Generalized seizures as the presentation of flecainide toxicity

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A 12-year-old girl developed generalized tonic-clonic seizures following ingestion of flecainide 1500 mg (15 tablets). At presentation, the electrocardiogram showed marked prolongation of the JT interval and marked increase in QRS duration. The initial plasma flecainide level was >4 μg ml⁻¹. Supportive therapy was instituted and complete recovery occurred within 48 h. The electrocardiogram returned to normal. The management of class 1 antiarrhythmic agent toxicity is briefly outlined and the association of antiarrhythmic drug toxicity with seizures is reviewed.

Introduction

Flecainide, an antiarrhythmic agent with class lc properties, is effective in the management of a wide range of supraventricular and ventricular arrhythmias. At therapeutic dosages the drug is well tolerated; the most common extracardiac adverse effects include dizziness (30%), visual disturbances (28%), headache (9%) and nausea (9%). Acute toxicity studies in animals using single doses of up to 500 mg kg⁻¹ have produced ataxia, dyspnoea and convulsions. These effects have not previously been documented in man. We describe a case of flecainide overdose presenting as generalized seizures associated with marked electrocardiographic abnormalities.

Case report

A 12-year-old girl presented with a 2 h history of headache, abdominal discomfort and blurred vision followed by a generalized tonic-clonic seizure lasting 2 min, which was observed by her mother. There was no previous history of fitting. The girl had a 6-year history of palpitations due to paroxysmal atrioventricular re-entrant tachycardia (AVRT) initially treated with digoxin and then verapamil. After 4 years, the attacks became more frequent and an electrophysiological study was undertaken at St George's Hospital, London, during which a spontaneous sustained AVRT was terminated using intravenous flecainide. Oral flecainide, 50 mg tds, was then commenced and during a repeat study 4 days later a non-sustained slower AVRT could be initiated by rapid atrial pacing. The patient improved symptomatically on flecainide and was maintained on 50 mg bd which achieved a plasma flecainide level of 0.56 μg ml⁻¹ (normal therapeutic range 0.4-1.0 μg ml⁻¹).

Following the seizure, the girl was admitted to hospital unconscious and mildly pyrexial, 37.5 °C. She weighed 35 kg. The pulse was 70 beats min⁻¹ and regular and the blood pressure was 80/50 mmHg. The limbs were hypotonic and both plantar responses were extensor. The electrocardiogram on admission showed a regular rhythm, 68 beats min⁻¹, with a PR interval of 120 ms, a QRS duration of 280 ms and a JT interval of 400 ms [Fig. 1(a)]. Serum potassium was slightly low at 3.1 mmol l⁻¹, and serum calcium and glucose were normal. White cell count was elevated to 15 x 10⁹ l⁻¹ (60% neutrophils). Arterial blood gases (while breathing 100% oxygen) were pO₂ 201 mmHg, pCO₂ 41 mmHg; the arterial pH was 7.33.

The patient experienced two further fits, each lasting 2 min, and was electively intubated, ventilated and transferred to this centre for further assessment. On arrival she was extubated and, in view of the electrocardiographic features, a temporary endocardial pacing electrode was inserted. Repeated serum potassium levels were normal. Computerized tomography of the brain, electroencephalography and lumbar puncture were normal. Over the ensuing 24 h the patient gradually

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regained consciousness and the electrocardiogram showed a persistent increase in QRS duration and JT interval with an increased PR interval (240 ms). No further fitting was observed. The girl was able to confirm that she had omitted her usual dose of flecainide for 1 week but had then taken 1500 mg (15 tablets) at once in order to ‘catch up’. Serial serum flecainide levels and corresponding electrocardiographic appearances (lead VI) are shown in Fig. 2. Electrocardiographic appearance returned towards normal after 40 h [Fig. 1(b)]. No evidence of deliberate self-harm or attention-seeking was elicited. The patient made a full recovery and was discharged on her usual dose of flecainide 5 days after presentation; repeated plasma flecainide levels were satisfactory with no evidence of drug accumulation. The patient was also given carbamazepine 200 mg twice daily for 3 months but no further fits occurred and, following this period, the drug was slowly discontinued.

Discussion

This case report is the first to describe generalized seizures as a complication of flecainide therapy. It also illustrates the marked effect of the drug on ventricular depolarization and repolarization at plasma flecainide levels previously unrecorded (personal communication with Guy’s Hospital, London).

Flecainide is a type Ic antiarrhythmic agent which slows cardiac cellular depolarization but has little effect on action potential duration. It depresses conduction within the myocardium, acting predominantly on the His–Purkinje system, prolonging the HV interval by 27–47%. Most studies also report increases in the PR interval (17–29%) and QRS duration (11–27%) but little change in the JT interval (an index of ventricular repolarization). In our patient, the electrocardiogram on presentation showed a marked prolongation of the JT interval (400 ms) and QRS duration (280 ms) but a short PR interval with normal P wave axis. Twelve hours later, the PR interval had increased to 240 ms with a similar P wave axis and at a similar heart rate. It is possible that the initial rhythm was junctional, with subsequent conversion to sinus node origin. There was no evidence that a second drug had been taken and the electrocardiographic effects therefore were probably due to the high plasma concentration of

Figure 1  Electrocardiograms at (a) 2 h, (b) 40 h following ingestion of flecainide 1500 mg. See text for details. (Leads II and III of the initial electrocardiogram are unavailable; the tracing has been enhanced for clarity).
flecainide. Atrioventricular nodal block with escape rhythm and increased QRS duration have previously been described following an overdose of flecainide in a patient with a plasma level of 3 μg ml⁻¹.[2]

As shown in Fig. 2 the return of the QRS duration and JT interval towards normal was associated with a return of the plasma flecainide level towards the therapeutic range. We do not know of any previous report of this electrocardiographic appearance associated with toxic levels of plasma flecainide. In particular, the effect of flecainide on ventricular repolarization at these plasma levels is of interest. Despite its lack of significant effects on repolarization at therapeutic dosages, proarrhythmic effects have been reported[4,5], although no ventricular arrhythmias were observed in this patient. Myocardial depression has been well documented following flecainide administration[6] but, apart from a low blood pressure at presentation, there was no evidence of impairment of ventricular function in this patient (her normal systolic blood pressure was 90–110 mmHg).

Flecainide is rapidly absorbed when given orally and has 90% bioavailability. Peak plasma levels are achieved approximately 3 h after ingestion (range 0.5–6 h) and the volume of distribution is 91 kg⁻¹. Fifty percent of the drug is plasma protein bound. Approximately 86% of the drug is excreted by the kidney in its active form and its two inactive metabolites. The elimination half-life in healthy subjects varies from 7–23 h and this may be increased in renal impairment, congestive heart failure and chronic liver disease[7]. The most common extra-cardiac adverse effects are dizziness, visual disturbances, headache and abdominal discomfort at therapeutic dosages[8] and these were experienced by our patient. They are usually relatively mild and transient and are dose-related, their incidence increasing when the plasma level exceeds 1 μg ml⁻¹.

Toxicity studies in animals have reported convulsions following single doses of 500 mg kg⁻¹ flecainide; death appeared to be due to respiratory depression and arrest. We believe this is the first reported case of flecainide toxicity associated with generalized tonic-clonic seizures in man. In our patient, the initial plasma level was >4 μg ml⁻¹.

The management of our patient consisted of exclusion of other causes of fits and supportive therapy; renal and hepatic function were normal on presentation and remained so. In our patient the estimated elimination half-life of flecainide following the overdose was 20 h (Fig. 2), which is greater than the 8–9 h previously estimated in single dose studies, but is probably consistent with chronic drug administration in this patient. Attempts to remove flecainide, for example using haemodialysis, have not been shown to be effective but acidification...
Seizures are a toxic feature of many antiarrhythmic drugs: one study reported that two of 349 patients treated with lignocaine for cardiac arrhythmias developed seizures, while the overall incidence of drug-induced convulsions was 1 per 1000 patients. Brief generalized seizures associated with marked acidosis have been reported following ingestion of 3-3.5 g of encainide, another class lc antiarrhythmic agent, in a 46-year-old man. Fitting was suppressed using diazepam and preceded cardiovascular manifestations. The clinical condition improved promptly following correction of the acidic state using hypertonic sodium bicarbonate. Following quinidine, severe cinchonism may present as lethargy, delirium, convulsions and coma and often precedes cardiovascular depression, although QT prolongation is invariably present. Convulsions may be suppressed using diazepam but, in resistant cases, underlying serum calcium or plasma glucose abnormalities are often present and require correction.

Seizures precipitated by lignocaine, a class lb agent, usually occur when plasma levels exceed 9 μg ml\(^{-1}\). Diazepam usually suppresses the convulsions but in the presence of hypoxia and hypercapnia cerebral penetration of lignocaine is increased and adequate ventilation and correction of acid-base status are therefore mandatory. Seizures have been reported following ingestion of 16 g tocainide, an oral class lb agent. Phenytoin, a drug with class lb properties and a commonly used anticonvulsant, may also precipitate seizures if plasma levels exceed 40 μg ml\(^{-1}\). Mexiletine and aprindine may also induce convulsions.

\(\beta\)-adrenoceptor antagonists, especially the lipidsoluble agents such as propranolol and, to a lesser extent, metoprolol and oxprenolol, may produce hallucinations, seizures, delirium and coma at toxic levels. Seizures have been described following atenolol, but we are unaware of any reports following use of the class III agent amiodarone. Overdose with verapamil has precipitated seizures in an infant and convulsions may be the terminal event following overdose with calcium antagonists, possibly related to poor cerebral perfusion.

Specific antidotes for overdose with class I antiarrhythmic agents are unavailable. In most situations, management is supportive, ensuring adequate ventilation with careful monitoring of blood pressure, cardiac rhythm, serum electrolytes and acid-base status. During the first 4 h following ingestion, and possibly later with some agents (for example disopyramide which has anticholinergic properties), gastric lavage and/or emesis with ipecacuahna syrup are beneficial but these measures should be avoided following drugs which induce an early onset of seizures, for example mexiletine and lignocaine. Activated charcoal and purgatives may be given and, for quinidine toxicity, repeated charcoal ingestion every 4 h increases removal from the gut. The effectiveness of measures to increase elimination of antiarrhythmic drugs depends on individual pharmacokinetics. Forced acid diuresis has been suggested for quinidine toxicity, but there is little increase in elimination since renal clearance is low. Haemodialysis is effective if the drug is of low molecular weight, has low protein binding and high water solubility and has a low volume of distribution. Haemoperfusion is not limited by the first three of these characteristics but is ineffective if the drug has a large volume of distribution (>400 l). Phenytoin and disopyramide may be removed by these methods, probably more efficiently by the latter. In renal failure, procainamide and quinidine clearance is increased by haemodialysis. In hepatic failure drugs such as mexiletine and lignocaine may be removed by haemoperfusion.

Drug-induced seizures may be suppressed using diazepam as described above. Carbamazepine should be avoided where there is class la drug toxicity and, similarly, phenytoin should be avoided if there is overdosage with a class lb agent.

Most tachyarrhythmias may be induced by drugs. Sinus tachycardia requires treatment with \(\beta\)-adrenoceptor antagonists if the patient is symptomatic. Ventricular tachycardia usually requires immediate cardioversion if the patient is compromised; an antiarrhythmic agent with different properties from the ingested drug may otherwise be used. Prolongation of the QT interval may precipitate torsade de pointes. QT prolongation is especially common following disopyramide and quinidine but is also a characteristic of most other class lb agents. It usually responds to an isoprenaline infusion or overdrive pacing.

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