

Therapeutic Drugs 2



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So far....

- Basic principals of managing poisoning
- Paracetamol overdose

Case scenario

- A 22 year old female is brought to the night casualty ward by her husband. She has had a quarrel with him and then taken some pills from her grandmothers medicine. She is drowsy and sweaty.

You are the house officer attending to this patient. What will be the next step of management ?

Poisoning with unknown drugs

- History
- Examination
- Investigations

History

- Agent
- Amount
- Timing

History

- Her husband has brought the left over drugs of what she has taken.



- What will be your next step to identify ?

- The grandmother has lost her clinic books one month back
- She is on treatment for diabetes, hypertension, psychiatric illness and heart disease
- The patient does not exactly remember what medicine and what amount she consumed
- Counting the pills also fails as the grandmother has not had good compliance

- What would you do.....

Examination

Cluster of symptoms

| Clinical features | Drug |
|---|----------------|
| Hypertonia Hyperreflexia | TCA,SSRI |
| Tachyarrhythmias/Seizures/Extensor plantar/Dilated pupils | TCA |
| Hypotonia,Hyporeflexia Respiratory depression(Hypoventilation) | Benzodizapines |
| Pinpoint pupils Respiratory depression(Hypoventilation) Hypotension | Opioids |
| Vomitting Tinnitus ,Deafness Acidotic breathing | Salicylate |

Investigations

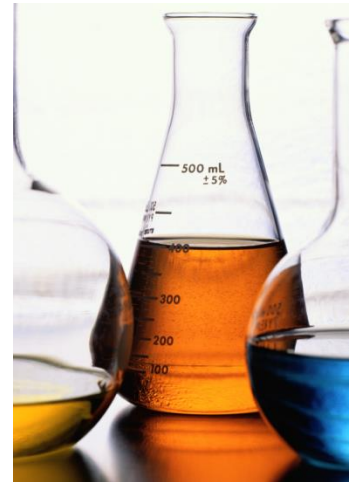
- **Toxicological investigations**

- blood levels :

- Paracetamol,Lithium,Iron,Theophylline

- Toxicological screening of urine and blood

- **Non toxicological investigations**

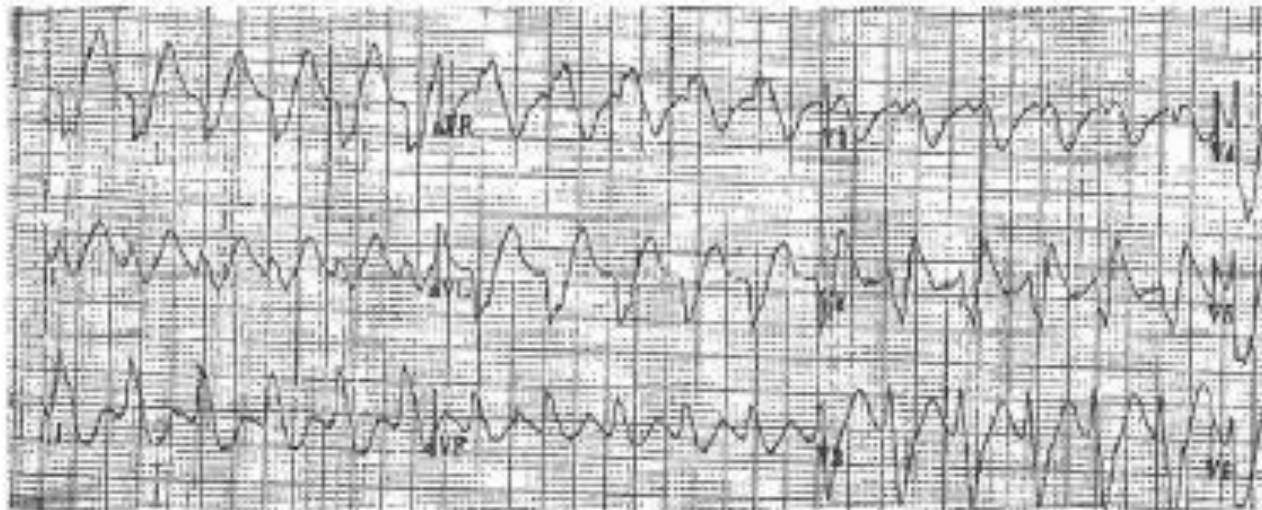


Non-toxicological investigations

| Investigation | Anticipated abnormality | Agent responsible |
|----------------------|-------------------------|---|
| Blood sugar | Hypoglycemia | Antidiabetic drugs Beta blockers Salicylates |
| ABG | Acid base disturbances | Salicylates |
| Serum electrolytes | Hypokalaemia | Theophylline Salbutamol Insulin Diuretics |
| | Hyperkalaemia | Digoxin |
| Liver function tests | Elevated transaminases | Paracetamol |
| Prothrombin time | Prolongation | Paracetamol Warfarin |
| ECG | Arrhythmias | QTc prolongation- Antipsychotics Tachyarrhythmias- TCA |

ECG changes anticipated in therapeutic drug poisoning

Figure 6. Wide Complex Tachycardia Due To Sodium Channel Blockade Resulting From Tricyclic Antidepressant Poisoning



Antidotes in drug poisoning

| Drug overdose | Antidote |
|--------------------------------------|-------------------------------------|
| Theophylline | Beta blocker |
| Oral hypoglycemic drugs | Octreotide |
| Iron | Desferrioxamine |
| Digoxin | Digoxin Immune Fab antibody |
| Benzodiazepine | Flumazenil |
| Beta blocker/Calcium channel blocker | Glucagon (Inotrope for hypotension) |
| Opioid | Naloxone |
| Heparin | Protamine sulfate |
| Beta blocker | Atropine (For bradycardia) |

Lets look into the management of some specific drug toxicities

- Benzodiazepines
- Antidepressants
- Opioids
- Digoxin
- Lithium
- Gentamicin-Home work

Benzodiazepines

- Sedative /hypnotic agents
- Act by potentiating the effects of the inhibitory neurotransmitter GABA within the CNS.

Examples include:

- Alprazolam
- Clonazepam
- Diazepam
- Midazolam

Features of Overdose

- Ataxia
- Drowsiness
- Nystagmus
- Slurred speech
- Decreased level of consciousness
- Respiratory depression
- Hypotension, bradycardia and hypothermia- in larger doses



Management

- Monitor for respiratory depression/cardiac monitoring
- Antidote-**flumazenil**-only indicated if respiratory depression
- Mechanical ventilation
- Supportive management

Antidepressants

- Tricyclic antidepressants –
Amitriptyline, imipramine
- MAO inhibitors
- SSRI

TCA toxicity

- Toxic effects due to
 - Inhibition of reuptake of monoamines at nerve endings (serotonin/noradrenaline)
 - Anticholinergic effects
 - Na/K channel blockage

Clinical features of TCA overdose

| Cardiovascular system | CNS | Anticholinergic symptoms |
|-----------------------|----------------------|--------------------------|
| Sinus tachycardia | Drowsiness | Dry mouth |
| Prolonged QRS/QT | Confusion | Blurred vision |
| ST/T wave changes | Hypertonia | Dilated pupils |
| Hypotension | Exaggerated reflexes | Urinary retention |
| Cardiogenic shock | Seizures | Sinus tachycardia |
| | Coma | Myoclonic jerks |
| | | Agitation |
| | | Hallucinations |

TCA overdose

- Cardio toxicity usually is the cause of death
- Usually appear within 4 hours
- ECG monitoring
- Give NaHCO_3 if arrhythmias, metabolic acidosis, hypotension
- Give IV glucagon or vasopressors for severe hypotension
- Give diazepam for seizures

Home work

- A 45 year old male is brought to the emergency treatment unit, found semiconscious in his room. He is on treatment with imipramine for depression. Examination findings are
 - drowsy
 - dilated pupils
 - hypertonia with exaggerated reflexes
 - BP-80/50mmHg
 - PR-120/min
- 1.What will be your tentative diagnosis ?
 - 2.State the most important investigation in this patient

SSRI

- Unlikely to cause fatal toxicity unless very large amounts are being ingested
- Cardiotoxicity less
- Can cause serotonin syndrome
 - restlessness
 - hypertonia
 - hyperreflexia
 - hyperpyrexia
- Supportive and symptomatic management

Opioids

- Clinical features
 - pinpoint pupils
 - respiratory depression
 - impaired level of consciousness
 - hypotension
 - vomiting

Management

- Antidote –IV naloxone
- Need repeated doses as short half life
- Caution – Precipitate withdrawal symptoms in opioid dependence

Beta blocker overdose

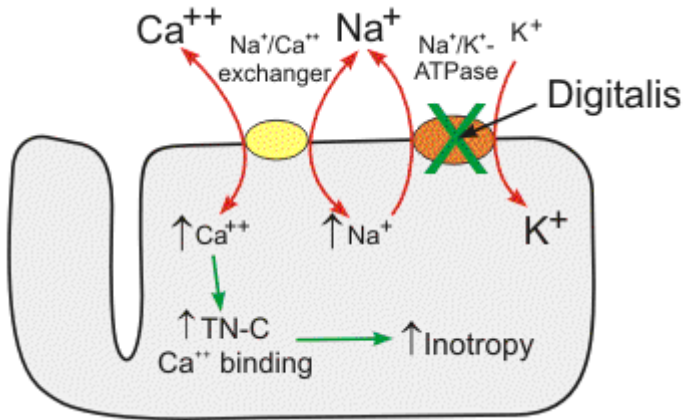
- Bradycardia
- Hypotension
- Cardiac failure
- Cardiac arrest
- Peripheral vasoconstriction
- Bronchospasms
- Seizures
- Drowsiness
- Hallucinations
- Coma
- Hypoglycaemia

Management

- Monitor HR, BP, ECG
- Hypotension - IV glucagon/IV dobutamine
- Bradycardia - IV Atropine(anticholinergic)
- Convulsions - IV diazepam
- Bronchospasms - Nebulize with salbutamol/IV aminophylline
- Hypoglycaemia - 50% glucose 50ml, IVI 10% glucose

Digoxin Mechanism of Action

- Inhibits Cardiac Na/K ATPase which indirectly increases intracellular Ca concentration
 - Increase cardiac excitability and contractility
 - Increases AV node refractory period by increasing vagal tone



Has a low therapeutic index...

Digoxin overdose –mechanism of toxicity

- Increase cardiac excitability and contractility



Ventricular ectopics/
tachyarrhythmias

- Increases AV node refractory period by increasing vagal tone



Bradyarrhythmias

- Hypokalaemia /hypomagnesaemia : increases risk of digoxin toxicity

Digoxin overdose –clinical features

- Nausea/diarrhoea
- Arrhythmias
 - ventricular ectopics
 - SVT/VT/VF
 - heart block
- Confusion /agitation
- Xanthopsia
- Hyperkalaemia

Reverse tick sign –ST depression with Digoxin –seen in therapeutic doses as well



Management of Digoxin toxicity

- Gastric lavage. Activated charcoal
- Bradyarrhythmias- IV Atropine
- Tachyarrhythmias- IV MgSO_4
- Antidote: digoxin binding antibody fragments (Fab, digibind)

Salicylate overdose –features

- Primary respiratory alkalosis
- Hypokalemia, hypocalcaemia
- Dehydration
- Acute renal failure
- Primary metabolic acidosis
- Hyper/hypoglycemia
- Pulmonary oedema
- Pyrexia
- Seizures
- Tinnitus
- Deafness
- Nausea and vomiting

Management

- Gastric decontamination
- Activated charcoal
- Mild to moderate- Oral or IV rehydration with attention to K^+ supplements
- If severe-Alkalinizing urine ($NaHCO_3$) while monitoring K^+
- Hemodialysis

Lithium

- Commonly used to treat bipolar affective disorder
- Low therapeutic index
- Toxicity
 - acute
 - chronic
- Multisystem dysfunction with toxicity
- T_{1/2}: 12-26h

Lithium toxicity

- Excretion- renal
- Reabsorbed in PCT- paired with Na absorption
- Reabsorption of lithium is increased and toxicity is more likely in patients who are hyponatremic or volume depleted

Identifying lithium toxicity

- *Clinically*

-fine tremors/ polyuria/polydipsia/metallic taste are side effects of lithium. Can occur in therapeutic doses

-Features suggestive of Li toxicity include

- ☐ Mild > 1.5mmol/l

- Anorexia
- Vomiting
- Severe diarrhea
- Coarse tremor
- Blurred vision
- Nystagmus
- Muscle weakness, twitching, myoclonus
- Ataxia
- Slurred speech
- Severe polyuria

- ☐ Moderate >2mmol/l

- Confusion
- Seizures

- ☐ Severe >3mmol/l

- Coma

Identifying lithium toxicity

- ***Biochemical parameters***



Lithium levels

Lithium levels

- Routinely monitored in patients on Lithium
- desired serum levels ----0.6-1.2 mEq/L
- Toxicity - > 1.5 mEq/L

Question – Home work

Find how monitoring of Lithium levels are done in patients on Lithium?

What are the other investigations recommended routinely in patients on lithium?

What are the drugs that will increase risk of Li^+ toxicity?

Management –Lithium toxicity

- Gastric lavage
- Activated charcoal is not useful
- Urgent lithium level and renal function
- Stop drugs which increase risk of toxicity
- Hydration
- Treat electrolyte imbalances
- Haemodialysis in severe toxicity(In chronic therapy only if $\text{Li}^+ > 4\text{mmol/l}$ or if neurological features are present)

Thank you....

