Marked junctional bradycardia, prolonged QT interval and torsade de pointes in acute phenothiazine intoxication in a schizophrenic patient
A Case Report

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Summary

A schizophrenic man ingested a mixture of psycho-active drugs during para-suicide, and presented with marked respiratory and psychomotor depression. Electrocardiographic abnormalities of marked junctional bradycardia, prolonged QT interval and ventricular tachyarrhythmias of the torsade de pointes type were documented. Cardioversion, lignocaine infusion, temporary cardiac pacing and beta-blockade finally controlled the unstable rhythm.

Introduction

Phenothiazines especially thioridazine, are known to cause QT prolongation and other electrocardiographic changes, including dangerous ventricular arrhythmias. [1,2] Sudden deaths have also been reported among patients on chronic phenothiazine therapy[1] as well as in those with acute overdose. Lately, with the renewed interest in QT prolongation syndromes and their association with atypical ventricular tachycardia i.e. torsade de pointes, more reports are emerging to definitively impute this peculiar arrhythmia which if prolonged may precipitate syncope, seizures and even sudden deaths from terminal ventricular fibrillation.[3]

We report here, a patient suffering from chronic schizophrenia and depression who ingested an overdose of a combination of psychotropic agents during parasuicide.

Case Report

A fifty-nine year old man with a long history of schizophrenia associated with recurrent bouts of depression and attempted suicides, was admitted to casualty after his family failed to rouse him from sleep. Apparently the night before, he complained of restlessness and insomnia and had ingested about twenty tablets of a combination of anti-psychotic agents, i.e. apohaloperidol 0.5 mg, haloperidol 100 mg, chlorpromazine 25 mg and thioridazine 100 mg tablets. The exact quantity of each type ingested was unknown, but certainly exceeded his daily recommended dose of chlorpromazine 50 mg nocte. The other drugs were left-overs from past treatment.

On admission, he was drowsy and confused with irregular shallow breathing. His blood pressure was 150/90 mm Hg supine and his pulse was a slow but regular 34 beats per minute. His pupillary reflexes were sluggish but equally reactive to light. He moved all four limbs in response to irritation, his reflexes were hypoactive but his plantars were downgoing. No neck stiffness or head trauma was evident. Fundusopy was normal. There was severe bradycardia with mildly elevated (4 cm) jugular venous pulse, some bilateral basal crepitations in the lungs and a soft systolic basal murmur, though no cardiomegaly. The other systems were normal.

A twelve-lead resting electrocardiogram showed a narrow-QRS junctional bradycardia of 34 per minute, and a QT-U interval of 0.78 second {QTc=0.59s} (Figure 1a). Notably, the T waves were abnormally notched (V1 to V5) and merged with giant U waves best seen in leads V1 to V3, 2, 3, and aVF. Intravenous atropine was repeatedly given but only temporarily increased the junctional rate. Ventricular bigeminy with typical R-on-T phenomena, couplets and later short salvos were also noted (Figure 2a). Longer runs of polymorphous ventricular tachycardia (Figure 2b) precipitated cardiorespiratory arrest, necessitating repeated direct current cardioversion, lignocaine infusion, mechanically-assisted ventilation, and later temporary transvenous overdrive pacing at 100 per minute, when an isoprenaline infusion failed to stabilise the rhythm.

Laboratory investigations were normal except for low serum calcium (2.08 mmol/l, albumin 46 g/l), low potassium (2.0 mmol/l) and a mild metabolic acidosis; which corrected promptly with supplements.

A second electrocardiogram (Figure 1b) taken the following day (pacing mode off) showed a junctional bradycardia (38 per minute) with residual QT prolongation of 0.58 second (QTc=0.47 second) but U waves and T wave notching had disappeared. Oral propanolol was added.

The patient remained drowsy, confused, and dysarthric, but gradually recovered whilst on a pacemaker rate of 75 per minute. However, he became progressively aggressive and confused, requiring psychiatric referral. Intramuscular flupenthixol 20 mg was given twice. Chlorpromazine 50 mg nocte was resumed as the patient recovered. The pacing wire was removed on day seven, when the patient became pacer-independent having regained a sinus bradycardia of 55 per minute. QT prolongation remained at 0.48 second. The patient recovered uneventfully afterwards, with parenteral antipsychotic therapy (intramuscular flupenthixol) and family support therapy.

DISCUSSION

Antipsychotic agents of the phenothiazine group particularly thioridazine and chlorpromazine are well known to cause QT prolongation, T-wave changes and prominent U waves even in therapeutic dosages. [1,2] These changes are seldom of any clinical consequence. However, at toxic levels, thioridazine can not only cause QT prolongation but also sinus bradycardia, atrioventricular block and dangerous recurrent ventricular tachycardia-fibrillation[1,2] as experienced by our patient.

Thioridazine has been shown to alter various phases of myocardial action potential, i.e. reducing the maximal rate of rise of phase 0, decreasing phase two duration and amlitude, and prolonging conduction time and phase three repolarisation. Our patient had marked junctional and sinus bradycardia interspersed with recurrent ventricular tachycardia initiated by premature ventricular depolarisations falling on the prolonged QT-U segment (typical R-on-T phenomena). Furthermore the morphology of the atypical ventricular tachyarrhythmias fits the criteria of torsade de pointes.[3] The mechanism of QT prolongation predisposing to torsade do pointe type ventricular tachycardia is thought to be inhomogeneous cardiac recovery with increased temporal dispersion of refractoriness thereby, favouring multiple reentrant circuits.

Treatment of these induced arrhythmias is quite different from the usual ventricular tachycardia or fibrillation. Class I antiarrhythmic drugs i.e. quinidine, procainamide, disopyramide further

Figure 1 a

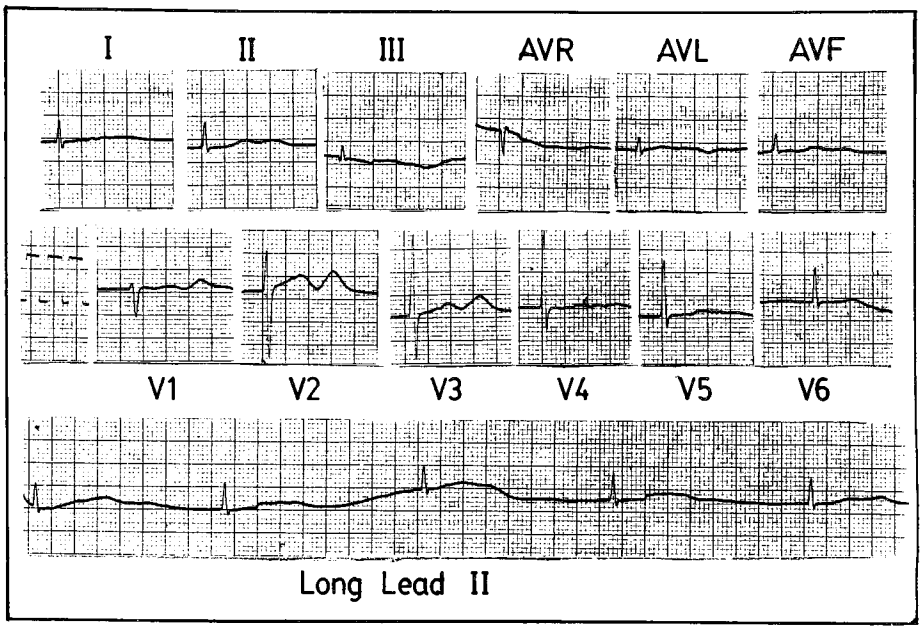

Figure 1 b

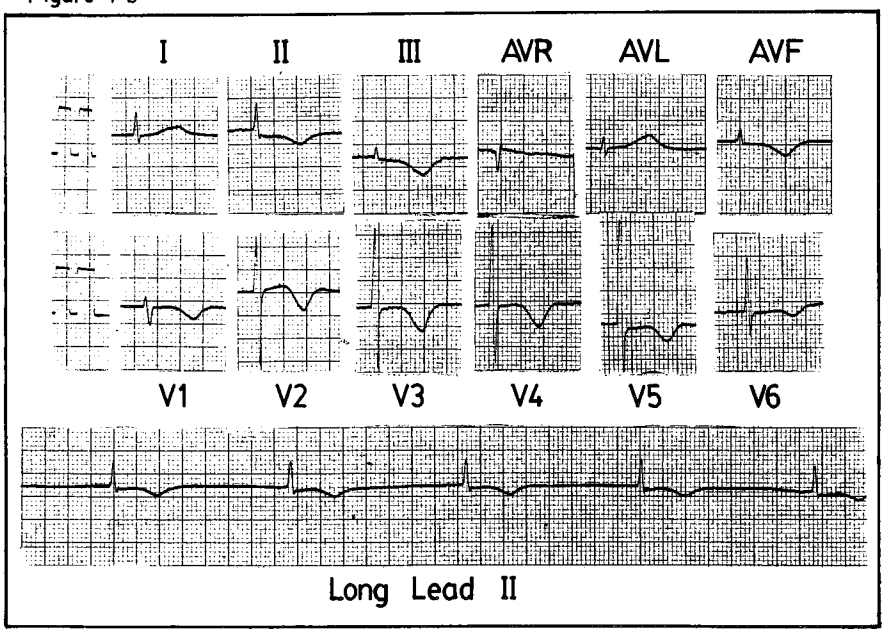

Figure1: **a.** Admitting 12-lead electrocardiogram showing marked junctional bradycardia of 34 beats per minute. The QT-U interval was prolonged to 0.78 second (QTc 0.59 second, by Bazzett's formula). The abnormally large and prominent U wave merging with the T wave was obvious in leads II, aVF and V1 to V3. In other leads, I, III V4, V5, the T wave appeared notched and widened showing abnormal ventricular repolarisation.
b. Following replacement of potassium and calcium, the abnormal notching of the T waves and the U waves disappeared. The QT however, remained prolonged at 0.58 second (QTc 0.47 second) with the rhythm of junctional bradycardia of 38 per minute.

FIGURE 2

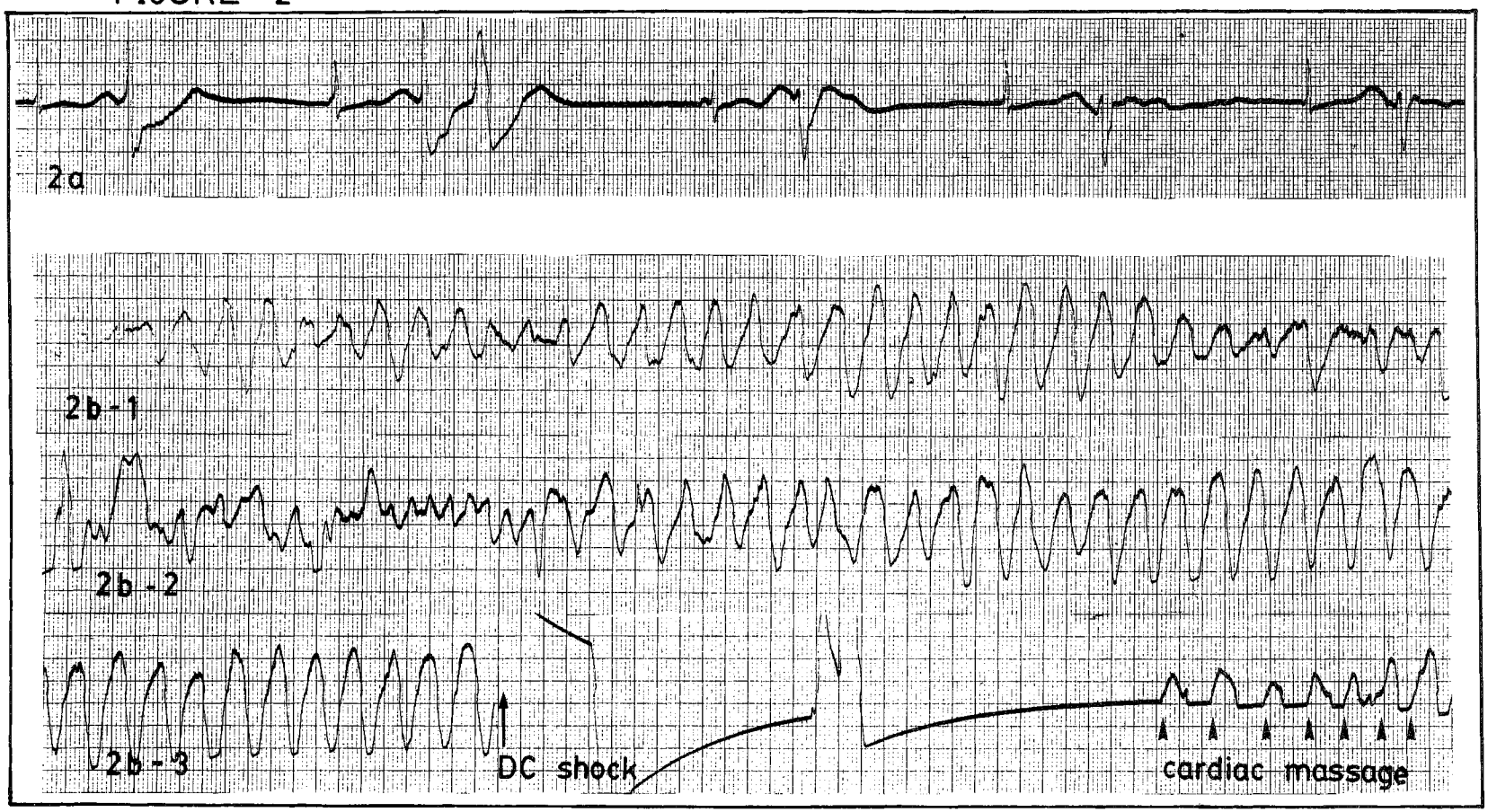

Figure 2: **a.** Electrocardiogram (continuous modified V5 lead) showing ventricular premature beats falling on the down-slope of the T waves in bigeminal pattern. The underlying rhythm was the very slow junctional bradycardia with prolonged QT interval.
b. Electrocardiogram (continuous b-1 through b-3) showing typical undulating polymorphous ventricular tachycardia of the torsade de pointes type. This sustained episode was terminated by direct current countershock which resulted in asystole necessitating external cardiac massage.

prolong the QT interval and are contraindicated. Although direct current shock may terminate the arrhythmia abruptly, this effect is often transient. The underlying unstable rhythm often returns provoking recurrent salvos of torsade phenomena which can be fatal. Although initially thought by Fowler and others[2] that lignocaine infusion is useful, many have found this peculiar arrhythmia resistant.[4,5] Isoprenaline infusion[4], artificial cardiac pacing[5] have been advocated. In our patient, only overdrive pacing successfully controlled the unstable rhythm. Lignocaine and isoprenaline infusions did not appreciably influence the outcome. We added beta-blockade to shorten the QT interval and stabilise myocardial recovery.[3] Most importantly, any predisposing cause should be treated. This patient's hypokalaemia and hypocalcaemia could have contributed to his electrocardiographic abnormalities; thus, these were promptly identified and treated. We could not eliminate the ingested drugs as he was admitted well over 12 hours post-ingestion and no history was forthcoming till much later. Nevertheless the typical torsade de pointe ventricular tachyarrhythmias should be recognised and treated accordingly.

We advise that lignocaine infusion and direct current electroconversion be delivered initially, whilst trying to correct all underlying electrolyte imbalance i.e. low potassium, calcium, magnesium or acidosis. Should these fail, an isoprenaline infusion should be started to increase the heart rate as well as to shorten the QT interval. This step is especially important in hospitals where temporary transvenous pacing is not available.

This can be life-saving. Where pacing can be performed, right atrial or ventricular pacing to overdrive the ventricular rate to 100-180 beats per minute nearly always control the unstable rhythm.

We further highlight the problem of psychiatric patients who often have within their reach, many potentially lethal amounts of drugs. Should they have depression or suicidal intent, these drugs could pose a most opportune hazard. We wish to emphasise that thioridazine and to a lesser extent chlorpromazine and trifluphenazine, are notorious in this aspect. Haloperidol and like drugs are much safer, even in toxic doses. Ideally perhaps, monthly depot injections should be recommended where patients then, would not have such ready access to self-intoxication.

Acknowledgement

We wish to gratefully acknowledge the meticulous care of the coronary care nurses of the General Hospital Kuala Lumpur. We would also like to thank Dr Maniam, Consultant Psychiatrist and lecturer University Kebangsaan Malaysia, for his advice and expertise on the care of this patient.

REFERENCES

1. Kelly HG, Fay JE. Laverty SG. Thioridazine hydrochloride (Mellaril): Its effects on the electrocardiogram and a report on two fatalities with electrocardiographic abnormalities. Can Med Assoc J 1963;89:546-554.
2. Fowler NO, McCall D, Chou T, Holmes JC, Hanenson IB. Electrocardiographic changes and cardiac arrhythmias in patients receiving psychotropic drugs. Am J Cardiol 1976;37:223-230.
3. Smith WM, Gallagher JJ. 'Les torsades de pointes': An unusual ventricular arrhythmia. Ann Intern Med 1980;93:578-584.
4. Kemper AJ, Dunlap R, Pietro DA. Thioridazine-induced torsade de pointes. Successful therapy with isoproterenol. JAMA 1983;249:2931-4.
5. Schoonmaker FW, Osteen RT, Greenfield JC Jr. Thioridazine (Mellaril)-induced ventricular tachycardia controlled with an artificial pacemaker. Ann Intern Med 1966;65:1076-8.