Procainamide hydrochloride

Chemical name: N-(2-Diethylaminoethyl)-4-amino-benzamide
CAS: 614-39-1
MF: $C_{13}H_{21}N_3O \cdot HCl$
MW: 271.8

MW for $C_{13}H_{21}N_3O$ is 235.4 (for calculation of blood concentration).
Solubility: soluble in water and ethanol.

Major use
Procainamide is an antiarrhythmic drug (since 1951) classified as type IA. To the same type belong quinidine and disopyramide (see in AcuBase). All these drugs are widely used for long term management of supraventricular and ventricular arrhythmias [1].

Human toxicity
Cases of serious toxicity and poisoning are not very common, but when they do occur, poisoning is often life-threatening [1]. With poisoning, dysrhythmias (ventricular tachycardia, junctional tachycardia), heart conduction abnormalities (QRS and QT prolongation), hypotension, mental status depression, lethargy and confusion, seizures, anticholinergic effects, respiratory depression, nausea, vomiting and diarrhea have been reported. Respiratory failure, pulmonary edema, the central nervous system (CNS) depression, cerebral ataxia, coma and death may occur at the high doses [2].

Therapeutic oral daily dose of procainamide hydrochloride is 50 mg/kg [3].

The minimum toxic dose of procainamide has not been established. Toxicity (but not fatality) has occurred in adults after ingestion of 7 and 19 g orally [2].

The therapeutic range for procainamide blood concentration level is 6 to 14 mg/l (25.5 to 59.5 μM) [2]. Plasma procainamide concentrations of 4-8 mg/l are considered safe and effective in most persons [3]. Total procainamide and its main metabolite *N*-acetylprocainamide (NAPA) therapeutic levels range from 5 to 25-30 mg/l [4].

Manifestations of procainamide toxicity usually appear at plasma concentrations in excess of 16 mg/l [4]. In four cases of sublethal toxicity, procainamide blood concentrations were in the range of 59-106 mg/l [5]. Four cases of fatal procainamide overdosage were reported in which post-mortem blood concentrations of 80-260 mg/l (average 145 mg/l) were estimated [3].

Kinetic data
Absorption: procainamide is absorbed rapidly and almost completely from the gastrointestinal tract[1].

Bioavailability: 50-95%. for NAPA bioavailability is 85% [2].

Toxicokinetics is linear [5].

Volume of distribution: 3.3-4.8 l/kg [3].

Distribution: rapidly distributed in the body. The drug is most extensively bound to heart, kidney, liver and lungs, i.e. organs which are well-perfused [6].

Passage of blood-brain barrier: there are not enough data, but coma in acutely intoxicated patients indicates distribution to brain [5].

Plasma half-life: therapeutic plasma half-life is 2-5 h for procainamide and approximately 6 h for NAPA. Half-lives are longer in patients with renal or cardiac failure. In overdoses, half-lives of 8.8 and 10.5 h for procainamide and 35.9 h for NAPA have been reported [1].

Biphasic kinetics have also been reported with a half-life of 3.5 the first 12 h and a half-life of 8.5 h between 16 and 24 h (reviewed in [5]).

Time to peak blood concentration: 1-2 h for procainamide, and 1-8 h for NAPA [3].

Plasma protein binding: 10% for procainamide and 15% for NAPA [2].

Elimination: via kidney. Up to 91% of a single oral dose of procainamide is eliminated in the 72 h urine [3].

Metabolism and excretion

Procainamide is acetylated in the liver to NAPA, which is nearly as effective in its antiarrhythmic effect as its parental compound. The rate of formation of this major metabolite is genetically determined by *N*-acetyltransferase activity: slow acetylators exhibit a longer half-life (4.1 h) for procainamide than fast acetylators (2.5 h) and tend to excrete less NAPA in the urine [3].

Two other metabolites, norprocainamide and N-acetylnorprocainamide, are about one-half as active as procainamide itself. These compounds are found in the plasma of treated patients at concentrations less than 0.5 mg/l and 0.4-3.9 mg/l, respectively (reviewed in [3]).

Excretion: in 24 h urine there are 31-56% of unchanged drug, 7-24% of NAPA, and 8-14% represents by other two metabolites [2].

Mechanisms of action

Procainamide decreases electrical impulse conduction velocity through atrial and ventricular tissue. It is manifested by a widened QRS* and PR** interval in the electrocardiogram (ECG). Procainamide also prolongs the effective refractory period, when the cells reset and prepare for the next wave.

NAPA retains similar clinical effects as procainamide; however, it has a slightly different electrophysiological profile [2].

Toxicological mechanisms

Procainamide is acutely toxic through an interference with cardiac contractility, leading to cardiac failure/hypotensive shock. The kidney is also damaged by procainamide and NAPA, which may lead to prolonged half-lives of these drugs, accumulation of NAPA and accentuated toxicity [5].

Target organs: heart, kidney, CNS.

References

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* 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.

** PR interval (ECG) is the period of time from the onset of the P wave to the beginning of the QRS complex, which normally ranges from 0.12 to 0.20 seconds in duration. This interval represents the time between the onset of atrial depolarization and the onset of ventricular depolarization.

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