Carbamazepine

CAS: 298-46-4
MF: C_{15}H_{12}N_{2}O
MW: 236.27
Soluble in chloroform, dimethylformamide, ethylene glycol monomethyl ether, or methanol; only slightly soluble in ethanol or glacial acetic acid; virtually insoluble in water [1].

**Major use**
Carbamazepine is an anticonvulsant. It is widely used in the treatment of epilepsy, neuralgic pain and bipolar affective disorder. The drug is a carbamylated iminostilbene, structurally related to the tricyclic antidepressants [2].

**Human toxicity**
Mild intoxication with carbamazepine could result in drowsiness, ataxia, slurred speech, nystagmus (rapid involuntary eye movement), dystonic reactions, hallucinations, hyponatremia, hypokalemia, combativeness, hypothermia, mydriasis, as well as decreased gastrointestinal motility.

Severe intoxication could result in coma, seizures, respiratory depression, dysrhythmias, decreased myocardial contractility, pulmonary edema, and hypotension. Severe cardiac toxicity generally occurs at doses >60 g. In rare cases intoxication may lead to elevated levels of liver enzymes, and oliguria (the decreased production of urine). Symptoms develop 1-3 hours after extended release capsule ingestion, with neuromuscular effects being prominent [3].

*Lethal symptoms*: coma, seizures, respiratory depression, dysrhythmias, decreased myocardial contractility, pulmonary edema, and hypotension.

Serious toxicity with survival has been reported after ingestion of 13.2-34 g [3]. Lethal doses are between 21 and 31 g. The lowest known lethal dose reported was 3.2 g in a 24-year-old woman (death due to cardiac arrest) and in a 24-year-old man (death due to pneumonia and hypoxic encephalopathy) [3].

The optimal therapeutic blood concentration levels are between 4-8 mg/l [5]. Toxic blood levels are usually greater than 20 mg/l [6].

**Kinetic data**
*Absorption* After therapeutic doses, 72-96% is absorbed, and 28% excreted in the feces [3]. In an overdose, absorption may be delayed [3].

*Volume of distribution*
Vd adult - 0.59 to 1.2 l/kg [3].
Vd adult, overdose - 3 l/kg [3].

*Distribution*: carbamazepine distributes rapidly to all tissues [7].

*The plasma half-life*
Carbamazepine and its epoxide metabolite range between 18 to 54 h in a single overdose; between 16 to 26 h in chronic therapy [3].

The half-life may be prolonged in overdose beyond the normally expected half-life. In a patient who overdosed on 20 g, the half-life prior to ingestion was 13 hours, and after the overdose was 25 hours.

Time to peak was calculated to be 33 (+/- 3) h after overdose [3]. However, the peak plasma concentrations may occur as late as 72 hours after an overdose [3].

Protein binding
Carbamazepine is 75% protein bound and its epoxide metabolite is approximately 50% protein bound [3]. Following a massive overdose, carbamazepine and its active epoxide metabolite are progressively less protein-bound, with an increasing percent of the total concentration being free serum concentration [3].

Elimination
Carbamazepine follows first order elimination kinetics in therapeutic doses. After extremely large doses, a long plateau-like plasma concentration-time curve has been reported. Three phases of absorption are described after massive overdose.

Metabolism and excretion
Carbamazepine is 98% metabolized in the liver. Radiolabeled studies on carbamazepine have shown 4 major metabolic pathways [3]: Epoxidation of the 10,11 double bond of the azepine ring (40%). Hydroxylation of the 6-membered aromatic ring (25%). Direct N-glucuronidation of the carbamoyl side chain (15%). Substitution of a sulfur group for the 6-membered ring.

More than 7 metabolites have been identified. The main metabolite is carbamazepine-10,11-epoxide, which has anticonvulsant activity of its own [3].

Only 1% of the administrated dose is excreted in urine in the unchanged form [4].

Metabolites more toxic than carbamazepine: none.

Toxicological mechanisms
Unknown.
Theories (reviewed in [7, 8]):
1. Decreased conduction of Na⁺ ions across nerve cell membrane, which reduces cAMP and elevates levels of brain serotonin;
2. Decreased turnover of GABA;
3. Increased rate of firing of adrenergic neurons;
4. Action as a partial agonist at adenosine receptors.

Target organs: unknown.

References
1. HSDB, TOXNET (2005).

*Written by Cecilia Clemedson, May 200;*, revised February 2007

*Cecilia@Stifud.se*