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Letter to the Editors

Acute amiodarone toxicity due to an administration error: could excipient be responsible?

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Amiodarone is widely used for ventricular and supraventricular tachyarrythmia and is a relatively safe choice of drug, particularly in its enteral form in paediatric patients, because of its low negative inotropic action. Severe side-effects have been described, mostly dose and treatment duration dependent. The use of the intravenous form has aroused concern because of the presence of excipients, polysorbate 80 and benzyl alcohol, considered as possible alternative causes for severe hypotensive events. We report the case of a newborn presenting with supraventricular tachycardia. After receiving a high loading dose of amiodarone intravenously instead of orally, the infant rapidly developed cardiogenic shock and multiple organ dysfunction.

This case report illustrates an underestimated side-effect of a supposiedly safe drug, probably related to the negative haemodynamic effects of the excipients.

A previously healthy newborn presented on day 4 with re-entrant supraventricular tachycardia, confirmed by electrocardiograph in a regional hospital.

The arrhythmia spontaneously ceased before any manoeuvre was attempted. In order to prevent recurrence of arrhythmia, the physician prescribed a loading dose (1200 mg/m^2 = 47 mg kg^{-1}) of amiodarone, without determining the route of administration. The 'oral' loading dose was administrated intravenously, over a 30-min period (preparation infused in glucose). The baby remained stable during the infusion.

Thirty minutes after the end of the infusion, the child suddenly deteriorated, with profound hypotension, requiring cardiopulmonary resuscitation for 20 min. Inotropic support with epinephrine and dobutamine at high doses was started.

On arrival of the PICU medical transport team, the baby was unreactive and presenting signs of systemic and peripheral hypoperfusion with severe lactic acidosis. Inotropic support treatment was adapted with introduction of milrinone and weaning of catecholamines, considering the haemodynamic stabilization.

During the first 24 h, he developed multiple organ failure with acute hepatic and renal failure, myocardial ischaemia and severe encephalopathy.

Organ function slowly recovered. No recurrence of supraventricular tachycardia occurred, but mild sinus bradycardia down to 90 min^{-1} spontaneously resolved. We eliminated every other major aetiologies (allergies, infection) causing profound shock, and therefore concluded that the 10 times recommended i.v. dose of Cordarone® was the most probable cause of this adverse event.

Serum amiodarone and desethylamiodarone (DEA) levels were monitored (Figure 1). The highest serum concentrations never exceeded the usual steady-state concentrations (between 1 and 3 μg ml^{-1}). Excipient dosage was unfortunately not available.

The child was discharged 1 week after admission with normal cardiac and neurological functions.

Amiodarone is a Vaughan-Williams class III antiarrythmic drug, with negative chronotropic and dromotropic effects. The vasodilatory action is responsible for decreased cardiac workload and myocardial oxygen consumption. Amiodarone accumulates in various sites, especially in adipose tissue. Amiodarone is metabolized to DEA by two cytochromes P450, CYP3A4 and CYP2C8. The CYP3A4 isoenzyme is present in the liver and the intestines, with large interindividual variability in its activity and consequently variable systemic availability of oral amiodarone (between 33 and 65%) [1]. Amiodarone and its metabolite are eliminated by hepatic metabolism and biliary excretion; neither amiodarone nor DEA is dialysable.

DEA has similar haemodynamic properties, but accumulates to a greater extent than its precursor.

Recommended loading dose ranges from 800 to 1200 mg m^{-2} orally and 5 mg kg^{-1} intravenously. Maintenance dose ranges from 200 to 500 mg m^{-2} orally and 5 to 20 μg kg^{-1} min^{-1} intravenously. After a single i.v. loading dose, the expected serum peak concentration in healthyvolunteers ranges from 5 to 41 mg l^{-1}. Serum

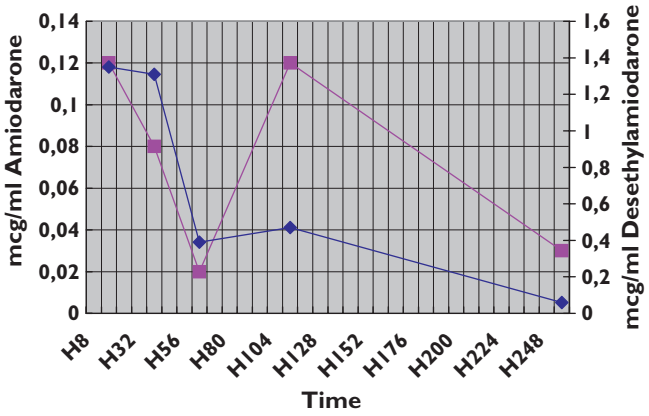

Figure 1

Time-dependent evolution (hours after administration) of desethylamiodarone and amiodarone levels. amiodarone (–■–); desethylamiodarone (–◆–)

concentration decreases to 10% of its peak value 30–45 min after the end of the loading dose [1].

The commercial presentation of amiodarone contains two solvents, benzyl alcohol and polysorbate 80. Those molecules exert haemodynamic effects [2–4].

Benzyl alcohol is an aromatic alcohol used as a bacteriostatic and solvent. Based on animal studies, it is estimated that in normal adults a rapid infusion with up to 4.5 mg kg^{-1} remains safe [5]. In the 1980s, numerous cases of neonatal death after the use of benzyl alcohol-containing intravenous solutions were published [6]. Benzyl alcohol has been responsible for metabolic acidosis, respiratory insufficiency, seizures, intracranial haemorrhage and hypotension leading to cardiovascular collapse [7]. Benzyl alcohol is metabolized to benzoic acid, glycino-conjugated into the liver and excreted as hippuric acid by the kidneys. This pathway could be underdeveloped in the newborn, resulting in metabolite accumulation and toxic side-effects [7].

Toxic effects have also been described with polysorbate 80 (Tween 80®). In 1982, Gough *et al*. studied the cardiovascular effects of the commercial form of amiodarone (amiodarone plus polysorbate) and amiodarone alone in anaesthetized dogs. Only the commercial form caused a 60% drop in mean blood pressure and left ventricular work. They concluded that those adverse events were related to the potent vasodilator and negative inotropic effects of polysorbate 80 [3].

Two studies (Gallik, and Somberg) have compared the classic Cordarone® formulation with the Amio-Aqueous® formula, free of the two previously incriminated solvents. Amio-Aqueous® formula infusion resulted in an increase of peripheral vascular resistance, compensating for an initial decrease in myocardial contractility. Conversely, the classic Cordarone® formulation containing polysorbate 80 resulted in vasodilation and hypotension [8, 9].

Amiodarone itself produces bradycardia and progressive negative inotropic effects [10], minimized by a slower rate of infusion, especially in hypovolaemic patients [2, 11].

One single study on amiodarone use for the treatment of supraventricular and ventricular tachycardias has been conducted in paediatric patients. It showed that amiodarone given intravenously was as safe and effective as the oral form. Half of the infants were haemodynamically unstable, under inotropic support. This instability may have altered the final results and underestimated the side-effects of amiodarone and its solvents [12].

The hypothesis that the two excipients, benzyl alcohol and polysorbate 80, precipitated the occurrence of the cardiogenic shock seems plausible, and appears particularly realistic because the plasma concentration of amiodarone and DEA never reached toxic level. Unfortunately, we were unable to measure the serum level of the two excipients to confirm the hypothesis.

This report underlines the potential for severe, even lethal, haemodynamic side-effects of a drug recognized as safe and widely used for paediatric arrhythmia. The actual i.v. formulation used in Belgium should be reconsidered and be replaced by an excipient-free formulation like Amio-Aqueous®, preventing serious side-effects.

We emphasize also the need to double check at both physician and nursing levels when unusual medications are prescribed.

Competing interests

None declared.

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