Maprotiline

CAS: 10262-69-8
MW: 313.9
MF: $C_{20}H_{23}N$
LogP: 4.52
Solubility: Soluble in ethanol; solubility in water is 1 in 700.

Major uses

Maprotiline is a tetracyclic antidepressant drug used to treat depressive neurosis (dysthymic disorder), as well as manic-depressive illness and anxiety associated with depression [1].

Human toxicity

Maprotiline produces effects similar to tricyclic antidepressants after overdose. There may be a greater incidence of seizures associated with maprotiline toxicity than with other antidepressants. CNS depression may persist for days. Tachycardia, torsade de pointes, heart block, QRS interval widening, and ventricular dysrhythmias have also been reported. Furthermore, respiratory depression, aspiration pneumonia and respiratory distress syndrome have been reported. Hallucinations and delirium are frequently reported during recovery from a maprotiline overdose [1]. Self-poisoning with maprotiline is not uncommon but very few deaths have been recorded [2].

The usual adult therapeutic dose is 50 to 150 mg/day. To minimize risk of seizures, maintenance therapy should not exceed 150 to 200 mg daily. Higher doses (up to 225 mg) have been used with caution in hospitalized patients for short term therapy. Seizures and dysrhythmias have developed in adults after ingestion of 4.5 g. One gram or less of maprotiline has produced CNS symptoms but no cardiovascular complications in adults [1].

Deaths have been reported following maprotiline ingestions of 2 to 10 g with and without coingestants. However, an adult has been reported to recover completely from a 5 gram overdose of maprotiline [1, 2].

At steady-state therapeutic plasma concentrations of 0.1 to 0.15 mg/l have been reported following an oral dose of 150 mg/day. It has been concluded that there is no relationship between serum levels and toxicity or efficacy. Seizures have been reported at serum concentrations of 0.237 to 0.317 mg/l. Two patients survived overdoses with levels of 0.83 mg/l and 1.5 mg/l. A postmortem maprotiline blood level of 1.3 mg/l was reported in a 37-year-old man taking 200 mg maprotiline at bedtime for 5 weeks [1]. The average maprotiline blood concentration observed in 9 victims of fatal poisoning was 5.4 mg/l (range 1.3-13 mg/l) {reviewed in [3]}.

Kinetic data

Absorption of maprotiline is slow but complete from the gastrointestinal tract [1, 2].

Distribution: Like other lipophilic bases, maprotiline is widely distributed throughout the body following absorption and readily crosses body membranes [2].

Volume of distribution: 23-70 l/kg [2].

Plasma half-life: It varies considerably between studies, ranging between 13-58 h, with a mean of 43 h [1, 2]. Average elimination half-life of the active metabolite (desmethylmaprotiline) ranges from 60 to 90 hours [1].

Time to peak: Following a 50 mg oral dose of maprotiline in healthy subjects, the peak plasma level occurred between 8 and 24 hours [1, 2].

Protein binding: Human serum proteins bind 85% to 93% of maprotiline [1, 2].

Metabolism and excretion

Maprotiline is metabolized in the liver. The cytochrome P-450 enzymes contributing to demethylation of maprotiline are CYP2D6 (high affinity binding site) and CYP1A2 (low affinity binding site) [1]. The principle metabolite is desmethylmaprotiline, which is an active metabolite [1, 2]. Also formation of hydroxylmaprotiline from maprotiline has been reported. Further degradation of these two metabolites into glucuronides is reported [2]. Numerous minor metabolites have been identified in urine. These are excreted in urine as conjugated glucuronides and as aromatic methoxyethers. The inactivation of maprotiline follows first-order pharmacokinetics [2]. Other metabolites are products of deamination, dihydroxylation, hydroxylation, and N-oxidation [1].

Metabolites more toxic than maprotiline: desmethylmaprotiline.

Excretion: About 30% of maprotiline is excreted in the faeces and about 70% in the urine**.** It is removed almost entirely as metabolites and only about 2% is unchanged maprotiline [2].

Pharmacological mechanisms

Maprotiline is similar to other tricyclic antidepressants in its effects on receptor blockade, biogenic amine pump reuptake inhibition, negative inotropy, and membrane effects. It has antihistaminic effects and is moderately anticholinergic. It strongly inhibits norepinephrine reuptake at the cellular membrane and may be a vascular alpha blocker. Finally, maprotiline may upregulate GABA binding in the cerebral cortex and may increase the concentration of endogenous substances that bind to benzodiazepine receptors [1].

Toxicological mechanisms

Maprotiline's higher epileptogenic potential may be the result of high brain concentration, lipophilicity, or selective norepinephrine re-uptake blockade with little or no effect on serotonin re-uptake. Its hypotensive effect is related to the norepinephrine and dopamine effects. Maprotiline binds preferentially to myocardial tissue; although minimal data are available, its similarity to other tricyclic antidepressants would suggest that this may involve the inward sodium transport during phase 0 of the action potential [1].

Target organ: CNS [1].

References

1. Poisindex, Thomson Micromedex (2006).
2. *Therapeutic drugs*, vol. 1, ed. C. Dollery, 1992, Churchill Livingstone.

3. Baselt, R.C. & Cravey, R.H. (1995) *Disposition of Toxic Drugs and Chemicals in Man*, 4th edn., pp. 445-447. Chemical Toxicology Institute, Foster City, CA, USA.

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