

## Meprobamate

Chemical name: 2-methyl-2-propylpropane-1,3-diol dicarbamate

CAS: 57-53-4

MF: C<sub>9</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>

MW: 218.3

pKa=9.2

Solubility: poorly soluble in water (0.34% at 20°, 0.79% at 37°C); freely solved in most organic solvents [1].

### Major uses

Meprobamate (synthesized in 1946) is an anxiolytic drug, which is used in the treatment of anxiety and tension. It is a mild tranquilizer and anticonvulsant, with sedative and hypnotic effects, used in many psychiatric conditions, e.g. depression, mental disorders, epilepsy etc. [2].

### Human toxicity

Following overdose, meprobamate produces CNS depression similar to the barbiturates. Neurological symptoms include lethargy, stupor, slurred speech, headache, weakness, and prolonged coma may be noted with massive poisonings. Coma may last for more than 48 to 72 hours. Cardiovascular symptoms are: tachycardia, hypotension, shock, and cardiac dysrhythmias. Respiratory depression and pulmonary edema may be noted. Among the gastrointestinal symptoms are listed anorexia, nausea and vomiting.

Meprobamate-related deaths are generally due to a dramatic acute circulatory failure. Fatal intoxications are usually associated with mixed ingestions (other drugs and/or alcohol), whereas death in pure meprobamate ingestions is rare [3].

Therapeutic oral doses are up to 400 mg three or four times a day. Oral administration of 400 mg of meprobamate produces peak plasma concentration of 5-39 mg/l (22.9-178.7 µM) within 1-3 h.

The minimum lethal dose of meprobamate is about 12 g, although recovery has occurred after ingestion of 40 g (reviewed in [4]).

The plasma concentrations of 30-100 mg/l (137.4-458.0 µM) are usually reached following mild overdose and are associated with stupor or light coma. The plasma concentrations of 100-200 mg/l (458.0-916.2 µM) are associated with deep coma and are potentially lethal [1]. Fatalities occurred when plasma concentrations were in the range of 156-237 mg/l (714.6-1085.7 µM) [5].

### Kinetic data

*Absorption:* meprobamate is well absorbed from the gastrointestinal tract following ingestion of therapeutic dose; absorption occurs primarily in the small intestine.

Absorption is prolonged in overdose, with a mean absorption half-life of 4 h (range 1 to 13 h) in one series of 38 patients (reviewed in [3]).

*Kinetics* is biphasic, at overdose situation.

*Volume of distribution:* 0.7l/kg [6].

*Distribution:* widely distributed in body tissues [2].

*Passage of blood-brain barrier:* free [2].

*Plasma half-life:* 10 h [2].

*Time to peak plasma level:* within 2 to 4 h, at therapeutic doses, but plasma levels at 8 h may equal to those at 4 h because of delayed gastric emptying [7].

*Plasma protein binding:* 15% [2].

*Elimination:* 90% of a drug is eliminated via the kidney in form of metabolites; 10% - in form of unchanged drug [2]. Elimination half-life after therapeutic dose is 6-17 h. Following an overdose, most of the drug will be metabolized and eliminated in 24 to 36 h (biphasic kinetics) [3].

### **Metabolism and excretion**

Meprobamate is rapidly metabolized in the liver, where it can induce liver microsomal enzymes. It is unclear whether it induces the enzymes responsible for its own metabolism.

Meprobamate metabolites are pharmacologically inactive and include 2-beta-hydroxymeprobamate, as well as glucosylurionide and glucuronide conjugates of meprobamate [3].

In the overall population, some persons can acetylate the drug rapidly ("fast acetylators") and thereby detoxify it quickly, whereas others acetylate meprobamate more slowly ("slow acetylators").

*Excretion:* about 10-12% of a dose of meprobamate is excreted in urine as unchanged drug within 24 h. The remainder is excreted in the urine as metabolites (see above). Five to 10% of a dose is excreted in the feces in 24 h. [2, 3, 7].

### **Pharmacological and toxicological mechanisms**

Meprobamate, like barbiturates, depresses CNS functions, although its detailed mechanism of action is unknown. It appears to inhibit interneurons in the hypothalamus, thalamus, limbic system, and spinal cord. It blocks the long internuncial (linking two neurons in a neuronal pathway; adapted from The Free Medical Dictionary, via Internet) neuron circuits between the cerebral cortex and the thalamus, without influencing autonomic function.

Meprobamate does not act on the medulla, reticular activating system, or autonomic nervous system. The skeletal muscle relaxing effect of meprobamate appears due to the sedative effect of the drug [3].

Unlike other CNS depressants meprobamate does not produce anesthesia at therapeutic doses. However, extremely high doses of this drug can induce anesthesia with concomitant depression of the respiratory and vasomotor centers [2].

In one fatal suicidal case, the drug was accumulated in the heart (meprobamate analysis of the autopsy specimens), confirming cardiac toxicity of meprobamate, which might result in cardiovascular failure in acute intoxication [4].

**Target organs:** CNS, heart [2, 7].

## References

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