Anticonvulsants

Overview

The common OD's produce dose-dependent CNS effects after erratic absorption that usually respond to supportive care. Large ODs can → fits, coma and other organ toxicities.

Phenytoin

Toxic mechanism

Sodium channel blocker and membrane stabiliser.

Toxicokinetics

Slow & erratic oral abs in OD. Peak level may be delayed 24-48h. Small Vd, highly protein bound. Hepatic P450 metab to inactive metabolite but genetic variability. Saturatable (zero order) in OD so $T_{\frac{1}{2}}$ may be 24-230h.

Clinical features

Early mild GIT symptoms with acute OD.
Slow onset of neurotoxicity (acute or chronic OD) – ataxia, dysarthria, nystagmus, tremor, involuntary movements, ophthalmoplegia which resolve over 2-4days.
Massive OD may occasionally cause seizures or coma. Also can cause HONK (as sodium salt).
Rapid IV admin can cause cardiotoxicity from carrier propylene glycol

Investigations

Screening: BSL, Serial ECGs, paracetamol
Specific bloods: Phenytoin level

Level	Clinical features
40-80μmol/L (10-20mg/L)	Therapeutic range
>80μmol/L (>20mg/L)	Nystagmus
130-160μmol/L (30-40mg/L)	CNS & anticholinergic effects
>200μmol/L (50mg/L)	Coma, seizures & cardiotoixicity

Risk assessment

Dose	Effect
<10-20mg/kg	Standard loading dose
>20mg/kg	Ataxia, dysarthria, nystagmus
>100mg/kg	Potential coma & seizures

Dose-dependent CNS (mainly cerebellar) effects.
Coma/seizures rare and cardiotoxicity not a feature of oral OD.

Management

Resus: ABCs as normal
Supportive Care: Beware falls when mobilising.
Decontamination: Activated charcoal if <4hrs from OD
Enhanced Elimination: MDAC does speed up elimination but little clinical benefit. Extracorporeal methods considered if severe intoxication.

Disposition

If CNS symptoms admit until able to walk safely. Rarely need ICU.

Carbamazepine

Toxic mechanism

Dirty drug – structurally related to TCAs. Inhibits inactivated Na channels preventing action potentials. Also blocks NA reuptake & is a muscarinic, nicotinic, NMDA & central adenosine antagonist.

Toxicokinetics

Slow & erratic absorption even in non-controlled release form. Anticholinergic effects may cause ileus in large OD and slow absorption to days. Small Vd. Hepatic P450 metabolism to active metabolite.

Clinical features

Onset of effects by 4h but may not peak until 8-12+hrs (with CR formulation or massive OD). Early anticholinergic effects common (↑HR, dry mouth, urine retention)

CNS:

- Mild-moderate effects: nystagmus, dysarthria, ataxia, sedation, delirium, mydriasis, ophthalmoplegia, myoclonus
- Large OD: fluctuating LOC, seizures, coma may be delayed 8-12h

Cardiotoxicity: In large/massive OD – hypoBP, cardiac conduction abnormalities (NaBlockade, arrhythmias – VT, VF, asystole)

Investigations

Screening: BSL, Serial ECGs, paracetamol

Specific bloods: Carbamazepine level

Level	Clinical features
34-51μmol/L (8-12mg/L)	Therapeutic range
>51μmol/L (>12mg/L)	Nystagmus
>85μmol/L (>20mg/L)	CNS & anticholinergic effects
>170μmol/L (>40mg/L)	Coma, seizures & cardiotoixicity

Risk assessment

Dose	Effect
<20-50mg/kg	Mild-mod CNS & anticholinergic effects
>50mg/kg	Fluctuating LOC/agitation with risk of → coma in first 12h. Risk of hypoBP and cardiotoxicity with massive OD

Teratogenic.

In massive OD coma can last days.

Management

Resus:

- ABCs as normal

Supportive Care:

- Treat Na channel blockade cardiotoxicity with bicarbonate
- Treat seizures & agitated delirium with BDZs

Decontamination: Activated charcoal if <50mg/kg, or larger OD of CR prep if early & asymptomatic. If CNS toxicity already evident can only give AC if & when intubated.

Enhanced Elimination: MDAC if intubated & extracorporeal methods if severe intoxication.

Disposition

If asymptomatic for 8hrs may be d/c. Consider admitting children with any level. ICU if coma.

Valproic Acid (VPA)

Toxic mechanism

Increase GABA and at large doses inhibits mitochondrial function.

Toxicokinetics

Abs becomes erratic in OD. Peak levls may be delayed 18h. Small Vd, highly protein bound. Hepatic met to active metabolites.

Clinical features

Often initially asymptomatic. Dose-dependent CNS depression.
In massive OD: coma ± metabolic abnormalities (high AG met acidosis, ↓BSL, ↓ Ca, ↑Na, ↑ammonia), hypoBP, renal dysfunction, marrow suppression, cerebral oedema, death

Investigations

Screening: BSL, Serial ECGs, paracetamol
Specific bloods: serial VPA levels

Level	Clinical features
<350-750μmol/L (<50-100mg/L)	Therapeutic range
<3500μmol/L (<500mg/L)	Not usually associated with multi-organ effects
>3500μmol/L (>500mg/L)	Coma ± other organ effects
>7000μmol/L (>1000mg/L)	Life threatening multi-organ effects
>14,000μmol/L (>2000mg/L)	Death expected

Others: serial UEC, ABG, FBC in coma to watch for multisystem toxicity.

Risk assessment

Dose	Effect
<200mg/kg	Asymptomatic or mild drowsiness/ataxia only
200-400mg/kg	Variable CNS depression. Rarely need to intubate
<400-1000mg/kg	Significant CNS depression and need to intubate more likely. Coma may be delayed 12hrs post ingestion. Multi-system toxicity more common.
>1000mg/kg	Potentially lethal. Prolonged coma. Multi-organ toxicity.

Management

Resus:

- ABCs as normal. Early intubation advised if falling LOC.

Supportive Care:
Decontamination: Activated charcoal if >400mg/kg (via NG likely to be intubated) may rpt at 3-4hr if no ileus and levels rising.
Enhanced Elimination: WBI possible if less than 4hr post-OD but early haemodialysis better.
Dialyse if:

- >1000mg/kg with level >7000μmol/L (>1000mg/L)
- Serum level >10,4000μmol/L (>1500mg/L) at anytime
- Severe VPA poisoning with cardiovascular instability or lactic acidosis

Antidote: Carnitine has been advocated by some for mitochondrial toxicity.

Disposition

If OD<200mg/kg and asymptomatic at 8hrs post ingestion, may be d/c. Otherwise admit ± ICU.