Pathogenetic principles and diagnostic approaches in toxicology. Treatment methods and principles of acute poisonings

Toxicokynetics- The toxokinetics of exogenous noxa is a major part in the pathogenesis of poisoning. The movement of the poison through the body goes through several stages and during these stages the interaction between the body and the toxic substance is determined by their physical and chemical properties and the permeability of cell membranes.

MEMBRANES
The more lipophyllic, less polar and smaller the molecules- the easier and quicker it is to pass through the biphospholipid membranes and get to the target( receptors, enzymes)

The more hydrophilic, ionized or polar - the more difficult to be distributed to the target organ and easier to be exreceted out of the body

THINK OF THE MANY BARIERS A TOXIN OR A DRUG NEEDS TO PASS

EPITHELLIUM→ INTERSTITIUM→BLOOD VESSELS→INTERSTITIUM→END ORGAN CELL MEMBRANE

If they can by pass a barrier they will have quicker drug or toxic effect ( desirable or not)

The stages of interaction between the body and the toxic substance are:

- stage of entry and resorption of the poison, in which the penetration of the toxic substance into the body through the respective entrance door, absorption and passage of the toxin through the barrier membranes until entering the circulation
-stage of distribution of the poison (hematogenous stage), during which distribution takes place -distribution in the blood and transfer to various tissues in the body
-biotransformation (metabolism) -mainly in the liver but also other

parenchymal organs- kidneys, lungs, adipose tissue
-stage of excretion of the poison from the body - excretion (elimination) -liver, kidney, but also with exhaled air, body fluids, accumulation in skin appendages

Routes of intoxication

Oral( ingestion) 80-90% of all intoxications – easy access to anything we can accidentally or deliberately put in our mouths.( children most prone)
depending on the physical and chemical characteristics absorbtion can start in **the mouth mucosa** ( Nitrates, midazolam, glucose- buccal way used in medical emergencies)
**esophagus**- passage time less then 12-15sec, sotechnically not much time for the toxin to be absorbed
-**stomach** - lipotropic substances such as alcohols and poisons with acidic properties (barbiturates) have a good coefficient of resorption and their penetration is carried out mainly by simple diffusion; poisons with weakly alkaline properties such as quinine, atropine and other alkaloids pass much more limitedly through the gastric mucosa

**-in the intestinal tract** - poisons with alkaline properties, oil solutions of toxic substances are quickly absorbed, and slower - poisons with slightly acidic properties due to the higher ionization coefficient in the alkaline environment of the intestinal juice

think 1) acidity 2) motility

Some basic chemistry reminders:

The more hydrogen ions in the system , the more the equilibrium is shifted to the left and the weak acids stay nondissosiated, hence less polar , hence easier to be absorbed.If we alkalinize the system we will shift the equilibrium to the right and the weak acid could be easily excreted ( example- aspirin/salicylic acid)

normal pH in stomach 1,5-3,5
antiacids, hystamin and proton pump inhibitors- decreased acidity,drug absorbtion might be hindered, like Omeprazole taken with NSAIDs ( nurofen ) can slow down its absorbtion

Available food content in the stomach, which slows down the absorption of the poison to varying degrees or changes its properties (monosaccharide-rich foods neutralize the toxic properties of cyanide compounds in the gastrointestinal tract, in the presence of fatty foods the absorption of lipotropic toxins is accelerated)

Changes in the blood circulation of the gastrointestinal mucosa - with hyperemia and acceleration of blood flow significantly accelerates resorption; in a state of shock, the penetration of the poison through the intestinal mucosa is very difficult and delayed. After overcoming the shock, the resorption increases, which contributes to a new acute deterioration of the condition.

motility – the slower/lazier the stomach and the guts- more time for the toxin to be exposed to the absorbing surface- higher toxic concentration later and possibly GI decontamination/emptying might be still considered if recommended at all for treating the patient

hypotermia, opiods, b-blockers, calcium channel blockers, atropine – all slow down motility

If we increase the motility of the guts and stomach, toxin will have less time to be absorbed and will get out of the body quicker. Another treatment consideration →we give patients laxatives as magnesium sulfate on top of the activated charcoal.
Don't forget to warn them that tar-colored diarrhea is an expected happening and we are happy when we see a black nappy( the charcoal has travelled all the waythrough GI tract )

INTESTINES AND LARGE BOWEL- very long and humongous absorbing surface, tens of square meters.
pH in guts- weakly alkaline so think opposite of the stomach- weak bases will

be non polar and readily absorbable- metoprolol, codeine

Once absorbed ,toxins follow the blood stream and if ingested they travel in the portal vein circulation and get to the liver.

INTOXICATIONS VIA INHALATION

intoxication can occur when inhaling fumes,vapors,dust during fires, smoking illicit substances, overdose with anaesthetic gases, working in hazardous environment in industrial plants, welfare

less membranes to be crossed
huge absorbing surface, massive vasculature→ quick absorbtion and toxic effects
gases follow the concentration gradient and are dissolved in the blood ( partial pressure is the key factor)
Toxic effects could be local- chlorine, acids are irritants and cause imminent laryngo and bronchospasm with acute respiratory failure, or generalized- psychoactive substances like tetrahydrocannabiol ( weed),crack,toxic vapors- ethanol, fuel, organic compounds-systemic effects
Always mind the duration of exposure and any comorbidities- elderly people, ischaemic heart desease, cerebral ischaemia, asthma, COPD- be ready for worse symptoms and higher risks

VOLATILE AGENTS- normally liquids that vaporize easily at room or body temperature, most organic industrial/domestic products – hydrocarbon mixtures as gas, kerosene,paints, alcohols ( as in if you are caught for drinking under influence ,DUI, and you are asked to blow in the dragger, the concentration of the ethanol in the exhaled air will correspond to the level in your blood streem))
They all have irritative effect on their first pass via the GI tract, but once

absorbed and distributed around with pulmonary circulation they diffuse in the alveolae and exert local toxic effect- bronchitis, toxic pneumonitis >36-48h after the exposure

**skin and mucosae**- lipophyllic substances can pass through and when in significant amounts can cause not only local tocic/irritative/allergic effects but generalized intoxication – alcohols, pesticides, toxic particles and organic compounds. Certain areas with a denser network of blood vessels pass the poison relatively faster (scalp, hyperemic areas of the skin obtained by mechanical friction, warming). In obese people there is a more extensive penetration of toxic noxa into the subcutaneous adipose tissue and a longer course of intoxication with periods of improvement and deterioration (more fat depots-> longer retention of lipophilic substances)

rectum and vagina – abundant blood supply, quicker absobrtion, rectal mucosa is used when administering drugs like antiflamatories- nurofen, paracetamol, diazepam in children as they act quicker.Easy to get a child overdosed this way ( always ask mothers for more details if she appears pro active or the grandmother if she still uses old but gold methods of putting the fever down)
per vagina- any suspicious bleeding ,discharge, pain in combination with systemic symptoms of intoxication- always consider pregnancy and attempt for illegal abortion

Parenteral route
intravenous/subcutaneous or intramuscular injection
Bypasses all compartments and barriers and drug is delivered straight in to the blood streem if given iv, hence effects are immediate ( nearly)
Circulation time of blood around the body <40s
IV drug abuse or drug errors( yatrogenic)
Always double /triple check
-right patient
-right drug

-right dose

Distribution

Part of the penetrated poison is not binded to the plasma - only it can cross the capillary wall and be involved in the processes of distribution and in the subsequent stages of toxicokinetics.

Protein binding
Albumins being the main carriers
Non covalent bound, protein toxin complex stability and dissociation depends on ph, concentration, binding sites, molecular structure
less protein (hypoproteinemia)= more free toxin fraction, more toxic effects
consider it with malnourished, frail patients, burns,comorbidities
alcohols, pesticides=0-10% protein binding
SSRI,antipsychotic drugs- 85-98% protein binding

Low Vd/Low protein binding → haemodyalisis beneficial (lots available in blood to be dyalized) barbiturates,salicylates, ethanol,methanol

High Vd/High protein binding →dyalisis unpractical, benzodiazepines,TCA,SSRI

Volume of distribution- the imaginary abstract volume of fluid /space that is needed for all the given dose of a toxin/drug to be contained if absorbed instantaneously and fully

Example:
Blood volume of 80kg man `~5litres of which ~2,4l plasma, so plasma/body weight = 2,4l/80kg= 0,03l/kg

Low Vd= most of the drug/toxin is contained within the blood Vd<1
pesticides
ethanol/methanol/etylenglycol

valproic acid(depakine)

High Vd- blood compartment can be potentially fully saturated and drug diffuses in other compartments- fat tissue, muscles, parenchimial organs
verapamil,TCA
SSRI

Metabolism (biotransformation)

Whatever the entrance route, toxin under go so called 1st pass metabolism, and as oral route most common it takes place mostly in the liver, but kidneys, GI, muscles, blood vessels, pulmonary interstium can be also involved

the basic principle- the body tries to make xenobiotics more difficult to be absorbed and to stimulate the excretion

non polar/lypophyllic→polar/ionized
oxidative-reduction reactions
hydrolysis
adding up glucoronyl or sulfonyl/methyl groups

Main enzyme involved Cytochrome P450 oxydase (CYP450)
class of >50proteins,abundant in liver
can be induced ( good if you want to get rid of a toxin, bad if you want a drug to stay in therapeutic concentrations)- rifampicin ,a tuberculosis drug→ ,most powerful inducer
inhibitors- grapefruit juice!!
Always use your BNF, toxbase sites, or Google it if you don't know the specific interactions of a mixture of drugs ( that's what clinical pharmacologist are paid for too)

liver or kidney elimination- kidneys not only filter, but actively metabolize xenobiotics and excrete them.

enterohepatic circulation – once a toxin is in the hepatic lobuli, some of it might be excreted in the bile back in the GI before it is metabolized and be redistributed to the liver numerous time, sustaining a toxic concentration enough for repeated or prolonged poisoning ( opiods, ssri) treatment hint- give repeated activated charcoal doses if that s the case (every 3-4hours)

Excretion- the way of the toxin out of the organism, entrance route might be exit routes as well.If we enhance the passage from these we can detoxicate patient faster
stool→ laxatives,whole bowel irrigation
urine→forced diuresis, change the pH if needed
blood→ haemodyalisis,carbohaemo perfusion,antidotes
exhaled air-increase tidal/minute volume, high flow 100% oxygen
bodily fluids- sweat, saliva,BREAST MILK, exhaled air, hairs, nails….

TOXICODYNAMICS

Toxicodynamics involves the interactions of a toxicant with a biological target and the functional or structural alterations in a cell that can eventually lead to a toxic effect. Depending on the toxicant's chemical reactivity and vicinity, the toxicant may be able to interact with the biological target. Interactions between a toxicant and the biological target may also be more specific, where high-affinity binding sites increase the selectivity of interactions. The targets are often receptors on the cell surface or in the cytoplasm and nucleus. Toxicants can either induce an unnecessary response or inhibit a natural response, which can cause damage.

Examples
-dna/genome toxicity- more with chronic exposures- professional, environmental – mutations,teratogenic and cancerogenic effects
-enzymes- inhibiting or disrupting enzymes involved in crucial cellular metabolic paths-

-toxic byproducts
methanol- formaldehyde-formic acid
metabolites cause severe acidosis, electrolyte derangement shock and cardiac arrest
paracetamol→ toxic metabolite that deprives the cell of glutation and hepatocytes die from oxidative stress

Toxidromes

Syndromes caused by specific toxins are called toxidromas. The main toxidromes are: anticholinergic, cholinergic, opioid, sympathomimetic, sedative-hypnotic.

Anticholinergic toxidrome

The anticholinergic syndrome occurs frequently because many common medications and other xenobiotics have anticholinergic properties. From sleep aids to muscle relaxants to antipsychotics have the potential to disrupt cholinergic function in the CNS with resulting delirium. Cholinergic activity is the primary mediator of attention, concentration, memory, reasoning, planning, and, to a large extent, communicating and understanding through language. Antimuscarinic toxicity in the CNS causes delirium, frequently accompanied by mumbling speech. Psychomotor activity is generally of high frequency and low amplitude when patients are awake. Vivid visual hallucinosis of living creatures occurs. Deep tendon reflexes are often hyperdynamic. Inhibition of secretory functions can can lead to dry mouth, flushed skin, and impaired heat dissipation. Suppression of cholinergic inhibition of heart rate may produce tachycardia. Unopposed sympathetic drive of the ciliary apparatus produces pupillary dilation. Cholinergic function also is required for normal peristalsis and bladder emptying, so this syndrome may be accompanied by fecal and urinary retention, as well.

- caused by anticholinergics - atropine, scopolamine:

-dry skin and mucous membranes
-warm skin
-heated temperature

-tachycardia and hypertension
-disorders of mental status – agitation
-mydriasis and cycloplegia
-reduced motility of the intestinal tract (constipation)
-urinary retention

Cholinergic toxidrome

Cholinergic toxicity produces a patient who presents “wet,” as opposed to the anticholinergic syndrome, which often causes the patient to be “dry.” The wetness is manifest by profuse sweating and excessive activity of the exocrine system, often accompanied by vomiting, diarrhea, and urinary incontinence. The mnemonic “SLUDGE” highlights specific elements of the syndrome: salivation, lacrimation, urination, defecation, gastrointestinal cramping, and emesis. The CNS (eg, confusion, seizures, coma) and skeletal muscles (eg, weakness, fasciculations, hyporeflexia) also can be involved. Cholinergic excess is frequently caused by accidental organophosphate or carbamate pesticide exposure, which may occur through dermal contamination. Cholinergic effects also are the cause of toxicity from “nerve gases” like sarin and from mistaken ingestion of Clitocybe and Inocybe mushrooms.

- caused by organic phosphorus compounds, carbamates, choline, fungi:

-tearing with blurred vision and miosis
-salivation
-frequent urination
-diarrhea (accelerated intestinal motility)
-bradycardia

Opioid toxidrome

Toxicity from opioids progresses from analgesia to anesthetic CNS depression, coma and death. Respiratory depression is particularly pronounced with opioid overdose, and the tidal volume or respiratory rate can be diminished before decreases in blood pressure or pulse occur. Patients will have minimal respiratory drive and quickly develop manifestations of shock. Miosis also is characteristic and, in pure opioid toxicity, a fairly reliable finding. A patient “found down” after several hours following opioid exposure will frequently have laboratory and imaging results consist with hypoxic and hypovolemic injury to multiple organ systems, including kidneys, liver, lungs, heart, skeletal muscle, and CNS. Noncardiogenic pulmonary edema with progression to acute respiratory distress syndrome is common. Rhabdomyolysis combined with hypotensive renal damage can result in a need for hemodialysis, sometimes for weeks.

- opioids are natural or synthetic substances that have morphine-like effects. Opiates of natural origin are morphine and codeine. Synthetic analogues are methadone, fentanyl. Symptoms:

-CNS suppression
-myosis
-respiration suppression
-bradycardia
-hypotension
-slow intestinal motility

Sympathomimetic toxidrome

The sympathomimetic syndrome is usually seen after acute or chronic abuse of cocaine, amphetamines, or decongestants. Blood pressure is elevated, the pulse is rapid, pupils are typically dilated. Mild toxicity rarely leads to cardiac complications, but large over-doses of sympathomimetic agents can produce hypertensive crisis, intracranial hemorrhage, arrhythmias, cardiovascular compromise, and shock. Some

compounds (eg, cocaine) cause seizures and arrhythmias due to their ability to interact with neuronal and cardiac sodium channels, so sodium bicarbonate infusions are essential in the critical care of severely poisoned patients.

- may develop as a result of the action of caffeine, cocaine, amphetamines, methamphetamines, LSD, theophylline (bronchodilator). Symptoms:

-psychomotor arousal
-tachycardia
-hypertension
-increased sweating
-hyperpyrexia
-mydriasis
-tremor
-reduced intestinal motility

Sedative-hypnotic toxidrome

When administered in sufficient dosage, sedative/hypnotics cause general anesthesia with diminished reflex activity and a complete loss of awareness. Sedation can be profound, but it is rare that benzodiazepine toxicity, alone, results in significant respiratory depression. Barbiturates, however, are sufficiently potent to produce shock and respiratory failure. “Pure” GABA-ergic toxidromes can sometimes be distinguished on the basis of history, lethargy or coma, relatively preserved pulmonary function, and the absence of constricted pupils (see Table 1). Patients also can be confused and disinhibited by benzodiazepines such that they display intermittent agitation, despite the CNS depression typically produced by these agents. This phenomenon, along with prolongation of delirial and comatose states, is a major iatrogenic complication of care in the ICU setting. Continuous infusions of midazolam remain common practice,22even though interrupted regimens have been associated with

decreased sedativeuse, lower rates of delirium, fewer complications, and shorter lengths of stay; andthus appear in the most current practice guidelines for critical care.23Even intermittentuse of benzodiazepines can yield neuropsychiatric complications with the potential tocontribute to long-term sequelae, so recognition of and definitive treatment for seda-tive toxicity is critical.When offending toxins operate at the benzodiazepine-binding site of the GABA-Areceptor complex, reversal of this syndrome can be accomplished with the admin-istration of flumazenil. It should not, however, be used in the setting of active toxicityfrom agents that are highly proarrhythmic or proconvulsant, because adverseevents can result.24With careful attention to neurologic status and autonomicindices, physical examination can identify patients (non-hyperreflexic, withouttachycardia or significant hypertension) who can safely receive a potentially thera-peutic test dose of flumazenil. If individual IV doses are kept low (0.2–0.5 mg) anddelivered over 30 seconds, the incidence of arrhythmias and seizures, even in pa-tients who take benzodiazepines chronically, is negligible.25A state of anxietymay emerge from the reversal of stupor,26but supportive psychological presenceis all that is required to manage such a side effect from the antidote.25Withdrawalis possible, but because such an outcome cannot be predicted and the effects willbe transient, a low dose of flumazenil can be used safely27as an initial alternative tothe standard practice, relatively lacking in an evidence base, of scheduling a pro-tracted taper of benzodiazepines for all patients who have been sedated forextended periods in the ICU.23,28Therapeutic effects include facilitation of extuba-tion, restoration of wakefulness and cognition, and relief of disinhibition with theresult that patients can advance to calm participation in their own care. Flumazenilis short-acting; multiple doses may be necessary to maintain the effect, so afterinitial benefit is achieved, repeating 0.5-mg doses every hour as needed isrecommended.25Although their mechanisms of action differ somewhat from benzodiazepines, thetoxic effects of nonbenzodiazepine sedatives (eg, zolpidem, zaleplon, and zopiclone)will respond to flumazenil. Flumazenil will not reverse either the effects of barbituratesor those of other sedatives that work via distinct mechanisms like ion channel modu-

lation. Although not a specific antidote, as it is in the setting of benzodiazepine toxicity,flumazenil has been used with benefit in some cases of muscle relaxant overdose.29See Box 2 for a list of toxins for which flumazenil may be antidotal. The suggestionof increased central GABA activity in the pathophysiology of hepatic encephalopathy and some limited clinical success indicate that flumazenil also may help to treat theneuropsychiatric complications of liver failure.

- observed in overdose with benzodiazepines, barbiturates, muscle relaxants, antiepileptics, ethanol and others. They have a dose-dependent effect on the CNS - in small doses they have a sedative effect; with increasing dose cause a soporific effect (hypnosis) and general anesthesia (anesthesia); an even higher dose leads to suppression of the respiratory center. Leads to:

-bradycardia and hypotension
-slow intestinal motility

GENERAL PRINCIPLES OF TREATMENT IN TOXICOLOGY

The therapeutic regimen for the treatment of acute poisoning includes:

1. Detoxification-depuration means and methods

2. Antidote means and methods

3. Resuscitation tools and methods

4. Organoprotective agents and methods

5. Symptomatic treatment

6. Rehabilitation methods

#1 priority
YOUR OWN SAFETY- YOU CANT HELP THEM IF YOU ARE DEAD OR INJURED
check your safety, patient's safety, assess the situation- relatives, psychotic

patients, exposure to poisonous substances when attending a patient

2. Are they dead or alive- you don't treat dead people you help the bereaved, you mind the possibility of legal actions being taken ()

3.If alive but appear dead or your not sure

DR-Airways-Breathing-Circulation→ CPR!!!

Use each 2min cycles to get more data for the reversible causes of arrest , here s where T for toxins stand for- drug charts, past medical history, evidence, packages, friends, witnesses, suicide ideas , notes

4. If you happen  to achieve ROSC, or patient present still conscious
ABCDE- review systems quickly and act on any problems as u go
draw samples for lab and tox levels
5.Start treating them if intoxication is your primary diagnose using the next few approaches

non specific

activated charcoal single or repeated dose, inert not absorbed by the body, very efficient if given within 1$^{st}$ hour following ingestion
DOSE 1g/kg
Not effective for alcohol, hydrocarbons,heavy metals, corosives
forms suspension with water, not tasty, but saves lives
prepacked as 30-50g doses
give it with a catharctic/laxative agent- Mg-sulfate

Worn patients that they are going to have black colored stool/diarrhea
One possible side effect – ileus , if GI motility slow, but very safe in general

Emesis- ipeca was used historically to induce it
patients might have already done it themselves, or you can encourage them to do it, 1l of water, two fingers at the back of the tongue

not yours, the patients ☺
only if adequate, cooperative and FULLY conscious, and not very reliable way

gastric lavage- legal requirement in BG, long time debunked in western medicine

comparable efficacy to charcoal but far more risky side effect, like aspiration, pneumonia, esophageal/stomach rupture, hyperhydration and hyponatremia in children

Indications- might be considered if
<1h of ingestion of a very toxic xenobiotic in large doses that has no antidote and gastric motility slow
If
>1h , small dose of relatively safe drug and antidote readily available-is it worth the risks??

NEVER EVER DO IT if
patient comatose or consciousness suppressed- no gag and coughing reflexes
INTUBATE first, otherwise you will drown them
corrosive intoxications- you will burn the stomach and esophagus again and double the damage
hydrocarbons-they just don't mix with water- patients will foam and will aspirate ( notorious example- kerosene)
patient seizuring or actively bleeding

If you do it ( falloid and organophosphate poisonings are probably the ones that are worth it)
- be gentle, neer use restrains or physical power
- sit the patient up or put the in left lateral position
-use orogastric or nasogastric tubes and make sure you have checked if properly placed in the stomach
use small amount of water 250-300ml
give a dose of activated charcoal at the beginning and the end

other methods

-whole bowel irrigation
-repeated doses of activated charcoal – in poisonings with toxins undergoing enterohepatic circulation( opiods, SSRIs)
-forced diuresis-
make sure they are not dehydrated- never give furosemide first, ,you will make them further hypovolemic
healthy person can be given 0,5-1l fluids/20 mins if no kidney injury
Hydrate first- aim for 250-300ml/h urine output
not if Hx of Acute or chronic kidney failure, pulmonary edema, heart failure

alkalize- will keep week acid polar and more difficult to be absorbed( salicylates)

hemodialysis – small polar less protein bound low VD molecules( alcohols, lithium,metformin, salicylates)) uses semipermeable membrane and opposite directed flows to maintain a concentration gradient
carbohaemoperfussion –blood is run through a cylinder with activated charcoal ( falloid poisoning)
plasmapheresis

specific

antidotes- Antidotes are substances that by specific action counteract the poison, reduce its effect, increase its elimination or prevent its absorption by the body.

Antidotes specifically act on the mechanism of poisoning by blocking enzymes, competing for receptors, blocking transport proteins, reducing the affinity of the toxin for enzymes, affecting metabolic chains

The main mechanisms of antidote action are realized through mechanical, physical and chemical processes, metabolic and immunological effects, functional antagonism and chelation.

Examples:
Carbo medicinalis (activated charcoal)- an universal antidote , see notes above

Naloxone - a competitive mechanism of antidote action in opiod poisoning

Flumazenil (Annexat) - a competitive antagonist of benzodiazepine drugs.

Glucagon - a metabolically active antidote for poisoning with beta-blockers, hypoglycemic drugs, acute insulin poisoning or overdose. Dosage: 0.5 mg-1 mg subcutaneously

Ethanol - a competitive metabolic mechanism with blocking alcohol dehydrogenase. In case of poisoning with methyl alcohol and polyhydric alcohols (ethylene glycol)

Protamine sulfate - neutralizing antidote effect to heparin.

Vitamin K – antidote for cumarine type anticoagulant poisoning

Acetylcysteine - accelerates the detoxification of potentially toxic metabolites. In paracetamol poisoning by restoring the glutathion

Atropine sulfate – functional antagonist in cholinergic poisonings by blocking the M-cholinergic receptors

Toxogonin( pralidoxim) – regenerates acetylcholinesterase but active up to 24-48 after exposure to war gases. organophosphates