

QT interval prolongation associated with sibutramine treatment

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Aims

To investigate a possible association of sibutramine with QT interval prolongation.

Methods

Post-marketing surveillance using prescription event monitoring in the New Zealand Intensive Medicines Monitoring Programme (IMMP) identified a case of QT prolongation and associated cardiac arrest in a patient taking sibutramine for 25 days. This patient was further investigated, including genotyping for long QT syndrome. Other IMMP case reports suggesting arrhythmias associated with sibutramine were assessed and further reports were obtained from the World Health Organisation (WHO) adverse drug reactions database.

Results

The index case displayed a novel mutation in a cardiac potassium channel subunit gene, *KCNQ1*, which is likely to prolong cardiac membrane depolarization and increase susceptibility to long QT intervals. Assessment of further IMMP reports identified five additional patients who experienced palpitations associated with syncope or presyncopal symptoms, one of whom had a QT_c at the upper limit of normal. Assessment of reports from the WHO database identified three reports of QT prolongation and one fatal case of torsade de pointes in a patient also taking cisapride.

Conclusions

This case series suggests that sibutramine may be associated with QT prolongation and related dysrhythmias. Further studies are required, but in the meantime we would recommend that sibutramine should be avoided in patients with long QT syndrome and in patients taking other medicines that may prolong the QT interval.

Introduction

Sibutramine (Meridia/Reductil, Abbott) is a serotonin and norepinephrine re-uptake inhibitor licensed worldwide for the management of obesity. The Associate Director of the Federal Drugs Authority's (FDA's) Office of Drug Safety has commented that sibutramine is one of five drugs currently on the market that may be endangering patients [1].

In March 2002 sibutramine was withdrawn from the market in Italy after two deaths from cardiovascular causes and 50 other adverse events, including tachycardia, other arrhythmias and hypertension [2]. Following this suspension, risk-benefit assessments were performed by several medicines regulatory authorities including Health Canada [3] and the FDA [4]. The European Committee for Proprietary Medicinal Prod-

ucts (CPMP) also reassessed sibutramine in June 2002, concluding that the risk-benefit ratio was favourable and marketing approval was subsequently re-instated [5].

The postmarketing safety of sibutramine is currently monitored by the New Zealand Intensive Medicines Monitoring Programme (IMMP). We present here a report of a patient who experienced a cardiac arrest shortly after starting sibutramine and was subsequently diagnosed with congenital long QT syndrome (LQTS). Additional case reports from the IMMP and from the World Health Organisation (WHO) international spontaneous reporting database that were used to further investigate this potential signal are also presented.

Methods

Setting

The New Zealand IMMP utilizes Prescription Event Monitoring (PEM) methodology pro-actively to study the safety of monitored medicines in postmarketing use [6]. Cohorts are established using prescription data obtained directly from pharmacies throughout the country [6, 7]. Collection of prescription data for sibutramine commenced on 1.02.01, when the medicine was first marketed in New Zealand. The cohort was closed on 31.3.04, by which time over 17 000 patients had received at least one prescription for sibutramine.

The IMMP obtains reports of adverse events from multiple sources, primarily from follow-up questionnaires sent to patients' doctors [6, 7], but also from prescription data, linkage to national mortality and morbidity databases, pharmaceutical company reports and spontaneous reports from health professionals. Following identification of the index case described below, all other cardiovascular events reported and assessed before 31.12.04 were identified from the IMMP database for sibutramine. At this time, follow-up of approximately 9500 patients in the cohort (prescriptions from 1.02.01 to 30.11.02) was in progress but not completed, with the remainder of the cohort (prescriptions from 1.12.02 to 31.03.04) not yet followed up.

Index case report

A 40-year-old Caucasian woman taking sibutramine 15 mg daily for 25 days was found collapsed, unresponsive and without a detectable pulse by her husband who successfully performed cardio-pulmonary resuscitation. On arrival at the emergency department a 12-lead ECG revealed atrial fibrillation with a ventricular rate of 80 beats min^{-1} . The QT interval appeared prolonged but was difficult to determine precisely as the ST segments were very flat.

Atrial fibrillation resolved spontaneously and subsequent ECGs detected sinus rhythm with marked QT prolongation with a heart rate corrected QT interval ($QT_c = QT/vR-R$ interval) of 0.60 s (Figure 1). Drug-induced QT prolongation was suspected and sibutramine was discontinued. Echocardiography, serum electrolytes and coronary angiography were normal. However, since the QT interval remained prolonged congenital LQTS was suspected. An intracardiac defibrillator was placed and nadolol was commenced. The patient progressed well and following discharge there have been no further cardiac events. Two years later her QT_c is normal (0.44 s).

Several months prior to this episode the patient saw a cardiologist because of palpitations. She had no family history of LQTS, syncope or sudden death in the young. A 12-lead ECG performed at that time was reported as normal, but in fact showed mild QT_c prolongation (0.50 s).

Genetic screening of index case for LQTS

The coding regions and intronic splice sites of five genes associated with channelopathy-onset LQTS (*KCNQ1*, *HERG*, *SCN5A*, *KCNE1* and *KCNE2*) were screened for mutations in the above patient and her siblings. The genes were analysed using Transgenomics dHPLC and ABI 3100 sequencing technology.

Assessment of further IMMP reports

All clinical events reported to the IMMP for monitored medicines are coded by clinical assessors, using terms from a dictionary based on WHOART [7]. In order to identify any reports suggesting QT prolongation or other arrhythmias associated with sibutramine, all case reports with events coded as 'circulatory collapse', 'syncope', 'dizziness/faintness', 'chest pain/tightness', 'angina', 'palpitations', 'tachycardia' and all other arrhythmias were reassessed.

Identification of other reports from international databases

The database of the WHO Uppsala Collaborating Centre for International Drug Monitoring (UMC) was searched for 'heart rate and rhythm disorders' (system organ class 1030 in WHOART) associated with sibutramine. High-level terms searched included 'arrhythmia' 'fibrillation cardiac', 'heart block', 'tachycardia' (includes the preferred terms 'palpitation', 'ventricular tachycardia' and 'supraventricular tachycardia' and 'torsade de pointes') with the additional preferred terms 'QT prolonged', 'bradycardia' and 'cardiac arrest'. For all reports with the event 'QT prolonged' or 'torsade de pointes' the case report was obtained and a

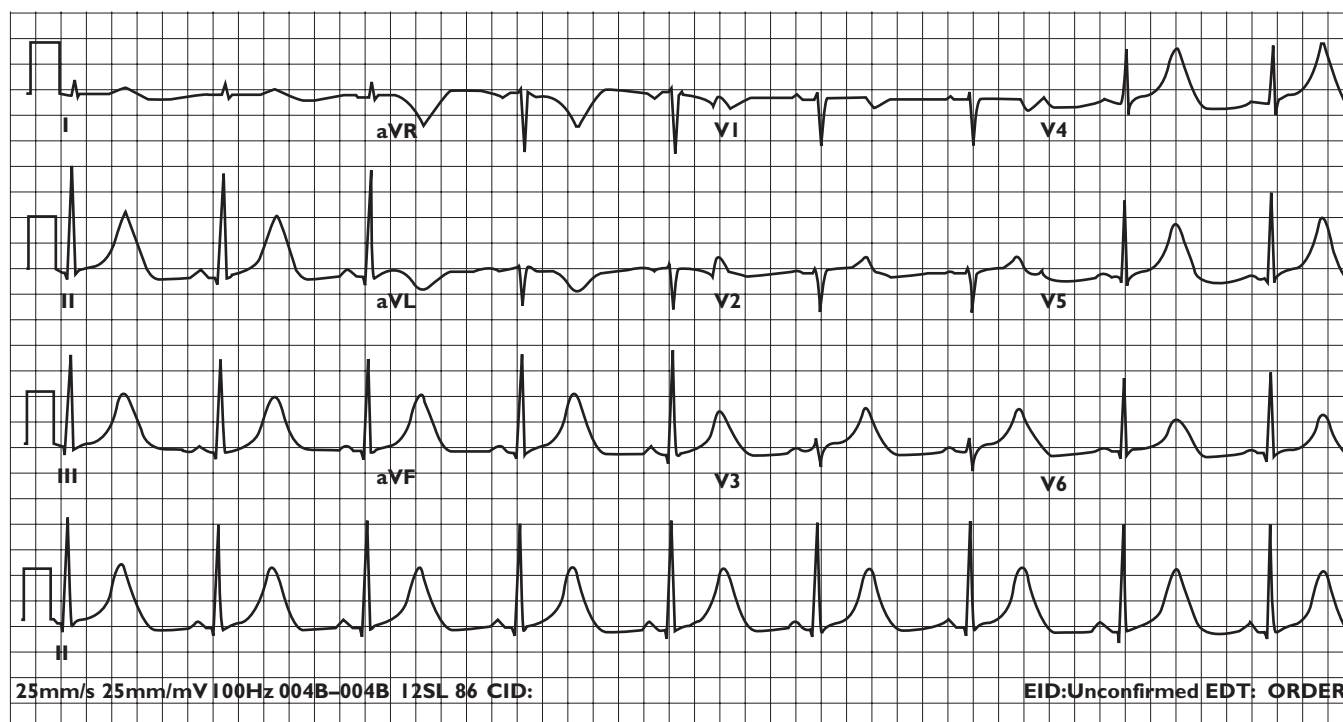


Figure 1

12 lead ECG taken 1 week after AC's cardiac arrest. This shows sinus rhythm with a very large broad-based T-wave (typical of long QT type 1), and a long QT interval. The QT interval is 0.64 s, R–R interval 1.15 s, giving a heart rate corrected QT interval (QT_c) of 0.60 s using Bazett's formula ($QT/\text{square root R–R interval}$) and 0.61 s using Fridericia's formula ($QT/R\text{--}R\text{ interval}/3$). The upper limit of normal for QT_c in an adult female is 0.47 s

causality assessment [8], using information available on outcome, date of reaction onset, dates of treatment, action taken and outcome of dechallenge, was performed to assess the strength of the association with sibutramine. Only those where there was sufficient information to classify the relationship as 'possible' or 'probable' were included.

Results

Genetic screening of index case for LQTS

A mutation was identified in the patient (and subsequently her children) in a potassium channel subunit gene, *KCNQ1* (c793t) causing a novel and previously undescribed T265I amino acid substitution (Figure 2A) in the *KCNQ1* polypeptide sequence. This mutation resulted in the gain of a *MamI* restriction site that was not detected in 192 control chromosomes by restriction fragment length polymorphism (RFLP) testing (Figure 2B). Mutations in this gene cause the LQTS type 1 phenotype and the discovery of the T265I mutation has facilitated the extended testing of affected and unaffected family members. The segregation of *KCNQ1* T265I was consistent with ECG-associated LQTS.

Further IMMP reports

A further 65 reports were identified and reassessed. In this group, the most frequent events reported were those already identified in the product information [9]. These were palpitations (26 cases), dizziness/faintness (20), and tachycardia (10). Of the 26 cases of palpitations, five were associated with syncope or presyncopal symptoms and three of these patients developed symptoms within 14 days of starting sibutramine (time to onset was not reported for two cases). One patient was referred for an exercise ECG (performed 1 month after stopping sibutramine), which revealed a QT_c of 0.47 s, which is at the upper limit of normal for a female. A cardiologist advised that this patient should not take medicines that prolong the QT interval. There was no ECG information for the other four patients.

Of the remaining nine cases in the group of 65 reports, six reported chest pain/tightness or angina and one of these patients was also reported to have tachycardia. Further reports included a case of circulatory collapse in a patient who was investigated in hospital (and recovered) but in whom no cause was identified, a case of supra-ventricular tachycardia (SVT) which occurred 7 days after starting sibutramine and a patient

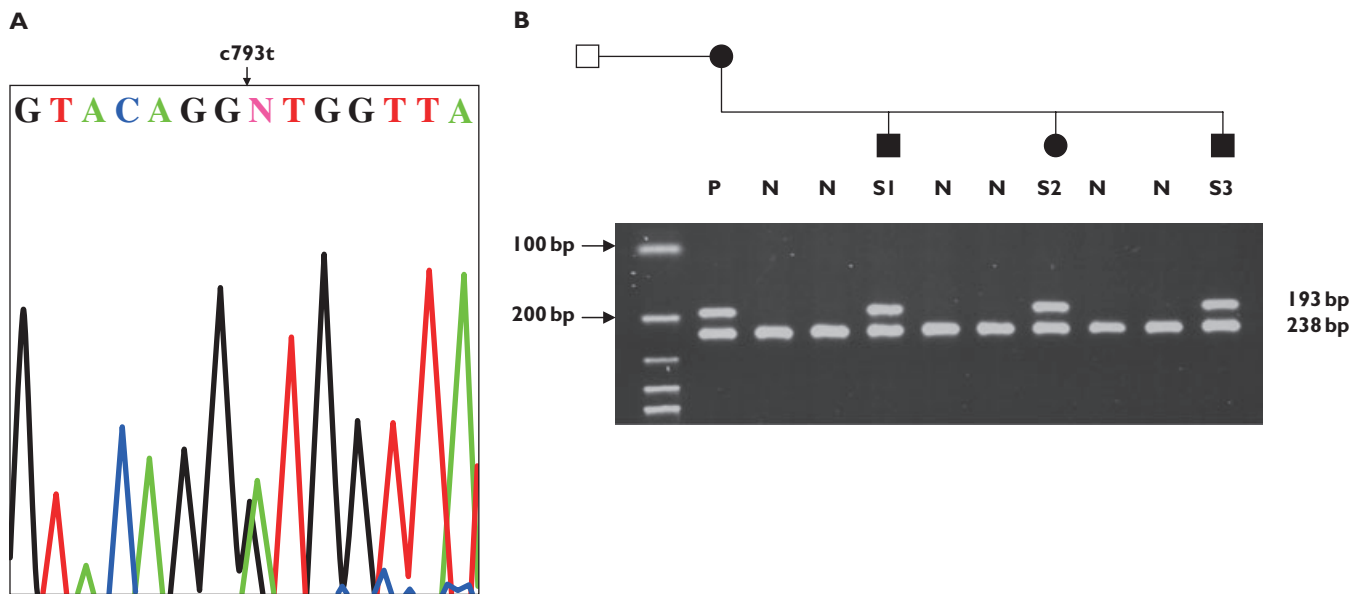


Figure 2

(A) Sequencing (reverse) of *KCNQ1* exon 6. This reveals a C→T at position 793 of the cDNA in the index patient. This results in a substitution of threonine with isoleucine at position 265 of the polypeptide sequence and is located in the S5 domain of the subunit protein. (B) An RFLP assay for *KCNQ1* c793t. This demonstrates that *Mam1* is an effective restriction enzyme for this sequence change. The patient (P) and three siblings (S1-S3) with the mutation are inter-dispersed with two control samples (N). The presence of *KCNQ1* c793t creates a novel *Mam1* site generating a 193bp fragment that is not detected in control samples

who experienced ventricular ectopic beats whilst taking sibutramine.

Identification of further reports from the WHO-UMC

Regarding the high level terms, there were 41 reports of arrhythmia, 43 reports of cardiac fibrillation (five of these were ventricular fibrillation), eight reports of heart block and 500 reports of tachycardia, of which four were ventricular tachycardia, 23 were SVT and one was torsade de pointes. In addition, there were three reports of QT prolongation and 21 reports of cardiac arrest.

Review of the three reports of QT prolongation from the WHO database identified a 38-year-old woman diagnosed with prolonged QT 61 days after starting sibutramine, a 48-year-old woman who developed ventricular fibrillation, but recovered 35 days after starting this medicine and a 13-year-old boy diagnosed with QT prolongation 1 year after starting sibutramine. There was also one fatal case of torsade de pointes identified in a 50-year-old woman (also taking cisapride) 29 days after starting sibutramine.

Discussion

We identified an index case report of cardiac arrest and profound QT prolongation in a patient taking sibutramine, who was subsequently diagnosed with hereditary

LQTS. We also examined other postmarketing case reports in order to identify any further cases of QT prolongation or associated arrhythmias in patients taking this medicine. From reports to the New Zealand IMMP, we identified another patient who experienced palpitations and syncope and displayed a QT interval at the upper limit of normal. From the WHO database we identified a further three reports of QT prolongation associated with sibutramine and an additional fatal case of torsade de pointes in a patient taking sibutramine and cisapride.

The index case was gene-positive for a novel *KCNQ1* T265I mutation, putatively conferring a predisposition to LQTS. In the absence of supportive electrophysiological data, mutational pathogenicity is suspected due to the exclusion of T265I from the normal control population and segregation of the mutation within family members revealing signs of LQTS. More suggestive evidence is provided by other S5 domain *KCNQ1* amino acid substitutions that are consistently associated with several LQTS families, revealing functional significance in relation to K⁺ pore selectivity and inactivation [10]. Despite the patient's genetic predisposition, her QTc was much shorter before and after the episode of cardiac arrest. It is therefore possible that sibutramine triggered an arrhythmia leading to her cardiac arrest, through pro-

longation of the QT interval. This presentation fits best with rapid ventricular tachycardia or torsade de pointes. After the event, she was haemodynamically stable with atrial fibrillation for a few hours, which was most likely a consequence of her cardiorespiratory collapse rather than the cause.

Sibutramine has a similar pharmacological action to some other QT-prolonging drugs such as tricyclic antidepressants in inhibiting neuronal norepinephrine and serotonin uptake [11]. Lists of drugs that prolong QT may be found in the literature [12, 13], standard texts [14] and internet sites [15] that are updated as new examples emerge. Many of these drugs can affect cardiac K^+ channels, mostly by blocking I_{Kr} or I_{Ks} currents and causing prolonged repolarization [12]. Although most drugs that are associated with an increase in QT_c block I_{Kr} channels, in recent years an increasing number of drugs that prolong QT_c have been found to actively block I_{Ks} channels [12]. With drugs similar to tricyclic antidepressants, which increase synaptic neurotransmitter concentrations, this may be augmented partly by regulation of action potential duration (APD) through an increase in sympathetic neurotransmission [16].

Hu and colleagues previously demonstrated that sibutramine and dexfenfluramine inhibit I_{Ks} currents in rat lingual taste cells [17]. In their study Hu *et al.* also tested dexfenfluramine on rat cardiac myocytes and demonstrated inhibition of I_{Ks} currents in these cells. If sibutramine also inhibits I_{Ks} currents in cardiac myocytes, this would suggest a potential mechanism for prolonging the QT interval and triggering an arrhythmia in LQTS-susceptible individuals.

The additional case reports identified provide supporting evidence for an effect of sibutramine on the QT interval, although this type of postmarketing data has limitations. Whilst we had full clinical details for the index case, this was not available for most of the other cases identified. The amount of information collected by the IMMP for each patient is dependent on how much detail each reporting doctor provides, but does not routinely include ECG or genotyping data. The WHO database contains summary reports received from national monitoring centres and full clinical details are not always provided. Further, the data are not homogenous with respect to origin or likelihood that the product caused the reaction. Although causality assessments have usually been performed based on the information provided to each national centre [8], for all the cases of QT prolongation/torsade de pointes identified in our search we performed further assessments on the data provided and only include reports where a causal relationship with sibutramine is at least possible.

Other limitations of postmarketing surveillance methods for examining this type of potential adverse event are under-reporting and under-detection of the effect. Under-reporting of adverse reactions to medicines is a well-recognized problem, although the methods used by the IMMP attempt to at least partially address this by proactive identification of reports from multiple sources [6, 7]. Identifying cases of long QT associated with medicines by postmarketing surveillance methods is particularly difficult as this adverse event cannot be diagnosed without ECG evidence. Therefore, some asymptomatic patients with this abnormality and others presenting with clinical symptoms (e.g. palpitations and syncope) may remain elusive if ECGs are not performed.

The IMMP case reports presented in this paper cannot be used to calculate the incidence of cardiovascular events associated with sibutramine because follow-up of the cohort is not yet complete. Although we intend to perform analyses of incidence in due course, presentation of case reports at this stage of the monitoring is useful in identifying previously unidentified adverse reactions to medicines ('signal detection').

Sibutramine has not been associated with long QT in the published literature, but interestingly, it is included in a recognized list of drugs that prolong the QT interval and/or induce torsades de pointes. This list states that the drugs included should be avoided by patients with congenital LQTS [15].

We conclude that the case reports presented here suggest that sibutramine may prolong the QT interval in some patients. This may result in potentially fatal arrhythmias in patients with LQTS or in those taking other medicines known to trigger long QT. Further studies are required to investigate this further, but until these have been performed we would suggest that sibutramine be avoided in patients with LQTS and in patients taking medicines that prolong the cardiac QT interval.

Conflict of interest statement: There are no conflicts of interest for any of the authors.

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