Theophylline

Chemical name: 1,3-dimethylxanthine
CAS: 58-55-9
MF: $C_7H_8N_4O_2$
FW: 180.2
Solubility: slightly soluble in water; moderately soluble in ethanol.

Major uses
Theophylline is a drug for treatment of pulmonary diseases, e.g. chronic bronchial obstructive disease, bronchial asthma, and pulmonary edema. Therapeutic use is limited due to considerable toxicity of this drug [1].

Human toxicity
Therapeutic doses of theophylline in adults vary between 300 and 600 mg/day, once daily [2]. The therapeutic serum concentrations can be within 10 to 20 mg/l; concentration >25 mg/l is regarded as critical [3]. Theophylline can be toxic at the therapeutic doses: about 30% of patients with serum theophylline concentrations grater than 15 mg/l had toxic reactions; and 78% with concentrations grater than 25 mg/l had symptoms of toxicity [1].

At the acute overdose, nausea, vomiting, abdominal pain, metabolic acidosis, heart arrhythmias, CNS excitation, agitation and seizures have been recorded; there are cases of fatal poisoning too. The minimum toxicity occurs between peak theophylline levels of 20-40 mg/l, moderate toxicity at 40 to 100 mg/l, and severe effects are developed at the serum concentrations about 100 mg/l and greater [4].

Kinetic data
Absorption: almost complete and rapid, from 30 min to 1 h after therapeutic dose. 90% of theophylline is absorbed within 4 h, after therapeutic dose (up to 200 mg/day, 6 weeks). Overdose may result in delayed absorption [2].

Kinetics is biphasic (at the overdose situation) [5].

Volume of distribution (V_d): from 02 to 0.7 l/kg (mean 0.5 l/kg) [4].

Peak blood levels occur within 2 h after ingestion. At therapeutic doses, blood levels follow first-order kinetics; but in overdose, mixed first- and zero-order (Michaelis-Menten) kinetics take place [4].

Protein binding: 40% at therapeutic serum concentration [1]; up to 56% at overdose [1, 2].

Elimination half-life: Overdose may produce a biphasic elimination pattern with a short half-life in the first phase (about 17 min) and prolonged half-life at a second phase (from 6 to 16 h) [4, 5].

Passage of blood-brain barrier is free [5].

Metabolism and excretion

Theophylline undergoes metabolism in the liver, mediated by cytochrome P-450 microsomal enzymes.

Major metabolites include 1,3-di-methyluric acid, 3-methylxanthine, and 1-methyluric acid, all of which are excreted in the urine [1].

The most active metabolite is 3-methylxanthine, which possesses 30 to 70 % of the biologic activity of theophylline [4].

Excretion: the kidney excretes 5 to 10 % of a therapeutic dose unchanged in the urine [4].

Mechanisms of action

The mechanisms are still poorly defined. Several mechanisms of theophilline action have been proposed, for example, inhibition of prostaglandins, phoshodiesterase inhibition, as well as alteration of intracellular calcium and cyclic AMP. Theophilline is also adenosine receptor antagonist [1].

Toxicological mechanisms

Theophylline intoxication can lead to potassium loss from the cells (hypokalemia). It may also induce the increased levels of catecholamines (epinephrine and norepinephrine) in blood, which can lead to hyperglycemia (increase in plasma glucose level) [3].

Target organs: CNS, heart, gastrointestinal tract [5].

References

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3. *Casarett and Douls Toxicology* (1986), C.D. Klaassen, M.O. Amdur, J. Doull (eds), 3rd edn., Macmillan Publishing Company.
4. Ellenhorn, M.J., Schonwald, S., Ordog, G., Wasserberger, J. (1997) *Ellenhorn's Medical Toxicology*: *Diagnosis and Treatment of Human Poisoning*, 2nd ed., pp. 828-835. Williams & Wilkins.
5. Ekwall, B., Clemedson, C., Crafoord, B., Ekwall, Ba., Hallander, S., Walum, E., Bondesson, I. (1998) MEIC evaluation of acute systemic toxicity. Part V. Rodent and human toxicity data for the 50 reference chemicals. ATLA 26, 571-616.

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