ANTICONVULSANT TOXIDROMES

NEWER AGENTS:

E.G. gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, vigabatrin

GENERALLY MUCH LESS TOXIC IN OVER DOSE THAN OLDER AGENTS → SEE LATER

SEDATION AND NON=SPECIFIC NEUROLOGICAL SYMPTOMS MAY OCCUR

TREATMENT IS SUPPORTIVE

RISK ASSESSMENT:

- Most overdoses with these agents produce no symptoms or mild transient CNS symptoms only
- Coma/seizures are rare

TOXIC MECHANISM:

- Most of these agents act by potentiating GABA neurotransmission (either by enhancing release or inhibiting re-uptake).
- Lamotrigine and topiramate also have effects on voltage-dependent Na+ channels
- Topiramate also inhibits carbonic anhydrase
- Pregabalin ↓s release of excitatory neurotransmitters, especially glutamate (by blockade of calcium channels)

TOXICOKINETICS:

- All are well absorbed and have linear kinetics
- Levetiracetam, pregabalin and topiramate are primarily excreted unchanged in the urine

CLINICAL FEATURES:

- GABAPENTIN → nausea, vomiting, hypotension, ↓GCS → mild and resolve within 10 hours
- LAMOTRIGINE → ataxia, nystagmus, slurred speech, ↓GCS. Rare → transient intraventricular conduction delay (Na channel blocking) and seizures
- LEVETIRACETAM → agitation, ↓GCS, coma and respiratory depression
- PREGABALIN → drowsiness ONLY
- TIAGABINE → sedation, coma, seizures
- TOPIRAMATE → ataxia, sedation, coma, seizures, metabolic acidosis (carbonic anhydrase blocking, non-anion gap and may last 7 days but is of little significance). CNS effects typified by rapid onset and resolve within 24 hours.
- VIGABATRIN → drowsiness and delirium

MANAGEMENT:

- Supportive care is central to good outcomes → esp coma, respiratory depression
- Seizures and delirium/agitation managed with diazepam
- No role for gastrointestinal decontamination due to mild effects, and rapid absorption
- Consider other toxicological causes of coma, as it is uncommon

BARBITURATES:

Includes pentobarbitone, phenobarbitone, primidone and thiopentone

UNCOMMON PRESENTATION, BUT CAN CAUSE PROFOUND AND PROLONGED COMA MIMICKING BRAIN DEATH

RISK ASSESSEMENT:

- Ingestion of 8mg/kg expected to produce toxic neurological symptoms in the non-tolerant individual
- Mechanics of self administration by IV route hopefully will induce coma prior to an otherwise lethal dose being administered

TOXIC MECHANISM:

- Cause CNS depression by enhancing GABA mediated neurotransmission by binding to GABAa receptor and ↑g duration of chloride channel opening
- Also block central glutamate activity
- Effects at medullary cardiorespiratory centres and hypothalamic nuclei → hypotension, hypothermia and respiratory arrest

TOXICOKINETICS:

- Only some are effective after oral administration
- Thiopentone and pentobarbitone have large volumes of distribution, highly lipid soluble and are rapidly redistributed from the CNS, hence are only useful IV
- Phenobarbitone and primidone are less lipid soluble and thus less rapidly redistributed, hence can be given orally

CLINICAL FEATURES:

- Overdose is characterised by profound, prolonged and potentially fatal CNS/CV depression
- CNS features:
    - Ataxia, lethargy → coma, hypotonia, hypothermia and respiratory arrest
    - Profound coma with complete loss of neurologic function can develop → features mimicking brain death (absent DTR, pupillary reflexes and vestibulo-ocular reflexes)
    - Central respiratory depression → apnoea
- CV SYSTEM:
    - Tachycardia
    - In very large ingestion → depression of medullary vasomotor nuclei as well as direct myocardial depression and peripheral vasodilatation.

INVESTIGATIONS AND MANAGEMENT:

- Consider levels to confirm an ingestion and serial levels to monitor progress
- Phenobarbitone level > 100mg/L prompts consideration of haemodialysis
- EEG may mimic brain death
- Need for intubation is anticipated and performed early if level of consciousness is declining

- ENHANCED ELIMINATION → phenobarbitone → consider multi-dose activated charcoal to ↑ rate of elimination by interrupting enterohepatic and enteroenteric circulation. Haemodialysis/filtration for markedly elevated levels or for those continuing to rise despite MDAC. MDAC has not been shown to ↓ length of ICU stay/duration of coma
- Decontamination only after airway secure

CARBAMAZEPINE:

PREDICTABLE DOSE-DEPENDENT CNS AND ANTICHOLINERGIC EFECTS → MANAGEMENT PRIMARILY SUPPORTIVE WITH SELCTED USE OF ENHANCED ELIMINATION

RISK ASSESSMENT:

- Clinical features are dose dependent, but onset depends on whether preparation is controlled release vs immediate
- Threshold dose ~ 50mg/kg → fluctuating mental status and risk of progression to coma within 12 hours. Risk of hypotension and cardiotoxicity with extreme doses
- Following larger overdoses, anticholinergic effects may be prominent prior to onset of coma
    - Following massive ingestions → coma anticipated to last days due to ongoing absorption, slow elimination and presence of active metabolite
- One 400mg tablet in toddler can induce intoxication

TOXIC MECHANISM:

- STRUCTURALLY SIMILAR TO IMIPRAMINE (TCA)
- Inhibits inactivated sodium channels, thus preventing further action potentials
- Also blocks noradrenaline reuptake and is an antagonist at muscarinic, nicotinic and NDMA receptors

TOXICOKINETICS:

- Slow and erratic absorption
- Following large overdose, anticholinergic-mediated ileus may result in ongoing absorption for days
- Hepatic metabolism produces active metabolite

CLINICAL FEATURES:

- Onset is unpredictable
- Coma may be delayed until 8-12 hours post-ingestion
- Anticholinergic effects → retention, tachycardia, dry mouth
- Large overdose → seizures, hypotension, conduction anomalies → VF, VT and asystole in massive overdose

INVESTIGATIONS AND MANAGEMENT:

- Serum levels confirm diagnosis and serial levels in coma to monitor course
- If level > 40mg/L → expect coma, seizures and cardiac conduction abnormalities. Ingestion > 50mg/kg may be associated with evidence of Na channel blockade on ECG (first degree AV block and ↑ QRS duration)
- In the rare event of ventricular dysrhythmia → SODIUM BICARBONATE
- Basics resuscitative measures ensure survival in most
- ACTIVATED CHARCOAL → early presentations who have ingested >50mg/kg or controlled release → after intubation if CNS depression
- ENHANCED ELIMINATION → cease MDAC as soon as bowel sounds disappear (ileus). Haemodialysis/filtration remove carbamazepine very effectively when levels are markedly elevated

- Patients with nystagmus, ataxia, drowsiness and anticholinergic effects are managed supportively in the ED/observation area

PHENYTOIN:

INTOICATION IS USUALLY BENIGN AND RESULTS IN DOSE-RELATED ATAXIA AND CNS DEPRESSION

CARE IS SUPPORTIVE

RISK ASSESSMENT:

- Dose-dependent CNS effects, mainly cerebellar, occur following acute overdose.
- Coma and seizures are RARE, even after massive overdose
- Cardiovascular effects are not associated with ingestions of any dose
- At >20mg/kg → ataxia, nystagmus and dysarthria, potential for coma and seizures at >100mg/kg

TOXIC MECHANISM:

- Blocks sodium channels and suppresses membrane post-tetanic potentiation and hyperexcitability

TOXICOKINETICS:

- Absorption slow and erratic following oral overdose
- Peak levels delayed up to 24-48 hours
- Metabolism is SATURABLE (MICHAELIS-MENTEN KINETICS) → HALF-LIFE RISES DRAMATICALLY EVEN AFTER SMALL CHANGES IN DAILY DOSE

CLINICAL FEATURES:

- Chronic toxicity usually presents with gradual onset of ataxia, dysarthria and nystagmus
- Following acute overdose → toxicity develops slowly over hours → slow horizontal nystagmus, dysarthria, ataxia/tremor
    - Resolve over 2-4 days
    - Coma, rigidity and seizures occur rarely
- Hypernatraemia, hyperglycaemia can result in non-ketotic hyperosmolar coma after massive ingestion
- Permanent cerebellar injury is rarely reported
- RAPID IV ADMINISTRATION → hypotension, bradycardia, ventricular arrhythmia and asystole (propylene glycol diluent implicated)

INVESTIGATIONS AND MANAGEMENT:

- Phenytoin levels → confirm diagnosis and correlates with toxicity, severe ataxia after levels of 30-40mg/L
- General supportive care ensures good outcome
    - ECG monitoring not necessary following oral overdose/chronic toxicity
- Patients are fit for discharge as soon as they are able to walk safely

VALPROIC ACID

MOST OVERDOSES RESULT IN CNS DEPRESSION → SUPPORTIVE CARE SUFFICIENT

HOWEVER, IN LARGE OVERDOSES → MULTI-SYSTEM ORGAN FAILURE AND DEATH→ PREVENTABLE WITH EARLY HAEMODIALYSIS!

RISK ASSESSMENT:

- **Dose-dependent CNS depression**
- Increasingly severe multi-system effects above 400mg/kg
- Ingestion above 1g/kg potentially lethal → profound/prolonged coma and multi-organ toxicity (cerebral oedema, hypotension, lactic acidosis, hypoglycaemia, hyperammonaemia, hypernatraemia, hypocalcaemia and bone marrow suppression)

TOXIC MECHANISM:

- Increases level of GABA
- In large doses → interferes with numerous MITOCHONDRIAL METABOLIC PATHWAYS

TOXICOKINETICS:

- Usually well absorbed, but may be erratic following overdose
- HIGHLY PROTEIN BOUND WITH VERY SMALL VOLUME OF DISTRIBUTION

CLINICAL FEATURES:

- Frequently presents relatively asymptomatic, even after large ingestions → progressive deterioration closely correlates with rising serum level
- Following large ingestions, coma is accompanied by:
    - METABOLIC ANOMALIES → anion-gap acidosis, ↑NH3, ↑Na, ↓BSL, ↓Ca2+
    - Renal impairment
    - Bone marrow suppression
    - Very severe poisoning → cerebral oedema, haemodynamic instability and death

INVESTIGATIONS AND MANAGEMENT:

- Serial valproate levels confirm diagnosis, refine risk assessment and guide therapy, especially in the comatose patient as they determine risk of multi-system dysfunction and the need for haemodialysis → URGENT LEVELS ESSENTIAL IN THE COMATOSE PATIENT TO STRATIFY RISK AND NEED FOR HAEMODIALYSIS
    - Levels >7000micromol/L frequently develop life-threatening multi-organ effects, at >14,000 death is expected without urgent haemodialysis
- Need for intubation is determined early

- ACTIVATED CHARCOAL IF INGESTION >400MG/KG AFTER SECURING AIRWAY → CONSIDER REPEAT DOSE AT 3-4 HOURS
- INDICATIONS FOR HAEMODIALYSIS (ideally perform prior to multi-system dysfunction):
    - WHENEVER LIFE-THREATENING TOXICITY IS ANTICIPATED
    - Ingestion >1g/kg and level >7000micromol/L
    - Level > 10,400 at any time
    - Severe valproic acid poisoning with lactic acidosis or CV instability
- **Consider valproate poisoning in unexplained coma with lactic acidosis, hypernatraemia or hypocalcaemia**
- The level may be normal initially → even after massive ingestions, so repeat if there is a change in level of consciousness