Class III Antiarrhythmics in Overdose
Presenting Features and Management Principles

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Summary

Class III (Vaughan-Williams classification) antiarrhythmic drugs prolong the cardiac action potential without affecting depolarisation. The 3 class III drugs currently in general use are amiodarone, sotalol and bretylium. The presenting features of acute toxicity are different for each agent and are, therefore, discussed separately. Several new class III antiarrhythmic agents are under development, including dofetilide and d-sotalol, but specific data on overdoses of these potent class III drugs are not yet available.

Amiodarone toxicity following acute overdose is rare because poor bioavailability and a large volume of distribution limit the peak serum concentration. Toxicity is low even if high serum concentrations are reached. The major risks from acute overdose are hypotension (intravenous administration only) and arrhythmia if other factors, such as hypokalaemia or additional antiarrhythmic agents are present. Management is chiefly directed at reducing absorption with activated charcoal or cholestyramine, and monitoring for arrhythmia.

Sotalol is a β-blocker with additional class III activity. Oral bioavailability is high, and overdosed patients can present with bradycardia, hypotension and major haemodynamic collapse. The combination of bradycardia and prolongation of the QT interval is associated with malignant arrhythmias such as torsade de pointes. Management principles include observation and correction of bradycardia with endocardial pacing, intravenous adrenergic drugs and glucagon. The risk of arrhythmia can be substantially reduced by intravenous potassium and magnesium supplements. d-Sotalol is a potent class III drug devoid of β-blocking activity and may be expected to share the
proarrhythmic affects of the racemic mixture in overdose, without pronounced hypotension and bradycardia.

Intravenous bretylium in overdose causes an initial hypertensive effect, followed by profound hypotension from systemic vasodilation. Management is directed at controlling hypotension with volume expansion and norepinephrine (noradrenaline).

Class III (Vaughan-Williams classification) [Singh & Vaughan-Williams 1970] drugs are antiarrhythmic agents which prolong the cardiac action potential without affecting depolarisation. There is only a small number of drugs that have this property and these include amiodarone, sotalol and bretylium. Sematilide and dofetilide are new, potent, class III drugs which are being tested in clinical trials at the time of writing.

1. Amiodarone

Most of the problems of amiodarone toxicity relate to its long term use. In acute overdose, amiodarone is generally less toxic because of low bioavailability and a large volume of distribution.

1.1 Pharmacology and Pharmacokinetics

Amiodarone decreases the slow outward potassium current in myocardial cells, causing a decreased slope of diastolic depolarisation. The pharmacological effects of amiodarone include delayed atrioventricular conduction, sinoatrial (SA) node inhibition and reduced cardiac automaticity which, with normal doses of amiodarone, cause lengthening of the PR interval and sinus bradycardia. Peripheral vascular resistance may be reduced (intravenous amiodarone) and coronary sinus blood flow is increased in some patients taking amiodarone (Cote et al. 1979). Oral amiodarone has no negative inotropic action, although intravenous amiodarone probably does have a small negative inotropic effect, especially if the left ventricle is diseased (Remme et al. 1985).

Amiodarone has extremely unusual and complex pharmacokinetics. The absorption of amiodarone from tablets is highly variable but is generally slow and usually incomplete. Absorption continues for up to 15 hours after a single dose (Holt et al. 1983). This becomes important in acute overdose because activated charcoal given even 6 to 12 hours after ingestion may be effective (see below).

Oral bioavailability is unpredictable and ranges from 22 to 86% (Riva et al. 1986). Peak plasma concentrations of amiodarone (0.38 to 0.45 mg/L) are reached 2 to 10 hours after a single 400mg dose (Kivisto & Neuvonen 1991; Riva et al. 1984). Amiodarone in plasma is 98% protein bound (Harris et al. 1983a) and has a very large volume of distribution (>6000L) [Holt et al. 1983].

Excretion occurs via the biliary route, and an enterohepatic loop exists (Andreason et al. 1981). There is considerable variation in the plasma half-life of the drug and its de-ethyl metabolite. The elimination half-life ranges from less than 20 days to 58 days (Cordarone 1992; Nitsch & Luderitz 1986).

1.2 Toxicity

In humans, the maximum recommended dose of the drug is in the region of 20 mg/kg/day (Sanofi 1990). The LD₅₀ (50% of the lethal dose) of amiodarone in the rat is more than 3 g/kg, and no mortality has been observed in dogs with oral doses greater than 3 g/kg.

Although there are many potentially serious adverse affects of long term amiodarone use, acute toxicity is rare. Knowledge of the acute toxicity of oral amiodarone is derived from a small number of case reports of amiodarone taken in overdose (Bouffard et al. 1985; Braganti 1985; Fortunati et al. 1983; Goddard & Whorwell 1989; Oreto et al. 1980) in which no fatalities occurred (see table I). These reports, together with animal studies, suggest that acute overdose of oral amiodarone is rarely the cause of life-threatening toxicity, but the