Disopyramide

CAS: 3737-09-5
MW: 339.5
MF: $C_{21}H_{29}N_3O$
LogP: 2.58
Solubility: In alcohol: 1 in 10, and in water: 1 in 200.

Major uses

Disopyramide is a quinidine-like class IA antidysrhythmic, cardiac depressant drug. It depresses myocardial excitability and conduction velocity [1].

Disopyramide has negative inotropic and anticholinergic properties and is effective in the treatment of various supraventricular and ventricular dysrhythmias. Inotropic effekts are ones that change the strength of contraction of the heart muscle.

Human toxicity

In overdose, cardiovascular and anti-muscarinic effects are pronounced. Depressed myocardial contractility is a significant feature of disopyramide poisoning which shares similar toxic effects with quinidine. Sinoatrial, atrioventricular, and his-ventricular depression of conduction may occur along with ventricular tachycardia and ventricular fibrillation. Toxic ECG manifestations, in addition to the aforementioned dysrhythmias, include significant QRS and QT interval prolongation (greater than 50% prolongation suggests toxicity), PR prolongation, ST depression, and T inversion. Severe effects also include apnea, pulmonary edema, loss of consciousness, loss of spontaneous respiration, and cardiac arrest [1, 2].

Usual adult therapeutic dosage is 400 to 800 mg per day in divided doses. Toxic dose has not been established, but ingestions greater than 2.5 g have caused severe toxicity in 5 of 14 cases. The toxic dose was 1.5 g in adults in a series of 106 cases [1].

Therapeutic blood plasma concentration range is reported to be 2 to 6 mg/l [1, 2]. Adverse effects have been reported with plasma levels of 3.6 and 10 mg/l, and deaths reported with levels of 16 mg/l. However, a patient with a serum level of 16.5 mg/l demonstrated impaired cardiac conduction and hypotension. Disopyramide plasma concentrations in fatal cases have ranged from 4.3 to 146 mg/l [1].

Kinetic data

Absorption: Disopyramide is well absorbed with 80% to 90% bioavailability [1, 2]. Following overdoses absorption may be delayed due to the anticholinergic actions of disopyramide with reduced gastrointestinal perfusion [1].

Volume of distribution: 0.5 to 1.3 l/kg [1, 2].

Distribution: In a case of a fatal overdose of disopyramide, concentrations of drug in the lung, heart, liver and spleen was comparable to that in plasma, but kidney concentrations were 2 to 3 times higher. Disopyramide has been reported to cross the placental barrier and is distributed into breast milk [1].

The plasma half-life: The average therapeutic half-life of orally administered disopyramide is 7 hours ranging from 5 to 37.1 h. Renal disease or heart failure increases half-life [1]. The plasma half-life is dose dependent [2].

Time to peak: Peak levels occur within 1 to 1.5 h of ingestion [1, 2].

Protein binding: Varies with drug concentration (protein binding decreasing as concentration increases) from 5% to 65%, averaging 40%. Patients with liver failure have decreased protein binding of disopyramide and increased clearance of unbound drug. Considerable interindividual variation occurs with binding of disopyramide to plasma proteins. Binding occurs mainly to alpha-1-acid glycoprotein, with higher concentrations of this protein associated with increased binding of disopyramide. Persons with a lower concentration of alpha-1-acid glycoprotein, such as Chinese people, women in the third trimester of pregnancy, and neonates, will have reduced binding of disopyramide [1].

Metabolism and excretion
Approximately 16% undergoes first-pass hepatic metabolism by mono-N-dealkylation [1, 2]. The major metabolite is nordisopyramide, which produces no significant cardiac effects following a single dose in healthy persons, but has resulted in greater antimuscarinic effects than disopyramide [1, 2].

Excretion: The major route of excretion occurs predominately via the urine with about 57% excreted unchanged, approximately 23% excreted as nordisopyramide, and 10% as other metabolites. Urine pH does not affect the excretion rate. Average clearance is 1.3 ml/min/kg. Approximately 10% of an oral dose is excreted in the feces [1, 2].

Pharmacological mechanisms
Although chemically unrelated to quinidine, disopyramide has similar electrophysiological effects as other type I antiarrhythmics. Therapeutic dosing decreases automaticity in the sinus node and Purkinje fibers. Its vagolytic action may, however, increase heart rate. Although disopyramide mildly prolongs intranodal conduction in patients with bundle branch block, it does not precipitate atrioventricular block. As with quinidine, the probable mechanism of disopyramide-induced ventricular tachycardia or ventricular fibrillation is temporal dispersion of refractoriness resulting from prolonged repolarization. This predisposes to reentry circuits. Disopyramide has antimuscarinic activity. It has no effect on alpha- or beta-adrenergic receptors [1].

Toxicological mechanism
Toxicity occurs by anticholinergic effects [2].

Target organs: CNS, heart [2].

References

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

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