Anticonvulsants in Psychiatry

Level 4, MBChB

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Valproate

- For treatment of manic episodes associated with Bipolar mood disorder
- Rapidly converted to valproic acid in the stomach
- Multiple formulations in the market
  - Valproic acid
  - Divalproex sodium

Valproate

- Rapidly and completely absorbed in 1-2 hours after oral admin
- Peak concentrations; 4-5 hours after oral administration
- Plasma half life: 10-16 hours
- It is highly protein bound. Unbound fraction is active and can cross the BBB

Mechanism of Action

- Complex and not fully understood
- Postulated to enhance GABA activity; Modulation of voltage sensitive sodium channels and action on extra-hypothalamic neuropeptides.

Valproate

Indications

- Complex partial seizures
- Simple and complex absence seizures
- Adjunct therapy for multiple seizures
- Divalproex for migraine prophylaxis

- Bipolar I disorder
  - Acute mania
  - Acute bipolar depression
  - Prophylaxis
- Schizophrenia and schizoaffective disorder
- Other mental disorders

Valproate

Adverse effects

- Gastric irritation
- Lethargy and confusion
- Weight gain
- Dose related tremors
- Hair loss
- Peripheral oedema
- Thrombocytopenia, leukopenia, red cell hypoplasia
- Pancreatitis
- Hyperandrogenism in women and linked to polycystic ovarian disease

Adverse effects

- Teratogenic: avoid in women of child bearing age, and where unavoidable, Folic acid and contraception
- Very rarely; Fulminant hepatic failure

Valproate

Beware of drug interactions

- Increased plasma concentrations of: diazepam, amitriptyline, nortriptyline, phenobarbital
- Decreased plasma concentrations of: phenytoin
- Decreased concentrations of valproate with: carbamazepine
- Increased concentrations of valproate with; guanfacine, amitriptyline, fluoxetine
- Valproate displaced from plasma proteins by: carbamazepine, diazepam, aspirin

Carbamazepine

- Initially synthesised as a potential antidepressant
- Approved for use in trigeminal neuralgia in the late 60s and for temporal lobe epilepsy in 1974
- Absorption is slow and unpredictable; food enhances absorption
- Peak plasma levels 2-8 hours after a single dose.
- 70-80% protein bound
- Half life about 26 hours (but with chronic admin- 12 hours)
- It is an enzyme inducer, inducing its own metabolism as well as for others
- Metabolised by the liver and the metabolite is active as an AED

Carbamazepine

- **Mechanism of action:**
  - Block voltage gated sodium channels (inhibiting repetitive neuronal firing)
  - Reduces glutamate release and decreases the turnover of dopamine and adrenaline
  - Other postulated effects: Reduction of currents through NMDA receptor channels, competitive antagonism of A_1 adenosine receptors and potentiation of CNS catecholamine neurotransmission

Carbamazepine

Indications

- Generalised and focal seizures
- Trigeminal neuralgia
- Bipolar disorder
  - Acute mania
  - Prophylaxis
  - Depression
- Other disorders
  - Symptoms associated with alcohol withdrawal
  - Non acute agitation in patients with schizophrenia and schizoaffective disorder

Carbamazepine

Adverse reactions

Relatively well tolerated

- Mild GI- nausea, vomiting, anorexia…..
- CNS- Ataxia, drowsiness
- Blood dyscrasias- aplastic anaemia, agranulocytosis
- Hepatitis
- Dermatologic- maculopapular rash, exfoliative dermatitis, erythema multiforme, SJS, toxic epidermal necrolysis
- Renal- Hyponatraemia
- Etc. (look them up)

Carbamazepine

Interactions

- Prominent induction of CYP3A4: antidepressants, most anti psychotics, benzos, cholinesterase inhibitors, methadone, thyroxine, theophylline, oestrogen levels may be reduced with carbamazepine
- Drugs that inhibit CYP3A4 will increase carbamazepine plasma levels and precipitate toxicity: cimetidine, diltiazem, verapamil, erythromycin, some SSRIs
- Anticonvulsant activity is reduced by drugs that lower the seizure thresholds e.g. antipsychotics

Lamotrigine

Pharmacokinetics:

- 98% bioavailability
- 55% protein bound
- Half life of 25 hours

MOA

- Blockade of voltage sensitive calcium channels
- Modestly increases plasma serotonin concentrations
- Weak inhibitor of $5HT_3$ receptors

Lamotrigine

Indications

- Bipolar disorder
  - Especially bipolar depression
  - Rapid cycling bipolar disorder
- Pain syndromes

Adverse reactions

- Well tolerated
- Mild dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea
- Rash

Gabapentin

- First introduced as an AED
- Metabolised largely unbound
- Eliminated unchanged by renal excretion
- Appears to increase cerebral GABA and may inhibit glutamate synthesis
- Increases blood serotonin levels; modulates calcium channels to reduce monoamine release

Gabapentin

Indications

- Treat generalised and partial seizures
- Reduce pain of post herpetic neuralgia
- Other neuropathic pain syndromes: diabetic neuropathy, neuropathic cancer pain, fibromyalgia, paraesthesia
- Improve mood in depressed patients
- May decrease craving in alcoholic patients
- Anxiety disorders (social phobia and panic disorder)

Gabapentin

Side effects

- Mild
- Daytime somnolence
- Ataxia
- Fatigue
- Avoid in pregnancy

Topiramate

Pharmacology

- 80% bioavailability
- 15% protein bound
- 70% by renal excretion
- Half life about 24 hours

MOA

- GABAergic effects and increases cerebral GABA

Topiramate

Indications

- AED
- Prevention of migraine
- Smoking cessation
- Pain syndromes
- PTSD
- Essential tremor
- Associated with weight loss
- Bulimia; binge eating
- May decrease self mutilating behaviour in borderline personality disorder

Topiramate

Adverse effects

- Paraesthesia
- Weight loss
- Somnolence
- Anorexia
- Dizziness
- Memory problems
- Sense of taste disturbances

Levetiracetam

- Initially developed as a memory enhancing drug
- MOA not well understood but appears to enhance GABA inhibition
- Not significantly plasma protein bound
- Not metabolised through CYP

Indications

- Potent anticonvulsant
- Off label to treat acute mania
- Add on for major depression
- Anxiolytic agent

Pregabalin

- Similar to gabapentin

Approved for

- Diabetic peripheral neuropathy
- Post herpetic neuralgia
- Adjunct treatment of partial onset seizures
- Panic disorder or social anxiety
- fibromyalgia

Phenytoin

Pharmacology

- Blockade of voltage activated sodium channels
- Half life: 22 hours
- Excreted in bile, reabsorbed then excreted through urine

Indications

- Generalised and complex partial seizures
- Acute mania

Phenytoin

- Dose related nystagmus, ataxia, slurred speech decreased coordination
- Dizziness, insomnia, transient nervousness, motor twitching, headaches
- Thrombocytopenia, agranulocytosis, pancytopenia

Interactions

- Acute R-OH, amiodarone, chlordiazepoxide, cimetidine, diazepam, disulfiram, oestrogen, fluoxetine, isoniazid, methylphenidate, salicylates may increase phenytoin levels
- Carbamazepine, chronic alcohol abuse, reserpine may lower phenytoin levels

Questions?