Sibutramine-Associated QT Interval Prolongation and Cardiac Arrest

David Ernest, Alexander Gershenzon, Carmela E Corallo, and Ramesh Nagappan

OBJECTIVE: To report on a probable association between sibutramine and QT interval prolongation leading to ventricular fibrillation and cardiac arrest.

CASE SUMMARY: A previously well 51-year-old woman with obesity but no other relevant past medical history or cardiac risk factors was prescribed sibutramine (initial dose 10 mg daily, increased to 15 mg daily after 10 wk). Four months after initiation of therapy, the woman developed ventricular fibrillation and was successfully resuscitated. On admission, an electrocardiogram (ECG) demonstrated sinus tachycardia without any ischemic changes and a prolonged QTc interval (545 msec). A subsequent coronary angiogram revealed normal coronary arteries and no other abnormalities. Her QTc interval returned to normal (432 msec) by day 2 and remained within normal limits (<440 msec) thereafter. Due to a favorable neurologic recovery and the absence of any cardiac structural abnormality, the patient was readmitted for implantation of an automatic implantable cardioverter-defibrillator on day 35 and remained well from a cardiac and neurologic standpoint at a 2-year follow-up examination.

DISCUSSION: Sibutramine acts centrally to inhibit noradrenaline, dopamine, and serotonin reuptake, thereby sharing similar actions of other QT interval–prolonging drugs. Therefore, sibutramine might be anticipated to also share a tendency to QT interval prolongation. The current prescribing information for sibutramine does not specifically list any precautions or adverse reactions related to QT interval prolongation. QT interval prolongation associated with sibutramine in this case is considered probable based on the Naranjo probability scale.

CONCLUSIONS: Clinicians prescribing sibutramine should monitor their patients for ECG abnormalities and be cautious in coprescribing drugs known to prolong the QT interval.

KEY WORDS: cardiac arrest, QT interval, sibutramine, ventricular fibrillation.

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Sibutramine acts centrally to inhibit noradrenaline, dopamine, and serotonin reuptake as well as peripherally to increase metabolic rate and thermogenesis. Licensed for use worldwide, sibutramine has been shown to produce modest weight loss, but adverse cardiovascular effects are a potential source of concern.[1] Postmarketing adverse reactions include arrhythmias, myocardial infarction, cardiac arrest,[2] and QT interval prolongation.[3] We report on a patient taking sibutramine who suffered near-fatal cardiac arrest from ventricular fibrillation associated with QT interval prolongation.

Case Report

A previously well 51-year-old woman who had recently been prescribed sibutramine for obesity collapsed while attending a social function. Her prior medical history included mild asthma, controlled with intermittent albuterol and regular fluticasone 250 µg/salmeterol 25 µg metered-dose inhalers, and menorrhagia, treated with levonorgestrel 125 µg/ethinylestradiol 50 µg. Sibutramine had been started 4 months prior to her presentation. The starting sibutramine dose was 10 mg daily, which was increased to 15 mg daily after 10 weeks. There was no past history or family history of any cardiac disorder, and she had never had an electrocardiogram (ECG) recorded.

Immediately prior to her collapse, the woman reported being "hot and unwell," with no chest pain, shortness of breath, or palpitations; she subsequently become pale and pulseless. Cardiopulmonary resuscitation was started immediately, and her initial rhythm was ventricular fibrillation, which reverted following cardioversion to a slow junctional rhythm with no output. Continued resuscitation included intubation and administration of epi-

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nephrine 4 mg (in 1-mg increments) and 1000 mL of cold lactated Ringer's solution to induce hypothermia. The time to return of spontaneous circulation was 26 minutes.

On admission to an emergency department, the woman was sedated and ventilated. Vital signs were temperature 35.1 °C, pulse 140 beats/min, and blood pressure 180/100 mm Hg; there were no abnormal cardiovascular findings. Relevant initial investigation revealed electrolyte levels and renal function within normal limits (serum potassium 4.0 mEq/L, reference range 3.5–5.0; serum magnesium 1.70 mEq/L, reference range 1.40–2.20), and troponin T 0.07 ng/mL (normal <0.03). An ECG showed sinus tachycardia and a prolonged QTc interval (545 msec), without any ischemic changes.

The patient was subsequently transferred to an intensive care unit for ongoing management. She remained hemodynamically stable. On day 2, a transthoracic echocardiography examination revealed mild concentric left ventricular hypertrophy with normal systolic function and no valvular abnormalities, an ECG showed sinus rhythm with a normal QTc interval (432 msec) without evidence of ischemic changes, and the serum troponin T level peaked at 0.34 ng/mL.

Hypothermia was induced to a temperature of 33 °C for 24 hours and supportive treatment was administered for 5 days before the woman showed features of neurologic recovery. During this period, she had frequent myoclonic jerking and investigations included a computed tomography scan of her brain, which was normal, and an electroencephalogram, which demonstrated features of moderately severe diffuse encephalopathy. A subsequent magnetic resonance imaging brain scan did not reveal any features of hypoxic cerebral injury. The patient was extubated on day 10 and discharged for ongoing neurologic rehabilitation.

Metoprolol and aspirin were started, and further cardiac investigation included serial ECGs that remained within normal limits (QTc interval <440 msec) other than a first-degree heart block and a coronary angiogram that revealed normal coronary arteries and a normal ejection fraction. An incidental diagnosis of hypothyroidism was made on the basis of an elevated serum thyroid-stimulating hormone TSH level (17.8 mIU/L; reference range 0.27–4.20), which fell to 0.78 mIU/L after oral thyroxine replacement therapy was initiated on day 2. Sibutramine, which was ceased on admission, was not reinitiated.

In view of the woman's favorable neurologic recovery and the absence of any cardiac structural abnormality, she was readmitted for implantation of an automatic implantable cardioverter-defibrillator on day 35. She remained well from a cardiac standpoint and was noted to have persisting dyskinetic movements and a jerky gait at a 2-year follow-up review.

Discussion

Our case report highlights a probable association between the use of sibutramine and QT interval prolongation, ventricular fibrillation, and cardiac arrest. In our patient, there were no apparent alternative risk factors for this life-threatening arrhythmia, and subsequent cardiac investigation failed to identify any evidence of coronary artery disease, cardiomyopathy, or valvular heart disease. It is noteworthy that our patient had evidence of QT interval prolongation (545 msec) on her initial ECG that resolved promptly with discontinuation of sibutramine.

The Naranjo probability scale showed a probable association between use of sibutramine and QT interval prolongation in this patient on the basis of (1) previous conclusive reports of QT interval prolongation associated with sibutramine, (2) the appearance of this effect after administration of the drug, (3) the absence of alternative factors that could have caused the reaction on their own, and (4) the possibility that the reaction was more severe when the dose was increased.[4]

Sibutramine acts centrally to inhibit noradrenaline, dopamine, and serotonin reuptake and peripherally to increase metabolic rate, thermogenesis, and energy expenditure by stimulating β_3-adrenergic receptors. Initial post-marketing surveillance reports linked sibutramine with a wide spectrum of adverse events, most notably cardiovascular events including increased blood pressure, chest pain, arrhythmias, and stroke.[5] Such reports led to the drug being temporarily withdrawn from the market in Italy in 2002 after 50 reported adverse reactions, including 2 deaths from cardiac arrest, with additional reports of 2 deaths in the UK, 10 serious adverse events in France, 397 adverse events in the US (143 cardiac arrhythmias, 19 cardiovascular deaths), and 28 adverse reactions in Canada.[2] A subsequent independent review by the European Committee for Proprietary Medicinal Products concluded that the risk-benefit profile of the drug remained positive and that clinicians could continue using it in clinical practice.[6]

A search of the database of the Australian Therapeutic Goods Administration's Adverse Drug Reaction Advisory Committee from June 2002 to June 2006 revealed 138 reports concerning 404 adverse reactions, predominantly nervous system (62), psychiatric (50), gastrointestinal (33), cardiac (31), vascular (26), and respiratory (15).[7] Within the reported cardiovascular events, sibutramine was the sole suspected drug in 27 cases and involved 11 cases of arrhythmia (including 1 case of ventricular fibrillation and cardiac arrest [the subject of this case report]), 9 cases of palpitations, 4 cases of chest pain (including 1 case of myocardial infarction), and 8 reports of hypertension.

While there appears to have been substantial reports of adverse cardiovascular events related to sibutramine to various regulatory authorities, a MEDLINE search up to

February 2008 showed only a few cases reported in the literature. The SCOUT (Sibutramine Cardiovascular Outcomes) trial found that treatment with sibutramine 10 mg/day was tolerated well by obese and overweight subjects with a high risk of cardiovascular events (history of coronary artery disease, peripheral arterial occlusive disease, cerebrovascular disease [stroke or transient ischemic attack], hypertension, diabetes).[8] Of the 15 (0.1%) subjects who died in that study, 10 deaths were attributed to a cardiovascular cause; this incidence was considered to be comparable to that in the placebo arms of similar studies with equivalent study populations. Recently, however, the use of sibutramine has been reported to be associated with the development of reversible cardiomyopathy,[9] QT interval prolongation,[3] and myocardial infarction.[10]

Harrison-Woolrych et al.[3] described a 40-year-old female with a congenital susceptibility to QT interval prolongation who sustained cardiac arrest 25 days after starting sibutramine 15 mg daily. Similar to our patient, their patient was treated with an automatic intracardiac cardioverter-defibrillator and was noted to have a normal QTc interval (440 msec) 2 years later. In addition, those authors searched the World Health Organization's international spontaneous reporting database (postmarketing surveillance) and identified 3 further reports of QT interval prolongation associated with sibutramine and an additional fatal case of torsade de pointes in a patient also taking cisapride.

With sibutramine's inhibition of noradrenaline, dopamine, and serotonin reuptake, it shares similar actions with other QT interval–prolonging drugs and therefore might be anticipated to also have a tendency to produce QT interval prolongation. The current prescribing information for sibutramine does not specifically list any precautions or adverse reactions related to QT interval prolongation,[11] whereas specific interest resources do list sibutramine as a drug to be avoided in patients with diagnosed or suspected congenital long QT interval syndrome.[12]

A potentially confounding variable in relation to our patient's apparent transient QT interval prolongation is the intercurrent diagnosis of hypothyroidism. While an association between hypothyroidism and QT interval prolongation has been described in the literature,[13] the same authors reported similar changes in patients with hyperthyroidism,[14] with identical baseline QTc interval values of 434 msec in each group, 20 msec greater than in the control group. Other investigators have described a decrease in QTc interval from a mean of 434 msec to 417 msec in hypothyroid patients treated with L-thyroxine.[15] Thyroid function does not seem to have played a role in our case, as the patient's QTc interval returned to a normal value after sibutramine was stopped and before thyroxine replacement therapy was started.

Conclusions

Our report of a probable association between sibutramine and QT interval prolongation leading to ventricular fibrillation should alert clinicians prescribing sibutramine to monitor their patients for ECG abnormalities. In addition, clinicians should be cautious when coprescribing drugs known to prolong the QT interval, such as tricyclic antidepressants, some typical and atypical antipsychotic agents, and certain antiarrhythmic agents. This adverse drug reaction of QT interval prolongation is assessed as probable based on the Naranjo probability scale. Moreover, our case highlights the ongoing requirement to undertake suitable postmarketing surveillance to identify clinically important but infrequent adverse events that may not be identified during the preapproval safety and efficacy trials.

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Sibutramina Asociada a la Prolongación del Intervalo QT y Arresto Cardíaco

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EXTRACTO

OBJETIVO: Reportar una asociación probable entre sibutramina y la prolongación del intervalo QT causando una fibrilación ventricular y arresto cardíaco.

RESUMEN DEL CASO: Una mujer de 51 años de edad previamente en buen estado de salud con obesidad pero sin historial médico pasado relevante o factores de riesgo cardíacos, quien había comenzado hace 4 meses en terapia de sibutramina (dosis inicial 10 mg diario, aumentado a 15 mg diario después de 10 semanas); desarrolló fibrilación ventricular de la cual fue resucitada exitosamente. Cuando fue admitida al hospital su electrocardiograma (EKG) mostraba taquicardia sinusal sin presentar cambio isquémico y una prolongación del intervalo QTc (545 msec). Un angiograma coronario subsiguiente reveló que las arterias coronarias estaban en estado normal y no había otras anormalidades. En el segundo día, el intervalo QTc regresó a la normalidad (432 msec y después se mantuvo dentro de los límites normales (QTc < 440 msec). Debido a que tuvo una recuperación neurológica favorable y ausencia de anormalidades en las estructuras cardíacas, la paciente fue readmitida para la implantación de un Desfibrilador Automático Cardio-vertidor el día 35 y se mantuvo bien desde el punto de vista cardíaco y neurológico por 2 años de seguimiento.

DISCUSIÓN: Sibutramina actúa a nivel central inhibiendo la entrada de noradrenalina, dopamina, y recaptación de serotonina; por esta razón comparte acciones similares a otras medicinas que prolongan el intervalo QT. Por esta razón se podría anticipar que sibutramina también comparte la tendencia de prolongar el intervalo QT. La información actual para recetar sibutramina no contiene un listado específico de reacciones adversas o precauciones relacionadas a la prolongación del intervalo QT. La información sobre reacciones adversas relacionadas con la prolongación del intervalo QT se evaluó con el uso de la Escala de Probabilidad del Naranjo para reacciones adversas y determinó que era probable.

CONCLUSIONES: El caso que reportamos describe una probable asociación entre sibutramina y la prolongación del intervalo QT como causantes de fibrilación ventricular y se debe alertar a los médicos que prescriben sibutramina, para monitorear a sus pacientes verificando anormalidades en el electrocardiograma y que tengan precaución al recetar otros medicamentos que prolongan el intervalo QT.

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Allongement de l'Intervalle QT et Arrêt Cardiaque liés à l'Utilisation de la Sibutramine

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RÉSUMÉ

OBJECTIF: Décrire une association probable entre la sibutramine et la prolongation de l'intervalle QT ayant causé de la fibrillation ventriculaire et un arrêt cardiaque.

SOMMAIRE DU CAS: Une femme de 51 ans se portant bien mais obèse et sans antécédents médicaux ou facteurs de risque cardiaque a reçu de la sibutramine. Après 4 mois de traitement (dose initiale 10 mg par jour, augmentée à 15 mg par jour après 10 semaines), la femme a présenté de la fibrillation ventriculaire pour laquelle une réanimation a été faite avec succès. Lors de l'admission à l'hôpital, on pouvait remarquer sur l'électrocardiogramme une tachycardie sinusale sans manifestations ischémiques et un prolongement de l'intervalle QT (545 msec). Ultérieurement, un angiogramme coronarien a montré des artères coronariennes normales et aucunes autres anomalies. L'intervalle QT est revenu à la normale au jour 2 (432 msec) et est demeuré dans les limites normales ensuite (QTc <440 msec). En raison d'une récupération neurologique favorable et en l'absence d'anormalité structurelle cardiaque, la patiente a été réadmise au jour 35 pour l'implantation d'un défibrillateur cardioverteur interne (DCI); 2 ans après l'intervention, la patiente ne présentait pas de troubles cardiaques ou neurologiques.

DISCUSSION: La sibutramine agit au niveau du système nerveux central par inhibition de la recapture de la noradrénaline, de la dopamine et de la sérotonine, mécanisme d'action similaire à celui d'autres médicaments provoquant un allongement de l'intervalle QT. C'est pourquoi on peut s'attendre à observer un allongement de l'intervalle QT lié à l'utilisation de ce médicament. L'information disponible sur les précautions à prendre et les effets indésirables liés à la prescription de la sibutramine ne mentionne en aucun temps la prolongation de l'intervalle QT. Selon l'échelle de probabilité d'effet indésirable médicamenteux de Naranjo, l'allongement de l'intervalle QT par la sibutramine est probable dans ce cas.

CONCLUSIONS: Ce rapport de cas décrit une association probable entre la sibutramine et la prolongation de l'intervalle QT, prolongation ayant causé une fibrillation ventriculaire. Les cliniciens prescrivant de la sibutramine à leurs patients devraient assurer un suvi étroit de la fonction cardiaque afin de déceler des anormalités et être prudents si le patient prend déjà un médicament connu comme pouvant prolonger l'intervalle QT.

Traduit par Denyse Demers