Carbamazepine

Chemical Structure
Closely related to Imipramine and the tricyclics –

Chemical Relatives
Among the iminostilbenes there is also Oxcarbazepine, which is the keto-analog of carbamazepine. Iminostilbene(dibenazepine) is a three-ringed precursor. You can even buy it online from China. All the other derivatives of iminostilbene are tricyclic antidepressants.

Administration and Absorption
- Available as an oral drug only.
- Enteric absorption rate is weird and erratic
- Peak plasma levels occur 4-8 hours after administration...
  BUT THE MORE YOU TAKE, THE LONGER IT TAKES TO ABSORB – AS LONG AS 24 HOURS. Eventually, 100% of it does get absorbed.
  ...an exception is the SYRUP: that gets absorbed very quickly, and there are effects within 30 minutes.
  Once it hits the bloodstream, 75% of it binds to plasma proteins.
  It has a large volume of distribution as it distributes to all tissues.
  Volume of Distribution = 1.4L / Kg

Metabolism and Clearance
- Carbamazepine induces the enzymes which are responsible for its own metabolism; as therapy progresses one must increase the dose, because rate of metabolism increases.
  Half life at the beginning of treatment is 36 hours, and then it drops to 8-12 hours with chronic treatment
  The half life of the 10,11-epoxide is 5-10 hours

ENTEROHEPATIC RECYCLING:
- Of the absorbed dose, about 28% gets back out into the gut lumen, and is reabsorbed.

From "Goodman & Gilman’s The Pharmacological Basis of Therapeutics" 11th ed by Brunton et al and "Poisoning and Drug Overdose" by Olson, as well as “Basic & Clinical Pharmacology” 8th ed. By Katzung et al
Mechanism of Action
- Voltage-gated sodium channel blocker, similar to Phenytoin
- Prevents repetitive firing of those neurons by slowing the rate of recovery of inactive (post-depolarization) neurons
- The 10,11-epoxycarbamazepine also does this to sodium channels.

Indications for Use
- Partial seizures and generalized tonic-clonic seizures
- Back in the day (1960) it was used for the treatment of trigeminal neuralgia, but it was reclassified as an antiepileptic, and now also find use as treatment for bipolar disorder (which is weird, because Phenytoin, which has the EXACT SAME mechanism of action, doesn't have any effects as a mood stabilizer)
- It also has an ANTIDIURETIC effect: somehow it interferes with ADH, there there is an antidiuretic effect, with decreased serum ADH levels.

Interactions
- It interacts with anything that gets metabolized by those induced enzymes; famously, it decreases the effectiveness of the oral contraceptive tablet.
- Causes increased rates of metabolism of primidone, phenytoin, ethosuximide, valproate, clonazepam…
- Propoxyphene and valproate may inhibit clearance and increase carbamazepine levels

Chronic Toxicity
- Bone marrow suppression; may cause APLASTIC ANAEMIA or AGRANULOCYTOSIS
- Hepatitis
- Cardiomyopathy
- Hyponatremia

Acute Toxicity and Overdose
Most of the toxicity is due to the CNS depression and anticholinergic effects

| Anything over 10mg/kg is considered toxic; |
| Typical maximum daily dose is 1.6-2.4 grams |
| Historically people have overdosed dangerously on 5.8 to 80 grams. |

You can monitor levels:
- Therapeutic range is 4-12 mg/L
- Anything over 10mg/L = nystagmus and ataxia

- Consequences of overdose:
  - Seizures, status epilepticus
  - QRS and QT prolongation
- They will be tachycardic, with mydriasis, dry mucous membranes, and delirious
- The urinary point of care drug screen with be positive for tricyclics

Management of acute toxicity
- Monitor its levels 4-6 hourly at first
- Monitor QTc and QRS length
- Administer charcoal – its essentially the only useful thing you can do.
- HEMODIALYSIS or CHARCOAL HEMOFILTRATION can be used to enhance clearance
- **DO NOT use physostigmine!** Its contraindicated. Embarrassing asystole will be your reward.

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