Ventricular fibrillation due to lithium withdrawal – an interaction with chlorpromazine?

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Summary: We report a case of primary ventricular fibrillation following withdrawal of lithium in a patient concurrently taking chlorpromazine. A potentially important drug interaction is discussed.

Introduction

Lithium and chlorpromazine are frequently prescribed concurrently for the treatment of chronic psychiatric disorders. We report a possible drug interaction whereby chlorpromazine toxicity may have been precipitated by the abrupt withdrawal of lithium therapy.

Chlorpromazine toxicity was manifested as sudden ventricular fibrillation associated with prolongation of the QTc interval on the electrocardiogram (ECG).

Case report

A 57 year old woman was admitted to the accident and emergency department following a sudden syncopal episode earlier in the day. She had a long history of manic-depressive illness for which she was treated with lithium 400 mg daily and chlorpromazine 200 mg four times daily. One week prior to admission she complained of non-specific abdominal pains which were thought to be an early sign of lithium toxicity. Lithium was therefore discontinued, though she remained on chlorpromazine at the same dose. Her abdominal symptoms subsided.

On arrival at hospital, the initial nursing observations were normal. Whilst waiting to be seen, she collapsed on the floor, unconscious and pulseless. She responded immediately to a blow on the chest, and when the cardiac arrest team arrived was fully conscious with a good cardiac output. A few minutes later she collapsed again, the monitor showing ventricular fibrillation. A single DC shock restored sinus rhythm,

following which the patient made a complete recovery.

There was no preceding history of chest pain or cardiovascular disease. She denied taking any drugs other than chlorpromazine. Physical examination revealed signs of mild mitral stenosis but was otherwise normal. There were no signs of cardiac failure. Routine haematology and biochemistry were normal other than a moderately low plasma potassium (3.0 mmol/l) immediately post-arrest. This was rapidly corrected with an intravenous infusion containing potassium chloride.

The chest radiograph was normal. The initial ECG showed sinus rhythm with a normal PR interval and normal QRS complexes. The QT interval was markedly prolonged (QTc 0.67 ms). The T waves were inverted in the anterolateral leads and bifid in lead V₂ (Figure 1). Serum calcium and magnesium levels were normal, as were cardiac enzymes and thyroid function tests.

Chlorpromazine was discontinued following admission and subsequent electrocardiograms reverted towards normality though the QT interval (QTc 0.46) remained mildly prolonged after three days (Figure 2). Echocardiography confirmed mild rheumatic mitral valve disease. The patient made an uneventful recovery. An ECG taken some weeks later was entirely normal.

Discussion

It is well recognized that chlorpromazine and other phenothiazines commonly cause abnormalities of the ECG. In particular, T wave deformities, accentuation of the U wave and prolongation of the PR and QT intervals are well described.^{1,2} Furthermore, these effects are dose-related, occurring at therapeutic

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Figure 1 ECG on admission (leads V₄–V₆) showing prolonged QT interval (QTc 0.67 seconds) and inverted T waves.

Figure 2 ECG on the third day of admission. The QT interval remains mildly prolonged (QTc 0.46 seconds).

plasma levels and are thought to be benign.^{2,3} Prolongation of the QT interval and changes in T wave morphology appear to be two independent effects of chlorpromazine.

In over-dose, cardiac arrhythmias are common. These include sinus tachycardia, atrial fibrillation, ventricular tachycardia and fibrillation. The phenothiazines may cause potentially lethal ventricular arrhythmias in young patients without underlying heart disease, receiving therapeutic doses.¹ Phenothiazines have been associated with sudden unexplained deaths and cardiac arrhythmias have

been strongly implicated.⁴

It is unclear whether prolongation of the QT interval *per se* is directly responsible for the development of ventricular arrhythmias, although they are common in the congenital long QT syndromes.⁵

Chlorpromazine is commonly prescribed concurrently with lithium in the treatment of a number of psychiatric conditions. The combined use of these drugs has been implicated in the production of neurotoxicity in a small number of patients. There have been reports of neurotoxicity in the form of confusion and severe extrapyramidal reactions occurring soon after the addition of lithium to stable regimes of chlorpromazine.⁶ A similar reaction occurred in a patient after 2 years of treatment with lithium and chlorpromazine.⁷ In all cases lithium levels were within the therapeutic range. A definite cause and effect relationship has not been established, but the drugs may act synergistically to effect dopamine related neurotransmission. Similar interactions between lithium and other neuroleptics have been reported.⁸

There appears, in addition, to be an important pharmacokinetic interaction between lithium and chlorpromazine. There is good evidence that serum levels of chlorpromazine can be substantially reduced by concurrent administration of lithium carbonate. When chlorpromazine was administered with lithium to healthy volunteers, peak plasma levels of chlorpromazine were 40% lower than those without lithium.⁹ Furthermore, it has been suggested that abrupt cessation of lithium therapy may result in rebound elevation of chlorpromazine levels precipitating toxicity in the form of hypotension and extrapyramidal symptoms.^{10,11} The mechanism of this interaction is not fully understood. Work performed in rats suggests that lithium may impair absorption of chlorpromazine by delaying gastric emptying.¹² Lithium has also been shown to delay gastric emptying in a group of psychiatric patients in whom low plasma levels of chlorpromazine were observed in those concurrently treated with lithium.¹³

We report a case in which an episode of ventricular fibrillation was associated with transient prolongation of the QT interval. Chlorpromazine is strongly implicated, particularly as the QTc returned to near normal limits following its withdrawal. Mild hypokalaemia is well recognized following cardiac arrest and this may explain the marginally low serum potassium on admission. We doubt whether this degree of hypokalaemia alone could have induced ventricular fibrillation. The incidence of serious cardiac arrhythmias consequent to chronic mild hypokalaemia is extremely small.¹⁴ Furthermore, the ECG abnormalities could not be explained by hypokalaemia since the QT interval remained prolonged for several days despite correcting the serum potassium. No other cause for ventricular arrhythmias was discovered. We propose that chlor-

promazine toxicity was probably precipitated by the withdrawal of concurrent lithium therapy.

If lithium and chlorpromazine are used in combina-

tion, the withdrawal of lithium is potentially dangerous. The dose of chlorpromazine should be reduced if lithium is to be discontinued.

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