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Fatal torsade de pointes following jaundice in a patient treated with disopyramide

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Summary: A case of fatal torsade de pointes in a 53 year old patient treated with disopyramide is described. The arrhythmia followed the development of acute hepatocellular dysfunction and may have been due to failure of the liver to efficiently degrade the drug to its metabolites.

Introduction

Disopyramide is a class I antiarrhythmic agent which is generally safe and well tolerated. Serious toxicity has been rarely encountered,[1] yet sudden death associated with an overdose of disopyramide can occur.[2] We report a patient treated with disopyramide who developed a fatal torsade de pointes type of ventricular arrhythmia, secondary to acute hepatocellular dysfunction.

Case report

A 53 year old white female was admitted after the onset of epigastric pain, nausea and vomiting of 24-hour duration. Her past medical history included acute myocardial infarction 4 years previously, complicated by rapid supra-ventricular arrhythmias which were treated at first with quinidine and for the last year with oral disopyramide phosphate 150 mg three times daily. There was no history of angina or congestive heart failure but the patient was obese and had non insulin-dependent diabetes mellitus treated by glibenclamide 5 mg/day, and mild hypertension.

On admission she was slightly jaundiced with a regular pulse of 100/minute and blood pressure of 180/90 mmHg. Physical examination also showed right upper quadrant tenderness with no hepatomegaly, and was otherwise unremarkable with no signs of congestive heart failure. Chest X-ray was normal. The electrocardiogram (ECG) showed an old anterior wall myocardial infarction with a PR interval of 0.22, a QT_c of 0.42 seconds and no ischaemia or ventricular premature beats. Abdominal ultrasound was normal. On the next day, the jaundice considerably deepened. Laboratory data revealed a predominantly direct bilirubinaemia of 133 μmol/l with alkaline phosphatase of 345 U/l and transaminases 195–225 U/l. Hepatitis B serology and hepatitis A IgM antibodies were negative. Creatine kinase was 80 U/l. Urinanalysis, kidney function tests and electrolytes were normal. The ECG was unchanged except for a QT_c interval of 0.50 seconds. On the evening of the second day of her admission and about 3 hours after she received the third capsule of disopyramide, the patient, who was feeling well, had a sudden loss of consciousness and apnoea. ECG showed torsade de pointes 200/min (Figure 1) which could not be controlled and the patient died despite a prolonged resuscitation effort. Blood drawn for creatine kinase determination revealed normal values.

Discussion

Antiarrhythmic drugs including disopyramide have been implicated in the pathogenesis of polymorphous ventricular tachycardia (torsade de pointes).[3] This arrhythmia can develop even during relatively low-dose disopyramide therapy[4] but is often related to increased serum drug concentrations[2,5] causing a prolonged QT interval which can be reversed with discontinuation of the drug. Plasma disopyramide concentrations of 2–5 μg/ml represent the usually effective therapeutic range while concentrations above 7 μg/ml carry a considerable risk of toxicity. The main factor which may be associated with increased serum disopyramide levels and toxicity is impaired renal function, since more than 50% of the drug is excreted unchanged in the urine and about a third as metabolites. The latter is dependent on hepatic degradation and this role of the liver is supported by the recognition of disopyramide-induced hepatitis[6] ranging from asymptomatic increase in serum transaminase levels to frank cholestatic jaundice.[6–8] This however, appears to be a rare complication.

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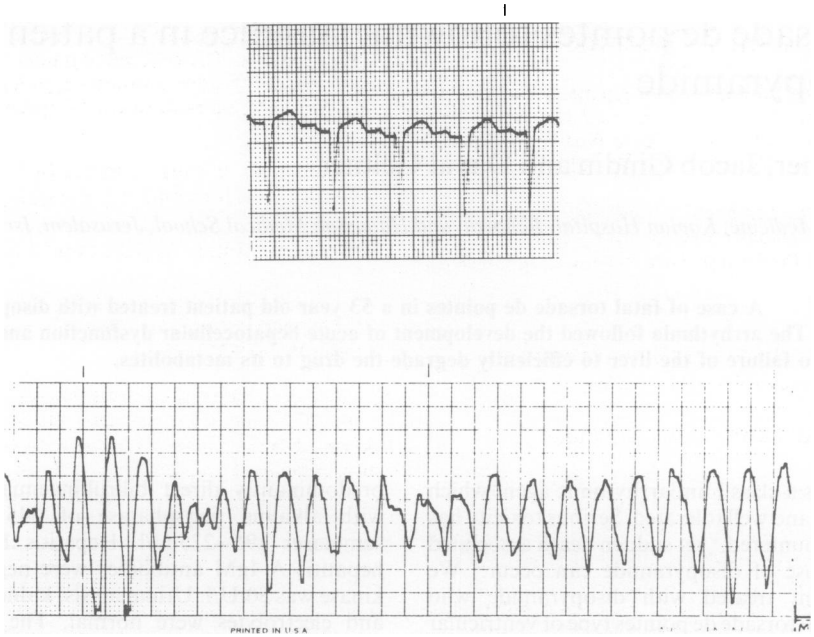

Figure 1 ECG strip one day before (upper trace) and during the fatal torsade de pointes.

The patient reported had normal renal function and disopyramide was administered uneventfully for over a year until the appearance of the jaundice. The hepatocellular disease may have been due to disopyramide or to another undetermined cause. However, the appearance of fatal ventricular arrhythmia of this type is very likely due to acute disopyramide toxicity as a result of a failure of the liver to degrade the drug efficiently to its metabolites. The ECG performed about a day before the patient's death could not predict the danger since it showed a normal QT_c, but liver function continued to deteriorate over the next day with deepening jaundice and a further prolongation of the QT_c interval (a less than 15% increase). Serum disopyramide levels were not done. However, torsade de pointes is an uncommon type of ventricular arrhythmia which is classically associated with drugs which lengthen the QT. It occurred 3 hours after administration of the drug, that is at a time of peak serum concentration[5] and no other cause for this arrhythmia (such as an electrolyte imbalance, or myocardial ischaemia) could be identified. We conclude that it is prudent immediately to discontinue disopyramide administration when jaundice or acute hepatocellular dysfunction appear.

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