Verapamil hydrochloride

CAS: 152-11-4
MF: $C_{27}H_{38}N_2O_4$.HCl
MW: 491.4
Verapamil hydrochloride is soluble in water and in alcohol.

Use
Verapamil hydrochloride (verapamil) is a synthetic drug, widely used for the treatment of hypertension, heart arrhythmia, tachycardia, angina pectoris and other cardiovascular disorders [1].

Human toxicity
Adverse effects associated with verapamil poisoning may include nausea, dizziness, weakness, hypotension, headache, bradycardia, and atrioventricular block [2]. Patients may also experience peripheral edema, coughing, and pulmonary edema [3].

Daily therapeutic oral doses of verapamil range from 240 to 480 mg. Three patients who acutely ingested 2.0–5.6 g of verapamil, survived (reviewed in [2].

Therapeutic blood concentrations in patients are in the range of 0.09–0.36 mg/l [4].

The average verapamil concentration in blood in 19 deaths due to acute overdosage was 11 mg/l (range 0.9-85), as reviewed in [2]. The mean lethal serum concentration, based on the data from several handbooks, was reported as 7.8 mg/l [5].

Kinetic data
Absorption: Over 90% of verapamil is absorbed following oral ingestion, with peak plasma concentrations occurring between 1 and 2 h. Verapamil is rapidly absorbed in the gastrointestinal tract; the drug has a distribution half-life of 15-30 min [6].

Kinetics is biphasic [5].

Volume of distribution (V_d) is 2.5-6.5 l/kg [2].

Accumulation in vital organs: verapamil is accumulated in liver [5].

Plasma protein binding is about 90%. Verapamil is mainly binding to albumin and α_1 acid glycoprotein.

The half-life of verapamil in plasma, after a single oral or intravenous dose, is between 4 and 8 h [6].

Passage of blood-brain barrier: restricted? [5].

Metabolism and excretion
Majority of verapamil is metabolized by *O*-demethylation, *N*-dealkylation and *N*-demethylation (40%, 25% and 15%, respectively). One of the metabolites,

norverapamil, has only 20% of the activity of the parental compound [7]. Verapamil undergoes extensive hepatic metabolism with nearly complete elimination by the liver [8].

Excretion: About 66-71% of verapamil is excreted in urine and about 9-16 % in feces over a 5 day period [2].

Pharmacological and toxicological mechanisms
Verapamil is a calcium (Ca^{2+}) channel blocker; and it is binding to the cytosolic surface of the channel. It leads to decrease of intracellular Ca^{2+} concentration, and thus less Ca^{2+} is available to interact with the contractile proteins. As a result, contractions of the myocardium are reduced and heart rate slows [7].

The cardiovascular toxicity of verapamil is due inhibition of transmembrane calcium influx stimulated by alpha-adrenergic receptors. Verapamil interferes with intracellular binding and release of calcium, as well as it is blocking alpha-adrenergic receptors, which may lead to sinus bradycardia, sinus arrest, and even heart block [3, 5].

Target organs: cardiovascular system, heart, liver.

References
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