Quinidine sulfate dihydrate

CAS: 6591-63-5
MF: $C_{40}H_{48}N_4O_4 \cdot H_2SO_4 \cdot 2H_2O$
MW: 783.0
Solubility: partially soluble in cold water; soluble in methanol and ethanol [1].

Quinidine (active part of chemical)
MF: $C_{20}H_{24}N_2O_2$
MW: 324.5 (to be used for the calculation of blood concentrations).

Quinidine sulfate salt contents 83% of quinidine [2].

Major use
Quinidine is an alkaloid originally derived from the bark of the *cinchona* tree. Other related compounds include the optical isomers of quinidine, such as quinine (antimalarial drug), clonidine, and cinchonine [3].

Quinidine salts (sulfate, gluconate and polygalacturonate) have been used in the treatment of supraventricular and ventricular dysrhythmias. Quinidine is classified as type IA anthiarrhythmic drug [2].

Human toxicity
Life-threatening effects include depression of atrial, atrioventricular, and ventricular condition, dysrhythmias (including ventricular tachycardia and ventricular fibrillation), severe hypotension, coma, apnea, and seizures. Ventricular dysrhythmias and hypotension are the most serious toxicities.

Among other symptoms of acute overdose are listed vomiting, diarrhea, tinnitus, blurred vision, headache, confusion, and delirium. Respiratory depression and pulmonary edema may also occur [2].

Symptoms and signs of quinidine toxicity are expected in adults ingesting greater than 1 g of this drug.

The therapeutic range of blood serum concentration of quinidine is 1 to 4 mg/l.

Toxic symptoms (cinchonism, from the "*cinchona* tree", marked by headache, dizziness, hearing loss, tinnitus etc.) may occur at levels above 5 mg/l. Cardiac toxicity (greater than 50% prolongation of Q-T* interval on electrocardiogram, ECG) is usually associated with levels above 14 mg/l. In one acute poisoning case (ingestion of 8 g of quinidine by 16-years old girl; she survived), peak serum concentration was 21 mg/l (reviewed in [2]). Based on data from several handbooks, the mean clinically measured acute lethal serum concentration, was 24 mg/l, whereas the minimum lethal concentration was 11 mg/l [4].

Kinetic data
Absorption: Quinidine salts are almost completely absorbed from the gastrointestinal tract. The amount of drug which reaches the circulation after oral administration of quinidine depends on the amount of drug metabolized on the first pass through the liver (see Metabolism and excretion).

Bioavailability: 70 to 80% [2].

Kinetics: First-order? (Data are not fully convinced) [5].

Volume of distribution: 2.7 l/kg (for the overdose situation).

Distribution: quinidine is distributed extensively to body tissues [5].

Accumulation in vital organs: liver, kidney, heart [4].

Passage of blood-brain barrier: restricted [4].

Plasma half-life: 6 to 8 h at therapeutic doses; half-lives in poisoned patients are unknown [6].

Time to peak blood concentration: 1 to 3 h at the therapeutic doses [2]; more than 2 h at an overdose [4, 5].

Plasma protein binding: 60-90% [4].

Elimination: via the kidney. Elimination half-life is 3 to 16 h [2]. At the overdose situation it is >7.8 h [4].

Metabolism and excretion

Quinidine (60 to 80% of a dose) is metabolized predominantly in the liver by hydroxylation and via the action of cytochrome P450. Metabolites may have some antiarrhythmic activity.

One of the active metabolites is 3-hydroxy-quinidine (10%), with a half-life averaging 12.4 hours, longer than that of quinidine. It has an effect similar to quinidine and can contribute to toxicity. About 25% of an oral dose of 3-hydroxy-quinidine is excreted unchanged in the urine [6].

Other known metabolites of quinidine are: 2'-oxoquinidinone (10%), 3-hydroxyquinidine-N-oxide (active, 1%), quinidine 10,11-dihydrodiol (3%), *O*-desmethyl-quinidine (1-2%), and quinidine-N-oxide [2, 7].

Excretion: approximately 20% of a dose is excreted unchanged in the urine when urine pH is less than 7. Urinary excretion increases in acid urine (pH lower than 6) [4, 6].

Mechanisms of action

Quinidine is prescribed for long-term management of supraventricular and ventricular arrhythmias. In therapeutic doses quinidine reduces conduction velocity, decreases excitability, and prolongs QRS** and Q-T intervals, as it is represented at the ECG.

The major electrophysiologic action of quinidine is to decrease the rate of inward sodium current through the sodium channel of the cardiac membrane during depolarization (reviewed in [6]).

Toxicological mechanisms

The mechanisms are not well understood.

Quinidine and its metabolite, 3-hydroxyquinidine are blocking cardiac sodium channels that prolonging heart action potentials [6]. They decrease electrolyte permeability of cell membranes leading to depression of heart excitability, conduction

velocity and contractility. Lethal action of quinidine may be due severe myocardial depression, cardiogenic shock and hypotension [2, 4, 6].

Target organs: heart, vascular system, CNS, kidney [4].

References

1. Material Safety Data Sheet (2006), via Internet.
2. Poisindex, Thomson Micromedex (2006).
3. Ellenhorn, M., Schonwald, S., Ordog, G., Wasserberger, J. (1997) *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. 2nd ed., pp. 510-513. Williams & Wilkins.
4. 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.
5. Crafoord, B., Ekwall, B. (1997) *Quinidine*. The MEIC Monograph. http://www.cctoxconsulting.a.se
6. Haddad, L.M. & Winchester, J.F. (1990) *Clinical Management of Poisoning and Drug Overdose*. 2nd ed., pp. 1360-1371. W.B. Saunders Company.
7. HSDB, Micromedex (2006). Via Internet.

* The Q-T interval (ECG) represents the time for both ventricular depolarization and repolarization, and therefore roughly estimates the duration of an average ventricular action potential. This interval can range from 0.2 to 0.4 seconds depending upon heart rate.

** The QRS (ECG) complex represents ventricular depolarization. The duration of the QRS complex is normally 0.06 to 0.1 seconds. If the QRS complex is prolonged (> 0.1 sec), conduction is impaired within the heart ventricles.

Written by Ada Kolman, February 2006; revised March 2007
ada.kolman@telia.com