Poisoning and Drug Overdose ManagementTrainingfor HealthCare Professionals

Participants' Manual

Addis Ababa, Ethiopia

March 2020

APPROVAL STATEMENT OF THE MINISTRY

The Federal Ministry of health of Ethiopia has been working towards standardization and institutionalization of In-Service Trainings (IST) at national level. As part of this initiative the ministry developed a national in- service training directive and implementation guide for the health sector. The directive requires all in-service training materials fulfill the standards set in the implementation Guide to ensure the quality of in-service training materials. Accordingly, the ministry reviews and approves existing training materials based on the IST standardization checklist annexed on the IST implementation guide.

As part of the national IST quality control process, this Poisoning and Drug Overdose Management Training IST training package has been reviewed based on the standardization checklist and approved by the ministry in June, 2020.

Assegid Samual Cheru
Director
Human resource development directorate
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Forward

Poisoning by chemicals is a significant risk in all countries where substantial quantities and increasing numbers of chemicals are being used in the development process. Similarly, in Ethiopia, various types of pesticides and herbicides are being used for agriculture and other types of chemicals are also being used for household, industries and public health. However, most of them may contain hazardous substances and impurities that can harm human health and environment, if not properly managed. These chemicals have been a source of both intentional and unintentional poisoning in all over Ethiopia, as the chemicals are vast and ever-changing management of patients in different set ups has been difficult and unharmonized.

Moreover, the type and number of drugs being available in the market is increasing including those which are inherently toxic. Taking too much of these drugs (overdose) at household and in hospital setups is not uncommon in our community. In addition, even though it has geographic differences, snake bite (envenomation) is also common particularly in the rural community.

Cognizant of this fact, Ministry of Health of Ethiopia has started the establishment of poison control centers andthe promotion of harmonized systems for recording data as one of its priority initiatives. In addition, in order to fill the gap of knowledge, attitude and practice of managing poisoning and drug overdose in facilities, poison management handbook and this training manual is prepared.

Therefore, this training manual provides guidance to all hospitals and health professionals to update their knowledge and to give appropriate care at all levels.

Finally, my sincere acknowledgement goes to the poison management technical working group and participants of consultative workshops for their commitment and unreserved contribution to the effort of developing this manual.

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Acknowledgment

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We also acknowledge FMOH IST/CPD team member, namely, Tegene Arega for their detailed review and comment of this training course.

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Acronyms

ABG	Arterial blood gas
ARDS	Acute respiratory distress syndrome
BUN	Blood urea nitrogen
BVM	Bag valve mask (BVM)
CBC	Complete blood count
CNS	Central nervous system
CO	Carbon monoxide
CO	Carbone monoxide
CPK	Creatinine phospho-kinase
ECG	Electrocardiogram
ED	Emergency department
FFP	Fresh frozen plasma
FMOH	Federal ministry of health
GCS	Glascow coma scale
GI	Gastrointestinal
ICU	Intensive care unit
IM	Intramuscular
INR	International normalized ratio
IV	Intra Venous
Kg	Kilogram
LD	Loading Dose
LFT	Liver function tests
MAOIs	Monoamine oxidase inhibitors
Mg	Milligram
ML	Milliliter
NAC	N-acetylcysteine
NG	Nasogastric
NGT	Nasogastric tube
NPA	Nasopharyngeal airway
NPO-	Nothing Per Ose

O2	Oxygen
OPA	Oropharyngeal airway
PIC	Poison information center
PT	Prothrombin time
PTT	Partial thromboplastin time
RBS	Random blood sugar
RR	Respiratory rate
SC	Subcutaneous
SW	Southwest
TCA	Tricyclic Antidepressant
TOT	Trainer of trainees
WHO	World Health Organization

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Introduction to the manual

Poisoning, whether accidental or intentional, is a significant global public health problem. According to WHO data, in 2012 an estimated 193,460 people died worldwide from unintentional poisoning. Of which, 84% occurred in low-and middle-income countries. Nearly a million people die each year as result of suicide, and chemicals take a major share of these deaths. It is estimated that deliberate ingestion of pesticides causes 370,000 deaths each year.Acute poisonings or drug overdoses constitute a significant source of aggregate morbidity, mortality, and health care expenditure. The true incidence is unknown due to under diagnosis and underreporting.

Even though, the diagnosis and management of poisonings are given at different level of care starting from the site of incident to health facility level, the management approach very much dependent on the knowledge and skill of the individual healthcare provider. In addition, managing acute cases requires an attitudinal change as survival and sequel of exposure can be prevented from early and aggressive handling of life-threatening conditions.Moreover, poisoning and drug overdose management is not adequately addressed in most of pre-service curriculums.

To this effect, developing a national training material on poison and drug overdose management is found to be critical comprising the mechanism of toxicity, toxic dose, clinical presentation of poisoning and the methods of diagnosis approach will make management of victims appropriate.In addition, it is high time that the primary care providers at the front line understand that poisoning is a preventable and treatable condition.Besides, it is at most important to equip providers with the necessary knowledge and attitude on poison information centers establishment.

The core competency of this training course is:

- Evaluate clients presented with acute poisoning and drug overdose
- Promptly manage clients presented with acute poisoning and drug overdose
- Identify the specific management options for acute poisoning and drug overdose
- Monitor therapeutic outcomes of acute poisoning and drug overdose
- Establish and run a Poison Information Centre

The course follows adult learning approach to build on the existing knowledge and skills of healthcare provider on poisoning and drug overdose.The main topics in this training course are introduction to poisoning, general evaluation and treatment of acute poisoning and drug overdose, diagnosis and treatment of poisoning by specific agents, diagnosis and treatment of poisoning by specific drug overdoses, and establishment and runningpoison information center.

Course syllabus

Course Description

This5-day training course on ‘poison and drug overdose management for healthcare professionals’ is designed to prepare healthcare providers in the prevention, treatment, and care of clients with acute poisoning and drug overdose. In addition, it aims to introduce the trainees about poison information center and poison control center. It contains an introduction of poisoning, the general approaches in the evaluation and management of clients with acute poisoning and the management of acute poisoning and drug overdose for specific agents.

Course Goal

The goal of this training course is to equip healthcare professionals with the necessary knowledge, skills and attitudes needed to manage clients with acute poisoning and drug overdose for better treatment outcome of emergency service.

Participant learning objectives

By the end of the training course, the participants will be able to:

- Recognize the global and national epidemiology of acute poisoning and drug overdose
- Identify the most common poisoning agents in our country
- Evaluate clients presented with acute poisoning and drug overdose
- Promptly manage clients presented with acute poisoning and drug overdose
- Identify the specific management options for acute poisoning and drug overdose
- Monitor therapeutic outcomes of acute poisoning and drug overdose
- Provide effective counseling and education for clients with intentional poisoning

- Establish and run a Poison Information Centre

Training methods

- Interactive presentation
- Group discussions
- Group work
- Demonstrations
- Case studies
- Individualreading

Learning materials and resources

- Participant manual
- Facilitator's guide
- PPT
- Flip charts
- Laptop and LCDs
- Markers, notepad, pens/pencils
- Demonstration equipment(manikins or dolls, nasopharyngeal airway, oropharyngeal airway, bag valve mask (BVM), different face masks, ECG monitor)

Participant selection criteria

- Participants for this course should be health professionals including physicians, Nurses, Health Officers and Pharmacists who are working in the emergency department, intensive care units (ICU), poison control centers and poison information centers. In addition, program managers and RHB/MOH officers can take the training for effective program support, and monitoring and evaluation.

Evaluation methods

- **Trainees evaluation**
  - Formative

- Pretest
- Question and answer
- Group discussion with feedback
- Presentations with feedback
- Case studies with feedbacks
- Participant attendance
- Recap
- Practical skill

❖ Summative

- Post-course test (75 %)
- End of course evaluation

➢ **Certification criteria**

- Certificate will be provided to participants who have scored more than 80% on summative assessments with 100% attendance.

➢ **Course evaluation**

❖ Daily evaluation

❖ End-of-course evaluation

❖ Participant oral feedbacks

Suggested class size

- The number of trainees shall be 20 - 25 in each training session and at least 4 trainers.

Trainer selection

- Trainers for this course should be health professionals who developed the training manual and/or healthcare professionals with TOT certificate on ‘poison and drug overdose management training course for health professionals.

Course duration

- 5-days training for basic and 7-days for TOT.

Training venue

- The training will be conducted at selected national and regional IST centers/CPD providers having appropriate facilities, trainers, and attachment health facilities.

Course schedule

Date &Time	Time	Topic	Presenter
Day 1	8:30-9:15	**Registration, introduction, Welcoming**	
	9:15- 10:00	**Pre-test**	
	10:00-10:15	Tea break	
	10:15-11:00	**Introduction to poisoning** • Definition • Epidemiology • Types and common causes • Prevention	
	11:00-12:00	**General approach to poisoned patients** • General principles • Resuscitation • Diagnosis	
	12:00- 1:30	Lunch	
	1:30-2:15	**Decontamination principles** • GI decontamination • Enhanced elimination	
	2:15-3:15	**Resuscitation and management of poisoned patients** • ABCDE approach • Life threatening complications & their management	
	3:15-3:30	Tea break	
	3:30-4:30	**Skill station on management of ABC** • Group practice on ABC management	
	4:30-5:00	**Daily evaluation**	
Day Two	8:30-9:00	Recap	
		Organophosphates and other Herbicides • Introduction • Common compounds • Diagnosis • Management	

	9:00-10:30	**Common poisoning agents in our set up (new chemicals)** • New chemicals • Toxidrome approach • Management	
	10.30-10.45	Tea break	
	10.45- 11;30	**Opioid poisoning** • Introduction • Common compounds • Diagnosis • Management	
	11:00- 12:15	**Paracetamol poisoning** • Introduction • Diagnosis • Management	
	12.00- 1.30	LUNCH	
	1:30-2:30	**Caustics and corrosives** • Introduction • Common compounds • Diagnosis • Management	
	2:30-3:15	**Alcohol poisoning** • Introduction • Diagnosis • Management • Complications	
	3:15-3:30	Tea break	
	4:30-5:00	**Daily Evaluation**	
Day Three	9:00-9:20	**Recap**	
	9:15-10:15	**Sedative hypnotics** • Introduction • Common compounds • Diagnosis • Management	
	10:15-10:30	Tea break	
	10.30- 12:30	**Anticonvulsants** • Introduction • Common compounds • Diagnosis	

		• Management	
	12.30- 1.30	Lunch	
	1:30-2.20	**Rodenticides** • Introduction • Common compounds • Diagnosis • Management	
	2:20-3-00	**Cyclic Antidepressants** • Introduction • Common compounds • Diagnosis • Management	
	3.00-3:30	Tea break	
	3.:30-4:30	**Household products poisoning** • Introduction • Common compounds • Diagnosis • Management	
	4: 30:5:00	**Daily evaluation**	

	9:00-9:15	**Recap**	
	9:15-9:45	**Carbon Monoxide poisoning** • Introduction • Common compounds • Diagnosis • Management	
	9:45-10:45	**NSAIDs** • Introduction • Common compounds • Diagnosis • Management	
	10.45-11:00	**TEA BREAK**	
Day Four	11:00-12:30	**Hydrocarbons**	
	12.00- 1.30	Lunch	
	1:30-:3:15	**Snake Bites** • Introduction • Diagnosis • Management • Antivenoms	
	3:15-3;30	**Tea break**	
	3:30-4:30	**Herbal Medicine and Mushroom poisoning** • Introduction • Common poisonous agents • Management	
	4:30- 5:00	**Daily evaluation**	
	8:30-9:00	**Recap**	
Day five	9:00-10-00	**Poison information center** • Introduction • Requirements to establish and run a PIC • Governance, organization, and operation of a PIC • Tasks of a PIC • Roles of a PIC in chemical incidents	
	10.00 -10:30	Tea	
	11:00-12:30	**Posttest& certificates**	
	12.30- 1.30	LUNCH	
		Closing remark& way forward	

Chapter 1: Introduction to Poisoning

Time: 45 minutes

Chapter description

This chapter will focus about overview of poisoning and drug overdose designed to enable participants to define poisoning, understand the epidemiology of poisoning and types and common causes of poisoning.

Primary objective

By the end of this chapter, participants will be able todefine poisoning, describe the global and national burden of acute poisoning.

Enabling objectives

- Define poisoning
- Explain route of exposure
- Describe the global and national burden of poisoning
- Explain poisoning types and their common causes
- List prevention methods of poisoning

Chapter Outline

1.1 Definition of poisoning

1.2 Route of exposure

1.3 Epidemiology of poisoning

1.4 Types and common causes of poisoning

1.5 Prevention methods of poisoning

1.6 Summary

1.1 Definition of poisoning

Learning Activities (5 minutes):

- What is poisoning
- List route of exposure for poisoning
- What type of poising agent do you know?
- Is adult or pediatric poisoning common?

- Poisoning is an exposure to an amount of substance that is likely to produce untoward effects in an individual. Or *Poisoning* occurs when exposure to a substance adversely affects the function of any system within an organism.
- Advances in technology and social development have resulted in the availability of most drugs and chemical substances in the community.
- These chemical substances pose a significant threat due to their poisonous effect and extensive use in medicine, agriculture, industry, and residential environments.

1.2 Route of exposure

- Route of exposure for poisoning can be through ingestion, Injection, inhalation insufflations and contact. Toxicity level of a poisoned agent depends on the type of agent, doses, route of exposure, timing and the host health conditions. Oral ingestion is identified as the primary route of poisoning.

1.3 Epidemiology of poisoning

- Poisoning is a common reason for emergency departments visit and hospitalization worldwide with major morbidity and mortality in many countries. It is the third most common emergencies of pediatrics leading to increased childhood morbidity and mortality. World Health Organization (WHO) estimated 0.3 million people die every year due to various poisoning agents.
- Accidental and intentional poisoning remains a major cause of morbidity, mortality and health care expenditure worldwide. The global incidence of poisoning is not known. It may be speculated that up to half a million people die each year as a result of various kinds of poisoning. In the US in the year 2014, 2,165,142 human exposures were reported, 9% per year since 2000. The top 5 substance classes most frequently involved in all human exposures were analgesics (11.3%), cosmetics/personal care products (7.7%), household cleaning substances (7.7%), sedatives/hypnotics/antipsychotics (5.9%) and antidepressants (4.4%). Sedative/Hypnotics/ Antipsychotics exposures as a class increased most rapidly (2,368 calls (12.2%)/year) over the last 13 years for cases showing more serious outcomes. Rates of poisoning cases among Emergency Department (ED) patients appear similar in other industrialized nations.
- WHO estimated that there were 16, 500 deaths in 2012 from unintentional poisoning in 16 African countries. In addition, unintentional poisoning caused the loss of 1 128 500 years of healthy life (disability adjusted life years, DALYs) in these countries. These

figures underestimate the true impact of poisoning since they do not include intentional self-poisoning or poisoning due to snakebite. It has been estimated, for example, that there are in the order of 7800 deaths per year in Africa due to deliberate ingestion of pesticides and between 1400 and 10 000 deaths from snakebite in eastern sub-Saharan Africa.

- Although there are few studies done on poisoning in Ethiopia, acute poisoning is an important problem. Out of 116 adult patients presented with poisoning to Tikur Anbessa Specialized Hospital (TASH) from January 2007 to December 2008, females outnumbered males and mean age was 21 years, most being (96.5%) intentional self-harm poisonings. Household cleansing agents were the leading causes (43.1%) followed by organophosphates (21.6%) and phenobarbitone (10.3%).
- A study done on childhood poisoning in four hospitals located in Addis Ababa showed that it is not an uncommon problem and most of the children were poisoned with drugs prescribed for themselves or family. Most of the incidents were unintentional and occurred at home. Another study done in Gondar University teaching hospital indicates that acute poisoning accounts for 0.45% of emergency admissions. Organophosphates, rat poison and alcohol were implicated in majority of the cases for suicidal as well as para-suicidal intentions.

1.4 Types and common causes of poisoning

- Acute pesticide poisoning is one of the most common causes of intentional deaths worldwide. High doses of analgesics, tranquillizers, and antidepressants are the commonly used agents for intentional poisoning in industrialized countries and majority of pesticide exposure is seen more in middle and low-income countries due to increased use of agrochemicals in agricultural sector.
- Most poisoned patients seen in the emergency department are adults with acute oral drug overdoses.
- Childhood poisoning is usually accidental and tends to be associated with a low morbidity and mortality. In Western Europe and North America, it is most often due to household products and pharmaceuticals; in developing countries, paraffin, traditional medicines, snakes bites and insect stings are more commonly involved.
- In adults, self-poisoning is usually deliberate (suicide or parasuicide) and has a higher morbidity and mortality rate. Analgesics and psychotropics predominate in Western Europe and North America as causes of admission to hospital, though carbon monoxide is responsible for most deaths (the majority of which occur outside hospital). In developing

countries, accidental and deliberate pesticide poisoning is probably the commonest cause of adult deaths.

- In Ethiopia, Organophosphates and household cleansing agents are the predominant agents of acute poisoning. This is not surprising in that organophosphate compounds (OPCs) are widely used in third world countries like Ethiopia to increase the yield of agriculture products to meet the highly increasing demand of the society.
  - If the toxic effects occur immediately, usually within hours from the time of exposure, is called acute poisoning. Acute poisonings or drug overdoses constitute a significant source of aggregate morbidity, mortality, and health care expenditure. The true incidence is unknown due to under diagnosis and underreporting.
  - Chronic poisonings or poisonings with delayed health effects are often more problematic in the long run.Chronic poisoning occur from drug abuse or from environmental, industrial, and agricultural chemical exposure; medication reactions or interactions; and envenomation.
- Poisoning can be intentional or unintentional. Intentional poisoning often occurs in patients with depression or coping difficulties and may need extra psychological, familial or social attention. While the medical burden of intentional poisonings seems to be equal for similar severe cases.Its burden includes physical as well as mental disabilities.

1.5 Prevention methods of poisoning

Here are some globally proven techniques to decrease the burden of poisoning

- Store medicine, cleaning and laundry products, (including detergent packets) paints/varnishes and pesticides in their original packaging in locked cabinets or containers, out of sight and reach of children.
- The safest place to store poisonous products is somewhere a child can't see or reach.
- Purchase and keep all medicines in containers with safety caps. Discard unused medications.
- Never refer to medicine as “candy” or another appealing name, when giving to children.
- Never place poisonous products in food or drink containers. For E.g. keeping kerosene in water bottles, children can mistake it for water.
- Keep natural gas-powered appliances, furnaces, and coal, wood or kerosene stoves in safe working order.

- Maintain working smoke and carbon monoxide detectors, when available. But always use cooking charcoal out of the house or in a well-ventilated area. Carbon monoxide poisoning is a serious health hazard.
- Secure remote controls, key fobs, greeting cards, and musical children's books. These and other devices may contain small button-cell batteries that can cause injury if ingested.
- Always be on the lookout for a depressed family member, advice on psychiatric care when needed.
- Advice family members to monitor and administer anti depressant and other drugs to family members. They may escape taking the drugs or may overdose of given a large amount till their next follow up.

1.6Chapter Summary

- Poisoning is an exposure to an amount of substance that is likely to produce untoward effects in an individual. Or *Poisoning* occurs when exposure to a substance adversely affects the function of any system within an organism.
- Route of exposure for poisoning can be through ingestion, Injection, inhalation insufflations and contact.
- Toxicity level of a poisoned agent depends on the type of agent, doses, route of exposure, timing and the host health conditions
- The global incidence of poisoning is not known. Accidental and intentional poisoning remains a major cause of morbidity, mortality and health care expenditure worldwide.
- Poisoning is a common reason for emergency departments visit and hospitalization worldwide with major morbidity and mortality in many countries.
- Although there are few studies in Ethiopia, acute poisoning is an important problem.
- Poisoning incidence could be acute or chronic.
- Poisoning can be intentional or unintentional.
- Poisoning is a preventable and manageable condition and there are globally proven techniques to decrease the burden of poisoning.
- Childhood poisoning is usually accidental with a low morbidity and mortality.

Chapter 2: General approaches to acute poisoning

Time allocated:4 hours

Chapter description

This chapter will focus on the general assessment and management approach for a poisoned patient in systematic and organized manner. It also familiarizesfamiliarize the trainees to resuscitation, common toxidromes, antidotes and different decontamination techniques.

Primary objective

At the end of this chapter, participants will be able tomanage patients with acute poisoning in systematic and organized manner.

Enabling objectives

- Explain how to diagnose and resuscitate patients with poisoning
- Define toxidromes
- Describe common type of Toxidromes
- Describe investigation modalities in poisoned patient
- Describe decontamination techniques
- Explain the common antidotes
- Describe the disposition of patients with poisoning

Chapter Outline

2.1 Introduction

2.2 Initial approach(resuscitation)

2.3 Diagnosis of Poisoning

2.4 Decontamination technique

2.5 Common antidotes

2.6 Disposition of patients with poisoning

2.7 Summary

2.8 Practical session

2.1 General approach to acute poisoning

Case study:

A 25-year-old female patient comes to ED after she ingested unknown substance of 6 hrs duration. At triage area, she was uncommunicative and with smells of garlic odor and her clothes are soaked with vomitus materials.

Vital signs were: 100/60 HR 72 RR 34 spo2 72 % with room air and 92% with facemask oxygen. After she immediately transferred to resuscitation area,her ABCDE assessment shows:

Airway: full of secretion?

Breathing: bilateral coarse cripitation and wheezing, Spo2 92% with facemask

Circulation. BP 100/60 HR 72

Disability: Pupils pinpointed bilaterally, GCS 7/15, RBS 126mg/dl

Exposure: wet skin and her under wear soaked with urine

A. How do you like to manage this patient?
B. What Toxidromes this patient had
C. What is the most likely diagnosis
D. What is the subsequent Management

2.1.1 Introduction

- In the management of acutely poisoned patients, we must consider the dose of the substance ingested, time since ingestion, clinical features, patient factors, geographical location, and available medical facilities.
- A highly organized approach is essential to ensure effective delivery of time-critical interventions while at the same time devising a management plan tailored to the individual patient's needs in that particular medical setting.
- The first priority in treating poisoned patients is assessment and stabilization of cardiopulmonary function (e.g., the ABCs, or *a*irway, *b*reathing, and *c*irculation).
- The general approach to the diagnosis and management of the poisoned patient can be described using a two-pronged model as depicted in Fig.1.1 as well as by the approach outlined in Box 1.1.

- The left-sided prong begins with basic emergency medical care-the ABCs (airway, breathing, circulation).
    - In most potentially poisoned patients, a rapid blood glucose measurement should be obtained, and any derangements corrected.
    - Supplemental oxygen, naloxone and thiamine should be considered in the appropriate cases and situations.
    - The various methods of decontamination should be considered in any poisoned patientbased on each individual clinical situation.
    - Once a poisoning has been identified, methods of enhanced elimination should be considered. Focused therapy involves antidote administration when appropriate or aggressive supportive care tailored to the poison in question.
    - Finally, when treating any poisoned patient, it is prudent to consider early consultation with a toxicology service or local poison control center for further
- The right-sided prong on the diagram focuses on obtaining the poisoningand other patient history, performing a focused physical examination withattention to toxidrome recognition, and deciding on the appropriate diagnostictests to be performed.

NB: The two prongs often occur simultaneously and are integral to the diagnosis and management of a poisoned patient.

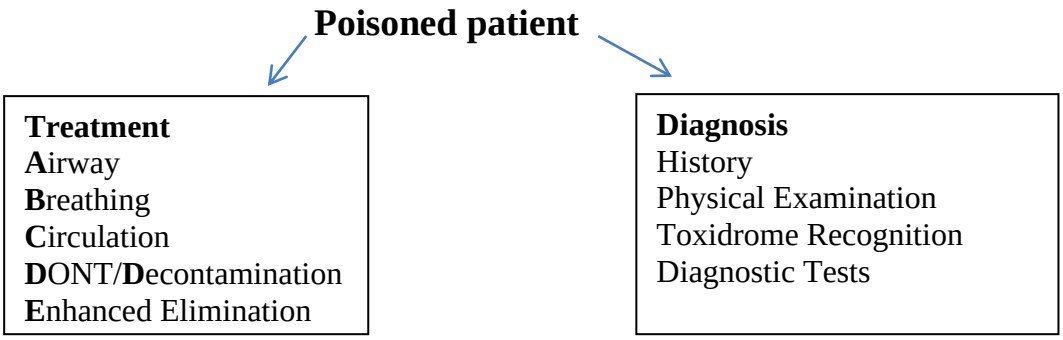


Fig 1.1: The two-pronged approach to the poisoned patient: DONT stands for dextrose, oxygen, naloxone, and thiamine. It applies in case of uknown poisoning with unconsciousness and coma. Treat hypoglycemia with IV dextrose (glucose). Patients at risk of Wernicke's encephalopathy also require thiamine, but do not require that it be administered before the dextrose. Altered mental status, when hypoglycemia cannot be excluded, is an indication for IV dextrose. Supplemental oxygen, thiamine, glucose, and naloxone are often administered empirically as a cocktail in cases of altered mental status.

Box 1.1: General approach to acute poisoning

i) Resuscitation – Airway – Breathing – Circulation – Seizure control – Correct hypoglycaemia – Correct hyperthermia – Resuscitation antidotes	ii) Risk assessment iii) Supportive care and monitoring iv) Investigations – Serum level (paracetamol, alcohol, aspirin – ECG v) Decontamination vi) Enhanced elimination vii) Antidotes viii) Disposition

2.1.2 Initial approach (Resuscitation)

Learning activity 1:

1. What are the components of ABCDE assessment?

I. Airway

- ✓ Loss of airway patency and reflexes may lead to obstruction, aspiration, or respiratory arrest.
- ✓ Maintain proper airway position; suction; use oropharyngeal or nasopharyngeal adjuncts as needed.
- ✓ Absent or depressed gag reflex in an unconscious or obtunded patient indicates an inability to protect the airway; so endotracheal intubation strongly considered if there is doubt about the patient's ability to protect the airway and avoid aspiration
- ✓ In-line cervical immobilization is required in patients with suspected occult trauma.

II. Breathing

- ✓ Respiratory failure is the most frequent cause of death in poisoned patients, and usually it is a result of (CNS) central nervous system depression.
- ✓ Assessing Breathing pattern, RR, Spo_2 measurement is very important
- ✓ Assist ventilation and administration of oxygen is important if the ventilation desaturation is compromised.
- ✓ Obtain and follow arterial blood gases.

III. Circulation

- ✓ Monitor blood pressure, pulse, and cardiac rhythm.
- ✓ Initiate intravenous line.
- ✓ If hypotension is present, administer fluid challenge with normal saline10–20 mL/kg.
- ✓ If hypotension persists, administer vasopressor such as norepinephrine can also be used.

IV. Disability

- ✓ Assessment of mental status (assessing GCS), gross motor movement, Pupillary size and reactivity to light.
- ✓ Determination of random blood glucose level. Rapid RBS test strips may be used to guide dextrose administration.
- ✓ Empiric administration of dextrose is recommended for the patient with altered consciousness when test strip glucose measurements are low or borderline low, not immediately available, or the accuracy of their results is questioned.

V. Exposure

- ✓ Complete exposure and examination of the patient
- ✓ Measurements of core temperature are essential.
- ❖ Indication for intubation in a poisoned patient or Suspected poisoning
- ✓ Respiratory failure
- ✓ Comatose patient who fails to protect air way
- ✓ Hypoxia refractory for no invasive oxygen administration
- ✓ Anticipation of Deterioration etc.

- ❖ Bradyarrhythmia associated with hypotension should be treated in the standard fashion with atropine or temporary pacing.
- ❖ In patients with calcium channel blocker or beta blocker intoxication, the administration of calcium and glucagon may obviate the need for further management.

- Drug-induced agitation is generally best treated with benzodiazepine administration, supplemented with high potency neuroleptics (haloperidol).
- Benzodiazepines to treat tachycardia secondary to sympathomimetic agents.
- Seizures, hypoglycemia, and hyperthermia must be detected and treated promptly to ensure good neurological outcome.
- Toxin-induced seizures tend to be global central nervous system (CNS) processes and are Grand mal or GTC in nature.
- Toxic seizures are usually controlled with iv benzodiazepines.
- Barbiturates are second line, and Pyridoxine is an additional option for seizures associated with poisoning from isoniazid.
- Phenytoin is not useful in the treatment of toxic seizures, and may worsen toxicity.

- Administration of an antidote may constitute an essential component of initial resuscitation.

2.1.3 Risk assessment

Following resuscitation, risk assessment is the next essential step in management of the poisoned patient (see box below). Risk assessment is a distinct cognitive process through which the clinician attempts to predict the likely clinical course and potential complications for the individual patient at that particular presentation. Risk assessment should be quantitative and take into account agent, dose, time of ingestion, current clinical status and individual patient factors (for example, weight and comorbidities). Risk assessment is vital as it allows the clinician to make specific decisions about all subsequent management steps (appropriate supportive care and monitoring; screening and specialized testing; decontamination; enhanced elimination; antidotes and disposition) that are appropriate to the individual patient at that particular time.

Box 1: Risk assessment

- Distinct cognitive step
- Quantitative
- Takes into account:
  - Agent(s)
  - Dose(s)
  - Time since ingestion
  - Current clinical status
  - Patient factors

2.2. Diagnosis of poisoning

Learning activity 2:

1. What is the importance of toxidromes in diagnosing patient with poisoning?

The history, physical examination, and routine and toxicological laboratory evaluations are used to establish and confirm the diagnosis of poisoning.

2.2.1 History taking

- It is often difficult to obtain a reliable and accurate history from overdose patients.
- These difficulties may result from a global alteration of mental status, but often there are underlying motivations, secondary gains, and perceived risk of arrest that may affect the history a patient provides.
- Obtain as much information as possible about the exposure.
- Ask about the agent or drug, estimated amount or dose, and route of exposure, as well as whether other individuals were exposed and duration of exposure
- If possible, the patient's intent should be determined.
- Corroborating information should be obtained from the patient's family members, prior medical records, witnesses.
- Ask about the environment in which the patient was found, the presence of empty pill bottles or containers nearby, any smells or unusual materials in the home, the occupation or hobbies of the patient, and the presence of a suicide note.

2.2.2 Physical examination

- An organized approach is recommended when evaluating patients with potential toxic exposures.
- Undress the patient completely.
- Check the patient's clothing for objects still retained in the pockets or substances hidden on the patient's body (waistband, groin, or between skin folds).
- Search clothing and belongings with care to avoid being injured by uncapped needles or sharp objects.
- Any odors on the patient's clothes should be noted.
- Assess the general appearance of the patient and note any agitation, confusion, or obtundation.
- Examine the skin for cyanosis or flushing, excessive diaphoresis or dryness, signs of injury or injection, ulcers, or bullae.
- Bruising may be a clue to trauma, a prolonged duration of unconsciousness, or coagulopathy.
- Examine the eyes for pupil size, reactivity, nystagmus, deconjugate gaze, or excessive lacrimation.

- Examine the oropharynx for hypersalivation or excessive dryness. Auscultate the lung fields to assess for bronchorrhea or wheezing, and the heart for its rhythm, rate, and regularity.
- Examine the abdomen, noting the presence of bowel sounds, enlarged bladder, and abdominal tenderness or rigidity.
- Evaluate the extremities for muscle tone and note any tremor or fasciculation.
- If the patient's condition allows, a more intensive neurologic assessment of cognition, cranial nerves, tendon reflexes, muscle strength, coordination, and gait is useful.
- The mental status, vital signs, and pupillary examination are the most useful elements and allow classification of the patient into either a state of physiologic excitation or depression
- Physiologic excitation, manifested by central nervous system stimulation and increased pulse, blood pressure, respiratory rate and depth, and temperature, is most commonly caused by anticholinergic, sympathomimetic, or central hallucinogenic agents, or by drug withdrawal states.
- Physiologic depression, manifested by a depressed mental status, blood pressure, pulse, respiratory rate and depth, and temperature, is most commonly precipitated by cholinergic (parasympathomimetic), sympatholytic, opiate, or sedative-hypnotic agents, or alcohols.
- Mixed physiologic effects occur in polydrug overdoses or following exposure to certain metabolic poisons (eg, hypoglycemic agents, salicylates, cyanide), membrane-active agents (eg, volatile inhalants, antiarrhythmic drugs, local anesthetic agents), heavy metals (eg, iron, arsenic, mercury, lead), or agents with multiple mechanisms of action (eg, tricyclic antidepressants).
- Discrepancies between the physical examination and the history may reflect an inaccurate ingestion history or a brief or prolonged time interval between exposure and physical examination. The physical examination, particularly the evaluation of mental status and vital signs, should be repeated frequently to determine the course of poisoning and the need for further intervention.
- Following the initial diagnostic evaluation and stabilization, other physical findings should be sought to further define a particular toxic syndrome (toxidrome) and to narrow the potential etiologies of poisoning.

2.2.3 Toxidromes recognition

- The term *toxidrome* refers to a syndrome or constellation of physical findings attributed to a specific class of toxins that can provide important clues to narrow the differential diagnosis.
- The most common toxidromes are the anticholinergic syndrome, Cholinergic syndrome, sympathomimetic syndrome, opioids, and serotonin syndrome.

Table 1 Common Toxidromes

2.2.4Laboratory tests

Toxidromes	**Mental status**	**Pupils**	**Vital signs**	**Other manifestation**	**Examples of toxic agent**
Sympathomimetic	agitation, hallucinations, paranoia	Mydriasis	Hyperthermia, Tachycardia; hypertension, tachypnea,	Diaphoresis, tremors ,hyperreflexia, seizures	✓ Cocaine ✓ amphetamines ✓ Ephedrine ✓ Theophylline
Anticholinergic	Agitation Hallucination delirium coma	Mydriasis	Hyperthermia, tachycardia, hypertension, Tachypnea	• Dry skin • decreased bowel sounds • urinary retention • Myoclonus	• Antihistamines • TCAs phenothiazines • atropine • scopolamine
Opioids	CNS depression Coma	Miosis	Hypotension Bradycardia Hypothermia Bradypnea, apnea	Hyporeflexia, pulmonary edema, needle marks	Opiates (eg, heroin, morphine, methadone, pethidine etc)
Sedative-hypnotic	CNS depression Stupor, confusion, coma	Miosis (usually)	Hypotension Bradycardia Hypothermia Bradypnea	Hyporefelxia	Benzodiazepines Barbiturate Ethanol
Cholinergic	Confusion, coma	Miosis	Bradycardia, HTN, Tachycardia Bradypnea	Salivation, Lacrimation, Urination, Emesis Defecation, fascicuation etc..	Organophosphates Carbamates etc
Serotonin syndrome	Confusion, agitation, coma	Mydrasis	Hyperthermia, tachycardia, hypertension, Tachypnea	Tremor,Myoclus, regidity,Clonus hyperreflexia,Trismus, diaphoresis,Diarrhea	MAOIs alone or with: SSRIs, meperidine, TCAs dextromethorphan,

❖ Symptomatic patients and those with an unreliable or unknown history should be investigated with at a minimum of:

- CBC
- Urinalysis

- Serum electrolytes
- BUN and creatinine
- Liver enzymes and Liver function test
- Serum glucose level
- Routine urine pregnancy testing is strongly recommended in all women of childbearing age

❖ The ordering of other laboratory studies should be individualized and is somewhat dependent upon the results of initial laboratory studies:

- Arterial blood gas, co-oximetry, and serum lactate measurements may be necessary in patients with acid-base, cardiovascular, neurologic, or respiratory disturbances.
- The presence of an anion gap metabolic acidosis may be the first clue to a toxic ingestion and should prompt measurement of serum salicylates, ethylene glycol, and methanol.\
- Co-oximetry can aid in the rapid diagnosis of carbon monoxide poisoning and methemoglobinemia.
- Toxic screening is rarely necessary when patients with a nonintentional ingestion are asymptomatic or have clinical findings that are consistent with the medical history.
- Drugs of abuse" immunoassay screens can be used to detect opiates, benzodiazepines, cocaine metabolites, barbiturates, tricyclic antidepressants,etc. in urine

2.2.5. Electrocardiogram (ECG)

It is a useful test to detect cardiac conduction abnormalities and identify patients at increased risk of toxin-induced adverse cardiovascular events. an ECG should be performed on all patients who are symptomatic or who have been exposed to potentially cardiotoxic agents.

Table 2 drug and toxin induced electrocardiographic abnormalities

Brady arrhythmias/AV blocks	**Supraventricular Tachyarrhythmia**	**Ventricular Tachycardia**	**QT and QT prolongation**
Beta blockers	Amphetamine	Amphetamine	Anti depressants
Calcium channel blockers	Cocaine	Cocaine	Anti Physchotics
Digoxin	Theophyline	Theophyline	Quinidine
Organophosphate	TCAs	TCAs	Amiodarone

Opoids	Atropine	Phenothiazines	Diphenyhydramine
Magnesium	Phenothiazines		
Sedative hypnotics	Epinephrine/Dopamine	Cardiac glycoside	Organophosphate

2.2.6 Radiographic studies

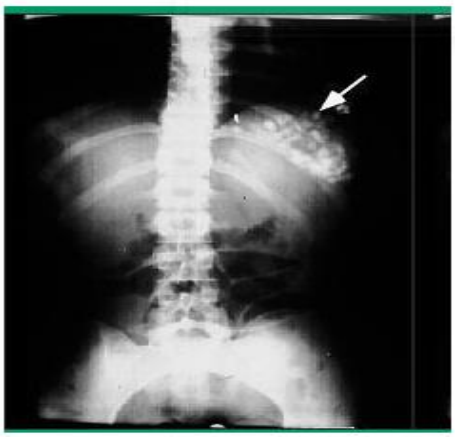
❖ Imaging studies are not required in every patient but may be useful in several situations

- Certain radiopaque toxins (summarized by the mnemonic "CHIPES") may be visualized by plain (Table-3)
- Ingested drug packets of "body packers" may be seen on plain film(figure-1)
- Noncardiogenic pulmonary edema and/or the acute respiratory distress syndrome due to exposure to certain toxic agents may be suggested by the appearance of the chest radiograph(patients with Organophosphate poisoning, CO poisoning, Beta Blockers etc..)

Table 3 Agents possibly radiopaque on plain x-ray

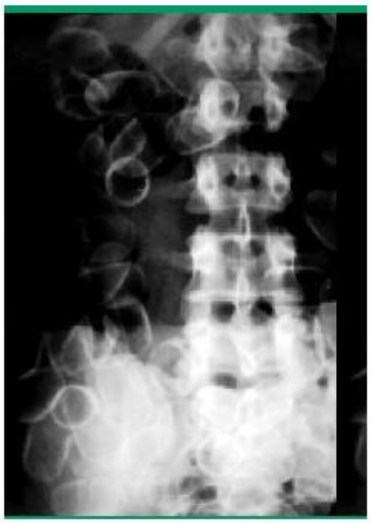
C	Chlorinated hydrocarbons(e.g chloral hydrate,carbon tetrachloride)
	Calcium salt (e.g calcium carbonate)
	Crack vials
H	Heavy metal (e.g iron,arsenic,mercury,thallium,lead)
I	Iodinated compound (e.g thyroxine)
P	Psychotropics (e.g phenothiazines, lithium, cyclic antidepressants)
	Packets of drugs (e.g cocaine and heroin “body packers”)
	Play-Doh
	Potassium salts
E	Enteric – coated tablets(e.g aspirin)
S	Salicylates
	Sodium salts
	Sustained – release preparations

Abdominal radiograph in iron overdose



Abdominal radiograph showing radiopaque iron (ferrous sulfate) tablets visualized in the stomach of an intentional overdose patient (arrow).
Courtesy of Michael J Burns, MD.

Drug packet ingestion



Abdominal radiograph showing radiopaque drug packets ingested by a "body packer."
Courtesy of Michael J Burns, MD.

2.3 Decontamination

- Following initial patient stabilization, patient decontamination may be performed if indicated. The sooner decontamination is performed, the more effective it is at preventing poison absorption.\
- Decontamination ideally occurs in a separate area adjacent to the ED, minimizing cross-contamination.

- Decontamination of severely poisoned patient must only be performed after careful consideration of the potential risks and benefits of the decontamination procedure.

2.3.1 Skin decontamination

- Corrosive agents rapidly injure the skin and must be removed immediately.
- Many toxins are readily absorbed through the skin, and systemic absorption can be prevented only by rapid action.
- Remove contaminated clothing and flush exposed areas with copious quantities of tepid (lukewarm) water or saline. Wash carefully behind ears, under nails, and in skin folds. Use soap and shampoo for oily substances.
- Health care providers should always wear personal protective equipments to prevent secondary contamination to themselves.

2.3.2 Ocular decontamination

- Eye exposures need prolonged irrigation with copious amount of water or saline
- Alkalis produce greater injury than acids due to deep tissue penetration via liquefaction so that prolonged irrigation (1 to 2 h) may be required.
- Ophthalmologic consultation is indicated for all ocular alkali injuries.

2.3.3 Gastrointestinal decontamination

- Gastric decontamination is not a routine part of poisoned-patient management
- Gastric decontamination may be considered in individual patients after a three-question risk-benefit analysis:
    - (i) is this exposure likely to cause significant toxicity?;
    - (ii) is gastrointestinal decontamination likely to change clinical outcome?; and
    - (iii) is it possible that gastrointestinal decontamination will cause more harm than good?
- Although gastrointestinal decontamination with activated charcoal and whole bowel irrigation may be of benefit particularly in early acute poisonings, it should only be attempted with careful consideration of the risks.

A. Gastric lavage

➢ Is the process of irrigating the gastric cavity to remove recently ingested material? (within two hours post ingestion)

Indication:

- Gastric lavage may be considered in cases of ingestion of a life-threatening amount of poison within the previous hour where institution of supportive care and antidotal therapy would not ensure full recovery once absorbed.
- In certain circumstances, such as delayed gastric emptying accompanying intoxication with anticholinergic drugs and phenobarbitone, benefit may be noted longer after ingestion.

Procedure:

- Ensure a protected airway if consciousness level is reduced.
- Use a 36 to 40F-gauge orogastric tube (22 to 24F in children).
- Position the patient on the left side with the head down 20 degrees.
- Pass lubricated tube down the esophagus, a distance equal to that between chin and xiphoid process.
- Confirm tube position by insufflation of air.
- Gently lavage with 200 mL (10 mL/kg in children) of warm tap water.
- Continue until returned fluid is clear.
- Consider administration of activated charcoal via orogastric tube before removal.
- Liquid agents can be lavaged with a smaller diameter nasogastric tube, but extraction of pill fragments requires use of a largebore tube (36–40 F).
- Large bore tubing may only be placed via the orogastric route to avoid trauma to the nasopharynx.

Complications:

- Placement of an orogastric tube is a distressing procedure to perform in an awake patient and may be complicated by gagging and aspiration.
- Other serious complications such as laryngospasm, dysrhythmia and perforation.
- Aspiration pneumonia/hypoxia
- Water intoxication
- Hypothermia
- Time consuming, resulting in delay instituting other definitive care

Contraindication:

- Contraindicated in cases of acid, alkali or hydrocarbon ingestion, and in comatose patients with absent gag reflex because of the risk of aspiration. (Airway should be protected by intubation first, in these patients).
- Supportive care/antidote likely to lead to recovery

- Unstable, requiring further resuscitation (hypotension, seizures)

B. Activated charcoal

Indications:

- Activated charcoal minimizes absorption of drugs by adsorbing them onto its surface.
- Charcoal administration has become the decontamination strategy of choice to prevent poisoning after toxicant ingestion and is most effective when used in the 1st hour after ingestion.
- Possesses large surface area that when administered orally, adsorbs ingested xenobiotics within the gastrointestinal tract thereby preventing systemic absorption.
- Some agents such as metals, ions and alcohols do not bind to charcoal.
- Significant increase in clearance for a number of drugs when repeated doses of 0.5 to 1 g per kg of activated charcoal are given every 4 to 6 h.

Contraindication:

- In patients with an unprotected airway (e.g., deeply comatous, depressed gag reflex) or a disrupted GI tract (e.g., after severe caustic ingestion, hypoactive bowel sound) or in patients in whom charcoal therapy may increase the risk and severity of aspiration (e.g., hydrocarbons).
- In addition, nontoxic ingestion, in this case toxin not adsorbed by activated charcoal and recovery will occur without administration of activate charcoal.

Complications:

- Bowel perforation or obstruction following multidose charcoal administration, vomiting, aspiration of the activated charcoal and impaired absorption of orally administered antidotes.

Dose and Administration:

- Poisoning (reduction of absorption), Oral: as soon as possible after ingestion of poison, **Adult,** 50–100 g as a single dose; **Infant,** 1 g/kg as a, single dose; **Child** 1–12 years, 25 g as a single dose (50 g in severe Poisoning).
- Poisoning (active elimination or multiple dose), Oral: **Adult,** 50 g every 4 hours (in case of intolerance 25 g every 2 hours); **Infant,** 1 g/kg every 4–6 hours; **Child** Over 1 year, 25–50 g every 4–6 hours.

C. Whole bowel irrigation

Indications:

- It uses a laxative agent such as polyethylene glycol to fully flush the bowel of stool and unabsorbed xenobiotics. Not recommended for routine use in the poisoned patient.
- May be considered for substantial ingestions of iron, sustained release products, enteric coated products and symptomatic acute lead toxicity with known lead particles in the gastrointestinal tract. It has been used for other metal ingestions (e.g., lead), overdoses of sustained-release medications (e.g., lithium, theophylline), ingested pharmaceutical patches, and ingestions of vials or packages of illicit drugs.
- It might also be useful in particularly massive and/or late-presenting overdoses for which the efficacy of gastric emptying and/or charcoal is expected to be suboptimal. The technique may be used by mouth in cooperative patients or by NG tube; the usual recommended dosing is 500 mL per hour (25ml/kg/hr, maximum 2L/h) in children and 2 L per hour in adolescents and adults.

Contraindication:

- In ileus, bowel obstruction or perforation, and in patients with hemodynamic instability. Unprotected airway, hemorrhage, Intractable vomiting

Complications:

- Nausea, vomiting, Pulmonary aspiration, Time consuming; possible delay instituting other definitive care

2.4Enhanced elimination

- In severely poisoned patient, enhancing the toxin elimination may improve outcomes for some poisonings.
- Procedures to enhance elimination of poisons include forced diuresis, urine ion trapping, hemodialysis, hemoperfusion, hemofiltration, and exchange transfusion. Various measures are useful in selected circumstances.

A. Urine alkalization:

Indication:

- It may be considered for agents that are excreted as weak acids in the urine (Moderate to severe salicylate toxicity not meeting criteria for hemodialysis).

- By alkalinizing the urine through use of iv sodium bicarbonate, these weak acids will remain in a more polar ionized form in the urine that limits reabsorption and enhances elimination.
- Urine alkalinization may be considered for, 2, 4-dichlorophenoxyacetic acid (2,4 D), methotrexate, phenobarbital and salicylates.

Contraindications:

- Preexisting fluid overload, renal impairment, and uncorrected hypokalemia.

Complications:

- Hypokalemia, volume overload, alkalemia and Hypocalcemia (usually mild)

B. Dialysis:

Dialysis is used to remove toxins or overdose of drugs and can be hemodialysis or hemoperfusion.

- **Hemodialysis:** Hemodialysis is movement of solute down a concentration gradient across a semipermeable membrane.

Indications: It may be considered for poisons that are amenable to filtration across dialysis membranes. These include agents that possess low volume of distribution (Vd), low protein binding, low endogenous clearance, low molecular weight. Examples of agents that are commonly encountered and may require hemodialysis include Lithium, Metformin lactic acidosis, Phenobarbital, Salicylates, Valproic acid, Methanol/ethylene glycol, Metformin-induced lactic

Contraindication: Hemodynamic instability, infants (generally), poor vascular access and significant coagulopathy.

- **Hemoperfusion:** Hemoperfusion is movement of toxin from blood, plasma, or plasma proteins onto a bed of activated charcoal (or other adsorbents).

Indications: It is useful for toxins with low VD, low endogenous clearance, and bound by activated charcoal. Examples of agents are Theophylline (high-flux hemodialysis is an alternative), Carbamazepine (multidose activated charcoal or high-efficiency hemodialysis also effective) and Paraquat (theoretical benefit only if instituted early after exposure).

Contraindication: Hemodynamic instability, infants (generally), poor vascular access, significant coagulopathy and toxin not bound to activated charcoal.

2.5 Antidotes

Although most poisonings are managed primarily with appropriate supportive care, several specific antidote agents may be employed.

The **Universal antidotes** are four classic compounds, which includes:

- **Oxygen:** for any cause of hypoxia
- **Dextrose:** insulin, hypoglycemics, coma, or protracted vomiting causinghypoglycemia
- **Naloxone:** Narcotics
- **Thiamine**: Wernicke`s or chronic alcohol abuse and in Malnourished patients.

The use of these antidotes should be individualized to the patient's condition.

Table 4 List of commonly used antidotes

S. No.	Antidote	Poisoning indication
1.	N-Acetyl cysteine injection, 140 mg/kg PO, then 70 mg/kg q4h for up to 17 doses.	Acetaminophen
2.	Polyvalent Immune Fab, ovine (Snake Venom Antiserum polyvalent Injection, 10ml)	Snake bite of unknown snake type
3.	Atropine Sulfate Injection, 1mg/ml in 1 ml ampoule	Organophosphorus and N-methyl Carbamates
4.	Calcium chloride *Injection, 10% (100mg/ml)*	Fluoride, Calcium Channel blockers
5.	Calcium gluconate *Injection, 10% in 10ml ampoule*	Fluoride, Calcium Channel blockers, Magnesium sulfate
6.	Calcium disodium EDTA†	Lead
7.	Calcium trisodiumpentetate (CaDTPA)	Plutonium, Americium or Curium
8.	Cyanide Antidote Kit* or Hydroxicobalamine HCl	Cyanide
9.	Deferoxamine mesylate	Iron
10.	Digoxin Immune Fab (Ovine) Digoxin specific, antibody fragments Powder for injection, 40mg	Cardiac glycosides/ Steroids
11.	Ethanol	Methanol or Ethylene glycol
12.	Flumazenil*	Benzodiazepine

	Injection, 0.1 mg/ml in 5 ml ampoule	
13.	Glucagon HCl	B-blocker, Calcium channel blockers
14.	Methylene blue	Methemoglobinemia
15.	Naloxone HCl Injection, 0.02mg/ml in 2ml ampoule, 0.4mg/ml in 1ml and 10ml ampoule, 1mg/ml	Opioid and Clonidine
16.	Octeriotide acetate	Sulphonylurea
17.	Physostigmine salicylate Injection, 1mg/ml in 1ml and 2ml ampoule	Anticholinergic syndrome
18.	Pralidoxime chloride Powder for injection, 1g/vial	Organophosphates and N-methyl Carbamate insecticides
19.	Pyridoxine hydrochloride *Injection, 50mg/ml in 2ml ampoule, 150mg/ml*	INH, Hydrazine
20.	Sodium bicarbonate Injection :	Sodium channel blockers;TCA
21.	Phytomenadione (Vitamin K inj.)	Warfarin, Rodent poisons
22.	Protamine Sulphate Inj.	Heparin
23.	Sodium Polystyrene Sulphonate Powder	Hyperkalemia
24.	Dextrose 40% injection	Insulin, oral hypoglycemic agents
25.	Thiamine	Alcohol intoxication
26.	Trimethoprim, methotrexate,	Leucovorin(Folinic acid)
27.	Penicillamine	Lead, copper, mercury,

2.6 Disposition

- Following initial evaluation, treatment, and a short period of observation, disposition of the patient is based upon the observed and predicted severity of toxicity.
- Patients who develop only mild toxicity and who have only a low predicted severity can be observed in the emergency department until they are asymptomatic.
- An observation period of four to six hours is usually adequate for this purpose.
- Patients with moderate observed toxicity or those who are at risk for such based on history or initial laboratory data should be admitted to the wards for continued
- Monitoring and treatment.

- Patients with significant toxicity should be admitted to an ICU.
- All patients with intentional overdose require psychiatric assessment prior to discharge.

2.7Chapter summary

- The general management and resuscitation of poisoned patients remains the same regardless of the specific toxicant.
- All patients should be approached in the basic ABC manner as any other emergency case.
- Ensure a patent airway, support breathing when needed and start crystalloid infusions in hypertensive patients.
- After patients are stabilized institute decontamination principles where appropriate.
- Gastric lavage and charcoal are indicated for patients that present within a couple of hours to hospital and always should be done after airway protection.
- Elimination techniques become in handy in severely poisoned patients presenting late to the hospital.
- Antidotes should be always be given after risk assessment is done for severe poisoning and after checking for any contraindications
- Toxidromes are constellations of sign and symptoms that can help us narrow down toxic agents to a certain group when the toxicant is unknown

Procedure for the practical session for resuscitation of poisoning patient

Parameter	Procedure
Airway opening maneuvers	Open airway using Jaw thrust maneuvers
	Open airway using head tilt and chin lift maneuvers
Use of airway adjuncts	Identify appropriate size of NPA
	Identify appropriate size of OPA
	Insert NPA appropriately on the manikins
	Insert OPA on manikins
Use of face mask	Identify different types of facemask
Use of BVM	Demonstrate how to use BVM on the manikins
ECG monitor	Demonstrate how to place ECG leads

Chapter 3: Diagnosis and Treatment of Poisoning by common chemicals and Envenomation

Time allocated: 8 hours 45 minutes

Chapter description

This chapter describes the evaluation and management of victims of poisoning by commonly used chemicals in our surroundings and poisonous snake bite. In each case of chemical exposure and envenomation; a summary about the nature/ route of the exposure, mechanism of toxicity, pharmacokinetics and toxic dose will be described. In addition, the clinical presentation, diagnostic methods, and treatment of each chemical and snake bite will be dealt. Under the treatment of each chemical and envenomation, specific treatment options including antidote therapy and anti-venom will be explained besides the general approaches of treatment.

Primary objective

At the end of this chapter, participates will be able to manage patients with specific chemicals and snake bite in an emergency.

Enabling objectives

- Explain the mechanism of toxicity for selected chemicals and envenomation.
- Identify the toxic doses of the specific chemical.
- Describe the clinical presentations of a specific chemical poisoning and envenomation.
- Discuss the diagnostic methods for specific chemical poisoning.
- Determine the treatment approaches for specific chemical poisoning.
- Discuss various species of snakes stressing on poisonous/venomous snakes.
- Discuss the general medical and surgical management of snake bite.
- Discuss the use of specific anti-venom and management of its allergic reaction.

Chapter outline

3.1 Organophosphates and Carbamates

Learning activity (5 minutes)

- **What are organophosphates?**
- **List common locally used chemicals of this type?**

Organophosphates and carbamates also known as cholinesterase inhibitors are widely used as pesticides that may cause human poisonings after accidental or intentional exposure. Poisonings are particularly common in rural areas where more potent agents are widely available as agricultural insecticides and home use. They can be absorbed via inhalation, ingestion, and skin contact.

Examples: Organophosphorus – malathion, parathion, TEPP, mevinphos (Phosdrin); and
Carbamates- methiocarb, carbaryl, Sarin, soman, tabun.

Mechanism of toxicity

- Organophosphates derivatives inhibit the enzyme acetyl cholinesterase, allowing the accumulation of acetylcholine at muscarinic receptors, at nicotinic receptors, and in the central nervous system. Permanent damage to the acetyl cholinesterase enzyme ("aging") may occur after a variable delay unless antidotal treatment with an enzyme reactivator is given. Afterwards, a period of weeks to months is required to regenerate inactivated enzymes.
- Carbamates also inhibit acetyl cholinesterase and produce similar clinical effects; however binding to the enzyme is reversible and toxicity is usually brief and self-limited, typically allowing reactivation of acetyl-cholinesterase within 24 hr.
- Some organophosphates may lead to delayed and persistent toxicity for several days after exposure.

Toxic dose

- There is a wide spectrum of relative potency of the organophosphates and carbamates.
- The degree of intoxication is also affected by the rate of exposure (acute versus chronic), the ongoing metabolic degradation and elimination of the agent, and for organophosphates, the rate of metabolism to their more toxic "-oxon" derivatives

Clinical presentation

- Signs and symptoms of **acute organophosphate poisoning** usually occur within 1–2 hours of exposure but may be delayed up to several hours, especially after skin exposure. Clinical manifestations may be classified into muscarinic, nicotinic, and CNS effects. In

addition, chemical pneumonitis may occur if a product containing a hydrocarbon solvent is aspirated into the lungs.

A. **Muscarinic** manifestations include vomiting, diarrhea, abdominal cramping, bronchospasm, miosis, bradycardia, and excessive salivation and sweating. Severe diaphoresis can actually lead to dehydration with systemic hypovolemia.
B. **Nicotinic** effects include muscle fasciculations, tremor, and weakness. Death is usually caused by respiratory muscle paralysis. Blood pressure and pulse rate may be increased because of nicotinic effects or decreased because of muscarinic effects.
C. Central nervous system poisoning may cause agitation, seizures, and coma.
D. Some organophosphates may cause a delayed, often permanent peripheral neuropathy.

Diagnosis

Based on the history of exposure and the presence of characteristic muscarinic, nicotinic, and CNS manifestations of acetylcholine excess.

There may be a solvent odor; some have a strong garlicky odor.

Specific levels measurement if available,Other studies include

Electrolytes, glucose, BUN, Creatinine, LFT, ABG, ECG monitoring, and CXR (if pulmonary edema or aspiration of hydrocarbon solvent is suspected).

Treatment

A. Emergency and supportive measures.

- Caution: rescuers and health care providers must take measures to prevent direct contact with the skin or clothing of contaminated victims, because secondary contamination and serious illness may result, especially with potent pesticides and nerve agents.
- ABC of life; Pay careful attention to respiratory muscle weakness; sudden respiratory arrest may occur. If intubation is required, better to use non-depolarizing neuromuscular blockers. Succinylcholine is degraded by plasma cholinesterase and may cause a prolonged paralysis. Administer supplemental oxygen.
- Treat hydrocarbon pneumonitis, seizures, and coma if they occur.
- Observe patients for at least 6–8 hours to rule out delayed-onset symptoms resulting from skin absorption.

B. Specific drugs and antidotes.

- Specific treatment includes the antimuscarinic agent atropine and the enzyme reactivator pralidoxime.
- After decontamination, antidotal therapy begins with the administration of atropine sulfate given:
    - 0.05 to 0.1 mg per kg to children and
    - 2 to 5 mg for adolescents and adults.
    - Doubled every 5 min as needed to obtain and maintain full atropinization, which is indicated by an end point of clearing bronchial secretions and pulmonary rales.
- Therapy is continued until all absorbed organophosphate has been metabolized and may require 2 mg to more than 2,000 mg of atropine over the course of a few hours to several days. The most clinically important indication for continued atropine administration is persistent wheezing or bronchorrhea.
- Note: Atropine will reverse muscarinic but not nicotinic effects.
- After atropinization has been instituted, severe poisonings should be treated with the addition of pralidoxime. This drug is particularly useful in poisonings characterized by profound weakness and muscle twitching.
    - A dose of 25 to 50 mg per kg should be administered in 100 mL of saline by infusion over approximately 30 minutes;
    - Adults may receive 1 to 2 g by IV.
    - In life-threatening situations, 50% of the initial pralidoxime dose may be infused over 2 minutes, followed by the remainder of the dose over 30 minutes. After loading, a 1% concentration may be infused continuously at the rate of 500 mg per hour in adolescents and adults, or approximately 10 mg per kg per hour in children, and can be titrated to clinical effect.
    - Occasionally, patients may require more than 48 hours of therapy; the end point should be persistent relief of neurologic and cholinergic signs.
- Pralidoxime (2-PAM, Protopam) is a specific antidote for organophosphate toxicity, that acts to regenerate the enzyme activity at all affected sites (muscarinic, nicotinic, and probably CNS; however, it does not reactivate plasma cholinesterase).
- Pralidoxime should be given immediately to reverse muscular weakness and fasciculations: It is most effective if started within the first 24 hours of the exposure

before irreversible phosphorylation of the enzyme, but may still be effective if given late, particularly after exposure to highly lipid soluble compounds.

- Pralidoxime is not generally recommended for carbamate intoxication, because in such cases the cholinesterase inhibition is spontaneously reversible and short-lived. However, if the exact agent is not identified and the patient has significant toxicity, pralidoxime should be given empirically.
- **Note:** Organophosphates are usually dissolved in hydrocarbon bases; thus, the clinician should be prepared to treat hydrocarbon pneumonitis if it develops. Also, bronchopneumonia that complicates the pulmonary edema has been observed in acute poisonings.
- Because the organophosphates cause elevated levels of acetylcholine in the plasma, compounds that affect the uptake of acetylcholine and/or its release should be avoided in the management of these patients. Specifically, aminophylline and phenothiazines are contraindicated.

C. Decontamination Note: The management of a patient who has ingested organophosphates must always include safeguards against exposure for the persons who treat the patient because the organophosphates are readily absorbed through the skin and mucous membranes. If there is heavy liquid contamination with a solvent, clothing removal and victim decontamination should be carried out outdoors or in a room with high-flow ventilation.

- Skin - Remove all contaminated clothing and wash exposed areas with soap and water, including the hair and under the nails. Irrigate exposed eyes with water or saline.
- Ingestion
    - Prehospital - Administer activated charcoal, if available. Do not induce vomiting because of the risk of abrupt onset of toxicity. (limited data on the effectiveness of charcoal)
    - Hospital - Administer activated charcoal (cathartics are not necessary if the patient already has diarrhea). Perform gastric lavage for large recent ingestions.

D. Enhanced elimination.

- Dialysis and hemoperfusion are not generally indicated because of the large volume of distribution of organophosphates and the effectiveness of the specific therapy described above.

An **"intermediate syndrome"** has also been described, characterized by recurrent muscle weakness occurring within several days (usually 1 to 5) of the exposure. Seen in around 40 % of patients following ingestion. It may be associated with inadequate pralidoxime therapy. Severe intoxications may also cause a toxic psychosis that resembles alcoholism.

Clinical features: include paralysis of neck flexor muscles, muscles inner-vated by the cranial nerves, proximal limb muscles, and respiratory muscles; respiratory support may be needed. Symptoms or signs of cholinergic excess are absent in this syndrome. Electromyography may assist in making the diagnosis. Aggressive, early antidote therapy and supportive measures may prevent or ameliorate the severity of this syndrome. Symptoms usually resolve within 7 days.

Chronic toxicityis seen primarily in agricultural workers with daily exposure, manifesting as symmetrical sensorimotor axonopathy. This mixed sensor motor syndrome may begin with leg cramps and progress to weakness and paralysis, mimicking features of the Guillain-Barré Syndrome.

Summary

- Organophosphate and carbamates are common compounds from the Cholinergic toxidrome group also known as ach-estrase inhibitors
- Common compounds include Malathion, Parathion, chloropyrophos from organophosphates and Sarin, Tabun etc from Carbamates.
- Organophosphates are usually used as herbicides and pesticides
- Carbamates are usually used as nerve gas agents
- Clinical presentation is DUMBELS or SLUDGE in mnemonics
- Management is mainly respiratory support and antidote administration.
- Antidote is Atropine for muscarinic features and pralidoxime, when available can prevent aging of the compounds at the cholinesterase bonding.
- After managing acute poisoning patients should be monitored for intermediate syndrome and delayed complications

3.2 Herbicide

Herbicides are used as a weed killer with different mechanism that includes inhibition of photosynthesis/ respiration/ protein synthesis.These agents can cause human toxicity; selected agents include:

3.2.1. ChlorophenoxyHerbicides

- The most common agent in this group are
    - **2,4-dichlorophenoxyacetic acid (2,4-D**); locally available also as Sura
    - 2,4,5-trichlorophenoxyacetic acid (2,4,5-T);
    - 4-chloro-2 Methylchlorophenoxyacetic acid;
- Human toxicity
    - can occur after dermal contact, inhalation or ingestion;
    - Mechanism is unknown;
    - Muscle is the primary target;
    - Minimum Toxic dose: 40-50 mg/Kg or 3-4 gm;

Clinical feature

- Eye and mucosal irritation after direct contact
- Nausea, diarrhea and vomiting after ingestion
- Dyspnea, tachypnea and pulmonary edema after inhalational exposure
- Systemic toxicity(If large exposure) result in :
    - Neurologic toxicity (Mental status changes and seizures);
    - Cardiac toxicity (hypotension, tachycardia, and dysrhythmias);
    - Skeletal toxicity (muscle tenderness, fasciculation, rhabdomyolysis)

Diagnosis

- Made by exposure history;
- No specific tests for its detection;
- Other:
    - Baseline;
    - CPK,
    - Urinalysis (occult heme test positive in the presence of myoglobin),
    - 12-lead ECG and monitoring

Treatment

- Supportive
- Decontamination measures,
    - Administer activated charcoal, then Perform gastric lavage;
    - After lavage, give a dose of charcoal;
    - Skin decontamination if exposed
- Respiratory support for myopathic-related respiratory failure,
- No specific antidote
- Urinary alkalinization will increase the elimination & is recommended for severely poisoned patients,
- Hemodialysis can also be used to enhance chlorophenoxy herbicide clearance,
- Patients should be monitored for rhabdomyolysis and treated as necessary.

Disposition:

- Asymptomatic or minimally symptomatic discharged after 4 to 6 hours of observation;
- Patients with muscle effects
    - Admit;
    - Close observation and monitoring.

3.2.2. Bipyridyl Herbicides

- Includes Paraquat and Diquat which are nonselective contact herbicides.

Paraquat (1, 1-dimethyl-4, 4'-bipyridylium chloride)

- Available as a liquid concentrate (20%), as granules (2.5-10%), or an aerosol (0.2%);
- Fast-acting, nonselective herbicide, used for killing grass and weeds by forming a toxic oxygen species like super-oxide, hydroxyl, and peroxide radicals that destroy lipid cell membrane;
- Human toxicity likely results from a similar oxidative mechanism; after which recruitment of inflammatory cells exacerbates injury;
- Plasma concentration peaks within minutes to 2 hours after ingestion, then distributed to most organs, with the highest concentrations found in the kidneys and lungs;
- In the lung paraquat accumulates and the high local oxygen tension generates a high levels of toxic oxygen species and subsequent damage;

- In the kidney paraquat is concentrated during excretion, often leading to acute tubular necrosis, which may occur soon after ingestion (within 24 hours); Paraquat-induced renal dysfunction may decrease paraquat excretion, thereby enhancing overall toxicity;
- A lethal oral dose of the 20% concentrate paraquat solution is about 10 to 20 mL in an adult and 4 to 5 mL in a child;
- Ingestion is responsible for the majority of paraquat deaths;
- Inhalation exposure to sprays can be very irritating to conjunctiva and the airway but are unlikely to cause systemic toxicity,
- Minimal transdermal absorption of paraquat in the absence of preexisting skin lesions.

Diquat

- Has similar structure and mechanism as paraquat,
- The lethal dose for diquat is similar to that of paraquat,
- Fewer occurrences of pulmonary injury and fibrosis because of diquat's lower affinity for pulmonary tissue,
- Caustic to the skin and GI tract, and exposure can result in renal and liver necrosis.

Clinical feature Bipyridyl poisoning (Paraquat)

- Depend on route of exposure and amount,
- Can result in local caustic effect or systemic toxicity from GI absorption,

  Direct local toxicity
- GI tract_ Ulceration of the lips, tongue, and pharynx within one to two days of ingestion, esophageal ulceration may proceed to esophageal perforation;
- Skin —skin rashes (particularly on scrotal and intergluteal areas), cracked nails, and epistaxis;
- Lungs — Inhalation may cause local toxic effects on bronchi, possibly resulting in cough, dyspnea, chest pain, pulmonary edema, epistaxis, and hemoptysis;
- Eyes —corneal exposure can cause ulceration and scarring;

  Systemic toxicity
    - Multisystem effects include acute renal failure, cardiac failure, hepatic failure, and extensive pulmonary injury,
    - Evident within a few hours following large ingestions, but more typical manifestations of renal failure and hepatocellular necrosis develop between the

second and fifth days, with progressive pulmonary fibrosis leading to refractory hypoxemia 5 days to several weeks later;

- Metabolic (lactic) acidosis is common as a result of pulmonary effects (hypoxemia) and multisystem failure;

Table 5 Paraquat toxicity from ingestion

Category	Clinical Features	Approximate Amount Ingested (In average adult)
Mild	Asymptomatic or Nausea, vomiting, and diarrhea; Renal and hepatic injury minimal or absent. Decreased pulmonary diffusion capacity may be present. Complete recovery expected.	<20 mg/kg or <7.5 mL of 20% concentrated solution
Severe	Initially nausea, vomiting, diarrhea, abdominal pain, mouth and throat ulceration. In 1–4 days: renal failure, hepatic impairment, hypotension. 1–2 week: cough, hemoptysis, pleural effusion, pulmonary fibrosis. Survival possible, but majority of cases die within 2–3 week from pulmonary failure.	20-40 mg/kg or 7.5-15 mL of 20% concentrated solution
Fulminant	Initially nausea, vomiting, diarrhea, and abdominal pain. Rapid development of renal and hepatic failure, GI ulceration, pancreatitis, toxic myocarditis, refractory hypotension, coma, convulsions. Death from cardiogenic shock and multi-organ failure within 1–4 d.	>40–50 mg/kg or >15–20 mL of 20% concentrated solution

Diagnosis

- Exposure history
- Paraquat test in urine/ blood
- Serial pulmonary function test
- Arterial blood gas determinations
- Upper GI endoscopy if indicated

- Laboratory abnormalities generally reflect multiorgan necrosis
    - Organ function test, serum electrolytee
    - Urine analysis
- CXR may show pneumomediastinum/pneumothorax due to corrosive rupture of the esophagus

Treatment

- Admit any patient with Paraquat poisoning even if asymptomatic,
- Supportive(ABC)care, includes:
    - Airway protection, maintaining intravascular volume, pain relief;
    - Treatment of renal failure and complications;
    - Treatment of infection,
- Do not administer supplemental oxygen unless the patient is severely hypoxic, because added oxygen stimulates superoxide radical formation and promotes oxidative stress,
- Maintain intravascular volume and urine output to prevent pre-renal kidney injury,
- Decontamination
    - Remove clothing for splash,
    - Skin washing with mild detergent for dermal contact,
    - Irrigate eyes with saline/ copious water if conjunctivae exposure,
    - Lavage not routinely recommended unless patient present early and for ingested,
        - Activated charcoal (1gm/kg up to 100 gm),and repeat dose in 1–2 hours
- Prolonged Hemoperfusion or Hemodialysis two to three weeks, 4-6 hours daily,
- Repeated pulse doses of glucocorticoids and cyclophosphamide may improve survival in severe cases,
- Treatment for diquat poisoning is similar to that for paraquat.

Organophosphate herbicides

- In addition to their use as insecticides, some organophosphate compounds are effective herbicides.
- Butiphos is used commonly as a cotton defoliant before mechanical harvesting.
- Treatment is identical to that for organophosphate insecticides.

Summary

- Herbicides eg. 2,4-D,Paraquat are used as weed killer and
- Human toxicity can occur un/ intentionally,
- Exposure can occur via skin contact, inhalational or ingestion
- Clinical feature depend on route of exposure and vary from local to systemic toxicity;
- Management should follow the general approach of a poisoned victim and usually supportive including hemodialysis.

3.3 Rodenticides

Are chemicals used for extermination of rodents like rat and mouse; sometimes used as a grain preservative by destroying insects; Classified based on whether the agent has anti-coagulant or non-anticoagulant effect,

3.3.1 Non-anticoagulant Rodenticides includes:

Arsenic, Barium carbonate/ hydroxide/ chloride/sulfide, Phosphorus (elemental/ yellow), sodium fluroacetate, Strychnine, Tetramine, Thallium Sulfate, Zinc/ Aluminum Phosphide, ANTU, Bromethalin, Dicaboximide, Vacor.

Zinc or Aluminum phosphide

Metal phosphides have been used as a means of killing rodents and are considered single-dose fast acting rodenticides (death occurs commonly within 1–3 days after single bait ingestion). A bait consisting of food and a phosphide (usually zinc phosphide) is left where the rodents can eat it, are used to preserve grain, especially wheat, and to kill rats.

Grain preservative is usually sold as tablets, and rat killer is sold as pellets.

Examples of locally available poisons include: Commando (Zn Phosphide) 80% , No Rat (Zn Phosphide), Celphos (Al Phosphide) 56% ,

Mechanism of action

Combines with water and gastric acid to produce phosphine gas heavier than air and has a characteristic fishy/ garlic odor;

Phosphine gas is a highly toxic gas, especially to organs of high oxygen flow and demand such as the lungs, brain, kidneys, heart, and liver;

Cause Cellular toxicity and necrosis to the GI tract, kidney, and liver if ingested and to the lungs if inhaled;

Toxic dose

The LD50 zinc phosphide in rats is 40 mg/kg; lowest reported lethal dose in humans is 4 g;

Ingestion of as little as 500 mg aluminum phosphide has caused death in an adult;

Clinical feature

The onset of symptoms is usually rapid, although delayed onset of pulmonary edema has been described;

Immediate nausea, vomiting, epigastric pain, phosphorous or fishy breath, black vomitus, and GI irritation or ulceration if ingested;

Inhalation of phosphine gas is associated with cough, dyspnea, headache, dizziness, and vomiting;

Myocardial toxicity, shock unresponsive to pressers, and acute lung injury, agitation, coma, seizures, hepato-renal injury, metabolic acidosis, hypocalcaemia tetany in both exposures has been observed;

Diagnosis

- Is based on a history of exposure to the agent;
- Other useful laboratory includes
    - BUN, Cr, electrolytes, liver transaminases, ABG or oximetry, and CXR;

Treatment

A. **Emergency and Supportive care**

- Maintain an open airway and assist ventilation if necessary,
- Administer supplemental O_2, and treat non-cardiogenic pulmonary edema if it occurs,

B. **Decontamination**

- Gastric lavage with potassium permanganate or combination coconut oil and 3-5%sodium bicarbonate
  (Reduce stomach acid and resulting production of phosphine gas);

C. **No specific antidote**

- Magnesium sulfate IV with low dose of dopamine may be beneficial;
- Consider acetylcysteine;

D. **Enhanced elimination.**

- Dialysis and hemoperfusion have not been shown to be useful in hastening elimination of phosphine.

E. **Disposition**

- Admit and observe for 48–72 hours for delayed onset of pulmonary edema,

3.3.2 Anti-coagulant rodenticides

First generation rodenticidal anticoagulants generally have shorter elimination half-lives require higher concentrations (usually between 0.005% and 0.1% of warfarin) and consecutive intake over days in order to accumulate the lethal dose, and are less toxic than second generation agents

Eg. Warfarin (Coumadin) is used therapeutically and as rodenticedes;

Second generation agents are far more toxic than first generation. They are generally applied in lower concentrations in baits — usually on the order of 0.001% to 0.005% — are lethal after a single ingestion of bait and are also effective against strains of rodents that became resistant to first generation anticoagulants; thus, the second generation anticoagulants are sometimes referred to as "superwarfarins"

Eg.of Super warfarin: Brodifacoum, Diphacinone, Bromadiolone, Chlorophacinone, Difenacoum, Pindone, and Valone;

Have profound and prolonged anticoagulant effects. Locally available brands include Zara.

Mechanism of Action

- By inhibiting the synthesis of Vit.K dependent clotting factors (F II, V, VII, and IX),
- Peak effects: not observed for 2–3 days because of the long half-lives of factors IX and X (24–60 hours),
- Duration of action: after a single dose of warfarin is 2-7 days while that of super warfarin stays weeks-months,
- Toxic dose: most warfarin-based rodenticides produce little effect after a single dose (10-20mg);While a single dose of superwarfarin (as low as 1 mg) produce a significant clinical effect,

Clinical feature

Seen as early as 8-12 hrs but mostly delayed by 1-2 days after ingestion and continue for days, weeks or months after superwarfarin ingestion, Sign and symptom of bleeding diathesis such as ecchymoses, subconjunctival hemorrhage, bleeding gums, or evidence of internal hemorrhage (eg, hematemesis, melena, or hematuria), the most immediately life-threatening complications are massive gastrointestinal bleeding and intracranial hemorrhage.

Diagnosis

- Based on exposure history;
- Clinical and laboratory features:
    - Elevated levels of PT (INR) from admission level suggest poisoning and a normal PT level after 48 hrs of exposure rules out significant exposure;
- Other useful laboratory studies include
- CBC and blood type and cross-match,
- Partial Thromboplastin Time (PTT),

- Bleeding time,
- Platelet count which may be used to rule out other causes of bleeding.

Treatment

A. Emergency and supportive treatment

- Treat hypervolemia/ shock with crystalloids,
- Transfusion with whole blood or FFP,
- Consult neurosurgeon if intracranial bleeding suspected,
- Minimize or avoid invasive procedures like NGT insertion or endotracheal intubation if possible,
- Avoid drug, which may decrease metabolism of warfarin like cimetidine, sulfonamides, NSAID;

B. Antidote

- Vitamin K (phytonadione),effectively restores the production of clotting factors,
- 5-10mg very slowly IV or subcutaneously (SC),
- Repeated may be required, especially in patients who have ingested superwarfarin product,
- Doses as high as 200 mg/d have been used,
- TitrateVit. K dose based on PTT level,
- May require FFP/ whole blood transfusion for active bleeding as Vit. K take effect (6-24hr later).

C. Decontamination: Activated charcoal can be used.

D. Enhanced elimination has no role.

Summary:

- Rodenticides are used as extermination of rodents and as grain preservative.
- Classified as anti-coagulant or non-anticoagulant.
- Clinical features differ according to the rodenticide type;
- Management includes supportive and decontamination,
- Magnesium sulfate and dopamine considered in case of aluminum phosphide;
- Vitamin k antagonist and fresh frozen plasma should be used in anti-coagulant rodenticide poisoning.

3.4 Ethanol

Case study

Unresponsive 6 years old girl was brought to ED by her family after she had been found at home. By the time she arrived she deteriorated.

Medical history was unremarkable.

The family brought an empty container labeled with alcohol-based hand sanitizer.

In ED her vital signs were BP 90/60 HR100 RR12 Temperature 35.7^0c SPO_2 98%

GCS was 9/15

A. How do you approach?
B. What differential diagnosis do you consider?
C. What is the most likely diagnosis?
D. What are the management principles?

- Ethanol is the most common alcohol ingested as a recreation or used with other chemical or drugs intentionally as suicidal means;
- Its principal effects are GI irritation and intoxication; and it doesn't by itself produce metabolic acidosis.
- Ethanol (CH_3CH_2OH, molecular weight 46.07) is:
- A colorless, volatile liquid that is the most frequently used and abused drug in the world. Morbidity from acute ethanol intoxication is usually related to secondary injuries rather than direct toxic effects.
    - Toxicity most commonly occurs from ingestion, but ethanol may also be absorbed via inhalation or percutaneous exposure.
- Ethanol is readily available in many different forms.
- A standard alcoholic beverage, such as 12 oz (355 mL) of beer (2% to 6% ethanol by volume), 5 oz (148 mL) of wine (10% to 20% ethanol by volume), or 1.5 oz (44 mL) of 80-proof spirits (40% ethanol by volume), contains about 15 grams of ethanol.
- Ethanol may be found in high concentrations in many other common household products such as mouthwash (may contain up to 75% ethanol by volume), colognes and perfumes (up to 40% to 60%), and as a diluent or solvent for medications (concentration varies widely between 0.4% and 65%), hand sanitizers (Up to 60 -70%)
- Such products are often flavored or brightly colored and may be attractive to children.

Mechanism of action

- Ethanol is rapidly absorbed after oral administration, and blood levels peak about 30 to 60 minutes after ingestion.
- The presence of food in the stomach prolongs absorption and delays the peak blood level. High concentrations of ethanol in the stomach may cause pylorospasm delaying gastric emptying. Some ethanol is broken down in the stomach by gastric alcohol dehydrogenase, which lowers the amount available for absorption.
- This enzyme is present at higher levels in men than in women, which may account for the fact that women usually develop a higher blood ethanol level than men after consuming the same dose per kilogram of body weight.
- The volume of distribution of ethanol is also gender dependent due to difference in body fat percentages: 0.6 L/kg in men and 0.7 L/kg in women.
- Ethanol is a CNS depressant.
- That enhances the inhibitory neurotransmitter γ-aminobutyric acid receptors and blockade of excitatory N-methyl-d-aspartic acid receptors.
- Modulation of these systems leads to the development of tolerance, dependence, and a withdrawal syndrome when ethanol intake ceases in dependent individuals.
- Because of the phenomenon of tolerance, blood ethanol levels correlate poorly with degree of intoxication.
- Although death from respiratory depression may occur in non habituated individuals at concentrations of 400 to 500 milligrams/dL (87 to 109 mmol/L), some alcoholic individuals can appear minimally intoxicated at blood concentrations as high as 400 milligrams/dL (87 mmol/L).
- Ethanol is predominantly eliminated by hepatic metabolism, with about 10% excreted in the urine, exhaled breath, and sweat.
- Alcohol dehydrogenase is the major enzyme involved in the metabolism of ethanol, producing acetaldehyde.
- At low ethanol concentrations, this process follows first-order kinetics, but as concentrations rise, alcohol dehydrogenase becomes saturated and metabolism switches to zero-order kinetics—a fixed amount is metabolized per unit of time.
- Also, as ethanol concentrations rise, the hepatic microsomal oxidizing system (specifically, cytochrome P-450 2E1 [CYP2E1]) plays a more important role in metabolism.

- Both alcohol dehydrogenase and CYP2E1 are inducible and thus are more active in chronic ethanol users.
- Therefore, rates of ethanol elimination from the blood vary from about 20 milligrams/dL per h (4 mmol/L per h) in non-habituated individuals 5 to up to 30 milligrams/dL per h (6 mmol/L per h) in individuals with chronic alcoholism.

Clinical features

- The hallmark of ethanol toxicity is clinical inebriation.
- Behavioral disinhibition may initially appear as euphoria or agitation and combativeness.
- As intoxication becomes more severe, slurred speech, nystagmus, ataxia, and decreased motor coordination develop.
- Severe intoxication may cause respiratory depression and coma.
- Nausea and vomiting often occur in conjunction with neurologic depression.
- Ethanol causes peripheral vasodilation and flushed, warm skin.
- Vasodilation causes heat loss to the environment promoting hypothermia, may also lead to orthostatic hypotension and reflex tachycardia.
- Ethanol-induced hypotension is usually mild and transient, so significant or persistent hypotension warrants investigation for alternative causes.
- Ethanol ingestion may cause hypoglycemia, usually in children and malnourished individuals due to low glycogen stores and reduced gluconeogenesis.
- When a chronic alcoholic suddenly stops consuming calories in the form of either ethanol or food, the body uses alternative fuel sources and begins to break down adipose tissue. This metabolism of fatty acids results in ketoacidosis.

Diagnosis

- Ethanol-intoxicated patients often have other disease processes, such as infections and traumatic injuries, so perform a detailed physical examination, looking especially for evidence of trauma, and obtain as much history as possible.
- Uncomplicated ethanol intoxication improves over a few hours.
- If depressed mental status fails to improve or deteriorates, consider other causes of altered mental status and evaluate aggressively. The clinical assessment guides the selection of laboratory tests.
- For altered levels of consciousness, obtain a point-of-care glucose level.

- Ethanol levels are not necessarily required in cases of mild or moderate intoxication when no other abnormality is suspected, but measure serum alcohol levels in patients with altered mental status of unclear cause. Clinical judgment of ethanol intoxication is unreliable, and self-reported drinking is also unreliable, particularly around levels of 100 milligrams/dL (22 mmol/L) or in alcohol-tolerant patients.
- Ask about concomitant drug use.
- The attraction of abusing these drugs together may relate to the formation of the cocaine metabolite coca ethylene that, although less potent than the parent compound, has a half-life that is three to five times longer.
- The risk of sudden death among users of both drugs simultaneously is higher than that among cocaine users alone.
- Ethanol ingestion is the most common cause of an osmolar gap metabolic Acidosis.

Treatment

- Management is observation until sobriety.
- Treat hypoglycemia with IV glucose 0.5 to 1 grams/kg
- Although acute Wernicke's encephalopathy can be precipitated by prolonged sustained administration of IV carbohydrate, there is no evidence that a single dose of IV glucose can cause this syndrome.
- The prevalence of vitamin deficiencies in acutely intoxicated ED patients is low and does not justify the routine use of IV vitamin-containing fluids.
- However, long-term drinkers are sometimes treated with IV fluids containing magnesium, folate, thiamine, and multivitamins, termed a banana bag because of the yellow color imparted by the multivitamin mixture.
- Wernicke's encephalopathy is characterized by abnormal mental status, ataxia, and nystagmus, and requires daily treatment with thiamine, 100 milligrams, until normal diet is resumed.
- Fluid administration does not hasten alcohol elimination, so establishment of IV access fluid administration alone is unnecessary in uncomplicated mild to moderate intoxication.

Disposition and follow up

- Patients with acute ethanol intoxication as the only clinical problem requires ED observation until sober. Prior to discharge, reassess for an underlying mental health

disorder, such as suicidal or homicidal ideation, that requires further care or hospital admission.

- Clinical judgment, rather than a serum ethanol level, determines the appropriateness of discharge. Discharge the patient in the care of a responsible companion.

Summary

- Ethanol is the most common alcohol ingested as a recreation
- Ethanol is rapidly absorbed after oral administration, and blood levels peak about 30 to 60 minutes after ingestion.
- The hallmark of ethanol toxicity is clinical inebriation.
- Severe intoxication may cause respiratory depression and coma.
- If depressed mental status fails to improve or deteriorates, consider other causes of altered mental status and evaluate aggressively
- Management is observation until sobriety.
- Treat hypoglycemia with IV glucose 0.5 to 1 grams/kg

3.5. Caustics and Corrosives

Corrosives include acidic, alkaline, or rarely, neutral pH (e.g., silver nitrate, concentrated hydrogen peroxide) compounds. In general, the burning sensation associated with ingestion inhibits patients from consuming much of the product. Because liquids do not stick, they are taken better than solid and can damage the whole esophagus. Liquids also may be aspirated into the airways, leading to airway obstruction.

Mechanism of toxicity

Alkali burns more common and worse than acid. Acid causes a coagulation-type necrosis. In contrast, alkalis' cause a liquefactive necrosis that leads to continuous penetration into deeper tissues, resulting in more extensive damage than acidic burns. Button batteries lead to esophageal perforation via leakage of the corrosive metal salts by direct impaction of the disk-shaped foreign body, and possibly by local discharge of electrical current at the site of impaction, can lead to esophageal perforation.

Toxic dose: there is no specific toxic dose or level.

Clinical presentation

- **After ingestion** of corrosive, hyper salivation, lethargy, polydipsia, vomiting, abdominal pain, dysphagia, pharyngeal edema, oral pain, drooling, and oral, esophageal, and/or gastric ulceration could occur.
- **Inhalation** of corrosive gases may cause upper respiratory tract injury, with strider, hoarseness, wheezing, and noncardiogenic pulmonary edema.
- **Eye or skin exposure** to corrosive causes instant pain and redness, followed by blistering. Conjunctivitis and lacrimation are common. Serious full-thickness burns and blindness can occur.

Diagnosis

- Is based on history of exposure to a corrosive agent and
- Characteristic findings of skin, eye, or mucosal irritation and the presence of injury to the gastrointestinal tract.
    - **Endoscopy:** esophageal or gastric injury is unlikely after ingestion if the patient is completely asymptomatic, but small number of patients will have injury in the absence of oral burns or obvious dysphagia. Endoscopy for all patients regardless of symptoms may be necessary.

- **X-rays:** of the chest and abdomen will show impacted button batteries, pneumomediastinum from esophageal perforation or free abdominal air from gastric perforation.
- **Specific levels:** depend on the specific chemical.
- **Other investigations studies:** CBC, electrolytes, glucose, arterial blood gases, chest x-ray, and upright abdominal x-ray.

Treatment

- **Emergency and supportive measures**
  - **Inhalation:**
    - Give oxygen, and
    - follow closely for signs of airway obstruction or for non-cardiogenic pulmonary edema.
  - **Chemical ingestion:**
    - Pre-hospital: immediately give water or milk to drink.
    - Do not induce vomiting or give pH-neutralizing agents (e.g., dilute vinegar or bicarbonate), or perform gastric lavage.
    - Give activated charcoal if the ingested agent can cause significant systemic toxicity.
    - If there is esophageal perforation, avoid giving water as it may also enter to the mediastinum.
    - If esophageal or gastric perforation is suspected refer immediately.
  - **Chemical eye and skin burn:**
    - Remove all clothing, wash skin, and irrigate eyes with copious water or saline.
  - **Button batteries:**
    - Immediately lodged endoscopy guided removal should be done immediately.

    ✓ There is currently no evidence of consistent benefit from systemic steroids, so steroids are not recommended as part of ED treatment. There is no also current evidence to support the ED administration of prophylactic antibiotics after caustic ingestions in humans.

    ✓ For most agents, there is no specific antidote.

Summary

- Suspect severe consequences if a large volume of caustic or an industrial-strength caustic product is ingested.
- Alkalis, by causing liquefaction, can cause damage until they are sufficiently diluted.
- Do not do gastric emptying or lavage with caustic ingestion because it re-exposes the upper GI tract to the caustic.
- Do not give activated charcoal.
- Do not attempt to neutralize caustic acid with an alkaline substance (and vice versa) because it will produce heat that may worsen tissue damage.
- Consider esophageal and stomach burns and do endoscopy, even if intraoral burns are absent.
- Treat perforation with antibiotics and surgery.
- Treatment with hyperbaric O2.

3. 6 Household Products

3.6.1 Detergents

Are synthetic surface-active agents containing chemical products used at home. Most products contain bleaching (chlorine-releasing), bacteriostatic (having a low concentration of quaternary ammonium compound), or enzymatic agents.

Mechanism of toxicity

Detergents may precipitate and denature proteins, are irritating to tissues, and possess keratolytic and corrosive actions. Detergents may cause skin irritation and have sensitizing properties.

Toxic dose: - No minimum or lethal toxic doses have been established. Mortality and serious morbidity are rare.

Clinical presentation:

Nausea, vomiting, and diarrhea, hematemesis may occur and as a result secondary dehydration and electrolyte imbalance may develop. Mild ocular irritation is possible. Large ingestions may produce intractable vomiting, diarrhea, and hematemesis. Dermal contact generally causes a mild erythema or rash.

Diagnosis:

- Based on history of exposure.
- Specific levels: there are no specific blood or urine levels.
- Other useful laboratory studies include
    - Electrolytes, glucose, calcium and
    - Phosphate (after ingestion of phosphate-containing products),
    - Methemoglobin (Cationic detergents).

Treatment

- In patients with protracted vomiting or diarrhea, administer IV fluids to correct dehydration and electrolyte imbalance. If corrosive injury, use the management guideline for corrosive ingestion. If hypocalcaemia occurs after ingestion of a phosphate-containing product, give IV calcium.
- **Decontamination:** dilute orally with small amounts of water or milk. Do not induce vomiting because of the risk for corrosive injury. Consider gastric lavage only for massive ingestions. Activated charcoal is not effective. In severe cases anti-emetics may be required (e.g., metoclopramide, 0.2–0.4 mg/kg, PO, SC, or IM, qid based).

- **Eyes and skin exposure**: irrigate with copious amounts of tepid water or saline. Consult an ophthalmologist if eye pain persists or if there is significant corneal injury.

3.6.2 Sodium Hypochlorite (Bleach)

Sodium hypochlorite is a chemical commonly found in bleach, water purifiers, and cleaning products**.** Sodium hypochlorite is a green/yellow liquid with the characteristic smell of chlorine and it is commonly known as bleach (berkina). Sodium hypochlorite is used as a disinfectant and as a bleaching agent. It is also used in the disinfectant process of drinking-water and in swimming pools. Household bleach usually contains approximately 5 % sodium hypochlorite, although some may contain up to 10 %. Chlorine is heavier-than-air, yellowish-green gas with an irritating odor. Hypochlorite is an aqueous solution produced by the reaction of chlorine gas with water. The addition of acid to hypochlorite solution may release chlorine gas. The addition of ammonia to hypochlorite solution may release chloramines, a gas with properties similar to those of chlorine.

Mechanism of toxicity:

If sodium hypochlorite is mixed with acidic products, chlorine gas is produced. Chlorine gas produces a corrosive effect on contact with moist tissues such as the eyes and upper respiratory tract.

Clinical presentation

- Airways and lungs: exposure to the fumes can cause burning in the eyes, ears, and nose, pain in the mouth, and pain in the throat, chest tightness, coughing and difficulty of breathing. In more severe cases increased breathing rate, wheezing, swelling of the airways and respiratory failure may occur, the onset of which may take up to 36 h.
- Skin: irritation of the exposed area. Burns and blistering have been reported.
- Stomach and intestines: stomach or abdominal pain, vomiting have been reported.
- Heart and blood vessels: Rare cases of cardiovascular collapse and shock are presumed to consider secondary to severe local injury.
- Nervous system: Lethargy, delirium and coma can occur in patients with severe respiratory effects.
- Chloramines' is less water-soluble and may produce more indolent or delayed irritation.

Toxic dose

- **Chlorine gas**: the recommended workplace limit for chlorine gas is 0.5 ppm (1.5 mg/m^3) as an 8 h time-weighted average. The short-term exposure limit is 1 ppm. The level considered immediately dangerous to life or health is 10 ppm.
- **Aqueous solutions**: dilute aqueous hypochlorite solutions (3–5%) commonly found in homes rarely cause serious burns but are moderatelyirritating. However, more concentrated industrial cleaners (20% hypochlorite) are much more likely to cause serious corrosive injury.

Diagnosis:

- Based on exposure history.
- Other useful laboratory studies include,
    - For ingestion, CBC, electrolytes, and chest and abdominal x-rays;
    - For inhalation, arterial blood gases and pulse oximetry.

Treatment

- **Emergency and supportive measures**
    - **Inhalation of chlorine gas:** immediatelyremove victim from exposure, give humidified supplemental oxygen. Observe carefully for signs of progressive upper-airway obstruction, and intubate the trachea if necessary. Use bronchodilators for wheezing and treat non-cardiogenic pulmonary edema if it occurs.
    - **Ingestion of hypochlorite solution:** if a solution of 10% or greater has been ingested, or if there are any symptoms of corrosive injury (dysphagia, drooling, or pain), flexible endoscopy is recommended to evaluate for serious esophageal or gastric injury. Obtain chest and abdominal x-rays to look for mediastinal or intra-abdominal air, which suggests perforation.
- **Decontamination**: for oral exposures, emesis and activated charcoal are contraindicated. Instead, immediately give water by mouth. Do not induce vomiting. Do not use activated charcoal; it may obscure the endoscopes' view.
- **Skin and eyes**: remove contaminated clothing, and flush exposed skin immediately with copious water. Irrigate exposed eyes with water or saline. Bathing with mild shampoo and thorough rinsing for significant dermal exposures is recommended.

3.6.3 Dettol®

Dettol is a commonly available household disinfectant. It contains Isopropyl alcohol (12%), Chlorxylenol (4.8%), and Pine oil (9%). Pine oil is made of secondary and tertiary terpene alcohols. As a result, it can cause CNS depression. The action is probably additive to the depressant action of Chlorxylenol. Similar to Chlorxylenol, Pine oil can cause renal failure and hepatitis. Iso-propyl alcohol can also cause CNS depression.

Mechanism of toxicity

It causes CNS depression, corrosion of oral mucosa and gastrointestinal tract, laryngeal edema, upper airway obstruction, nephrotoxicity, hepatitis and cardiac arrhythmias. However the main risk of poisoning is aspiration with subsequent development of acute respiratory distress syndrome (ARDS), pneumonia andsudden cardio-respiratory arrest. Micro-aspiration has been hypothesized to be the reason for delayed upper airway obstruction that may occur in totally asymptomatic patients up to 48 h after admission.

Clinical presentation:

CNS drowsiness, upper GI hemorrhage, air way obstruction, bronchospasm, pneumonia, adult respiratory distress and sudden cardio- respiratory arrest, renal toxicity and hepatotoxicity.

Treatment:

The mainstay of dettol poisoning is supportive management along with close observation in hospital for stridor.

- Emesis and gastric lavage should not normally be attempted. The only indication for gastric lavage in the acute setting is a patient who has consumed other poison along with Dettol. Patient should be started on IV fluids with regular monitoring of electrolytes.
- Adolescents and adults who have consumed more than 200 to 300 ml and children who have consumed lesser amounts should be kept nil per oral (NPO) and watched carefully for signs and symptoms of nephrotoxicity and CNS depression.
- In case of severe poisoning or any evidence of hematuria or azotemia, forced alkaline diuresis should be attempted to aid in excretion of the poisons. Exchange transfusion, and early dialysis for isopropyl alcohol can be attempted in rare patients who are deteriorating steadily despite adequate supportive measures.

- Even patients who arrive comatose to the ED frequently demonstrate a rapid and complete recovery. It is, however, important to remember that even patients who recover completely should be monitored closely in hospital for strider for a minimum of 48 hours after admission.

Summary

Precautions to prevent poisoning caused by household products: To prevent the risk of accidents:

- Keep cleaning and maintenance products out of the reach of children: in high places if possible, or fit door and drawer safety locks on low storage furniture
- Only buy dangerous products when you actually need to use them. Throw packaging in the bin, not in the fire, as a trace of leftover product could be enough to cause an explosion or fire
- Leave cleaning and maintenance, gardening or DIY products in their original packaging: decanting them into old food containers is one of the principal causes of poisoning by ingestion
- Never use two products together or one straight after another, for example baking soda for unblocking toilets and bleach. The chemical reactions caused when two products are mixed can result in the emission of toxic gases
- Read the instructions carefully before using a product
- Should you have any doubt about a product, seek advice on its characteristics by contacting the manufacturers' consumer service department listed on the label. Centres for Poisons can also provide advice on the dangers associated with particular products and ways to prevent the accidents which they can cause
- Learn to recognize hazard symbols. There are a number of leaflets, which show the hazard symbols. Sticking one up in the kitchen is a good way of learning the symbols and making the whole family aware of them: adults and children.

3.7 Carbon Monoxide Poisoning

CO is an odorless, colorless, tasteless, and non-irritating gas produced by the incomplete combustion of any carbon-containing material (e.g., wood, coal). Common sources of human exposure include smoke inhalation in fires, faulty or poorly ventilated charcoal, kerosene or gas.

Mechanism of toxicity

Toxicity results from cellular hypoxia and ischemia.

- CO binds to hemoglobin with an affinity 200 to 300 times greater than that of oxygen resulting in reduced oxyhemoglobin saturation and decreased blood oxygen-carrying capacity.
- CO may also directly inhibit cytochrome oxidase, further disrupting cellular function.
- Fetal hemoglobin is more sensitive to binding of CO, and fetal or neonatal levels may be higher than maternal levels.
- Tissue hypoxia increases cerebral blood flow, cerebrospinal fluid pressure, and cerebral capillary permeability, which predispose the patient to cerebral edema.
- CO also binds to myoglobin, which may lead to development of cardiac ischemia and/or dysrhythmias.

Clinical Manifestations:

High index of clinical suspicion is important

- ***Acute carbon monoxide poisoning:***
  - ✓ Mild levels: headache, dizziness, weakness, nausea, malaise
  - ✓ Moderate: confusion, lethargy, syncope, nystagmus, ataxia
  - ✓ Severe: coma, convulsions, pulmonary edema, myocardial infarction, cardiac arrest. Acute renal failure and rhabdomyolysis have also been reported with severe toxicity
- ***Sub-acute clinical squeal of CO poisoning:***
  - ✓ Persistent neurologic dysfunction is the most common long term sequealae of carbon monoxide poisoning.
  - ✓ Onset occurs between several days and several weeks or even months following exposure.
  - ✓ Decreased cognitive function, personality changes, dementia, Parkinson and decelerate rigidity.
  - ✓ Exposure during pregnancy may result in fetal death.

Diagnosis:

- ✓ History and blood levels of carboxyhemoglobin may help document the diagnosis and may aid prognosis.
- ✓ Other laboratory studies are helpful in evaluating the extent to the toxicity and include CBC, electrolytes, glucose, BUN, creatinine and CPK.

Treatment

- ➢ The most important measure is to remove the victim from the source,,
- ➢ Rescuers exposed to high exposure CO should wear protective self-contained breathing apparatus,
- ➢ Maintain an open airway and assist ventilation if necessary,
- ➢ If smoke inhalation has also occurred, consider early intubation before airway edema,
- ➢ If carbon monoxide poisoning is strongly suspected based on history, immediately provide supplemental oxygen in the highest concentrations available. Administer 100% oxygen. Breathing 100% oxygen speeds the elimination of CO from hemoglobin to approximately 1 h, compared with 6 h in room air. Use a tight-fitting mask and high-flow oxygen with a reservoir (non-re-breather) or administer the oxygen by endotracheal tube. Treat until the carboxyhemoglobin level is less than 5%.
- ➢ Continuously monitor ECG for several hours after exposure. Because smoke often contains other toxic gases, hence, consider the possibility of cyanide poisoning, methemoglobinemia, and irritant gas injury. The possibility of coexistent cyanide poisoning should be considered (especially where nitrogen-containing synthetic materials have burned) in patients who have a persistent metabolic acidosis in the context of normal carboxyhemoglobin and methemoglobin. Cyanide has high fatality but a short half-life (approximately 1 h).

Hyperbaric oxygen: provides 100% oxygen under 2–3 atm of pressure and can enhance elimination of CO (half-life reduced to 20–30 min). The role of hyperbaric oxygen is controversial. Some evidence supports the use of hyperbaric oxygen to prevent delayed cognitive and neurologic sequelae. Some of the suggested indications include syncope, altered mental status or neurologic deficits, evidence of cardiac injury and persistent or severe metabolic acidosis. Pregnancy especially with fetal distress is generally considered an indication for hyperbaric therapy. It may be useful in patients with severe intoxication who do not respond rapidly to oxygen at atmospheric pressure.

Summary

- CO poisoning is one of the most common fatal poisonings.
- Consider toxicity in patients with nonspecific symptoms (eg, flu-like symptoms in winter) or unexplained metabolic acidosis.
- Measure CO level with a CO-oximeter.
- Do not rule out toxicity based on a normal CO level because levels can decrease rapidly, particularly after treatment with supplemental O_2.
- Treat with 100% O_2.
- For severe poisoning, consult an expert or poison control center to discuss

3.8 Hydrocarbonpoisoning

Hydrocarbons, or petroleum distillates, are widely used in the petroleum, plastic, agricultural, and chemical industries as solvents, degreasers, fuels, and pesticides. Examples—kerosene, turpentine substitutes, petrolatum, and benzene.

Mechanism of toxicity:

Caused by direct injury from pulmonary aspiration or systemic intoxication after ingestion, inhalation, or skin absorption. Aspiration leads to a necrotizing, potentially fatal chemical pneumonitis.

CNS toxicity is manifested as alterations in mental status, including narcosis, inebriation, and frank coma.

In addition to these toxicities, the solvents possess additional toxicities, including the risk of bone marrow injury (in the case of benzene). Aliphatic hydrocarbons and simple petroleum distillates such as lighter fluid, kerosene, furniture polish, and gasoline are poorly absorbed from the gastrointestinal tract and do not pose a significant risk of systemic toxicity after ingestion, as long as they are not aspirated. In contrast, many aromatic and halogenated hydrocarbons, alcohols, ethers, ketones, and other substituted or complex hydrocarbons are capable of causing serious systemic toxicity, such as coma, seizures, and cardiac arrhythmias. Inhalation of any hydrocarbon vapors in an enclosed space may cause intoxication as a result of systemic absorption or by displacing oxygen from the atmosphere. Dermal absorption can be significant for some agents but is insignificant for most of the simple, aliphatic compounds.

Toxic dose: the toxic dose is highly variable depending on the agent involved and whether it is aspirated, ingested, or inhaled.

Clinical Presentation:

Pulmonary presents as coughing, gagging, or choking. This may progress within a few hours' to tachypnea, wheezing, and severe chemical pneumonitis. Death may ensue from secondary bacterial infection and other respiratory complications. Ingestion often causes abrupt nausea and vomiting, occasionally with hemorrhagic gastroenteritis. Some compounds may be absorbed and produce systemic toxicity which includes confusion, ataxia, lethargy, and headache.

With significant exposure, syncope, coma, and respiratory arrest may occur. Cardiac arrhythmias may occur owing to myocardial sensitization (with chlorinated and fluorinated compounds)

Diagnosis:

- ✓ based on history of exposure and typical findings.

A. Aspiration pneumonitis: If symptoms are not present within 6 h of exposure, it is very unlikely that chemical pneumonitis will occur. Chest x-ray and arterial blood gases or oximetry may assist in the diagnosis.

B. Systemic intoxication: diagnosis is based on history of ingestion or inhalation, accompanied by the appropriate systemic clinical manifestations.

C. Specific levels: are generally not available or useful.

D. Other useful laboratory studies: ABG, pulse oximetry, chest x-ray , and electrolytes, glucose, BUN, creatinine, liver transaminases, and ECG monitoring for suspected significant inhalation or ingestion.

If the patient has any respiratory symptoms upon arrival to the ED, a chest radiograph should be obtained immediately. Symptoms occur as soon as 30 min after aspiration or may be delayed for several hours. Lung radiographic changes usually occur within 2-8 h, peaking in 48-72 h. Pneumatoceles and pleural effusions may occur.

Other organ systems, especially the liver, central nervous system, and heart, may suffer serious injury. Cardiac dysrhythmias may occur and may be exacerbated by hypoxia and acid-base or electrolyte disturbances.

Treatment

A. **Emergency and supportive measures:**

- Provide basic supportive care for all symptomatic patients.
- Because most hydrocarbons cause clinical toxicity only when aspirated, the mainstay of treatment is to leave ingested compounds in the gut (when possible) and to prevent emesis or reflux.
- Gastric emptying is generally reserved only for those compounds with the potential for systemic toxic effects. Gastric emptying is always contraindicated in other cases.
- Treatment is generally supportive, consisting of oxygen, fluids, and ventilatory support as necessary.
- The pneumonic **CHAMP** refers collectively to the following hydrocarbons: **c**amphor, **h**alogenated carbons, **a**romatic hydrocarbons, and those associated with **m**etals and **p**esticides. Patients who ingest these compounds in volumes >30 mL,

such as might occur with intentional overdose, may benefit from gastric emptying. This is still a high-risk procedure that can result in further aspiration.

- Antibiotics should not be used prophylactically but should be reserved for specific infections if they develop.
- The use of corticosteroids in the treatment of aspiration is not recommended.
- In the event of hypotension or bronchospasm, epinephrine and other catecholamine containing pressors,(Dopamine and Norepinephrine) are contraindicated because hydrocarbons are known to cause ventricular irritability and predispose to fibrillation, an effect that is exacerbated by catecholamines.

B. Specific drugs and antidotes

There is no specific antidote for hydrocarbons.

A. Decontamination

Inhalation: move the victim to fresh air and administer oxygen if available.

Skin and eyes: remove contaminated clothing and wash exposed skin with water and soap. Irrigate exposed eyes with copious tepid water or saline and perform fluorescein examination for corneal injury.

Ingestion: for agents with no known systemic toxicity, gut decontamination is neither necessary nor desirable because any gut-emptying procedure may increase the risk of aspiration.

Summary

- Hydrocarbons, or petroleum distillates, are widely used in the petroleum, plastic, agricultural, and chemical industries
- Commonly used as solvents, degreasers, fuels, and pesticides. Examples—kerosene, turpentine substitutes, petrolatum, and benzene
- Mechanism of action is caused by direct injury from pulmonary aspiration or systemic intoxication after ingestion, inhalation, or skin absorption
- Aspiration leads to a necrotizing, potentially fatal chemical pneumonitis.
- Management is mainly providing basic supportive care for all symptomatic patients.
- Because most hydrocarbons cause clinical toxicity only when aspirated, the mainstay of treatment is to leave ingested compounds in the gut.

3.9. Snake Bite

Snakes live in grasses, forests, on tree branches, under rocks, or in desert and victims can be exposed because of their various activities. Snakes are carnivores and depend on small to large, land or water animals either by paralyzing through their venom or by suffocating their prey.

Most snakes are not harmful to humans but become aggressive when they are hungry, attacked/ confronted, or while trying to escape. Poisonous snakes are those that produce venom which are injected or spitted into a prey; this venoms use different mechanism of human toxicity depending on the snake species. Non poisonous snake use their large body to squeeze and suffocate their victims.

There are more than 3700 species of snake worldwide. Of these 400 species are found in Africa which are relatively harmless; approximately the 100 species are medically important of which 30 species are known to cause harm to humans. In Ethiopia according to a recent guide book there are 92 species of snake and 23 of these species are harmful to humans. The venomous species of medical importance are *Atractaspididae, Colubridae, Elapidae and Viperidae.*

.Snakes which are venomous have a characteristic appearance that are used to differentiate them from harmless snakes; these character include triangular head, elliptical pupil, presence of heat sensing pit between the eye and nostril, fangs/ fang mark on victim body, rows of scales at the tail and aposematic body color.

Clinical presentation

- Snake venoms are complex mixtures of enzymes, low-molecular-weight polypeptides, glycoproteins, metal ions, and other constituents;
- Mechanism of toxicity includes:
    - Hemorrhagins that promote vascular leakage and cause both local and systemic bleeding;
    - Proteolytic enzymes cause local tissue necrosis, affect the coagulation pathway at various steps, and impair organ function;
    - Myocardial depressant factors reduce cardiac output, and
    - Neurotoxins act either pre- or post-synaptically to inhibit peripheral nerve impulses;
    - Most snake venoms have multisystem effects on their victims

- Bites even by venomous snakes may not always result in envenomation. In a victim of snake bite sign and symptom may result from fear, treatment (first aid, medical or traditional) or envenomation
- Envenomation may be divided into local and/ or systemic symptoms and signs.

Local signs and symptoms

- There will be an immediate pain. Local bruises and persistent bleeding from fang puncture suggesting a hemostatic disturbance. Swelling begins within 10-20 minutes. It may become extensive after viper and spitting cobras, involving whole limb or adjacent trunk or whole body in children. Draining lymph nodes may become enlarged, painful and tender within 30-60 minutes.

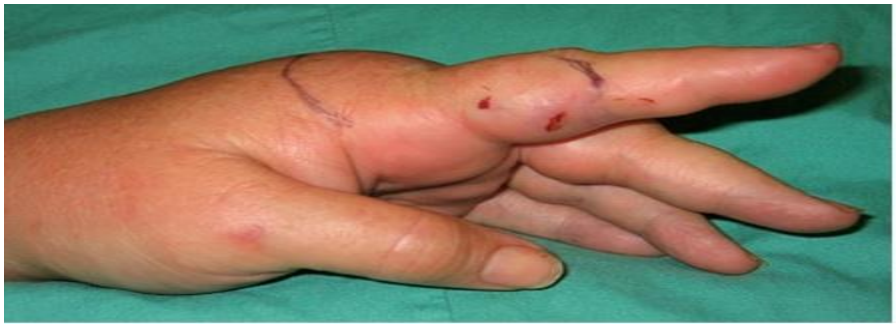


Figure 1: Moderately severe envenomation.

Note edema and early ecchymosis 2 h after a bite to the finger

(Kasper, Braunwald, et al (2015). Harrison's Principles of Internal Medicine, 19th edition, McGraw-Hill).

- Blisters, may appear near the fang marks in 12-24 hours. Demarcated pigmentation or depigmentation with anesthesia and a distinctive smell of putrefaction are sign of necrosis. This progresses to frank necrosis with sloughing of dead tissue.
- Increasing myalgia, blisters advances to tissue necrosis and gangrene will develope.

Figure 2: Severe envenomation. Note extensive ecchymosis 5 days after a bite to the ankle

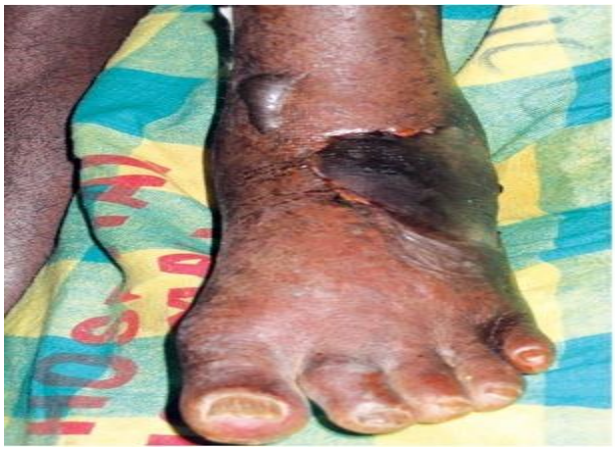


Figure 3: Early stages of severe, full-thickness necrosis 5 days after a viper

Systemic signs and symptoms

- Bleeding and clotting disorder: There is local bleeding from wound, fang puncture and venipuncture site and systemic bleeding from coagulation abnormality and impaired platelets. Spontaneous systemic bleeding (e.gs from gum and nose, hematemesis, rectal bleeding, hemoptysis, hematuria, retroperitoneal, intracranial bleeding and in pregnant woman ante-partum hemorrhage).
- Shock (hypotension): could be anaphylaxis or bleeding related or cardiotoxic effect.
- Progressive descending paralysis starting with droping eyelids (ptosis) and pupillary abnormality, paralysis of eye movement causing diplopia(ophthalmoplegia),; paralysis of facial muscle, jaw, tongue, neck flexors causing “broken neck” sign, and other cranial palsies, difficulty of producing speech(dysphonia), difficulty of handling secretions(drooling) finally respiratory muscle and total flaccid paralysis.
- Acute renal failure may ensue because of hypotension or rhabdomyolysis.

Diagnosis

- Bite history and reptile identified if possible;
  - Determine severity of envenomation:
    - None ("dry bite"): fang marks only
    - Mild: local findings only
      - e.g., pain, local ecchymosis, non-progressive swelling
    - Moderate: swelling (clearly progressing),systemic signs or symptoms, and/or laboratory abnormalities

- Severe: Respiratory distress, Neurologic dysfunction, and/or Cardiovascular instability/shock

Management of snakebite

- A significant proportion of snake bites do not result in envenomation……observe if no clinical features of local/systemic sign and/ or symptoms;
- Management includes general measures and anti-venom provision;
  - Assess and manage the ABCDE of life,
    - Includes treatment of shock and respiratory arrest .
      - Establish large-bore IV lines in unaffected limb or intraosous in children:
      - Give normal saline infusion (bolus of 20–40 mL/kg) if the patient is hypotensive; if hypotension persists, consider anti-venom. Only after aggressive volume resuscitation and antivenom administration; if the shock unresponsive, vasopressors (e.g., adrenaline, dopamine) should be added.
      - With any evidence of difficulty swallowing or breathing, proceed with endotracheal intubation and ventilatory support (may be required for days or weeks).
      - Paralysis of respiratory muscles can last for days and requires intubation and mechanical ventilation or manual ventilation;

  - Measures applied in the field (such as constriction bands) should be removed once IV access has been obtained,
  - Splint the limb below the level of the heart to reduce movement and absorption of venom if the limb is the affected organ; apply a firm bandage to affected limb from fingers or toes to proximal site of bite.
  - Irrigate and dress the wound;
  - Avoid intramuscular injections;
  - In acute renal failure dialysis (peritoneal or hemodialysis), usually reversible
  - If any evidence of neurologic dysfunction (e.g., any cranial nerve abnormalities such as ptosis or inability to maintain upward gaze):
    - Pretreat with atropine: 0.6 mg IV (children, 0.02 mg/kg; min. of 0.1 mg)
    - Followed by a trial of anticholinesterase inhibitors
      - Neostigmine: 1.5–2.0 mg IM (children, 0.025–0.08 mg/kg)
      - If objective improvement is evident at 5 min, continue neostigmine at a dose of 0.5 mg (children, 0.01 mg/kg) IV or SC every 30 min as

needed, with continued administration of atropine by continuous infusion of 0.6 mg over 8 h (children, 0.02 mg/kg over 8 h).

Antivenom

- The goal is to allow antibodies (or antibody fragments) to bind up circulating venom components before they can attach to target tissues and cause deleterious effects;
- May be monospecific (for a particular snake species) or polyspecific (covering several medically important species in the region).
- Indications for antivenom:

  - Any evidence of systemic envenomation (systemic symptoms or signs, laboratory abnormalities) and
  - Significant progressive local findings (e.g., soft tissue swelling crossing a joint or involving more than half the bitten limb)
  - After the bites of neurotoxic elapids, at the first sign of any evidence of neurotoxicity [cranial nerve dysfunction (e.g., ptosis) or peripheral neuropathy]
  - For viperid bites, antivenom administration generally should be continued as needed until the victim shows definite improvement (e.g., stabilized vital signs, reduced pain, restored coagulation)

- Prepare IM epinephrine (adrenaline) and IV chlorpheniramine, be ready if allergic reaction occurs when antivenum given.
- Give polyvalent anti-venom if the species is not known; follow the directions given on the anti-venom preparation;
- Dilute the anti-venom in 2–3 volumes of 0.9% saline and give intravenously over 1 hour.
- Give more slowly initially and monitor closely for anaphylaxis or other serious adverse reactions Before we give the anti-venom perform skin test with 0.02 to 0.03 ml in 1:10 dilution. If itching/urticarial rash, restlessness, fever, cough or difficult breathing develop, then stop anti-venom and give epinephrine (adrenaline)..
- More anti-venom should be given after 1–2 hr if the patient is continuing to bleed briskly or has deteriorating neurotoxic or cardiovascular signs. Start giving the anti-venom with minimal dose for mild cases with a minimal dose of 22-40 ml and give a maximum of 200-400 ml. Blood transfusion should not be required if anti-venom is given..

- Clotting function returns to normal only after clotting factors are produced by the liver.
- Response of abnormal neurological signs to anti-venom is more variable and depends on type of venom
- Neurotoxicity from elapid bites (cobra and mamba) may be harder to reverse with antivenom. Once neurotoxicity is established and endotracheal intubation is required, further doses of antivenom are unlikely to be beneficial. In such cases, the victim must be maintained on mechanical ventilation until recovery, which may take days or weeks.
- If acute reaction to antivenom develops and depending on severity of reaction:
    - Stop infusion.
    - Treat with standard doses of epinephrine (IM or IV; the latter route only in the setting of severe hypotension),
    - Antihistamines (IV) e.g., Diphenhydramine, 1 mg/kg to a max. 100 mg, +
        - Cimetidine, 5–10 mg/kg to a maximum of 300 mg
    - IV glucocorticoids
    - When reaction is controlled, restart antivenom as soon as possible if still indicated (may further dilute in a larger volume of normal saline).

Surgical Management

- Seek surgical opinion if there is severe swelling in a limb, it is pulseless or painful or there is local necrosis
- Surgical care will include:
    - Intact serum-filled vesicles or hemorrhagic blebs should be left undisturbed. If ruptured, they should be debrided with sterile technique.
    - Excision of dead tissue from wound
    - Incision of fascial membranes to relieve pressure in limb compartments, if necessary
    - Skin grafting, if extensive necrosis
- Antibiotic treatment is not required unless there is tissue necrosis at wound site
- Tracheostomy (or endotracheal intubation) if paralysis of muscles involved in swallowing occurs
- Bite in the hand, fore-arm or leg may be complicated by muscle-compartment syndrome

Supportive care

- Give fluids orally or by NG tube according to daily requirements

  Keep a close record of fluid intake and output.
- Pain management: acetaminophen and/or narcotics as needed (avoid salicylates and no steroidal anti-inflammatory agents) Elevate limb if swollen Give prophylaxis for tetanus
- Prophylactic antibiotics are unnecessary unless prehospital care included incisions or mouth suction.

Monitoring

- Monitor very closely immediately after admission, then hourly for at least 24 hours as envenomination can develop. Any patient with signs of envenomation should be observed in the hospital for at least 24 h, Patients whose condition is not stable should be admitted to an intensive care setting
- Measure/record circumferences of the bitten extremity every 15 min until swelling has stabilized; while monitoring, the extremity should be positioned at approximately heart level.
- Admit to hospital. (If no evidence of envenomation, monitor for 8 h before discharge.)
- Institute monitoring (cardiac and pulse oximetry)
- Vital signs, cardiac rhythm, oxygen saturation, urine output.

Investigation

- Send laboratory studies (CBC, metabolic panel, PT/INR/PTT, fibrinogen level, FDP, blood type and screening, urinalysis for presence myoglobin or blood).
- The 20-min whole-blood clotting test can be used for reliable diagnosis of coagulopathy. A few milliliters of fresh blood are placed in a new, clean, plain glass test tube and left undisturbed for 20 min. The tube then is tipped once to 45° to determine whether a clot has formed. If it has not, coagulopathy is diagnosed.
- Blood products and coagulation factors are rarely needed; if required, they should be given only after antivenom administration.
  - Give further CroFab (two vials q6h for three additional doses; close monitoring).
  - Monitor for evidence of rising intracompartmental pressures.
  - At discharge, warn patient of possible recurrent coagulopathy and signs/symptoms of delayed serum sickness
  - At discharge, victims of venomous snakebite should be warned about signs and symptoms of wound infection, antivenom-related serum sickness

Summary

- More than 3700 species of snake worldwide and 400 species are found in Africa;
- Around 100 species are medically important in Africa of which 30 species are known to cause harm to humans;
- A significant proportion of snake bites do not result in envenomation;
- The venomous species of medical importance in Africa are Atractaspididae, Colubridae, Elapidae and Viperidae;
- Bite can cause local or systemic/ life threatening envenomation;
- Management has to follow ABC;
- Identify the offending reptile if possible;
- Determine severity of envenomation;
- Antivenom provision for those with sign and symptom of systemic envenomation.

Chapter 4: Diagnosis and Treatment of Specific Drug Overdoses

Time allocated: 9 hours

Chapter description

This chapter describes the evaluation and treatment of clients presented with overdoses of specific drugs. In each specific drug overdoses, a summary about the nature of the specific drug's toxicity, its mechanism of toxicity, pharmacokinetics and toxic dose will be described. In addition, the clinical presentation, diagnostic methods, and treatment of each drugs overdose will be dealt. Under the treatment of each drug overdose, specific treatment options including antidote therapy will be explained besides the general approaches of treatment.

Primary objective

At the end of this chapter, participates will be able to manage specific drug overdoses in an emergency setup.

Enabling objectives

- Explain the mechanism of toxicity for selected specific drugs overdose.
- Identify the toxic doses of the specific drugs overdoses.
- Describe the clinical presentations of an overdose for specific drugs.
- Discuss the diagnostic methods for each of the specific drugs overdoses.
- Determine the treatment approaches for specific drug overdoses.

Chapter outline

4.1 Acetaminophen/paracetamol

4.2 Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

4.3 Cardiac glycosides

4.4 Opiates and Opioids

4.5 Phenothiazines and other antipsychotics

4.6 Benzodiazepines

4.7 Barbiturates

4.8 Anticonvulsants

4.1 Acetaminophen overdose

Learning activity

- Do you think paracetamol can be toxic to humans?
- If yes, list few symptoms of overdose?

Introduction

Acetaminophen or Paracetamol having many brand names is a widely used drug found in many over the counter and prescription analgesics and cold remedies. When it is combined with another drug such as codeine, the more dramatic acute symptoms caused by the other drug may mask the mild and non-specific symptoms of early acetaminophen toxicity, resulting in missed diagnosis or delayed antidotal treatment.

Mechanism of toxicity

- **Hepatic injury:** One of the minor products (N-acetyl p-benzoquinone imine) of normal metabolism of acetaminophen by the cytochrome P-450oxidase system is highly toxic. Normally this reactive metabolite is rapidly detoxified by glutathione in liver cells. However, in an overdose, production of the toxic metabolite exceeds glutathione capacity and the metabolite reacts directly with hepatic macromolecules, causing liver injury.
- **Renal damage:** may occur by the same mechanism, owing to renal metabolism.
- **Fetal death** and **spontaneous abortion:** overdose during pregnancyhas been associated with fetal death and spontaneous abortion.

Toxic dose

- **Acute ingestion** of more than 150–200 mg/kg in children or 6–7 g in adults' is potentially hepatotoxic. Children younger than 10–12 years of age appear to be less susceptible to hepatotoxicity because of the smaller contribution of cytochrome P-450 to acetaminophen metabolism. But, the margin of safety is lower in patients with induced cytochrome P-450 microsomal enzymes, because more of the toxic metabolite may be produced.
- **High-risk patients** include alcoholics' and patients taking anticonvulsant medications or isoniazid. Fasting and malnutrition also increase the risk of hepatotoxicity, presumably by lowering cellular glutathione stores.

- **Chronic toxicity** has been reported after daily consumption of high therapeutic doses (4–6 g/day) by alcoholic patients. Children have developed toxicity after receiving as little as 60–150 mg/kg/day for 2–8 days.

Clinical Presentation

Clinical manifestations depend on the time after ingestion.

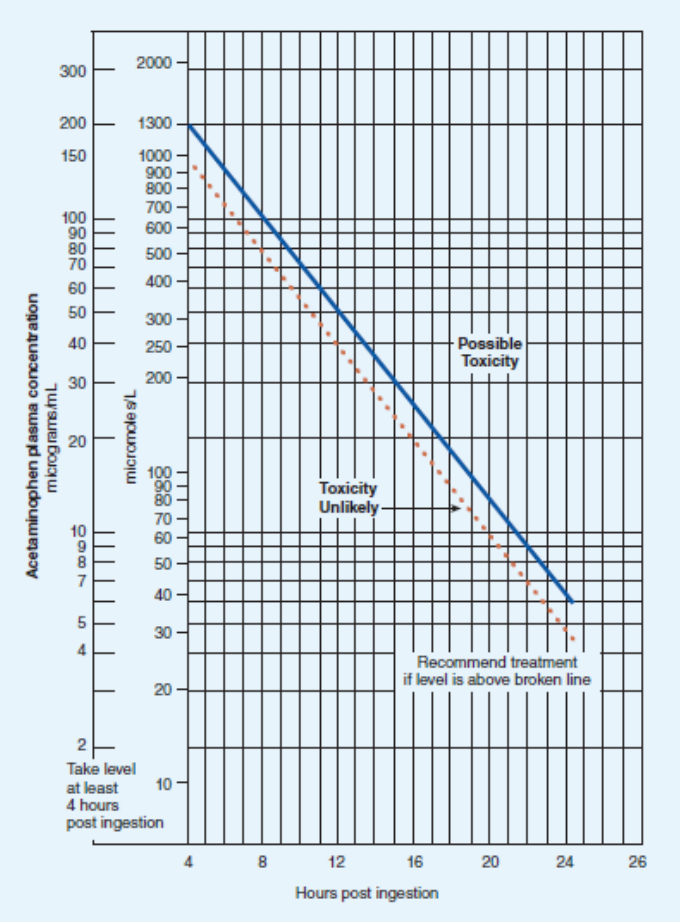
- **Early:** after acute acetaminophen overdose, there are usually no symptoms other than anorexia, nausea, or vomiting. Rarely, a massive overdose may cause altered mental status and metabolic acidosis.
- **After 24–48 hrs** when transaminase levels (AST and ALT) rise, hepatic necrosis becomes evident. If acute fulminant hepatic failure occurs, encephalopathy and death may ensue. Encephalopathy, metabolic acidosis, and a continuing rise in the prothrombin time (PT) indicate poor prognosis. Acute renal failure occasionally occurs, with or without concomitant liver failure.

Diagnosis

- Prompt diagnosis is possible only if the ingestion is suspected and a serum acetaminophen level is obtained. However, patients may fail to provide history of acetaminophen ingestion, because they are unable (e.g., comatose from another ingestion), unwilling, or unaware of its importance. Therefore, if it is available, order acetaminophen levels in all overdose patients, regardless of the history of substances ingested.
- Interpretation of serum acetaminophen level lab result is based on Rumack-Matthew nomogram (Figure 5.1) for single ingestion but not repetitive or chronic ingestion. The nomogram only directly applies to an acetaminophen concentration obtained after a single oral exposure and during the window between 4 and 24 h post-ingestion. After an acute overdose**,** obtain a 4-h-post-ingestion acetaminophen level to predict the likelihood of toxicity. Hence, use of n-acetylcysteine (NAC) is guided by serum concentration after single ingestion. The nomogram line separating possible toxicity from unlikely toxicity is based on a 4-h acetaminophen concentration of 150 µg/mL or 150 mg/L (1000 µmole/L) to increase the safety margin for treatment decisions.

- Multiple closely spaced acetaminophen ingestions and extended-release acetaminophen ingestions represent two unique aspects of acetaminophen poisoning for which the Rumack-Matthew nomogram cannot be readily applied because a single time of ingestion does not exist. After ingestion of extended relief tablets (e.g. Tylenol) which are designed for prolonged absorption, there may be a delay before the peak acetaminophen level is reached. This can also occur after co-ingestion of drugs that delay gastric emptying, such as opioids or anticholinergics. In such circumstances, repeat the serum acetaminophen level at 8 hours and possibly 12 hours.

Figure 4: Rumack-Matthew nomogram: a serum acetaminophen (APAP) level 4-hours postingestion > 150 mg/L shows possible toxicity.



- Other useful laboratory studiesinclude electrolytes, glucose, BUN, creatinine (the renal injury manifested after 2-3 days), liver transaminases, and PT, INR, ECG (to exclude the

presence of coingested cardiotoxic substances). Abdominal ultrasound may reveal hepatic enlargement, renal abnormality, and inflammatory changes.Human chorionic gonadotrophin (hcg) because acetaminophen cross placenta by 14 weeks.So, antidote should be considered in pregnancy as soon as possible. For patients with altered mental status, CT to see cerebral edema and encephalopathy.

Treatment

- ***Emergency and supportive measures:***
  - ✓ Spontaneous vomitingmay delay the administration of antidote and charcoal (see below) and should be treated with metoclopramide or ondansetron.(dose???)
  - ✓ Provide general supportive care for hepatic or renal failure if it occurs. Encephalopathy, metabolic acidosis, hypoglycemia, and progressive rise in the prothrombin time are indications of severe liver injury.
  - ✓ Emergency liver transplantmay be necessary for fulminant hepatic failure, if available. Treatment for acetaminophen-induced fulminant hepatic failure includes acetylcysteine therapy, correction of coagulopathy and acidosis, monitoring for and aggressive treatment of cerebral edema, and early patient referral to a liver specialty/transplant center.
- ***Specific drugs and antidotes:***
  - ✓ If stat serum levels are not immediately available, initiate antidotal therapy with NAC, with a loading dose of 140 mg/kg orally, followed by 70 mg/kg every 4 h for 17 more doses over 72 h (a total of 18 doses). The effectiveness of NAC depends on early treatment, before the metabolite accumulates. It is of maximal benefit if started within 8–10 h and of diminishing value after12–16 h. However, treatment should not be withheld, even if the client comes as late as 48 h post ingestion.
  - ✓ If the patient vomits, repeat the dose. If vomiting interferes with oral acetylcysteine administration, give it by gastric tube and use metoclopramide or ondansetron or give the NAC iv if necessary. Intravenous NAC is recommended if there is altered mental status or severe vomiting. However, mostly oral NAC has bad odor and unpleasant test.
  - ✓ Continuous IV infusion is recommended for acute ingestion, as follows:
    - Loading dose: 150 mg/kg IV; mix in 200 mL of D5W and infuse over 1 hr.
    - Dose 2: 50 mg/kg IV in 500 mL D5W over 4 hrs.

- Dose 3: 100 mg/kg IV in 1000 mL D5W over 16 hrs.

✓ Intermittent iv infusion may be considered for late-presenting or chronic ingestion. A loading dose of 140 mg/kg iv (diluted in 500 mL D5W) is infused over 1 hr. Maintenance doses of 70 mg/kg IV are given every 4 hours for at least 12 doses (dilute each dose in 250 mL of D5W and infuse over a minimum of 1 hr.).

✓ The duration of NAC treatmentis17 doses of oral NAC given over approximately 72 hrs. If IV NAC is needed, give for only 20 hrs. Once the standard treatment duration has elapsed, only discontinue therapy if the serum acetaminophen level is below the limits of detection, liver transaminase levels are normal, and the patient is asymptomatic. If there is evidence of hepatic toxicity, then NAC should be continued until this has resolved.

✓ In clients with chronicacetaminophen ingestions, patients may give a history of several doses taken over 24 h or more. In such cases, NAC treatment is advised if the amount ingested was more than 150–200 mg/kg or 6–7 g within a 24-hour period, if liver enzymes are elevated, or if the patient falls within a high-risk group (see above). Treatment may be stopped 36 h after the last dose of acetaminophen if the liver enzymes are normal.

- ***Decontamination:***

✓ **Prehospital.** Administer activated charcoal, if available. Ipecac-induced vomiting may be useful for initial treatment of children at home if it can be given within 30 min of exposure.

✓ **Hospital.** Administer activated charcoal if the patient has a stable mental and clinical status, patent airway, and presents to the emergency department within 1 hour of ingestion. Measurea 4-hour serum acetaminophen concentration to assess the potential risk for hepatotoxicity and interpret using the Rumack-Matthew nomogram. Activated charcoal should not be administered if the patient is mentally compromised and does not have an intact or protected airway. Gastric emptying is not necessary if charcoal can be given promptly. Do not administer charcoal if more than 3-4 h have passed since ingestion, unless delayed absorption is suspected (e.g., Tylenol or co-ingestion of others).

- ***Enhanced elimination.***

✓ Hemoperfusion effectively removes acetaminophen from the blood but is not generally indicated because antidotal therapy is so effective.

NB

- ✓ In general, consider giving NAC if the patient is at increased risk for toxicity, e.g., the patient is alcoholic, malnourished, or fasting, or taking drugs that induce P-450 activity (e.g., anticonvulsants, INH); multiple or subacute overdoses; or time of ingestion is uncertain or unreliable.
- ✓ If we are giving activated charcoal, it should be given before po NAC. This is because activated charcoal will adsorb the po NAC.
- ✓ All patients requiring acetylcysteine therapy should be admitted to the hospital until the completion of the therapy. In general, admission to a hospital bed is adequate unless the coingestant is of concern, hepatotoxicity is severe, or the patient is suicidal, and 24-hour direct observation cannot be arranged.
- ✓ Patients who are not at risk for developing acetaminophen-induced hepatotoxicity (e.g., acetaminophen concentration below the nomogram or unmeasurable acetaminophen concentration with normal hepatic transaminase concentrations) should be observed in the ED for 4-6 hours to exclude potentially toxic coingestants before disposition.

Summary

- Acetaminophen overdose is common, particularly accidental poisoning in children.
- Hepatic injury and renal toxicity are the common mechanisms of acetaminophen overdose from its toxic metabolite called N-acetyl p-benzoquinone imine.
- Acute ingestion of > 150–200 mg/kg in children or 6–7 g in adults' is potentially hepatotoxic.
- The early clinical presentation of acetaminophen overdose includes from no symptoms to anorexia, nausea, or vomiting; whereas hepatic necrosis may become evident after 24-48 hrs.
- Prompt diagnosis is possible if overdose is suspected & serum acetaminophen level is obtained.
- Interpretation of serum acetaminophen level is based on Rumack-Matthew nomogram for single ingestion, but not for repetitive or chronic ingestion.

- In acetaminophen overdose, the management approaches include emergency and supportive measures, specific drugs and antidotes (NAC), decontamination (activated charcoal), and enhanced elimination (hemoperfusion).
- For acetaminophen overdose, activated charcoal should be given before po NAC.

4.2 NSAIDs Overdose

Introduction

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse group ofagents that share similar pharmacologic properties and are widely used for control ofpain and inflammation. Overdose by most NSAIDusually produces only mild GI upset.When we talk about their pharmacokinetics,NSAIDs are generally well-absorbed, and Vd values are relatively small (e.g., 0.15 L/kg for ibuprofen). Most agents are highly protein bound, and most are eliminated through hepatic metabolism andrenal excretion with variable half-lives (e.g., 1.5-2.5 hrs. for ibuprofen and 13-15h for naproxen).

Mechanism of toxicity

NSAIDs produce their pharmacologic and most toxicologiceffects by inhibiting the enzyme cyclooxygenase (COX). This results in decreasedproduction of prostaglandins (PG) and decreased pain and inflammation. CNS, hemodynamic, pulmonary, and hepatic dysfunction also occur with some agents, butthe relationship to PG production remains uncertain. Prostaglandins are also involved in maintaining the integrity of the gastric mucosa and regulating renal blood flow. Thus, acute, or chronic intoxication may affect these organs.

Toxic dose

Human data are insufficient to establish a reliable correlation between amount ingested, plasma concentrations, and clinical toxic effects. Generally, significant symptoms occur after ingestion of more than 5-10 times theusual therapeutic dose.

Clinical presentation

In general, patients with NSAID overdose are asymptomatic or have mild GI upset (nausea, vomiting, abdominal pain, and sometimes hematemesis). Occasionally, patients exhibit drowsiness, lethargy, ataxia, nystagmus, tinnitus, and disorientation. With the more toxic agents

and with massive ibuprofenoverdose, seizure, coma, renal failure, and cardiorespiratory arrest may occur. Hepatic dysfunction, hypoprothrombinemia, and metabolic acidosis are also reported.

Diagnosis

Diagnosis is usually based primarily on history of ingestion of NSAIDs, because symptoms are mild and non-specific and quantitative levels are not usually available.*Specific levels*are not usually readily available and do not contribute to clinical management.*Other useful laboratory tests* include CBC, electrolytes, glucose, BUN, creatinine, liver transaminases, PT, and urinalysis.

Treatment

- ***Emergency and supportive measures:***
  - ✓ Maintain an open airway and assist ventilation if necessary (see chapter 2).
  - ✓ Administer supplemental oxygen.
  - ✓ Treat seizure, coma, and hypotension if they occur(chapter 3).
  - ✓ Antacids may be used for mild GI upset. Replace fluid losseswith IV crystalloid solutions.
- ***Specific drugs and antidotes:***
  - ✓ There is no antidote. Vitamin K (see chapter 5) may be used for patients with elevated PT caused by hypoprothrombinemia.
- ***Decontamination:***
  - ✓ **Prehospital:**consider activated charcoal if available and the patient is alert.
  - ✓ **Hospital:**consideractivated charcoal. Gastric emptying is not necessary for most ingestion if activated charcoal can be given promptly. Consider gastric lavage for massive overdoses.
- ***Enhanced elimination:***
  - ✓ NSAIDs are highly protein bound and extensively metabolized. Thus, hemodialysis, peritoneal dialysis, and forced diuresis are not likely to be effective.
  - ✓ Charcoal hemoperfusionmay be effective for phenylbutazoneoverdose, although there are limited clinical data to support its use.
  - ✓ There are no data on the use of repeat-dose activated charcoal therapy.

Summary

- Overdose by most NSAID usually produces only mild gastrointestinal upset.
- NSAIDs produce their most toxicologic effects by inhibiting the enzyme cyclooxygenase.
- Patients with NSAID overdose are asymptomatic or have mild GI upset.
- Significant symptoms occur after ingestion of more than 5-10 times the usual therapeutic dose.
- Diagnosis of NSAID overdoseis usually based primarily on history of NSAID ingestion.
- Treatment includes emergency and supportive measures, and decontamination (activated charcoal if available and the patient is alert and gastric lavage for massive overdoses).

4.3 Cardiac glycosides overdose

Introduction

Cardiac glycosides are found in several plants. They are used therapeuticallyas digoxin and digitoxin. The bioavailability of digoxin ranges from 60–80% and the absorption of digitoxin is more than 90%. Digoxin has very large Vd (5-10 L/kg), whereas it is small for digitoxin (about 0.5 L/kg). Peak effects occur after a delay of 6-12 h. The elimination half-life of digoxin is 30–50 h and for digitoxin it is 5–8 days (owing to enterohepatic recirculation).

Mechanism of toxicity

Cardiac glycosides inhibit the function of the sodium/potassium-ATPase pump. The increase in intracellular sodium leads to increased activity of the sodium-calcium exchanger and thus increased levels of intracellular calcium.This can lead to early after depolarization, cardiac irritability, and dysrhythmias. After acute overdose, the blockade of the Na-K ATPase pump also can result in hyperkalemia (with chronic intoxication, the serum potassium level is usually normal or low, owing to the concurrent diuretic therapy). Vagal tone is potentiated, and sinus and atrioventricular (AV) node conduction velocity is decreased. Automaticity in Purkinje fibers is increased.

Toxic dose

Acute ingestion of as little as 1 mg of digoxin in a child or 3 mg of digoxin in an adult can result in serum concentrations well above the therapeutic range. Healthy adults may develop symptoms after ingestions of more than 2-3 mg of digoxin but rarely develop severe toxicity with ingestions less than 5mg.Toxic effects in children are likely with ingestions of more than 0.1mg/kg of

digoxin and ingestions of 4 mg can be fatal. Generally, children appear to be more resistant than adults to the cardiotoxic effects of cardiac glycosides.Why do you think this is so?

Clinical presentation

Intoxication may occur after acute accidental or suicidal ingestion or with chronic therapy. Signs and symptoms depend on chronicity of the intoxication.

- ✓ **With acute overdose:**vomiting, hyperkalemia, sinus bradycardia, sinoatrial arrest, and second-or third-degree AV block are common.Ventricular tachycardia or fibrillation may occur. Hyperkalemia is a marker of severe acute toxicity and serum potassium is the best predictor of cardiac glycoside toxicity after an acute overdose.
- ✓ **Withchronic intoxication**: visual disturbances, weakness, sinus bradycardia, atrial fibrillation with slowed ventricular response rate or junctional escape rhythm, and ventricular arrhythmias (ventricular bigeminy or trigeminy, ventricular tachycardia, bidirectional tachycardia, and ventricular fibrillation) are common. Accelerated junctional tachycardia and paroxysmal atrial tachycardia with block are frequently seen. Hypokalemia and hypomagnesemia from chronic diuretic use may be evident and appear to worsen the tachyarrhythmias.

Diagnosis

Diagnosisis based on history of recent overdose or characteristic arrhythmias (e.g., bidirectional tachycardia and accelerated junctional rhythm) in a patient receiving chronic therapy. Hyperkalemia suggests acute ingestion but may also be seen with very severe chronic poisoning. Serum potassium levels higher than 5.5 meq/L are associated with severe poisoning.

- ✓ Specific levels:stat serum digoxin or digitoxin levels are recommended, although they may not correlate accurately with severity of intoxication. This is especially true after acute ingestion, when the serum level is high for 6-12 h before tissue distribution is complete. After use of digitalis-specific antibodies, the radioimmunoassay digoxin level is falsely markedly elevated. Therapeutic levels of digoxin are 0.5-2 ng/mL; of digitoxin, 10-30 ng/mL.
- ✓ Other useful laboratory studiesinclude electrolytes, BUN, creatinine, serum magnesium, and ECG monitoring. In general, we may need severallaboratory tests for diagnosis of digoxin

toxicity and complications like hypoxic seizure, encephalopathy or ischemic stroke, MI or ATN.

Treatment

- ***Emergency and supportive measures:***

✓ Maintain an open airway and assist ventilation if necessary (see Chapter 3).

✓ Monitor the patient closely for at least 12–24 h after significant ingestion because of delayed tissue distribution.

✓ Treat **hyperkalemia**(chapter 3), if greater than 5.5meq/L, with sodium bicarbonate (give 1-2mEq/kg iv bolus over 1-2 min; repeat as needed to improve cardiotoxic manifestations), glucose (0.5 g/kg iv) with insulin (0.1 U/kg iv). Administer regular insulin 10 U iv along with 50 mL of 50% dextrose (children: 0.1 U/kg insulin with 2 mL/kg of 25% dextrose), or sodium polystyrene sulfonate (Kayexalate, 0.5 g/kg po (0.3–0.6 g/kg PO) in 2 mL/kg 70% sorbitol, is effective but takes several hours.). Do *not*use calcium as it may worsen ventricular arrhythmias. Mild hyperkalemia may actually protect against tachyarrhythmias.In general, hyperkalemia in acute digoxin poisoning indicates severe toxicity and digoxin-Fab should be given to reduce mortality.

✓ Treat **bradycardia** or **heart block:** atropine is usually the drug of choice in this circumstance.For adults, give 0.5-1mg iv. For children, give 0.02 mg/kg iv up to a maximum of 0.5 mg and 1 mg in adolescents. Repeat as needed. Note that 3 mg is a fully vagolytic dose in adults. If response is not achieved at 3 mg, the patient is unlikely to benefit from further treatment unless bradycardia is caused by excessive cholinergic effects (e.g., carbamate or organophosphate overdose). A temporary pacemaker may be needed for persistent symptomatic bradycardia.

✓ **Ventricular tachyarrhythmias:**may respond to lidocaine. Administer 1-1.5 mg/kg (usual adult dose 50-100 mg; children, 1 mg/kg) iv bolus at a rate of 25-50 mg/min, followed by infusion of 1-4 mg/min (20-50 mcg/kg/min) to maintain serum concentrations of 1.5-5 mg/L. If significant ectopy persists after the initial bolus, repeat doses of 0.5 mg/kg iv can be given if needed at 10-min intervals (to a maximum 300 mg or 3 mg/kg total dose; children may be given repeat 1 mg/kg doses every 5-10 min to a maximum of 5 mg/kg). In patients with congestive heart failure or liver disease, use half the recommended maintenance infusion dose or phenytoin (a loading dose of 15–20 mg/kg iv slowly at a rate not to exceed 50

mg/min or 1 mg/kg/min in children) orto correction of low potassium or magnesium. Avoid quinidine, procainamide, and bretylium.

- ***Specific drugs and antidotes:***

✓ Fab fragments of digoxin-specific antibodies(Digi bind) are indicated for **(**acute**)** significant poisoning (e.g., severe hyperkalemia i.e. potassium>6.0mEq/L)and symptomatic arrhythmias not responsive to drugs described above) or chronic toxicity with any life-threatening dysrhythmia and possibly for prophylactic treatment in a massive oral overdose with high serum levels.

✓ Digi bind rapidly binds to digoxin and, to a lesser extent, digitoxin and other cardiac glycosides. The inactive complex that is formed is rapidly excreted in the urine. A full neutralizing dose of digoxin-Fab is based on an estimation of the total-body load of digoxin, which can be calculated from either the dose ingested or a steady-state serum digoxin level.

✓ In an acute poisoning, each vial of digoxin-Fab reverses approximately 0.5 milligram of ingested digoxin. In hemodynamically stable patients, half the calculated full neutralizing dose is infused, and the other half is given if an adequate clinical response is not seen in 1 to 2 h. A total of 200 to 480 mg of digoxin-Fab (5 to 12 vials) is required to effectively treat severely digoxin-toxic patients.

✓ When the ingested dose is unknown and serum level is unavailable, 10 vials are recommended as initial treatment in life-threatening situations. Digoxin-Fab are administered iv through a 0.22-mm filter over 30 min, except in cardiac arrest, when the dose is given as an iv bolus.

- ***Decontamination:***

✓ **Prehospital:**administer activated charcoal, if available and the patient can protect his/her airway (meaning alert) and is not vomiting.

✓ **Hospital:**administer activated charcoal. Gastric emptying is not necessaryif activated charcoal can be given promptly.

- ***Enhanced elimination:***

✓ Because of its large Vd, digoxinis not effectively removedby dialysis or hemoperfusion. Repeat-dose activated charcoal maybe useful in patients with severe renal insufficiency, in which clearance of digoxin is markedly diminished.

- ✓ Digitoxinhas a small Vdand undergoes extensiveenterohepatic circulation. As a result,repeat-dose charcoal can markedly enhance its elimination.

Summary

- Cardiac glycosides toxicity is by inhibiting the function of Na-K ATPase pump.
- Toxic effects in children are likely with ingestions of > 0.1mg/kg of digoxin, whereas adults develop severe toxicity with ingestions of > 5mg digoxin.
- Signs and symptoms of digoxin toxicity depends on chronicity of the intoxication.
- Diagnosisis based on history of recent overdose or characteristic arrhythmias and using serum potassium levels, in a patient receiving chronic therapy.
- Treatment include emergency and supportive measures (treatment of hyperkalemia, bradycardia/heart block and ventricular tachyarrhythmias), specific drugs and antidotes (Digi bindfor acutesignificant poisoning),decontamination& enhanced elimination.

4.4 Opiates and opioids overdose

Introduction

This group includes naturally occurring opiates (e.g., morphine, heroin, codeine, and hydrocodone) as well as syntheticopiate analogues (e.g., fentanyl, meperidine/pethidine, and methadone (Table 2.6). A wide variety of prescription medications contain opioids, often in combinationwith aspirin or acetaminophen. Dextromethorphanis an opioid derivativewith potent antitussive but no analgesic or addictive properties. Tramadolis a newer analgesic that is unrelated chemically to the opiates but acts onmu (μ) opioid receptors.

Usually, peak effects occur within 2–3 h, but absorption may be slowed by their pharmacologic effects on gastrointestinal motility.The timing of peak effects is related to the mode of ingestion. When used iv, peak effects are in 10-20 min.Oral dosing gives peak effects in 1-2 h.Most drugs have large Vd (3-5 L/kg). The rate of elimination is highly variable, from 1-2 h for fentanyl derivatives versus 15-30 h for methadone (see table 5.1 below).

Mechanism of toxicity

In general, opioids share the ability to stimulate several specific opiate receptors in the CNS, causing sedation and respiratory depression. Death results from respiratory failure, usually

because of apnea or pulmonary aspiration of gastric contents. In addition, acute noncardiogenic pulmonary edema may occur by unknown mechanisms.

Toxic dose

The toxic dose varies widely depending on the specific compound, the route and rate of administration, and tolerance to the effects of the drug because of chronic use. Some newer fentanyl derivatives have potency up to 2000 times that of morphine.

Table 6 Common opiates and opioids

Drug	Type of activity	Usual adult dose* (mg)	Elimination $t_{1/2}$ (hr.)	Duration of action (h)
Codeine	Agonist	60	2-4	4-6
Fentanyl	Agonist	0.2	1-5	0.5-2
Meperidine	Agonist	100	2-5	2-4
Methadone	Agonist	10	20-30	4-8**
Morphine	Agonist	10	2-4	3-6
Pentazocine	Mixed	50	2-3	2-3

*Usual dose: Dose equivalent to 10 mg of morphine.**Sedation and coma may last 2–3 days.

Clinical presentation

- **With mild or moderate overdose:** lethargy is common. The pupils are usually small, often "pinpoint" size. Blood pressure and pulse rate are decreased, bowel sounds are diminished, and the muscles are usually flaccid.
- **With higher doses:** coma is accompanied by respiratory depression, and apnea often results in sudden death. Noncardiogenic pulmonary edema may occur, often after resuscitation and administration of the opiate antagonist naloxone.
- **Seizures** are not common after opioid overdose but occur occasionally with certain compounds (e.g., dextromethorphan, meperidine, propoxyphene, and tramadol). Seizures may occur in patients with renal impairment who receive repeated doses of meperidine, owing to accumulation of the metabolite normeperidine.
- **Cardiotoxicity:** like that seen with tricyclic antidepressants and quinidine, it can occur in patients with severe propoxypheneintoxication.

- Some newer synthetic opioids have mixed agonist and antagonist effects with unpredictable results in overdose.
- Opioid **withdrawal syndrome** can cause anxiety, piloerection (goosebumps), abdominal cramps and diarrhea, and insomnia.

Diagnosis

Diagnosis is simple when typical manifestations of opiate intoxication are present (pinpoint pupils, and respiratory and CNS depression), and the patient quickly awakens after administration of naloxone. Signs of iv drug abuse (e.g., needle track marks) may be present.

- ✓ Specific levels:are not usually performed because of poor correlation with clinical effects. Qualitative screening of the urine is an effective way to confirm recent use. Fentanyl derivatives, tramadol, and some other synthetic opioids may not be detected by routine toxicologic screens.
- ✓ Other useful laboratory studiesinclude electrolytes, glucose, arterial blood gases or oximetry, chest x-ray, and stat serum acetaminophen or salicylate levels (if the ingested overdose was of a combination product).

Treatment

- ***Emergency and supportive measures:***
  - ✓ Maintain an open airway and assist ventilation if necessary (see Chapter 3).
  - ✓ Administer supplemental oxygen.
  - ✓ Treat coma, seizure, hypotension and noncardiogenicpulmonary edema if they occur.
- ***Specific drugs and antidotes:***
  - ✓ **Naloxone** is a specific opioid antagonist with no agonist properties of its own; large doses may be given safely.Administer naloxone, 0.4–2 mg iv. As little as 0.2–0.4 mg is usually effective for heroin overdose. Repeat doses every 2–3 min, if there is no response, up to a total dose of 10–20 mg if an opioid overdose is strongly suspected.***Caution:*** the duration of effect of naloxone (1–2 h) is shorter than that of many opioids. Therefore, do not release the patient who hasawakened after naloxone treatment until at least 3–4 h have passed since the last dose of naloxone. In general, if naloxone was required to reverse opioid-induced coma, it is safer to admit the patientfor at least 6–12 h of observation.

- ✓ **Sodium bicarbonate** may be effective for QRS interval prolongation or hypotension associated with propoxyphene poisoning.

- ***Decontamination:***
  - ✓ **Prehospital:** provide general supportive care**.** Activated charcoal isgenerally not indicated because of the risk of aspiration. Do *not*induce vomiting because of the potential for developing lethargy and coma.
  - ✓ **Hospital:** Administer activated charcoal if a patient presents soon after ingestion and is not manifesting signs of toxicity. Activated charcoal is not recommended in patients showing signs of toxicity because of the risk of aspiration. Gastric emptying is not necessary if activated charcoal can be given promptly.
- ***Enhanced elimination:***

✓ Because of the very large Vd of opioids and the availability of an effective antidotal treatment, there is no role for enhanced elimination procedures.

Summary

- Opioids stimulate several specific opiate receptors in the CNS, causing sedation and respiratory depression.
- The toxic dose varies widely depending on the specific compound, the route and rate of administration, and tolerance to the effects of the drug because of chronic use.
- With mild or moderate overdose, lethargy is common. But, with higher doses, coma is accompanied by respiratory depression, and apnea often results in sudden death.
- Diagnosis is made when typical manifestations of opiate intoxication are present, and the patient quickly awakens after administration of naloxone.
- Treatment for opiates and opioids overdose include emergency and supportive measures, specific drugs, and antidotes (naloxone), decontamination & enhanced elimination.

4.5 Phenothiazines and other antipsychotic drug overdose

Introduction

Phenothiazines, butyrophenones, and other related drugs (Table 5.2) are widely used to treat psychosis and agitated depression. In addition, some of these drugs (e.g., prochlorperazine, promethazine, and droperidol) are used as antiemetic agents. Suicidal overdoses are common, but because of the high toxic-therapeutic ratio, acute overdose seldom results in death. Many newer agents have been developed but overdose experiences with these new agents is limited. These drugs have large Vd (10-30L/kg), and most have long elimination half-lives (e.g., chlorpromazine = 18-30 h). Elimination is largely by hepatic metabolism (see table 5.2 below)

Mechanism of toxicity

A variety of pharmacologic effects are responsible for toxicity involving primarily the cardiovascular and central nervous systems.

- ✓ **Cardiovascular:** anticholinergic effects produce tachycardia. Alpha-adrenergic blockade causes orthostatic hypotension. With very large overdoses ofsome agents, quinidine-like membrane-depressant effects on the heart may occur.
- ✓ **Central nervous system:**centrally mediated sedation and anticholinergic effectscontribute to CNS depression. Alpha-adrenergic blockade causes smallpupils, despite anticholinergic effects on other systems. Extrapyramidal dystonicreactions are relatively common with therapeutic doses and are probablycaused by central dopamine receptor blockade. Unknown mechanisms may lower the seizure threshold. Temperature regulation is alsodisturbed, resulting in poikilothermia

Toxic dose

Extrapyramidal reactions, anticholinergic side effects, and orthostatic hypotension are often seen with therapeutic doses. Tolerance to the sedating effects of the antipsychotics is well-described, and patients on chronic therapy may tolerate much larger doses than other persons. The toxic dose after acute ingestion is highly variable. Serious CNS depression and hypotension may occur after ingestion of 200–1000 mg of chlorpromazine in children or 3–5 g in adults.

Table 7 Common Phenothiazines and other antipsychotic drugs

Drug	Usual adult daily dose (mg)	Toxicity
Chlorpromazine	200–2000	E, A, H
Haloperidol	1–100	E
Promethazine*	25-200	A, E

E = Extrapyramidal reactions; A = Anticholinergic effects; H = Hypotension.*Used primarily as an antiemetic

Clinical presentation

Major toxicity is manifested in the cardiovascular and CNS. Also, anticholinergic intoxication (see chapter 2) may occur because of ingestion of benztropine or other co-administered drugs.

- ✓ **Mild intoxication:** causes sedation, small pupils, and orthostatic hypotension. Anticholinergic manifestations include dry mouth, absence of sweating, tachycardia, and urinary retention. Paradoxically, clozapine causes hypersalivation through an unknown mechanism.
- ✓ **Severe intoxication:** may cause coma, seizures, and respiratory arrest. The ECG usually shows QT interval prolongation and occasionally QRS prolongation (particularly with thioridazine). Hypothermia or hyperthermia may occur. Clozapine can cause a prolonged confusion state and rarely cardiac toxicity. Risperidone can cause QT interval prolongation, but delirium is less severe.
- ✓ **Extrapyramidal** dystonic side effects of therapeutic doses include torticollis, jaw muscle spasm, oculogyric crisis, rigidity, bradykinesia, and pill-rolling tremor.
- ✓ Patients on chronic antipsychotic medication may develop the **neuroleptic malignant syndrome** characterized by rigidity, hyperthermia, sweating, lactic acidosis, and rhabdomyolysis.
- ✓ Clozapine use has been associated with agranulocytosis.

Diagnosis

Diagnosisis based on history of ingestion and findings of sedation, small pupil, hypotension, and QT interval prolongation.Dystonia in children should always suggest the possibility of antipsychotic exposure, often because of intentional administration by parents. Phenothiazines are occasionally visible on plain abdominal x-rays.

- ✓ Specific levels:quantitative blood levels are not routinely available and do not help in diagnosis/treatment. Qualitative screening may easily detect phenothiazines in urine or gastric juice, but butyrophenones such as haloperidol are usually not included in toxicologic screens.
- ✓ Other useful laboratory studiesinclude electrolytes, glucose, BUN, creatinine, CPK, arterial blood gases or oximetry, abdominal x-ray (to look for radiopaque pills), and chest x-ray.

Treatment

- ➢ ***Emergency and supportive measures:***
  - ✓ Maintain an open airway and assist ventilation if necessary.
  - ✓ Administer supplemental oxygen.
  - ✓ Treat coma, seizures, hypotension, and hyperthermiaif they occur.
  - ✓ Monitor vital signs and ECG for at least 6 h and admit the patient forat least 24 h if there are signs of significant intoxication. Children with antipsychotic intoxication should be evaluated for possible intentionalabuse.
- ➢ ***Specific drugs and antidotes:***
  - ✓ There is no specific antidote.
  - ✓ **Dystonic reactions:** give diphenhydramine, 0.5–1 mg/kg im or iv or benztropine (see chapter 3).
  - ✓ **QRS interval prolongation:**treat quinidine-like cardiotoxic effects with bicarbonate, 1-2 mEq/kg iv (see chapter 3).
- ➢ ***Decontamination*:**
  - ✓ **Prehospital:** general supportive measures. Administer activated charcoal if available and the patient is awake, and the ingestion is relatively recent. Do ***not*** inducevomiting.
  - ✓ **Hospital:**consider activated charcoal if the patient has no altered mental status and if s/he could protect the airway and come within 1 h. Gastric emptying is not necessaryif activated charcoal can be given promptly.
- ➢ ***Enhanced elimination:***
  - ✓ Owing to extensive tissue distribution, these drugs are not effectively removed by dialysis or hemoperfusion. Repeat-dose activated charcoal has not been evaluated.

Summary

- For phenothiazines and other antipsychotic drugs, different pharmacologic effects are responsible for toxicity involving primarily the cardiovascular and central nervous systems.
- The toxic dose of acute ingestion of phenothiazines and other antipsychotics is highly variable.
- Major toxicity is manifested in the cardiovascular and CNS.Mild intoxicationcauses sedation, small pupils, and orthostatic hypotension whereas severe intoxicationmay cause coma, seizures, and respiratory arrest.
- Diagnosisis based on history of ingestion and findings of sedation, small pupil, hypotension,QT interval prolongation and dystonia (for children).
- Treatment of overdose include emergency and supportive measures, treatments for dystonic reactions and QRS interval prolongation, decontamination & enhanced elimination.

4.6 Benzodiazepines Toxicity

Introduction

- Benzodiazepines to varying degrees, have in common six major pharmacologic effects: Sedative ,hypnotic, anxiolytic, amnestic, anticonvulsant and muscle relaxant.
- Benzodiazepines are commonly used for the short-term treatment of anxiety, insomnia, seizures, and alcohol and sedative-hypnotic withdrawal.
- Isolated benzodiazepine overdose is notable for the relative lack of significant rates of morbidity and mortality. Most reported cases of serious toxicity have occurred in the setting of co-ingestion of other agents or with parenteral administration.
- Death due solely to benzodiazepine overdose is rare in otherwise healthy individuals. However, deaths in seemingly isolated overdoses have been reported and appear to be more likely with short-acting derivatives such as alprazolam, temazepam, and triazolam.

Pharmacology and mechanisms of toxicity

- Benzodiazepines stimulate the α subunit of the postsynaptic γ-aminobutyric acid (GABA) receptor in the CNS. Stimulation of this receptor affects the ligand-gated chloride channel on the cell membrane, altering the transmembrane resting potential to below stimulation threshold and rendering the postsynaptic neuron less excitable. Stimulation of this GABA receptor leads to inhibitory effects throughout the neuroaxis, producing the typical clinical effects of sedation, anxiolysis, anticonvulsant activity, and striated muscle relaxation.
    - In general, benzodiazepines are well absorbed from the GI tract. The onset of action after oral ingestion is limited more by the rate of absorption from the GI tract than by the relatively rapid passage from the bloodstream into the brain. With the exception of lorazepam and midazolam, IM injection of benzodiazepines results in unpredictable absorption and diazepam can be give rectally.
    - Benzodiazepines are relatively lipid-soluble, with some variation among the agents. Increased lipid solubility is associated with more rapid diffusion across the blood–brain barrier. After single doses, the more highly lipophilic benzodiazepines have a shorter onset of action but also a shorter duration of activity. This short duration of activity occurs because of rapid egress of the drug from the brain and blood stream into inactive tissue storage sites. For this reason, the serum half-life is not a good indicator of the duration of action in an acute ingestion.

- Benzodiazepine derivatives undergo metabolism by hepatic biotransformation through either oxidation or conjugation.

Table 8 Benzodiazepines
Lorazepam

Generic Name	Time to peak Effect (hours)	Elimination Half-Life (hours)	Duration of Action (hours)	Active Metabolite Half-Life(hours)	Oral Dose Equivalent in Milligrams
Short Acting					
Midazolam*	IV 1-2min IM 10-15 min po 0.5-1	3-6	Iv 2 IM 4-6 PO 4-6	Yes	5
Intermediate Acting					
Bromazepam	1-3	10-20	<12	Yes	5—6
Lorazepam*	Iv 5-20 min IM 20-30min po 0.5 - 1	9-16	6-8	No	1
Long Acting					
Clonazepam*	0.3 -0.5	20-80	<12	No	0.5
Diazepam*	IV 1-5 min po 15-45min PR 5-45min	20-50	IV0.25-1 po 12-24	Yes (36-200)	10

Clinical Features of benzodiazepine toxicity

- The clinical presentation of benzodiazepine intoxication is nonspecific and may be highly variable because of the frequent co-ingestion of other agents. Except for additive effects, drug interactions of benzodiazepines with other sedative-hypnotics are unusual.
- The predominant manifestations of benzodiazepines are neurologic and are characterized by somnolence, dizziness, slurred speech, confusion, ataxia, incoordination, and general impairment of intellectual function. Coma, particularly if prolonged, is atypical and should prompt suspicion of intoxication with other agents or a non-toxin–related medical condition. In the elderly, infants and children, protein-deficient persons, and those with hepatic disease, the neurologic effects of benzodiazepines may be prolonged or enhanced.
- Paradoxical reactions, including excitement, anxiety, aggression, hostile behavior, rage, and delirium, have been reported but are quite uncommon. Although unclear, the etiology of such

effects is probably not idiosyncratic. This reaction may occur more with hyperactive children and in psychiatric patients. Benzodiazepines may have a disinhibiting effect, which, in the presence of various extrinsic factors, can lead to such actions as aggressive or hostile behavior. Other effects that have been reported and that have unclear etiologies include headache, nausea, vomiting, chest pain, joint pain, diarrhea, and incontinence.

- Some benzodiazepines may cause short-term anterograde amnesia. This effect may be desired, especially in procedural sedation. Agents most often associated with anterograde amnesia are lorazepam, midazolam, and triazolam, although this may occur with the other benzodiazepines.
- Uncommonly, respiratory depression and hypotension may occur, generally with either parenteral administration or in the presence of coingestants. IV administration is more likely to cause serious cardiorespiratory effects with rapid administration of large doses. In addition, the elderly and those with underlying cardiorespiratory disease are more susceptible to adverse effects of IV administration.
- Propylene glycol as a diluent in parenteral preparations of diazepam and lorazepam may cause severe metabolic acidosis, nephrotoxicity, and hyperosmolar states when infused at doses >1 mg/kg/d for an extended period of time. During such treatment, an osmolar gap >10 is predictive of elevated propylene glycol concentrations. Treatment of propylene toxicity may require hemodialysis.
- Extrapyramidal reactions have been associated with the use of benzodiazepines. Various allergic, hepatotoxic, and hematologic reactions also have been reported, but they are infrequent. In general, benzodiazepines have no long-term organ-system toxicity other than that which can be ascribed to indirect effects from neurologic or cardiorespiratory depression.

Differential diagnosis

- Benzodiazepine overdose is usually suspected or diagnosed because of the clinical presentation. Many patients are arousable and can provide supporting information. Atypical or focal findings can be clues to the presence of other conditions.
- Profound coma or cardiopulmonary instability with pure benzodiazepine overdose is rare, and the presence of either should prompt the search for a co-ingestant.

- Nontoxicologic causes of CNS depression should also be considered.

The following conditions can be the differential diagnosis :

A. Drugs and toxins
   - Sedative hypnotic agents and Opoids intoxication
   - Ethanol and toxic alcohols(Ethylene glycol and Methanol) poisoning
   - CO poisoning
   - Antipsychotics etc

B. Metabolic condition and environmental emergencies
   - Electrolyte disturbance(hyponatremia, hypernatremia..)
   - Oran failure(uremic encephalopathy, hepatic encephalopathy)
   - Endocrine emergencies(Hypoglycemia, Thyroid storm, Myxdema coma, HHS..etc..)

C. Brain disorders:

   - Meningitis, head injury, stroke etc..

Diagnosis

i. ***Routine laboratory evaluation of the poisoned patient should include the following***:

- Fingerstick glucose, to rule out hypoglycemia as the cause of any alteration in mental status
- Acetaminphen and salicylate levels, to rule out these common coingestions
- Electrocardiogram (ECG), to rule out conduction system poisoning by drugs that effect the QRS or QTc intervals
- CBC, RFT, LFT with Liver enzymes
- Arterial blood gas analysis
- Pregnancy test in women of childbearing age

ii. ***Testing for benzodiazepine toxicity***

Qualitative immunoassays for benzodiazepines in urine are available but do not aid management decisions. Many of these tests detect only benzodiazepines that are metabolized to oxazepam glucuronide; therefore, clonazepam, lorazepam, midazolam, and alprazolam are not detected on a urine drug screen.Serum drug concentrations are not routinely available and do not correlate with clinical severity

Management

Initial treatment — As with any poisoning, the management of benzodiazepine (BZD) overdose begins with a rapid assessment of the patient's airway, breathing, and circulation. Endotracheal intubation should not be delayed if needed. Oxygen is administered, intravenous access established, and continuous cardiac monitoring employed. A fingerstick serum glucose is immediately obtained. End tidal CO2 (ie, capnography) can be useful for monitoring patients at risk for hypoventilation, as can occur with severe benzodiazepine overdose. The vast majority of benzodiazepine overdoses can be managed expectantly. Activated charcoal is generally not beneficial in overdose. Hemodialysis, and whole bowel irrigation are not indicated or effective in benzodiazepine overdose.

Antidote

Flumazenil- a nonspecific competitive antagonist of the benzodiazepine receptor, can reverse benzodiazepine-induced sedation after general anesthesia, procedural sedation, and overdose, but is not recommended for the reversal of benzodiazepine overdose in the ED. Although theoretical benefits of flumazenil use include cost savings and avoidance of procedures and tests such as endotracheal intubation and lumbar puncture, several studies have not been able to demonstrate an actual benefit. Seizures and cardiac dysrhythmias can occur with flumazenil administration, and fatalities have been reported. Flumazenil is especially hazardous when given to patients who are habituated to benzodiazepines, in whom acute benzodiazepine withdrawal, including refractory seizures, can be induced, and also when seizure-causing drugs (such as cocaine or a tricyclic antidepressant) have also been ingested, due to loss of the benzodiazepine’s protective anticonvulsant properties. Co-ingestants that cause dysrhythmias, such as carbamazepine or chloral hydrate, may increase the likelihood of cardiac effects.

Indication of flumazenil

- Isolated benzodiazepine overdose in nonhabituated user (e.g., accidental pediatric exposure)
- Reversal of conscious sedation
- The initial adult dose of flumazenil is 0.2 mg given intravenously over 30 seconds. A second dose of 0.3 mg may be given, followed by 0.5-mg doses at 1-minute intervals, to a total of 3 mg. Most patients respond within 3 mg. In children, the initial dose is 0.01 mg/kg (up to 0.2 mg). Because the duration of action of flumazenil is short (0.7–1.3 hours), re sedation occurs in up to 65% of patients and requires either re dosing or continuous infusion (0.25–1.0 mg/hr)

Absolute contraindications

- Known or suspected co-ingestant that lowers seizure threshold
- Tricyclic antidepressants, cocaine, lithium, methylxanthines, isoniazid, propoxyphene, monoamine oxidase inhibitors, bupropion, diphenhydramine, carbamazepine, cyclosporine, chloral hydrate
- Patient taking benzodiazepine for control of a potentially life-threatening condition (e.g., seizures)
- Concurrent sedative-hypnotic withdrawal
- Seizure activity or myoclonus
- Hypersensitivity to flumazenil or benzodiazepines
- Patient with neuromuscular blockade

Relative contraindications

- Chronic benzodiazepine user, not taking for control of life-threatening condition
- Known seizure disorder not treated with benzodiazepines
- Head injury
- Panic attacks
- Chronic alcoholism

Disposition

- Patients remaining asymptomatic after 4 to 6 hours of Emergency department(ED) observation may be medically cleared.
- For cases of deliberate overdose, appropriate psychiatric consultation should be obtained.
- Indications for observation or hospital admission include significant alterations in mental status, respiratory depression, and hypotension. If mental status depression persists or is profound, other agents or conditions must be considered.

Summary

- Benzodiazepine overdose requires only supportive care (including, in some cases, intubation).
- Flumazenil may precipitate seizures or acute withdrawal. It should be used only in highly selected cases, such as small children with accidental poisoning or for reversal of accidental overdose of benzodiazepines during procedural sedation.
- When flumazenil is used, careful monitoring is necessary because of the risk for persistent respiratory depression or re sedation.

4.7. Barbiturates poisoning

Introduction

Barbiturates are addictive, producing physical dependence and a withdrawal syndrome that can be life-threatening. While tolerance to the mood-altering effects of barbiturates develops rapidly with repeated use, tolerance to the lethal effects develops more slowly, and the risk of severe toxicity increases with continued use.

Mechanism of toxicity

- The main action of barbiturates is to depress activity in the nervous and musculoskeletal systems. In the CNS this is accomplished by enhancing the action of the primary inhibitory neurotransmitter γ-aminobutyric acid (GABA) .
- Barbiturates inhibit the activity of the predominant excitatory neurotransmitter, glutamate,

- Barbiturates inhibit calcium-mediated excitatory neurotransmitter release at the presynaptic terminal. The blockade of the calcium channel may contribute to the cardiac contractility impairment seen with barbiturate overdoses.
- Barbiturates act directly on the medulla to produce respiratory depression.

Classification of Barbiturates

- Barbiturates are classified according to their onset and duration of action:
    - Ultra short-acting (onset immediate after intravenous dose, duration minutes) E.g. Methohexital, Thiopental
    - Short-acting (onset 10–15 minutes after oral dose, duration 6–8 hours)E.g. Pentobarbital, scobarbital
    - Intermediate-acting (onset 45–60 minutes, duration 10–12 hours)

E.g.Amobarbita, Aporbarbital

    - Long-acting (onset 1 hour, duration 10–12 hours) .E.g. Phenobarbital
- Only long-acting preparations have anticonvulsant effects in doses that do not cause sedation. increased morbidity and mortality with barbiturate overdoses compared to benzodiazepines.
- Because phenobarbital is a weak acid (pKa 7.2), alkalinizing the urine will increase the amount of drug present in ionized form, minimizing tubular reabsorption and increasing drug clearance.

Clinical Features

- Mild barbiturate toxicity mimics ethanol intoxication, presenting with drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional liability, and impaired cognition.
- In severe acute intoxication, CNS depression progresses from stupor to deep coma and respiratory arrest. Although pupils are usually normal or small and reactive, concomitant hypoxia can cause pupils to be fixed and dilated. Corneal and gag reflexes may be diminished or absent, muscle tone flaccid, and deep tendon reflexes diminished or absent.
- Flexor (decorticate) and extensor (decerebrate) posturing can occur in patients comatose. These neurologic signs are variable and do not always correlate with severity of intoxication or depth of coma. A fluctuating level of consciousness is commonly seen. High barbiturate levels depress gastrointestinal motility, delaying drug absorption. As the drug is metabolized

and blood levels drop, peristalsis and drug absorption may increase, causing drug levels to rise.

- The life threat of severe barbiturate toxicity is respiratory depression. Because respirations can be rapid but shallow, the degree of hypoventilation may not be apparent on clinical examination, but pulse oximetry or capnography will detect the ventilation compromise.
- Hypotension is common in patients with severe intoxication.
- Barbiturate overdose has been associated with non-cardiogenic pulmonary edema. Other
- Common complications include hypoglycemia(perhaps due to starvation),aspiration pneumonia, and acute lung injury.

Diagnosis

Investigation in a patient with barbiturate poisoning should include:

1. **Routine lab. investigations**
   - ✓ Glucose levels
   - ✓ Blood chemistries(RFT, LFT, serum electrolyte)
   - ✓ CBC
   - ✓ Arterial blood gas (if indicated),
2. ***EEG:*** Since the electroencephalogram may be silent as a result of barbiturate overdose, no patient should be declared "brain dead" if barbiturates are present at therapeutic levels or greater.
3. **Toxicology screen**

a) <u>Barbiturate serum levels</u>:

- Useful for the diagnosis of a comatose patient; however, acute treatment decisions should be clinically based.
- Serum barbiturate levels reported in lethal overdoses vary widely, and measurements are not reliable in predicting clinical course after an overdose because they do not reflect brain barbiturate concentrations and may underestimate the clinical condition of a patientin the setting of polydrug exposure.
- Barbiturate levels are also invalid in chronic barbiturate abusers who have developed physiologic tolerance and in patients with renal or hepatic disease who have decreased clearance.

- The therapeutic level of phenobarbital is 15 to 40 μg/mL (65–172 μmol/L). A serum level greater than 50 μg/mL can be associated with coma, especially in a patient who is not a chronic user. Levels greater than 80 μg/mL are potentially fatal.

b) **Urine barbiturate screening:**

- A false-positive result on the barbiturate screen has been reported with ibuprofen and naproxen.

4. Imaging

- Chest radiographs can detect noncardiogenic pulmonary edema or pneumonia.
- CT of the head should be obtained in comatose patients with evidence of trauma, focal neurologic signs, papilledema, or uncertain diagnosis.

Management

1. ABCDE Assessment and Initial Stabilization

- Airway assessment and stabilization are the first management priorities.
- Intubation with mechanical ventilation in severe sedative-hypnotic overdose is often required and should take priority.
- Barbiturate toxicity also results in decreased cardiac output and vascular tone, often resulting in profound hypotension. Volume expansion is the mainstay of circulatory support in the absence of cardiac failure.If fluid resuscitation fails to correct hypotension, vasopressors such as dopamine and norepinephrine should be initiated.
- Check hypoglycemia and treat
- Hypothermia between 30°C (86°F) and 36°C (96.8°F) is common and should be treated with rewarming measures.

2. Decontamination

- With very large overdoses, antecedent gastric lavage may be considered.
- A single dose of activated charcoal should be given to cooperative, clinically stable patients who present with in 1 hour of acute oral overdose. For patients who have a compromised airway, endotracheal intubation is advised prior to giving charcoal

- Multi-dose activated charcoal is consider if a patient has ingested a life-threatening amount of phenobarbital.
- A typical adult regimen for multi-dose activated charcoal is an initial dose of 50 to 100 grams PO followed by 12.5 to 25 grams PO every 4 hours.The dose for pediatrics is of 1g/kg for a child (for adolescents give 50g). Concurrent administration of cathartic agents remains unproven and is not recommended. Careful attention to and monitoring of the patient's airway is paramount to decrease the risk of aspiration or bowel obstruction.

3. Urinary Alkalinization

- Urinary alkalinization has been shown to enhance the clearance of phenobarbital and primidone, which is metabolized to phenobarbital. But it is said Zless effective in reducing toxic phenobarbital levels when compared to multi-dose activated charcoal in a small study.
- Urinary alkalinization is not considered a first-line treatment for phenobarbital poisoning and **it is not effective for shorter-acting barbiturates.**
- Urinary alkalinization is typically achieved by the administration of sodium bicarbonate as an IV bolus of 1 to 2 mEq/kg or an IV infusion of 3 to 4 mEq/kg over an hour.Urinary pH should be monitored frequently (every 15 to 30 minutes) until the urine pH is 7.5 to 8.5.
- Urinary alkalinization is sustained by either intermittent bolus or continuous infusion of bicarbonate. Serum pH should not be allowed to rise above 7.5 to 7.55. Adequacy of therapy should be monitored frenquently, typically every 2 to 4 hours.
- Pronounced hypokalemia may result from this technique. Hypokalemia induces the kidneys to reabsorb potassium and excrete hydrogen ions, inhibiting the production of alkaline urine. This may result in relatively acidic urine when compared to the serum pH.Thus serum potassium must remain above 4 mEq/L to reliably achieve continuous urinary alkalinization.
- Risks associated with urinary alkalinization include volume overload (heart failure and pulmonary edema), pH shifts, and hypokalemia.
- Therefore, contraindications to this procedure include patients who cannot tolerate the volume or sodium load, hypokalemic, or have renal insufficiency.

4. Extracorporeal Elimination

- Hemodialysis, hemoperfusion, and hemodiafiltration have all been used to enhance elimination of phenobarbital; however, they are reserved for patients who are deteriorating despite aggressive supportive care.
- These modalities are not useful for poisoning from barbiturates other than phenobarbital.
- Exchange transfusion has also been reported useful in neonatal phenobarbital toxicity

Disposition and Follow-Up

- Mild to moderate barbiturate intoxication responds well to general supportive care, including a single dose of activated charcoal, if appropriate.
- Improvement in neurologic status and vital signs over 6 to 8 hours signals eventual patient discharge or transfer. When indicated, assessment by mental health services should be performed or arranged.
- For phenobarbital, a long-acting agent, serial serum levels should be obtained during the initial 6 hours after an overdose before concluding the patient can be safely discharged or transferred.
- Evidence of toxicity after 6 hours will require hospital admission, and patients with severe toxicity should go to the intensive care unit.

Summary

- Barbiturates are addictive, producing physical dependence and a withdrawal syndrome that can be life threatening.
- Barbiturates are classified according to their onset and duration of action.
- Mild barbiturate toxicity mimics ethanol intoxication, presenting with drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional liability, and impaired cognition.
- In severe acute intoxication, CNS depression progresses from stupor to deep coma and respiratory arrest
- Airway assessment and stabilization are the first management priorities.
- Evidence of toxicity after 6 hours will require hospital admission, and patients with severe toxicity should go to the intensive care unit.

4.8 Anticonvulsants poisoning

Introduction

Anticonvulsants, or antiepileptics, are used to treat acute seizures and prevent convulsions in patients with epilepsy. The first generation of antiepileptics was developed between 1939 and 1980. Since 1993, 15 additional agents have been introduced into clinical use, termed the second and third generation" of antiepileptic drugs. In general, these new anticonvulsants have fewer serious adverse side effects and fewer drug interactions than the first-generation agents. The first-generation drugs have an established therapeutic range for serum levels that can guide therapy during long-term management and that correlate with acute toxicity from an overdose.This chapter reviews the pharmacology, clinical features, and treatment for commonly used anticonvulsants.

Table 9 Anticonvulsant drugs

First generation	***Second and third generation***
• Carbamazepine • Ethosuximide • Phenobarbital • Phenytoin and fosphenytoin • Primidone • Valproate	• Lamotrigine • Eslicarbazepine acetate • Ezogabine or retigabine • Felbamate • Gabapentin • Lacosamide • Levetiracetam • Oxcarbazepine • Pregabalin • Rufinamide • Stiripentol • Topiramate • Tiagabine • Vigabatrin • Zonisamide

4.8.1 Phenytoin and fosphenytoin poisoning

Introduction:

- Phenytoin is a primary anticonvulsant for partial and generalized tonic clonic seizures. It is useful in the treatment of non–drug-induced status epilepticus in conjunction with rapidly

acting anticonvulsants. Phenytoin has been used to prevent seizures due to head trauma (in the immediate post-traumatic period) and in the management of some chronic pain syndromes.

- Serious complications are extremely rare after intentional phenytoin overdose if supportive care is provided. Most phenytoin-related deaths have been caused by rapid IV administration or hypersensitivity reactions.
- Phenytoinis available in oral and injectable forms. Phenytoin has poor solubility in water, so the vehicle for the parenteral formulation is 40% propylene glycol and 10% ethanol, adjusted to a pH of 12 with sodium hydroxide. The acute cardiovascular toxicity seen with IV phenytoin infusion has frequently been ascribed to the propylene glycol diluent. Other limitations with parenteral phenytoin are the irritating nature of the vehicle and a tendency to precipitate in IV solutions.
- **Fosphenytoin** (a disodium phosphate ester of phenytoin) is a prodrug thatis converted to phenytoin by phosphatases in the body with a conversion half-life of 10 to 15 minutes.
- The advantage with parenteral fosphenytoin is that it is soluble in aqueous solutions, is buffered to a pH of 8.8, is nonirritating to the tissues, and can be given by IM injection.

Mechanism of action and toxicity

- Phenytoin exerts its anticonvulsant effect by blocking voltage-sensitive and frequency-dependent sodium channels in the neurons, suppressing repetitive neuronal activity, and preventing the spread of a seizure focus.
- At higher concentrations, phenytoin delays activation of outward potassium currents in nerves and prolongs the neuronal refractory period. It also may exert an anticonvulsant effect by influencing calcium channels and γ-aminobutyric acid receptors or by inhibiting adenosine reuptake.

Pharmacokinetics

- Phenytoin is a weak acid with a p*K*a of 8.3. In the acid milieu of the stomach and even at physiologic pH, more of the drug is non ionized, and its aqueous solubility is limited.
- Absorption after oral ingestion is slow, variable, and often incomplete, especially after an overdose.
- Different phenytoin preparations can possess major differences in bioavailability. **Consequently, it may be necessary to obtain serial measurements of serum level in**

suspected overdose to determine peak levels. Peak levels typically occur between 3 and 12 hours after a *single therapeutic* oral dose. After absorption, phenytoin is distributed throughout the body, with a volume of distribution of 0.6 to 0.8 L/kg.

- Brain tissue concentrations equal those in plasma within about 10 minutes of IV infusion and are correlated with therapeutic effects, whereas cerebrospinal fluid and myocardium equilibrate within 30 to 60 minutes.

Protein Binding

- Phenytoin is extensively (about 90%) bound to plasma proteins, especially albumin. The free, unbound form is the biologically active moiety responsible for the drug's clinical effect and toxicity.
- The unbound fraction of the drug is greater in neonates, the elderly, pregnant women, renal failure, hypoalbuminemia (cirrhosis, nephrosis, malnutrition, burns, trauma), and hyperbilirubinemia.
- Drugs that displace phenytoin from binding sites (salicylate, valproate, phenylbutazone, tolbutamide, and sulfisoxazole) also result in an increased unbound fraction.
- Patients with decreased protein binding have higher levels of free phenytoin and experience a greater biologic effect despite lower levels of total phenytoin. Free phenytoin concentrations are more useful in predicting toxicity.
- Corrected serum phenytoin levels(the concentration that would be present if a patient's serum albumin level were normal) can be calculated as follows:
    - **Corrected phenytoin concentration =** (measured phenytoin concentration × 4.4)/(albumin concentration), with phenytoin concentration measured in micrograms/ml and the albumin concentration measured in grams/dl.

Metabolism

- After absorption and distribution, only 4% to 5% of phenytoin is excreted unchanged in the urine.
- The remainder is metabolized by hepatic microsomal enzymes, primarily hydroxylated through a series of inactive compounds.
- The metabolism of phenytoin is capacity limited (dose dependent). At plasma concentrations of <10 micrograms/ml, elimination is **first-order kinetics** (a fixed

percentage of drug metabolized per unit of time). At higher concentrations, including those in the therapeutic range of 10 to 20 micrograms/mL, the metabolic pathways may become saturated, and the elimination may change to **zero-order kinetics** (a fixed *amount* metabolized per unit of time). With zero-order kinetics, small increases in maintenance doses may saturate the enzyme systems, markedly prolonging the half-life of phenytoin, and result in a disproportionate increase in the plasma level. **Thus incremental dose increases should be limited to 30 to 50 milligrams at a time, and levels should be carefully monitored when it is necessary to raise phenytoin doses above 300 milligrams (or above 5 milligrams/kg) per day.**

- Concomitant use of drugs that inhibit or enhance hepatic microsomal activity may result in an increase or decrease of phenytoin level, respectively. Phenytoin also affects the metabolism of various other agents

Table 10 Phenytoin Drug Interactions (Partial List)

Phenytoin increases Serum levels of	**Phenytoin levels are increased by**
Acetaminophen	Amiodarone
Acetazolamide	Chloramphenicol
Amiodarone	Cimetidin
Oral contraceptives	Disulfiram
Primidone	Fluconazole
Zidovudine	Isoniazid
Phenytoin increases serum levels of	Oral anticoagulants
Carbamazpine	Phenylbutazone
Oral anticoagulants	Salicylate (high dose)*
Phenytoin decreases serum levels of	Trimethoprim
Cyclosporine	**Phenytoin levels are decreased by**
Disopyramide	Antineoplastic drugs
Doxycycline	Calcium
Ethanol(chronic use)	Ethanol
Furosemide	Diazepam
Glucocorticoids	Diazoxide
Levodopa	Folic acid
Methadone	Phenobarbital
Mexiletine	Rifampin
Quinidine	Sucralfate
Theophylline	Sulfonamides*
Valproate	Theophyline
	Tolbutamide*
	Valproate*

Clinical manifestations

Clinical manifestation associated with Central Nervous System Toxicity

- As toxic phenytoin levels are reached, inhibitory cortical and excitatory cerebellar and vestibular effects begin to occur.
- The initial sign of toxicity is usually nystagmus, which is seen first on forced lateral gaze and later becomes spontaneous.
- Vertical, bidirectional, or alternating nystagmus may occur with severe intoxication.
- A decreased level of consciousness is common, with initial sedation, lethargy, ataxic gait, and dysarthria. This may progress to confusion, coma, and even apnea in a large overdose. Nystagmus may disappear as the level of consciousness decreases, and complete ophthalmoplegia and loss of corneal reflexes may occur. Therefore, absence of nystagmus does not exclude severe phenytoin toxicity.
- Nystagmus returns as serum drug levels decrease and coma lightens.
- Paradoxically, very high levels of phenytoin may be associated with seizures, although this is a rare occurrence, and such phenytoin-induced seizures are usually brief and generalized and almost always are preceded by other signs of toxicity, especially in acute overdose.
- Cerebellar stimulation and alterations in dopaminergic and serotonergic activities may cause acute dystonias and movement disorders, such as opisthotonos and choreoathetosis. Hyperactive deep tendon reflexes, clonus, and extensor toe responses also may be elicited.
- Chronic neurologic toxicity includes peripheral neuropathy and cerebellar degeneration with ataxia.

Clinical manifestations associated with Cardiovascular Toxicity

- Cardiovascular complications have been almost entirely limited to cases of IV administration, in large part due to the constituents of the parenteral vehicle, or in rare cases of chronic oral toxicity.
- Cardiac toxicity after oral phenytoin overdose in an otherwise healthy patient has not been reported and, if observed, is due to other causes (e.g., hypoxia and other drugs).

- Reported cardiovascular complications include hypotension with decreased peripheral vascular resistance, bradycardia, conduction delays progressing to complete AV nodal block, ventricular tachycardia, primary ventricular fibrillation, and asystole.
- ECG changes include increased PR interval, widened QRS interval, and altered ST segments and T waves.
- Cardiovascular toxicity is more common in the elderly, those with underlying cardiac disease, and the critically ill patients.
- Even though fosphenytoin does not contain the propylene glycol diluent, cardiovascular toxicity can occur with IV administration.
- Hypotension is seen in about 8%, and rare cases of bradycardia, AV nodal block, and asystole have been observed.

Vascular and Soft Tissue Toxicity

- IM injection of *phenytoin* may result in localized crystallization of the drug with hematoma, sterile abscess, and myonecrosis at the injection site.
- IV extravasation may produce skin and soft tissue necrosis, compartment syndrome, and limb gangrene. Delayed bluish discoloration of the affected extremity ("purple glove syndrome") followed by erythema, edema, vesicles, bullae, and local tissue ischemia has been described.

Hypersensitivity Reactions

- Hypersensitivity reactions usually occur within 1 to 6 weeks of beginning phenytoin therapy and can present as a febrile illness with skin changes (erythema multiforme, toxic epidermal necrolysis or Stevens-Johnson syndrome) and internal organ involvement (hepatitis, rhabdomyolysis, acute interstitial pneumonitis, renal failure, lymphadenopathy, leukopenia and/or disseminated intravascularcoagulation).
- Patients with a history of previous hypersensitivity reactions should not receive phenytoin, and because of similar reactions to phenobarbital, lamotrigine, felbamate, and carbamazepine,

Miscellaneous Effects

- Gingival hyperplasia is relatively common and is associated with poor dental hygiene gingivitis and dental plaques).

Diagnosis

- **Random blood glucose level(RBS)-**To rule out hypoglycemia as the cause of any alteration in mental status.
- **Determination of Complete blood count(CBC)-** rarely affects management.
  patients may have leukocytesis after seizure. CBC with differential will frequently show eosinophilia or marked leukocytosis in anticonvulsant hypersensitivity syndrome.
- **Organ function tests-** In patients with anticonvulsant hypersensitivity syndrome, liver function tests will often show elevated aminotransferases.
- **Pregnancy test-** should be done in women of childbearing age.
- **Serum Phenytoin level-** The therapeutic phenytoin serum level is 10 to 20 micrograms/mL (40 to 80micromoles/L), which generally corresponds to a free phenytoin level of 1 to 2 micrograms/mL.

Table 11 Correlation of plasma phenytoin level and toxic effects

Total plasma level(micrograms/ml	**Toxic effects**
<10	Usually none
10–20	mild nystagmus
20–30	Ataxia, slurred speech, nausea and vomiting
30–40	50 Lethargy, confusion
40–50	Lethargy, confusion
>50	Coma, seizures

- **Serum albumin level**- Hypoalbuminemia results in a higher free phenytoin concentration at any given total phenytoin level. Because it is the free phenytoin concentration that determines toxicity but the total phenytoin concentration that is reported, hypoalbuminemic patients with a therapeutic or mildly elevated phenytoin concentration may exhibit significant toxicity.

- **Electrocardiogram**-reveals the arrhythmias, atrioventricular block, or sinus arrest with junctional or ventricular escape that may occur after intravenous (or very rarely oral) exposure

Management

Airway and breathing

- For patients who require endotracheal intubation, standard rapid sequence intubation (RSI) protocols can be used. Most medications used in RSI are safe in patients with phenytoin intoxication, with the exception of lidocaine, which shares phenytoin's antidysrhythmic properties

Cardiovascular

- Symptomatic bradydysrhythmias following intravenous phenytoin administration are rare. Most resolve soon after stopping the infusion, but some may require transcutaneous or transvenous pacing.
- Hypotension can be treated with IV boluses of isotonic saline. Atropine, epinephrine, and dopamine remain first line medical treatment for symptomatic bradydysrhythmias.

Decontamination

- Activated charcoal (AC) may be useful in the setting of a recent ingestion. Multiple doses may remove some unbound phenytoin undergoing enterohepatic circulation, even if the phenytoin was administered intravenously.
- It is suggested that a single dose of activated charcoal be administered to patients with phenytoin overdose, unless they manifest a depressed mental status.
- It is not routinely use multiple doses of activated charcoal..

Seizures

- Seizures from phenytoin toxicity have been reported, but may stem from a patient's preexisting seizure disorder. Seizures should be treated with benzodiazepines and barbiturates as needed.

Disposition and Follow-Up

- Given the long and erratic absorption phase of phenytoin after oral overdose, the decision to discharge or medically clear a patient for psychiatric evaluation cannot be based on one serum level.
- After acute ingestions, serum level should be measured every few hours. Patients with serious complications after an oral ingestion (seizures, coma, altered mental status, or significant ataxia) should be admitted for further evaluation and treatment.
- Those with only mild symptoms may be observed in the ED and discharged once their levels of phenytoin are declining.
- Mental health or psychiatric evaluation should be obtained, as indicated, in cases of intentional overdose.

Summary

- The main presentation of patients with phenytoin overdose is related to cardiovascular and CNS involvement.
- Always you need to have high index of suspicion with other drugs toxicity when you have patient with phenytoin overdose.
- The main stay of management for phenytoin overdose is supportive.

4.8.2. Carbamazepine poisoning

Introduction:

- Carbamazepine is a primary anticonvulsant used in the treatment of partial and tonic-clonic seizures. Other uses include trigeminal neuralgia, chronic pain disorders, manic disorder, and bipolar disorder.

Pharmacokinetics and Toxicokinetics

- Carbamazepine inhibits sodium channels and interferes with muscarinic acetylcholine receptors, nicotinic acetylcholine receptors, *N*-methyl-d-aspartate receptors, and central nervous system adenosine receptors.
- Carbamazepine also possesses anticholinergic, antiarrhythmic, antidepressant, sedative, and neuromuscular-blocking properties.
- Carbamazepine is a potent cytochrome P-450 enzyme inducer and enhances its own metabolism over time. Autoinduction of the enzymes that metabolize carbamazepine occurs with about 1 month of continuous use. Because of this, the drug's half-life shortens over time: the half-life after an isolated carbamazepine dose is about 35 hours, much longer than the 10 to 20 hour half-life at steady state after 3 to 5 weeks of continuous therapy.
- Gastrointestinal absorption is slow, and peak serum concentrations usually occur within 8 hours but may be as late as 12 hours after ingestion
- Carbamazepine has a protein binding of about 80% and a volume of distribution of 0.8 to 1.2 L/kg. It is metabolized by liver cytochrome P-450 isoenzymes to an active metabolite (10,11-epoxide). The epoxide concentration comprises 15% of the parent compound in adults and slightly higher in children. The epoxide metabolite is responsible for much of the neurotoxicity seen in overdose.

Clinical manifestations

- Neurologic signs and symptoms and possibly some cardiovascular effects characterize acute carbamazepine toxicity. The initial neurologic disturbances include nystagmus, ataxia, and dysarthria. In patients with large overdoses, fluctuations in level of consciousness and coma occur.
- Carbamazepine toxicity may cause seizures in both in epileptic and nonepileptic patients. the mechanism underlying carbamazepine-induced seizures is poorly understood. In somecases, an increase in seizure frequency, without neurologic symptoms, is the presenting symptom of carbamazepine toxicity. Status epilepticus may complicate acute carbamazepine toxicity. Children may experience seizures at even lower concentrations.
- Cardiovascular effects include sinus tachycardia, which occurs in 35% of overdoses as a result of an anticholinergic mechanism, hypotension with myocardial depression, and

cardiac conduction abnormalities. High concentrations of carbamazepine may cause depression of phases 0, 2, and 4 of the action potential in cardiac tissue. In a large case series of carbamazepine overdoses, a 15% incidence of QRS complex prolongation (>100 msec), 50% incidence of QT interval prolongation(>420 msec), and no cases of terminal 40-msec axis deviation of the QRS complex in limb leads were observed.

- These abnormalities can be delayed for as long as 20 hours and may occur with chronic therapy but are not associated with life-threatening dysrhythmias or permanent sequelae. The toxicity of carbamazepine in children differs slightly from that in adults. Children experience a higher incidence of dystonic reactions, choreoathetosis, and seizures and have alower incidence of electrocardiographic abnormalities.
- Chronic carbamazepine overdose can result in headaches, diplopia, or ataxia. Idiosyncratic adverse events are common.

Diagnosis

- Complete blood count
- Urine analysis-
- Blood glucose level
- **Organ function test(OFT) and serum electrolyte**
    - The incidence of carbamazepine-induced hyponatremia ranges from 1.8% to 40%. in acute toxicity patient could have elevated liver enzymes
- **Pregnancy test**- should be done in women of childbearing age.
- **ECG-** To diagnose different arrhythmia
    - Carbamazepine can cause QRS prolongation and arrhythmia.
    - Sinus tachycardia is the most frequently observed cardiac effect of carbamazepine, but bradycardia, atrioventricular block, premature ventricular contractions, ventricular tachycardia, and junctional escape rhythms have all been attributed to carbamazepine toxicity
- **Serum carbamazepine level**
    - Serum carbamazepine concentrations should be followed serially in an acute overdose. Serum concentrations may not peak for over 96 hours; levels should be obtained every four to six hours until there is a definite downward trend and the

patient is improving clinically. Therapeutic concentrations of carbamazepine range from 4 to 12 mcg/mL (17 to 51 micromol/L).

- Carbamazepine concentrations above 40 mg/mL (170 micromol/L) correlate with an increased risk for apnea, dystonia, hypotension, and coma

Management

Airway, breathing and circulation

- Patients with significant CNS depression may lose protective airway reflexes and should be intubated, particularly in light of their lower seizure threshold.
- Short-acting neuromuscular blocking agents (eg, succinylcholine) are preferable, so as not to mask subsequent seizure activity. Induction agents with GABA agonist activity (eg, midazolam) may be preferable depending upon the patient's hemodynamic status.
- Hypotension is initially treated with isotonic crystalloid. Caution should be exercised in patients at risk for volume overload, such as those with underlying heart disease or carbamazepine-induced myocardial dysfunction. Vasopressors are used if intravenous fluids fail to correct the hypotension.

QRS interval prolongation

- Sodium channel blockade may cause QRS interval prolongation and predispose to ventricular arrhythmias.
- QRS prolongation is treated with sodium bicarbonate. A clear treatment threshold based upon the QRS duration has not been established.
- However, a reasonable practice is to give boluses of 100 to 150 meq of sodium bicarbonate intravenously for QRS intervals longer than 110 milliseconds, particularly in patients with hypotension.

Seizures

- Seizures caused by carbamazepine overdose should be treated with agonists of gamma-aminobutyric acid (GABA), such as benzodiazepines (eg, lorazepam).

- Propofol administered as a continuous infusion for the sedation of intubated patients also functions as an effective anticonvulsant.
- There is **no role** for phenytoin in the management of drug-induced seizures. electroencephalogram monitoring may be necessary in some patients.

Gastrointestinal decontamination

- **Activated charcoal** — Activated charcoal (AC) remains the most common method of gastrointestinal (GI) decontamination for acute carbamazepine poisoning.
- It is acceptable to give a single dose of AC (1 g/kg; maximum dose 50 g) to patients with a normal mental status who present within one to two hours of an acute overdose and are able to protect their airway.
- AC should be withheld in unintubated patients with CNS sedation who may not be able to protect their airway.
- **Multidose activated charcoal** — In cases of severe carbamazepine poisoning, multiple dose activated charcoal (MDAC) may be warranted. Carbamazepine demonstrates prolonged absorption and enterohepatic circulation in overdose, and some toxicologists advocate treatment with MDAC to prevent absorption and enhance

Extracorporeal elimination

- In patients with severe toxicity and multiorgan dysfunction, hemodialysis, hemoperfusion, or hemodiafiltration is effective.

Disposition and follow up

- Patients can be medically cleared from the ED if at least two carbamazepine measurements obtained a few hours apart show decreasing levels (preferably below 15 micrograms/mL) and the patient is awake, ambulatory, and free of cardiac conduction abnormalities.

Summary

- The neurologic manifestation of carbamazepine depends on the dose taken and the time of presentation after ingestion.
- Patients with carbamazepine overdose who presented with seizure should be treated with Benzodiazepine.

- Patients with carbamazepine overdose with serum level of <15mcg/ml, asymptomatic and with no ECG finding can be discharged from ED.

4.8.3 Valproate(valproic acid) poisoning

Introduction

- Valproate (or valproic acid) is used to treat tonic-clonic seizures, absence seizures, partial complex seizures, and post-traumatic epilepsy. Valproate is also used in migraine headache prophylaxis, to control manic episodes in bipolar disorder, and to treat neuropathic pain.

Pathophysiology

- Valproate affects neurotransmitters and the function of electrically excitable cells. Valproate increases γ-aminobutyric acid concentrations, reduces release of γ-hydroxybutyrate, and blocks *N*-methyl-d-aspartate receptors.
- Valproate prolongs recovery of inactivated sodium channels, enhances potassium conductance, and reduces T-type calcium current firing. With standard preparations at therapeutic doses, peak serum concentrations occur within 4 hours after ingestion. If the enteric-coated or controlled-release formulation has been ingested, peak serum concentration may be delayed for 12 to 17 hours.
- Valproate is metabolized by the liver by glucuronic acid conjugation and mitochondrial beta oxidation. Valproate enters mitochondria by using l-carnitine as a cofactor. Protein binding is extensive and influenced by serum concentration, with 90% of the drug protein bound at concentrations of 40 micrograms/mL.
- Valproate is an eight-carbon fatty acid and has a small volume of distribution of 0.13 to 0.23 L/kg. The half-life of valproate is 8 to 21 hours but may be two or three times longer after overdose.

Clinical features

- After an overdose with acute toxicity, the most frequent sign is CNS depression, ranging from drowsiness to coma.
- Other findings include respiratory depression, hypotension, hypoglycemia, hypocalcemia, hypernatremia, hypophosphatemia, and anion gap metabolic acidosis that may persist for days.

- Anion gap metabolic acidosis following overdose is a poor prognostic sign. It results from accumulation of ketoacids, lactic, carboxylic, and proprionic acids.
- Bone marrow suppression occurs 3–5 days following acute massive overdoses of VPA and is characterized by pancytopenia.
- These hematopoietic disturbances usually resolve spontaneously within a few days.
- Toxicity to the liver produces elevated serum levels of aminotransferases, ammonia, and lactate.
- Pancreatitis may occur, and thrombocytopenia may be clinically significant and severe.
- Valproate increases renal ammonia production and blocks hepatic ammonia metabolism.
- Hyperammonemia in the absence of liver failure has been reported following valproate overdose and during long-term therapy.
- Cerebral edema has been seen in acute overdose. During long-term therapeutic use, increased serum liver enzyme levels occur in >50% of patients with therapeutic valproate serum concentrations.
- Liver enzyme levels typically normalize with dosage reduction or discontinuation of the drug. Hepatic failure, histologically evident as microvesicular steatosis, occurs in about 1 in 20,000 patients receiving long-term therapy.
- Valproate-induced hepatotoxicity may be either intrinsic and benign (reversible, reproducible, and dose dependent) or idiosyncratic and fatal (unpredictable, not dose dependent, with a long latent period).
- Children <3 years of age who are receiving multiple antiepileptic agents and have additional medical problems are at highest risk for fatal hepatotoxicity, with an incidence of about 1 in 500. Serum levels of transaminases and ammonia should be checked in children on valproate therapy who demonstrate somnolence or lethargy.

Work up

- **CBC-** as a baseline and to see complication of Valproicacid toxicity(Pancytopenia, thrombocytopenia)
- **Urine analysis-**Valproate is eliminated partly as ketone bodies and may cause a positive test result for ketones in the urine or blood.
- **Serum electrolyte**-hypernatremia, hypocalcemia can be complication of valproate poisoning
- **Liver function and Enzyme tests**- To see hepatotoxicity

- **Lipase and amylase**- To assess Acute pancreatitis
- **Serum blood glucose level**-to rule out hypoglycemia as the cause of any alteration in mental status or
- **Arterial blood gas analysis-** To See anion gab metabolic acidosis and treat accordingly
- **ECG**- to rule out conduction system impairment by drugs that prolong the QRS or QTc intervals
- **Pregnancy test**-in women of childbearing age
- **Serum acetaminophen and Salicylates level**-to rule out these common congestions
- **Serum valproic acid concentration**
    - Therapeutic valproate concentrations are 50 to 100 micrograms/mL.
    - Although serum concentration does not correlate well with either seizure control or toxicity, adverse side effects increase as concentrations rise above 150 micrograms/mL, and coma may occur with levels above 800 micrograms/mL.
    - When serum valproate concentrations are measured, the enzyme-multiplied immunoassay technique yields higher values than gas-liquid chromatography, so a consistent analytic methodology should be used when monitoring treatment. Serum ammonia and glucose concentrations should be measured with suspected valproate toxicity.

Treatment

- Single-dose activated charcoal alone is sufficient for the vast majority of patients with a valproate overdose.
- Consider multidose activated charcoal and/or whole-bowel irrigation after ingestion of entericcoated, **delayed-release preparations** to prevent the ongoing absorption that may occur from delayed capsule or tablet dissolution.
- Because of delayed peak serum levels after an overdose, serial concentrations should be measured.
- Administration of high-dose naloxone has been reported to reverse valproate-induced neurologic depression, possibly by reversal of valproate- induced release of endogenous opioids or reversal of valproate induced blockade of γ-aminobutyric acid uptake. Because the serious toxic effects of valproate involve more than just these two mechanisms, naloxone is unlikely to be helpful in the management of a comatose patient after valproate overdose.

- **Hemoperfusion and hemodiafiltration** have been used to treat severe valproate overdose. Although valproate should not be amenable to dialysis due to significant protein binding, unbound (free) drug is markedly increased in overdose, and removal of valproate from this

Disposition and follow up

- Patients with signs or symptoms (eg, somnolence) of severe valproic acid (VPA) poisoning are admitted to an intensive care setting.
- In addition, adult patients who ingest greater than 200 mg/kg of VPA and/or have plasma concentrations greater than 180 µg/mL (1260 µmol/L) usually develop some degree of CNS depression and warrant admission to a closely monitored setting.
- Asymptomatic patients who ingest immediate-release preparations should be observed closely for six hours. If the VPA level is low and the patient remains asymptomatic, further clinical deterioration is highly unlikely.
- Patients who ingest sustained-release preparations should be observed for at least 12 hours.

Summary

- CNS manifestation is the most common presentation in of patients with Valporic acid overdose
- Determination of **Serum acetaminophen and Salicylates level** is very important in patients with Valproic acid overdoses to rule out co ingestions
- Supportive treatment and administration of activated charcoal is the main stay of treatment, if the patient comes to early
- Dialysis is the last resort of treatment in patients with Valproate overdose

4.9Tricyclic Antidepressant poisoning

Introduction

Structure: All have three ring molecular cores with a side chain, share pharmacologic and clinical actions and named tricyclic anti-depressant.

Action: act on the metabolism of monoamine neurotransmitters and their receptors at cellular level and includes:

- Inhibition of pre-synaptic norepinephrine and serotonin neuronal reuptake
- Interact negatively with peripheral adrenergic receptors,
- Anti-cholinergic effect especially on central and peripheral muscarinic receptors,
- Blockage of cardiac fast sodium channel

Absorption and bioavailability: therapeutic dose of TCA are well absorbed after oral administration and serum peak achieved within hours (2-8 hrs); in overdose due to anticholinergic effect, slowing of gastric activity and gastric emptying time results in slow/ erratic absorption and complicating management of acute overdose.

Has a lipophilic affinity and strongly bind to plasma proteins and tissues making its clearance by different methods difficult like hemodialysis, hemoperfusion, peritoneal dialysis, or forced diuresis..

Usually metabolized by liver and elimination occurs over several hours(12-24hrs) may increase up to 72 hours in overdose.

Actual use: tricyclic antidepressants (TCAs) were used extensively in the management of a range of psychiatric disorders; used in the treatment of panic disorder, obsessive compulsive disorder, and chronic pain syndromes.

Toxic dose:

- Clinical toxicity in intentional and pediatrics age group occurs in >2.5 mg/Kg of drug ingestion, especially in geriatric, underlying heart or neurologic comorbidities, concomitant ingestion of cardiotoxic or sedative –hypnotic drug.
- Life threatening symptoms in drug ingestion 10-20 mg/Kg, Fatal dose > 1 gm

Clinical presentation of TCA toxicity

Depending on the dose and drug ingested, patient may experience some or all of the toxic effect of TCA. Symptoms begins 30-40 minutes of ingestion but may be delayed due to slowed gastric emptying and erratic gut absorption.

- Mild-moderate overdose/ toxicity,anti-muscarinic effect predominates and presentation includes: Central effect: agitation, confusion, hallucination, seizure,ataxia, drowsiness, sedation, coma
- Peripheral: dry skin and mucosa, mydriasis, tachycardia, mild hypertension, hyperthermia,
- Urinary retention, ileus, tremor, myoclonus, hyperreflexia
- Severe toxicity: usually occurs within 6 hours if ingestion, consist of:
- Coma, cardiac conduction delays, supraventricular and ventricular tachycardia, hypotension, Respiratory depression, seizure.

In summary TCA poisoning may produce any of the three major toxic syndromes: **anticholinergic effects, cardiovascular effects and seizure disorder**.

Secondary complications in overdosed patient can happen and among these, Aspiration pneumonia, pulmonary edema, anoxic encephalopathy, hyperthermia, rhabdomyolysis can contribute to morbidity and mortality.

Death from TCA overdose may result from ventricular fibrillation, intractable cardiac shock, or status epileptics and from secondary complications.

Diagnosis

Cyclic antidepressant toxicity is diagnosed using a combination of criteria: history of exposure, clinical symptomatology, characteristic ECG findings, and positive cyclic antidepressant urine drug screen (if available) results.

Qualitative (urine) and quantitative (blood) TCA testing has limited therapeutic or prognostic utility in the acute setting..

ECG abnormalities are common with cyclic antidepressant toxicity and are useful in identifying patients at increased risk for seizures and ventricular dysrhythmias especially widening of QRS.

The classic ECG with cyclic antidepressant toxicity shows sinus tachycardia, right axis deviation, and prolongation of the PR, QRS, and QT intervals and less commonly aBrugada pattern (incomplete RBBB with ST elevation in V1-3 leads) and various block type. ECG abnormalities develop within 6 hours of ingestion and typically resolve over 36 to 48 hours.

The following signs suggest cardio toxicity:

- Prolongation of the QRS >100 msec
- Abnormal morphology of the QRS (eg, deep, slurred S wave in leads I and AVL)
- Abnormal size and ratio of the R and S waves in lead AVR: R wave in AVR >3 mm; R to S ratio in AVR >0.7.

Treatment

Initial resuscitation

Evaluate patients for alterations of consciousness, hemodynamic instability, and respiratory impairment.

- Establish an IV line,
- Initiate continuous cardiac rhythm monitoring, and obtain serial ECGs.
- Manage Air-way as indicated; many patients require tracheal intubation;
- Supplemental oxygen provision;
- Urinary catheterization to prevent urinary retention, and a nasogastric tube may be needed if ileus is present.
- laboratory studies include serum electrolytes, creatinine, and glucose
- Patients who are initially asymptomatic may deteriorate rapidly and therefore should be monitored closely for 6 hours.

Hypotension

- Treated initially with isotonic saline fluids in IV boluses in increments of 10 mL/kg to a maximum of 30 mL/kg.
- With impaired cardiac contractility, pulmonary edema can develop if excessive fluids are administered.

- Hypotension that does not improve with appropriate fluid challenges should be treated with sodium bicarbonate (regardless of QRS complex duration).
- Vasopressors (Norepinephrine and epinephrine)should be used when hypotension is unresponsive to fluids and sodium bicarbonate therapy.
- Start the IV infusion at 1 microgram/min and titrate according to blood pressure.
- Vasopressin can be tried if there is no response to norepinephrine or epinephrine.
- Dopamine is less effective than norepinephrine

GI decontamination

After the airway, breathing and circulation have been secured; attention may be turned to gastrointestinal decontamination if there is no suspicion of perforation, ileus or obstruction.

- A single 1 gm/kg (up to 50gm) dose of activated charcoal PO if patients are awake, have a patent airway/ intubated, and arrive within 2-3 hour of ingestion.
- Lavage if ingested >20mg/Kg
- Don't induce emesis.

Sodium bicarbonate

Used to treat cardiac conduction abnormalities (QRS interval >100 msec), ventricular dysrhythmias, or hypotension refractory to IV fluid;

- LD: 1-2mEq/Kg of 8.4 % of sodium bicarbonate through a wide bore needle,
- Monitor with 12 lead ECG for narrowing of QRS, R wave amplitude decrement in AVR, or resolution of arrhythmia.
- MD: mix 125 to 150 mEq of sodium bicarbonate in 1 liter of 5 percent dextrose (D5W), and infuse at 250 mL/hour
- reduce the infusion by about 25 percent per hour over four hours if patient respond
- Should the QRS interval widen during tapering, give an additional bolus of sodium bicarbonateand restart the original infusion
- Monitor pH (urine/ plasma) goal: >7.50-7.55 and clinical response.
- Also watch for volume overload, hypokalemia, hypernatremia.
- Torsades de pointes should be treated initially with 2 grams of IV magnesium sulfate.

- Identify and treat electrolyte disorders that are associated with torsades de pointes
- Contraindicated in the treatment of cyclic antidepressant–induced dysrhythmias: all class I antiarrhythmic agents, β-blockers, calcium channel blockers, and all class III antiarrhythmic agents.

Seizures or agitation

- Benzodiazepines for seizures or agitation
- Phenobarbital 10–15 milligrams/kg for seizures refractory to benzodiazepines;
- Do not give physostigmine, flumazenil, or phenytoin

Pediatric considerations

- TCA poisoning in the pediatric population generally follows a course similar to that in adults.

Disposition

- Patients with an alteration in mental status, hypotension, cardiac conduction abnormalities, or seizures should be admitted to an intensive care unit.
- Patients with mild symptoms, such as an isolated tachycardia without evidence of conduction abnormalities (i.e., QRS <100 msec), could conceivably be admitted to a monitored bed/ setting.
- Asymptomatic patients who have no conduction abnormalities on ECG and are monitored for at least six hours in an acute care setting can be safely discharged or transferred to a psychiatric service for evaluation.
- Hospitalized patients can be cleared medically after 24 hours if they are asymptomatic, with a normal or baseline ECG, normal mental status, and resolution of all antimuscarinic symptoms.

Summary

- TCA have three ring molecular cores with a side chain, and therefore named tricyclic.
- Well absorbed after oral administration and peak within hours (2-8h);
- Have erratic absorption because of delayed gastric emptying and complicate management of overdose.
- Strongly bind plasma proteins and therefore make clearance difficult.
- Overdose mainly affects CVS and CNS
- Management is supportive

Chapter 5: Establishment and Running Poison Information Center

Time allocated: 90 minutes

Chapter description

This chapter is all about how to establish and run a poison information center at national and regional level. It also discusses on the requirements to establish and maintain a PIC to ensure sustainability of the service. Further, it deals with the tasks (roles and responsibilities) of a PIC. Finally, it highlights the role of a PIC in chemical incident, disaster preparedness, and response.

Primaryobjective

At the end of this chapter, participants will be able to establish and run a poison information center at national and regional level.

Enabling objectives

- Describe what poison information centers are
- Discuss the requirements to establish and run a poison information center
- Explain the governance, organization, and operation of a poison information center
- Identify the roles and responsibilities of a poison information center
- Identify the roles of a poison information center in chemical incidents

Chapter outline

5.1 Introduction

5.2 Requirements to establish and run a PIC

5.3 Governance, organization, and operation of a PIC

5.4 Tasks of a PIC

5.5 Roles of a PIC in chemical incidents

5.6 Chapter summary

5.1 Introduction to Poison Information Center (PIC)

Brainstorming

- Have you ever heard of a poison information center?
- What do you think the function of the center is?

A poisons control center is a specialized unit that advises and assists with the prevention, diagnosis and management of poisoning cases, provision of laboratory analytical services, toxicovigilance activities, research, education and training in the prevention and treatment of poisoning. As part of its role in toxicovigilance, the center advises and actively involved in the development, implementation and evaluation of measures for the prevention of poisoning. In association with other responsible bodies, it also plays an important role in developing contingency plans for responding to chemical disasters, monitoring the adverse effects of drugs and in handling problems of substance abuse.

The structure and function of poisons centers varies around the world, however, at a minimum, a poison control center provides poison information services. Some poisons centers may also include a toxicology laboratory and/or a clinical treatment unit.

A poison information service should be available at national and regional level. Ideally there will be one national poison information center with a series of regional satellite centers. A regional poison information center should serve a population of 5-10 million and there should be close collaboration among them. Depending on the availability of other services that provide information, a poison information center may have to advise on a wide range of problems.

Establishing a national poison center requires political and financial support, technical input, and material resources. Political support is needed from the relevant ministries, particularly health, agriculture, and environment, which should also be prepared to provide funding. In addition, the poison center must have the support of the main professional groups of users; i.e. nurses, physicians, and pharmacists. Sustainable financial support is also essential.

A poison information center needs certain minimum requirements to function optimally, but a modest establishment that can be expanded in the future is preferable to no service at all. The national poison information center shall better have all the required facilities. However, the regional ones can begin the service by establishing a PIC in a leading hospital with better

emergency and critical care services. Poison information databases shall be developed for recording and documentation of calls and cases, and such databases can be shared in country.

5.2 Requirements to establish and run a PIC

Location of a PIC

Where feasible, the center should be located or affiliated at a leading hospital with better emergency and intensive care services, as well as a medical library and a good laboratory facility. It should be linked directly with a hospital emergency department where poisoned patients are treated. The laboratory facilities of such institution can usually be expanded to allow toxicological laboratory services to be undertaken and appropriate quality control to be exercised. The center should have a formal working relationship with laboratory, emergency, and ICU services.

Staff of a PIC

A poison information center needs a team of poison information specialists. The term "poison information specialist" is used to recognize all health professionals at poison information centers who are involved in providing the poison information service. The center should be headed by a director who is trained and experienced with toxicology and have sufficient time to perform the duties of the center on 24/7 basis. The director will be fully responsible for the operation of the center and should be employed on a full-time basis. A poison information specialist helps to prepare and provide expert information and advice on dealing with poisoning and drug overdose.

The PIC team include fulltime physicians, clinicalpharmacists, nurses, health officers, and IT personnel. When necessary the center will consult other part-time experts such as mental health professionals, toxicologists, and others as appropriate. The team shall have experiences in emergency and critical care services and trainings in applied/clinical toxicology. Additional advantage will be training or course in health informatics or drug informatics. When there are staff shortages, part-time staffs can work with the above trainings and experiences.

The numbers of staff in the various categories must be sufficient to provide an adequate and continuous service. While the enquiry load may vary according to the time of day, it would be desirable to have a minimum of four poison information specialists at national poison information centers to manage the activities. But, regional poison information centers can adjust

their need according to their number of population. The center should operate 24 hours a day all year round for receiving calls and providing service.

Equipment and facilities for a PIC

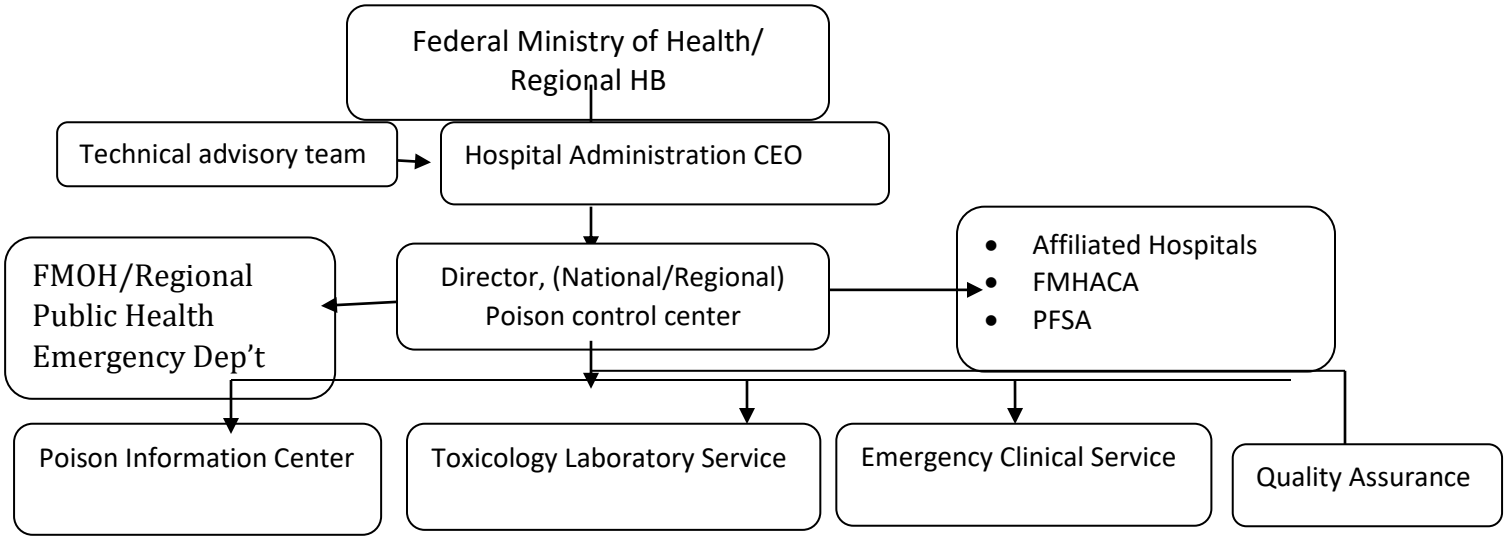
If a PIC is to function effectively, certain basic equipment is essential, including suitable office furniture and facilities for the safe storage of data. Internet connection for web browsing and email service is important. There should be collection of information resources in toxicology, poisoning and drug overdose including textbooks, guidelines, protocols, formularies, offline and online databases. There should be standard operating procedure for service provision. Optimum area shall be set out considering space for answering telephone calls, desk space for computers, preparation of documents, staff meetings and administrative works. Office chairs with tables, shelve(s), file cabinets, printers, copier, and telephone are necessary for running the service.

5.3 Governance, organization, and operation of a PIC

The national and regional poison information centers will be under Federal Ministry of Health and Regional Health Bureau (RHBs), respectively. Experienced and dedicated director will head the PICs. The FMOH or RHBs may delegate hospitals to oversee the poison information centers. The PICs should operate 24 hours a day all year round for receiving calls and providing service.

Twinning arrangements between PICs can be very valuable permitting exchanges of information and staff, training, research, provision of antidotes and documentation of case data on unusual types of poisoning. As a means of technical cooperation, twinning should also be encouraged between new and established centers within the country and outside. Cooperation at the international level between PICs, their national and regional associations, relevant professional bodies, governments, and organizations could do much to improve in the control of poisoning.

Organization of PICs will be at national and regional level.



1. *Developing and distribution of educational and information materials and algorithms:*
   - It shall prepare, publish, and distribute poison information bulletins, newsletters, brochures, algorithms,and posters targeting the public and health professionals.
   - It shall prepare national or regional formularies for relevant antidotes, poison treatment guidelines, and other reference materials in collaboration with stakeholders.
2. *Answering poison prevention and management related enquires to professionals and public*
   - The center shall answer poison related enquiries coming from health professionals
   - The center shall answer poison related enquiries coming from the public.
   - The center shall handle answers given to public enquiries carefully and results should be followed up by the center/provider.
3. *Organizing and providing in-service training, preservice education and general information*
   - It shall provide education and trainings on poison prevention and management to health professionals through preservice and in-service opportunities.
   - It shall provide public health education on poison prevention and management to the public/consumers through mass media.
   - It shall train other poison information officers and specialists.
4. *Conduct research and/or participate in poison related studies:*
   - It shall conduct researches on poison information service delivery, poison prevention and treatment activities, and toxicological laboratory services.

- It shall conduct epidemiological studies, morbidity and mortality rate and trends, quality of service audit and evaluation studies, and outcome researches.

5. *Maintain and promote ethical and legal provision of poison information services:*
   - Shall provide poison information that should not compromise patient's confidentiality. The legal status of the center should enable it to maintain the confidentiality of data it handles.
   - Shall provide poison information for medico-legal cases to the right body.
   - Shall provide independent, evidence-based, and reliable information supported by references
   - Information should be provided free of charge to enquirers, particularly in emergencies and for research.
6. *Collaborate & coordinate with regional, national, and international poison information centers*
   - The national PIC shall coordinate information resources and cooperate with other centers to avoid unnecessary efforts and to provide extensive coverage of the literature.
   - The national PIC shall make all the necessary efforts to keep contacts between regional, national, and international centers to exchange information materials and antidotes.
   - The PIC shall make efforts to exchange experiences on the provision of poison information between regional, national, and international centers.
   - The national PIC should support regional poison information centers
   - The national PIC should collaborate with pre-hospital caregivers and FMOH public health emergency department for special cases.
7. *Perform and maintain quality assurance activities to ensure a high standard quality of services.*
   - The center shall adhere, in quality assurance programs, to the following:
     - Assessment and identification of problems
     - Timely provision of solution and response to enquiry
     - Monitoring and evaluation of activities
     - Recording, documentation, and reporting of activities
     - Maintaining data confidentiality
     - Extent and quality of services provided
     - Collaborations and communications made

- Researches/assessments conducted

- The national and regional centers shall monitor and evaluate the status of their poison information services.
- The national PIC shall conduct monitoring and evaluation activities on regional PICs.

5.5Role of PICs in chemical incidents

A poison information center often has the advantage of providing a 24-hours service and may play a central role in chemical incident and disaster preparedness, and response activities. The fire and emergencyrescue services, together with the police, are usually the first to notice and report to the center during chemical incidents. By providing appropriate information, poison information centers havean important contribution to the handling of major incidents involving chemicals, and the clinical services may be involved in the treatment of victims. Centers should take an active part in contingency planning, education, and training for chemical incidents. They should also initiate research and follow-up studies when appropriate.

The staff of a poison information center should:

- Receive specific instructions on how to act in the case of a chemical disaster.
- Be prepared to provide information on the chemicals involved or alert procedures, to those handling the emergency, decision-makers, and the mass media.
- Know how to recognize the magnitude/level of the incident (whether it is operational, local, regional, or international) and should alert the center's director, other staff, and health and other authorities, according to established procedures.
- Be trained how to deal with the public, either directly or through the mass media.
- Be instructed on how to release information, build resilience and understanding in responding to disasters and, while providing reassurance and a clear message.

Maintaining and providing Information

The PIC may act as the focal point for action in case of chemical accidents and should be prepared to provide adequate information rapidly in acute phases. Hence, it is important to have information ontoxic chemicals and their effects, high-risk areas and processes and/or activities involving risk, which chemical(s) might be released, in what forms and quantities, and possible protective and remedial measures.

The exact location, capabilities, and capacities of treatment services, toxicological laboratory services and emergency transport services must be known. Centers must also be aware of the responsibilities and roles of all bodies involved in and establish close communication links with emergency rescue services and the police.In the event of a major chemical accident, PICsshould expect a flood of telephone calls. They should be prepared to deal with this type of situation, avoiding panic and providing advice rapidly to all concerned parties.

Making contingency planning

Poison information centers should cooperate with other agencies in contingency planning for chemical accidents. If contingency plans have already been established, a PIC may become an emergency control center in the event of a chemical disaster. The regional information centers should therefore have the foresight to consider what chemical disasters could occur within their region and be prepared to provide fast and accurate advice and orientation.

Emergency plans must be extended to cover chemical accidents, and close collaboration should be established between the planners and the PIC. The center should provide the planners with guidelines on measures for risk assessment, decontamination *in situ* and within hospitals, first-aid measures, general and specific therapy, and measures to ensure the availability of antidotes.

PICsshould also be aware of the facilities available for dealing with large numbers of victims in terms of number of beds, pharmaceutical supplies, and availability of specific antidotes.

Staff at clinical departments may be involved in the treatment of victims of chemical incidents or disasters. They need to provide guidance to the medical rescue teams on the triage of poisoned patients, on their initial treatment procedures before they reach hospital, and on decontamination at the site of the incident. Any hospital that manages poisoned patients may need to provide decontamination facilities out of its emergency admission area to prevent contamination by toxics.

Provision of education and training

Poison information centers should play an active role in the education and training of all members of rescue teams and health professionals for their role in the event of chemical accidents. This education and training should be geared to the educational level of each group being trained (e.g. fire and emergency, polices, supervisors, health professionals).Training

should cover decontamination, protective,and triage techniquesfor staff treating contaminated patients.

Conducting follow-up studies

Close follow-up studies of both major and minor chemical incidents may yield much valuable information on their handling. In the event of a major incident involving chemicals, PICs should be ready to mobilize one or more competent personnel to assist.A staff member from the center may need to go to the scene of the incident or to the place where patients are being treated to take an active part in evaluation and risk assessment, coordinate advice to health care personnel and organize analytical tests. This would also provide an opportunity to collect human toxicological data valuable for advice on future occasions and for planning with respect to chemical incidents.

5.6 Summary

- A poison information center (PIC) is a unit established to provide an evidence-based, UpToDate and timely toxicological information related to chemical poisoning, drug overdose, envenomation and chemical disasters to health professionals, and/or the public.
- A poison information service should be available at national and regional level.
- A PIC needs certain minimum requirements to function optimally, but a modest establishment that can be expanded in the future is preferable to no service at all.
- Where feasible, a PIC should be located/affiliated at a leading hospital with better emergency and intensive care services, a medical library and a good laboratory facility.
- A PIC needs a team of poison information specialists. The PIC team include fulltime physicians, clinical pharmacists, nurses, health officers, and IT personnel.
- If a PIC is to function effectively, certain basic resources are essential, including adequate and furnished office, internet connection, collection of information resources, and SOP.
- Organization of PICs shall be at national and regional level, and the national and regional PIC will be under FMOH & RHBs, respectively.
- Tasks of a PIC includes preparation and distribution of informational materials, answering poison related queries, providing education and training, conducting research and toxicovigilance, and perform monitoring and evaluation.
- A PIC has a role in the management of chemical disasters.

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