Lesson of the month 1: Acute flecainide overdose and the potential utility of lipid emulsion therapy

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ABSTRACT

Lipid-emulsion therapy (Intralipid®) has been advocated as a potential treatment for the management of cardio-toxicity arising from lipid-soluble drugs, particularly those acting upon sodium channels. This, on the basis of a number of *ex vivo* studies and animal models, suggests that partitioning a drug into lipid could alter its pharmacokinetics and result in significant clinical improvements. Its subsequent use in clinical case series has been seen as confirmation of this mechanism of action. While there are undoubtedly instances where lipid emulsion therapy has been associated with a desirable outcome in humans, as described in this case report, clinicians are reminded that they should not attribute causality, on this basis alone.

KEYWORDS: Flecainide, toxicity, overdose, lipid emulsion therapy, Intralipid

Background

Lipid emulsion therapy (Intralipid®) is an established treatment for the management of acute toxicity resulting from local anaesthetics.[1] In recent years, it has increasingly been advocated for the management of severe cardiovascular toxicity arising from a variety of other lipid-soluble drugs eg flecainide.[2,3]

We report upon an instance of acute flecainide toxicity in a child where intravenous lipid emulsion therapy (ILE) was associated with a favourable outcome, with analytical confirmation of flecainide ingestion and the impact of this treatment on flecainide concentrations. We also discuss two previous instances where ILE has been associated with a desirable outcome in humans, when exposed to supratherapeutic concentrations of flecainide. By critically evaluating our experience along with these previous case reports, we remind clinicians that a causal benefit should not be presumed.

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Case report

A 13-year-old girl attended her local emergency department (ED) 90 minutes after consuming 25 mg bisoprolol, 900 mg flecainide and 225 mg aspirin. Her weight was 45 kg and she had no significant medical history. On arrival, she was alert (GCS 15/15) with a normal respiratory rate (12 breaths per minute) and oxygen saturations of 100% on room air; although her heart rate was 65 bpm, she was found to be hypotensive (70/39 mmHg). The initial 12-lead ECG demonstrated a sinus rhythm (ventricular rate 70 bpm), first-degree AV nodal blockade (PR interval 215 ms), right bundle branch block (QRS duration 164 ms) and a QT_c of 452 ms. Her serum sodium was 137 mmol/l, potassium 3.7 mmol/l and magnesium 0.83 mmol/l; a four-hour salicylate level was <50 mg/l, while her four-hour paracetamol level was <10 mg/l. The venous pH was 7.55, bicarbonate 24.1 mmol/l and BE +3.0. Two 900 ml boluses (20 ml/kg) of 0.9% sodium chloride solution were given and advice sought from the medical toxicology service.

The clinical toxicologist on call recommended intravenous glucagon therapy in view of her bisoprolol ingestion; however 4 mg was given intramuscularly. 8.4% intravenous sodium bicarbonate was also advised in an effort to maintain a pH of 7.45–7.50, along with an infusion of magnesium sulphate (20 mmol). Despite these interventions, the patient had a VF arrest one hour after presenting to the ED. Following successful cardiopulmonary resuscitation, she was transferred to a tertiary care centre, intubated, ventilated and with ionotropic support *in situ*. Prior to transfer and immediately after the return of cardiac output, a 70 ml bolus of 20% ILE (1.5 ml/kg) was administered, followed by a further 225 ml (0.25ml/kg/min) over the next 20 minutes.

For the next 8 hours, severe cardiovascular instability was observed with the cardiac rhythm frequently alternating between a sinus tachycardia with right bundle branch block, Torsades de Pointes, a Brugada-like syndrome, coarse VT and ventricular standstill. Intravenous bicarbonate and ionotropes were continued throughout this period; although a temporary transvenous pacing wire was inserted, this was never utilised.

Twelve hours after the initial presentation, cardiac stability returned; serial 12-lead ECGs demonstrated sinus rhythm, a

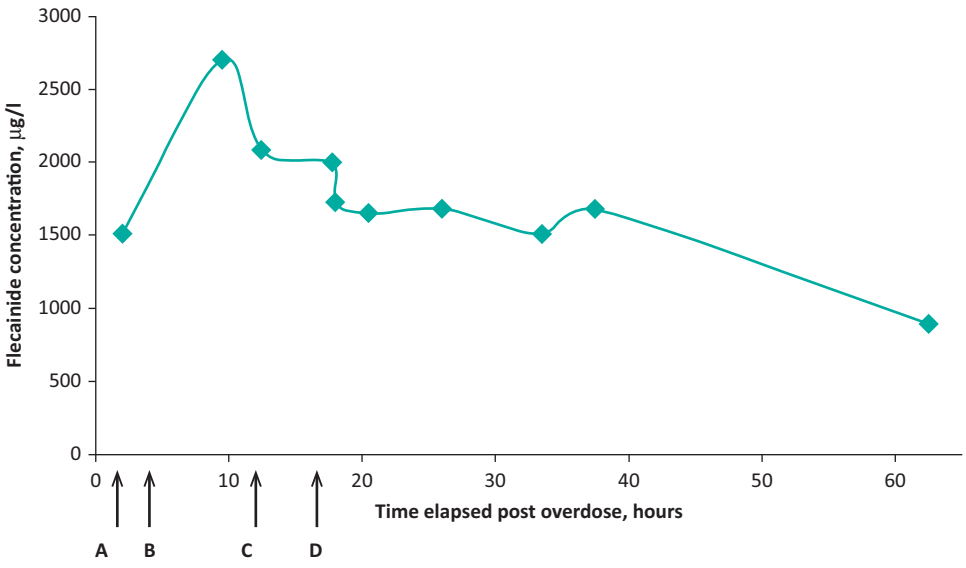

Fig 1. Serum flecainide concentrations and ECG features post overdose. A = presentation to ED; PR interval 215 msec; QRS duration 164 msec; QTc duration 452 msec. B = VF arrest; 20% Intralipid 1.5 ml/kg bolus followed by 0.25 ml/kg/min (over 20 mins). C = PR interval 185 msec; QRS duration 124 msec; QTc duration 601 msec. D = PR interval 185 msec; QRS duration 124 msec; QTc duration 601 msec.

QRS duration of <120 ms and a QT_c of <450 ms. The pacing wire was withdrawn, the inotropes weaned and the patient successfully extubated. A degree of ischaemic liver injury was noted, with the serum aspartate transaminase (AST) and alanine transaminase (ALT) peaking at 3,781 and 3,110 IU/l respectively, 60 hours post overdose. With progressive improvement in these indices and after a period of psychiatric assessment, the patient was discharged home with no obvious sequelae.

Flecainide toxicokinetics

The total flecainide concentration 90 minutes post overdose was 1,512 µg/l, increasing to 2,699 µg/l 9 hours post ingestion. At 12, 24, 60 and 140 h this had fallen to 2,075, 1,680, 895 and <100 µg/l respectively (Fig 1). With an elimination half-life of 32 hours, the use of Intralipid did not appear to have significantly altered the toxicokinetic profile of flecainide; previous toxicokinetic reports have established the elimination half-life of flecainide to be 28–30 h.[3,4] However, such toxicokinetic data should be interpreted with caution, as total, not free flecainide concentrations were measured, and ILE was administered during the likely absorption of flecainide.

Discussion

The reported mortality rate from overdoses of class Ic Vaughan Williams anti-arrhythmics is 22.5%.[5] Accepted treatments include aggressive fluid resuscitation, the administration of hypertonic sodium bicarbonate and intravenous magnesium.[6,7]

Equally, ILE has been heralded a lifesaving treatment in the context of flecainide toxicity. However, the evidence for this assertion is poor; animal data from Cave *et al*, failed to demonstrate the efficacy of ILE in this setting, when compared with hypertonic sodium bicarbonate.[8] Moreover, while ILE may act as a 'lipid sink', removing lipid-soluble drugs from the serum and thus limiting any clinical sequelae, this mechanism of action is, at best, putative.[3,9]

In that vein, a number of human case reports have also been cited as evidence for the efficacy of ILE in life-threatening flecainide toxicity.[10,11] In the first instance, a 72-year-old female developed haemodynamic compromise after ingesting 1,500 mg flecainide, 150 mg oxazepam and 1.5 mg thyroxine.[10] On arrival in the ED, her blood pressure was 70/50 mmHg, heart rate 55 bpm, QRS >200 ms and QT interval 'prolonged'. Following initial resuscitation with intravenous fluids, sodium bicarbonate and adrenaline, lipid emulsion therapy was administered. Thirty minutes later, the authors reported that 'haemodynamic stabilisation allowed a dramatic decrease in the dose of epinephrine (adrenaline)'. However, the exact haemodynamic parameters pre- and post-lipid emulsion therapy were not reported nor were details of flecainide concentrations. The second case report was of a 51-year-old male who ingested 2,500mg of flecainide 90 minutes prior to his arrival in an ED; at presentation his systolic blood pressure was 140 mmHg, heart rate 44 bpm, QRS 162 ms and QT_c 427 ms.[11] He was then treated with intravenous fluids, sodium bicarbonate, atropine, magnesium and lipid emulsion therapy. While the authors attribute the successful outcome to the use of ILE, the associated graphic suggests that the QRS duration was beginning to 'normalise' prior to the administration of ILE, casting doubt over the impact of ILE in this instance too.

Although we describe a third positive outcome following the use of ILE in the context of a life-threatening flecainide overdose, we remain cautious when attributing therapeutic efficacy. ILE was not administered in isolation of other antidotes/treatments, cardiovascular instability continued to be observed for several hours after its administration and the elimination half-life of flecainide appeared unchanged. Although ILE may have removed flecainide from the circulation into a 'lipid sink', thereby preventing it from causing further cardiovascular toxicity, such an analysis is speculative as we, along with others, are unable to measure free flecainide concentrations.[10,11] Thus, while ILE may have a role as a 'rescue' therapy in this setting, we would counsel clinicians against the presumption of causality. ■

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