The effects of thioridazine on the QTc interval — cardiovascular safety in a South African setting

Cathlene Seller, FCPsych (SA), MMedPsych
Piet Oosthuizen, MMedPsych, PhD
Department of Psychiatry, Stellenbosch University, Tygerberg, W Cape

Background. Thioridazine has long been used as a first-line antipsychotic in South Africa without any apparent problems. Recently the American Food and Drug Administration (FDA) and Novartis have warned of potentially lethal arrhythmias that may result from the use of thioridazine. Abnormal QT-interval prolongation on the electrocardiogram (ECG) seems to be the most reliable indicator of risk of arrhythmias, such as torsade de pointes and ventricular fibrillation.

Objective. The purpose of this study was to determine whether these warnings are of clinical relevance in a setting where there are already a limited number of antipsychotics available.

Method. Thirty hospitalised subjects who required switching from a high-potency to a low-potency antipsychotic were included. All subjects were commenced on thioridazine 300 mg per day and had an ECG 1 week after initiation and 48 hours after each dose adjustment. QTc was determined using Bazett's formula.

Results. Thioridazine induced a significant increase (p = 0.0001) in QTc interval from baseline values of 400.6 (± 27.3) milliseconds to 429.1 (± 44.2) milliseconds. The QTc interval increased to above 450 milliseconds in 7 subjects (23%) and thioridazine was discontinued in 2 subjects because of a QTc interval greater or equal to 500 milliseconds.

Conclusion. Thioridazine caused a significant, although asymptomatic, increase in QTc interval in almost one-quarter of subjects who received the medication as second-line treatment. Thioridazine should no longer be used as a first-line treatment and if used it should be accompanied by regular ECG monitoring.

Modern psychiatry is in the fortunate position of having access to a wide range of medications, with differing efficacy and side-effect profiles, available for the treatment of psychotic disorders. Among these are the phenothiazines, butyrophenone and thioxanthene derivates, also known as the typical antipsychotics, and the newer so-called second-generation or atypical antipsychotics.

Although antipsychotics offer hope of a normal life to many patients with psychotic illnesses, their usefulness has been limited by their side-effect profile. Antipsychotics are best known for their neurological, particularly extrapyramidal, side-effects but may also have a range of other, non-neurological side-effects. Among these is an association between the use of antipsychotic medications and ventricular arrhythmias and even sudden death.[1] The implicated drugs prolong ventricular repolarisation, reflected by T-wave changes and prolongation of the QT interval on the electrocardiogram (ECG).

The QT interval is an ECG measure that includes both ventricular depolarisation and repolarisation. It begins with the onset of ventricular depolarisation (Q-wave) and ends with the completion of repolarisation (T-wave). Because the QT interval shortens with increasing heart rates, this is usually corrected for. The formula most commonly used to obtain the corrected QT interval (QTc) is Bazett's formula: $QTc = \frac{QTo}{\sqrt{RR}}$ where the QTo is the observed QT interval. QTc intervals below 440 milliseconds are considered normal. The greater the duration of QTc, the more likely cardiac arrhythmias become, with 500 milliseconds considered the threshold for safety. QTc intervals longer than this are associated with substantially higher risk of arrhythmias.[2] Potentially lethal ventricular arrhythmias include polymorphic ventricular tachycardia, torsades de pointes and ventricular fibrillation.[3] Torsades de pointes is a particularly malignant ventricular arrhythmia associated with syncope and sudden death. The term refers to a characteristic pattern of polymorphic ventricular tachycardia.[1] Known risk factors for QTc interval prolongation include female sex, advanced age, electrolyte

imbalance, congenital long QT syndrome, cardiac disease, endocrine or metabolic abnormalities and central nervous system abnormalities.[4]

Although phenothiazines commonly give rise to nonspecific ECG abnormalities in psychiatric subjects,[5-8] the antipsychotic drug most commonly implicated in arrhythmias and sudden death is thioridazine.[9-15] Thioridazine affects the potassium rectifier channel, and therefore an important part of the repolarisation process of cardiac muscle. By blocking this channel thioridazine may prolong repolarisation and therefore the QT interval, increasing the risk of ventricular arrhythmia. Of the phenothiazines, it is the most likely to cause ECG abnormalities[5] and appears to be most cardiotoxic in overdose, even at therapeutic dosages in susceptible individuals.[16] At dosages of 100 - 400 mg/day in healthy individuals, thioridazine-induced ECG abnormalities include minimal prolongation of the QT interval, a decrease in T-wave amplitude, and prominent U-waves. These changes are seldom of clinical significance. At toxic levels thioridazine might cause prolongation of the QRS interval, sinus bradycardia, atrioventricular block, considerable prolongation of the QT interval, recurrent ventricular tachycardia and ventricular fibrillation.[6,15]

Despite the cardiovascular risk that it may present, thioridazine has long been used as a first-line antipsychotic in many institutions in this country, with little apparent adverse effect. More recently, however, many South African health institutions have followed the advice of the Food and Drug Administration (FDA) in the USA, namely that thioridazine should no longer be used as a first-line antipsychotic medication. Although we have applied the same restrictions at our hospital, we were interested to know whether this issue was clinically relevant in our population, as this would further limit the number of antipsychotic medications available and also restrict the use of a seemingly well-tolerated alternative to the high-potency antipsychotics. The purpose of this study was therefore to establish whether thioridazine causes clinically significant QTc interval changes, at the dosages used at our institution.

Methods

This was an open-label study, with subjects serving as their own controls. All subjects were inpatients at Stikland Hospital in Cape Town aged between 18 and 60 years (inclusive) at the time of the study. Subjects were considered for inclusion if they had a *Diagnostic and Statistical Manual* (*DSM-IV*) diagnosis of a psychotic disorder for which they required a change of therapy from another antipsychotic (usually haloperidol) to a low-potency medication such as thioridazine. This change of therapy could have been due to side-effects, non-response, or patient request. Subjects were excluded if they had any co-morbid cardiovascular disease (ischaemic heart disease, arrhythmias) or were on treatment with propranolol, pindolol or any medication known to inhibit the cytochrome P450 system. Concomitant treatment with any medication known to increase the QT interval was also not allowed. Other exclusion criteria were subjects with immediate suicide risk, known hypersensitivity to thioridazine, electroconvulsive therapy in the past 3 months and medical conditions in which thioridazine is contraindicated, e.g. hepatic dysfunction and glaucoma. The study protocol, patient information and consent procedures were approved by the Institutional Review Board of Stellenbosch University.

After receiving information on the purpose and method of the study, all subjects provided written, informed consent before any study procedures were undertaken. Demographic details, vital signs, medical, surgical and treatment history as well as ECG were obtained at baseline. Thereafter, the first-line medication was discontinued and thioridazine commenced at a dosage of 300 mg/day. Dosages were increased on a weekly basis in increments of 100 mg/day until the desired antipsychotic effect was achieved, intolerable side-effects developed or a total daily dosage of 800 mg/day was reached. Downward titration was allowed at any time. The maximum allowed daily dosage of thioridazine was 800 mg/day. Thioridazine was discontinued immediately in any subject found to have a QTc interval equal to or greater than 500 milliseconds.

Follow-up ECGs were obtained 1 week after initiation of thioridazine, and 48 hours after any dosage adjustment. Measurement of the QT interval was performed manually by counting the small marked squares on the ECG paper, each square representing 0.04 seconds. All measurements were done by a single rater (CS).

Statistical methods

Statistical analysis was performed with the help of a specialised computer software package, Statistica version 6 (Statsoft, Inc.).

Categorical variables were compared using chi-square or Fisher's exact test (two-tailed in all cases), depending on expected frequencies. All numerical variables were tested for normality of distribution using the Kolmogorov-Smirnov method. In cases where unrelated groups were compared in terms of numerical variables, we used either the Student's *t*-test (parametric) or the Mann-Whitney *U*-test (non-parametric). For correlations between pairs of numerical variables, we calculated Spearman's rank order correlation coefficients. A significance level of 0.05 was used throughout.

Results

A total of 36 subjects were evaluated for inclusion during the recruitment period. Six subjects failed to meet inclusion criteria and therefore the final sample consisted of a total of 30 subjects, of whom 17 (57%) were male. The mean age for the whole sample was 35.3 (± 11.6) years, and 31.8 (± 10.9) years and 38.9 (± 11.8) years for males and females, respectively. Twenty-five subjects had a diagnosis of schizophrenia, 3 had a diagnosis of schizophreniform disorder and 2 were diagnosed with bipolar disorder. The mean baseline QTc was 400.6 (± 27.3) milliseconds (range 335 - 439 milliseconds), and for males and females 398.8 (± 24.1) milliseconds and 403 (± 31.95) milliseconds, respectively. The mean daily antipsychotic dosage (in chlorpromazine equivalents) before initiation of thioridazine was 397.5 (± 141.3) mg (range 100 - 800 mg) for the whole group, and 447.1 (± 143.3) mg and 332.7 (± 186.4) mg for males and females, respectively.

The mean daily dosage of thioridazine at endpoint was 300.3 (± 71.8) mg (range 100 - 500 mg) and 305.9 (± 74.8) mg and 300.0 (± 70.7) mg for males and females, respectively.

Thioridazine induced a significant increase ($p = 0.0001$) in QTc interval from the abovementioned baseline values to 429.1(± 44.2) (range 335 - 447 milliseconds), and for males and females 424.3 (± 28.5) milliseconds and 435.3 (± 59.6) milliseconds, respectively. There was no significant difference between males and females with regard to increase in QTc interval. There was no correlation between QTc interval increase and age or thioridazine dosage.

The QTc interval increased above the arbitrary value of 450 milliseconds in 7 subjects (23%) after initiating thioridazine. These QTc interval values were 453, 454, 458, 460, 467, 500 and 600 milliseconds. Only 1 patient (3%) had a QTc interval above 500 milliseconds. In another patient, thioridazine was discontinued at the borderline QTc interval of 500 milliseconds, making the incidence of significantly long QTc intervals 6%. The first patient was a 54-year-old woman, with a QTc interval of 600 milliseconds, on 300 mg thioridazine (baseline QTc 421 milliseconds). The second patient was a 39-year-old woman, with a QTc interval of 500 milliseconds on 300 mg thioridazine (baseline QTc 400 milliseconds). Both subjects' QTc intervals normalised after discontinuation of thioridazine. Neither subject had clinical symptoms related to QTc-interval prolongation.

Subjects with a QTc interval above 450 milliseconds had a significantly longer baseline QTc interval than the rest of the study group (409.1 ± 22.8 milliseconds v. 398 ± 28.5 milliseconds, $p = 0.0051$). We failed to find any significant differences between subjects with a QTc interval ≥ 450 milliseconds and < 450 milliseconds with regard to age, increase in QTc above baseline or sex.

Discussion

Following discussions with the American FDA in 2000, Novartis has made the following major modifications to the labelling of Melleril (thioridazine).

1. A prominent boxed warning was added to the packaging advising clinicians that Melleril has been shown to prolong the QTc interval in a dose-related manner, and that drugs with this potential, including Melleril, have been associated with torsades de pointes-type arrhythmias and sudden death.

2. Treatment with Melleril is limited to use in schizophrenic subjects who fail to achieve an acceptable response to adequate courses of treatment with other antipsychotic drugs.

3. Melleril is contraindicated with certain other drugs, in subjects with congenital long QT syndrome or a history of cardiac arrhythmias.

4. Subjects being considered for treatment with Melleril should have a baseline ECG performed and serum potassium levels measured. Subjects with a QTc interval greater than 450 milliseconds should not receive Melleril. Periodic ECGs and serum potassium levels during Melleril treatment may be useful and Melleril should be discontinued in subjects with a QTc interval greater than 500 milliseconds.[17]

These changes are based primarily on the FDA's review of three published studies. In the first of these studies, von Bahr *et al.*[18] demonstrated altered pharmacokinetics and increased serum levels of thioridazine in subjects with a genetic defect resulting in slow hydroxylation of debrisoquin. This study population consisted of 19 healthy subjects, who were each given a single 20 mg dose of thioridazine. Findings were abnormal in 6 subjects.

In the second study, Hartigan-Go *et al.*[19] did a randomised, double-blind, three-period crossover study involving 9 healthy male subjects. They reported a dose-related prolongation of the QTc interval, using single doses of 10 mg and 50 mg thioridazine. The third study by Carrilo *et al.*[20] demonstrated an increase of thioridazine concentration in 10 males with schizophrenia, on concomitant treatment with thioridazine (mean dose 88 mg) and fluvoxamine.

Over more than four decades of use, thioridazine has gained wide acceptance among clinicians and patients worldwide because of its lower risk of extrapyramidal reactions compared with other first-generation antipsychotics. It is a relatively inexpensive agent with the same efficacy as other antipsychotics and a receptor profile not unlike that of the second-generation medications. In South Africa, where access to second-generation antipsychotics is severely limited, thioridazine has offered a viable alternative to the high-potency medications. Our study confirms that thioridazine has a potentially dangerous effect on the QTc interval when used in standard doses in our population. It increased the QTc interval to abnormal levels in almost one-quarter of subjects and to dangerous levels in 2 patients. Furthermore, these changes were asymptomatic and would not have been picked up had ECG monitoring not been done. As in other studies, we found that the increase was greater in females than in males, although the difference did not reach statistical significance. However, both subjects whose medication had to be discontinued were female. In contrast to what is suggested in the 'black box' warning, we did not find any association between dose and QTc prolongation; however a longer baseline QTc did seem to increase the risk.

Although pimozide, sulpiride and droperidol may also prolong the QTc interval and have also been associated with torsades de pointes and sudden death, they were never used as widely as thioridazine. Even haloperidol can induce torsades de pointes and may cause sudden death at normal therapeutic doses, but it does so substantially less frequently than thioridazine.[21] It should also be noted that, despite their generally enhanced safety and tolerability, some atypical antipsychotics have also been associated with QTc interval prolongation.[22] Sertindole has been associated with serious but non-fatal arrhythmias but also with cases of sudden death.[23] Although olanzapine, quetiapine and risperidone prolong the QT interval, it is not clear that they cause torsades de pointes or ventricular fibrillation.[22]

At this time, the most compelling evidence for antipsychotic drug-induced cardiac arrhythmias and sudden death exist with thioridazine.[24] It has been associated with numerous cases of torsades de pointes and sudden death.[25] When QT-interval prolongation of antipsychotics have been compared, they were found to be — in decreasing order of magnitude — thioridazine, sertindole, ziprasidone, quetiapine, risperidone, olanzapine, and haloperidol.[22] However, it is important to remember that despite being the best predictor variable of torsades de pointes, the QTc interval is at best only modestly associated with this arrhythmia. No absolute value of QTc interval is predictive of, or present in, all episodes of torsades de pointes. Nonetheless, a QTc value greater than 500 milliseconds is considered an unacceptable clinical risk.

There are some obvious limitations to our study. Other factors such as electrolyte disturbances, particularly hypokalaemia and hypomagnesaemia, may contribute to or even cause QT-interval prolongation. This study did not include routine potassium levels to establish the presence of hypokalaemia. Thioridazine levels might also have been a more objective indicator than the thioridazine dose, potentially differentiating between individual oversensitivity and possible pharmacokinetic factors. More attention should have been paid to a family history of cardiac problems and sudden death. The sample size was fairly small which might have compromised some of the results.

Despite the limitations, this study confirms that significant QT-interval prolongation may be a problem at normal therapeutic doses of thioridazine in our population. Until we have better predictors available for assessing cardiovascular safety, we suggest pretreatment and follow-up ECG, and adherence to FDA stipulations as set out above.

Additional suggestions as prescribed in previous studies are:[24,25] (*i*) medical history concentrating on previous episodes of syncope, previous heart disease, relatives with long-QT

syndrome, and family history of sudden death; and (*ii*) enquiring about the use of other medications that may also prolong the QT interval.

References

1. Thomas SHL. Drugs, QT interval prolongation and ventricular ar hy hmias. *Adverse Drug React Toxicol Rev* 1994;**13**: 77-102.
2. Glassman AH, Bigger JT. Antipsychotic drugs: Prolonged QTc interval, Torsade de pointes, and sudden dea h. *Am J Psychiatry* 2001;**158**:1774-1782.
3. Ban TA, St Jean A. Electrocardiographic changes induced by pheno hiazine drugs. *Am Heart J* 1965;**70**: 575-576.
4. Vieweg WVR. Mechanisms and risks of electrocardiographic QT interval prolongation when using antipsychotic drugs. *J Clin Psychiatry* 2002; **63**:18-24.
5. Barr CS, Naas A, Freeman M, *et al*. QT dispersion and sudden unexpected dea h in chronic heart failure. *Lancet* 1994; **343**: 327-329.
6. Huston JR, Bell GE. The effect of thioridazine hydrochloride and chlorpromazine on the electrocardiogram. *JAMA* 1966; **198**: 16-20.
7. Burda CD. Electrocardiographic abnormalities induced by hioridazine (Mellaril). *Am Heart J* 1968; **78**: 138-146.
8. Fletcher GF, Kazamias TM, Wenger NK. Cardiotoxic effects of Mellaril: conduction disturbances and supraventricular ar hy hmias. *Am Heart J* 1960; **78**: 135-138.
9. Kelly HQ, Fay J, Laverty FG. Thioridazine hydrochloride (Mellaril): its effect on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. *CMAJ* 1963; **89**: 546-554.
10. Desautels S, Filteau C, St Jean A. Ventricular tachycardia associated with administration of thioridazine hydrochloride (Mellaril). *CMAJ* 1964; **90**: 1030-1031.
11. Hollister LE, Kosik JC. Sudden death during treatment with phenothiazine derivates. *JAMA* 1965; **192**: 1035-1038.
12. Giles T, Modlin R. Death associated with ventricular arrhythmias and hioridazine hydrochlordie. *JAMA* 1968; **205**: 98-100.
13. Alexander CS, Nino A. Cardiovascular complications in young patients taking psychotropic drugs: a preliminary report. *Am Heart J* 1969; **78**: 757-759.
14. Kemper A. Thioridazine-induced torsade de pointes. Successful therapy with isoproterenol. *JAMA* 1983; **249**: 2931-2934.
15. Fowler NO, McCall D, Choiut T, *et al*. Electrocardiographic changes and cardiac arrhy hmias in patients receiving psychotropic drugs. *Am J Cardiol* 1976; **37**: 223-230.
16. Buckley NA, Thyte M, Dawson AH. Cardiotoxicity more common with hioridazine overdose han with other neuroleptics. *Clin Toxicl* 1995; **33**: 199-204.
17. Mellaril product label. New York: Novartis, 2003.
18. von Bahr C, Movin G, Nordin C, *et al*. Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation phenotype. *Clin Pharmacol Ther* 1991; **49**: 234-240.
19. Hartigan-Go K, Bateman DN, Nyberg G, *et al*. Concentration-related pharmacodynamic effects of hioridazine and its metabolites in humans. *Clin Pharmacol Ther* 1996; **60**: 543-553.
20. Carrilo JA, Ramos SI, Herraiz AG, *et al*. Pharmacokinetic interaction of fluvoxamine and hioridazine in schizophrenic patients. *J Clin Psychopharmacol* 1999; **19**: 494-498.
21. Fayer SA. Torsades de pointes ventricular tachyar hythmias associated with haloperidol (Letter). *J Clin Psychopharmacol* 1986; **6**: 375-376.
22. *FDA Briefing Document for Zeldox Capsules (Ziprasidone)*. New York: Pfizer Inc., 2000.
23. Lewis R, Bagnall A, Leitner M. Sertindone for schizophrenia. Cochrane Database System, rev. 2000, CD 001715. 2000.
24. Buckley NA, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. *Drug Saf* 2000; **23**: 215-228.
25. Mehtonen OP, Aranko K, Malkonen L, *et al*. A survey of sudden dea h associated wi h the use of antipsychotic or antidepressant drugs: 49 cases in Finland. *Acta Psychiatr Scand* 1991; **84**: 58-64.