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Sotalol induced torsades de pointes precipitated during treatment with oseltamivir for H1N1 influenza

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Abstract

Background—Striking prolongation of the QT interval and the morphologically distinctive polymorphic ventricular tachycardia torsades de pointes can occur in patients treated with antiarrhythmic drugs and certain non-cardiovascular medications. However, there have been no reported cases of QT prolongation and torsades de pointes associated with the antiviral agent oseltamivir.

Objective—To determine whether exposure to oseltamivir is associated with increased risk of QT prolongation and torsades de pointes in patients treated for H1N1 influenza.

Methods—Two unusual case histories of patients exposed to oseltamivir who developed marked QT prolongation and torsades de pointes were examined.

Results—Two patients on stable doses of sotalol for atrial fibrillation developed marked QT prolongation and torsades de pointes following administration of the antiviral agent.

Conclusions—The recent H1N1 pandemic has necessitated treatment of suspected or confirmed cases of H1N1 influenza with oseltamivir. Although the precise mechanism for this drug-drug interaction is not clear, given the large number of people expected to receive oseltamivir this winter, it is important to highlight this potentially adverse event.

Keywords

Long QT syndrome; drug interaction; sotalol; oseltamivir; torsades de pointes; ventricular tachycardia; sudden death

Novel influenza A (H1N1) is a flu virus of swine origin that first caused human illness in Mexico and the United States in March and April of 2009. By June of 2009, all 50 states had reported cases of novel H1N1 infection.¹ On June 11, 2009, the World Health Organization (WHO) elevated the worldwide pandemic alert to Phase 6, indicating wide spread human to human transmission and recognition that H1N1 spread had reached pandemic proportions.² The WHO has recommended that antiviral agents, including oseltamivir, be used in the treatment of suspected or confirmed cases of H1N1 influenza in at risk patients, such as the

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very young, elderly, pregnant woman, immunosuppressed patients, and those with co-morbid conditions.

Oseltamivir is the preferred therapy for those who present with severe or progressive illness.³ With increased utilization of antivirals, including oseltamivir, previously undescribed drug-drug interactions and adverse events may emerge. We describe two recent cases of patients tolerating long-term sotalol who developed marked QT interval prolongation and required resuscitation from polymorphic ventricular tachycardia (torsades de pointes, TdP) during oseltamivir treatment for H1N1 influenza.

CASE HISTORIES

Case 1

A 79-year-old Caucasian female was admitted with one week of worsening abdominal discomfort and hematochezia. Her past medical history was significant for atrial fibrillation (AF) and hypertension, and she had been maintained on a stable dose of sotalol 40 mg twice daily for 4 months. Her other medications included aspirin 81 mg daily, warfarin, lisinopril, furosemide, potassium chloride, calcium, lecithin, glucosamine, and a multivitamin. Vital signs and physical examination performed in the emergency department were unremarkable. Her admission laboratory values included a white blood cell count of 17,100/ μ L, hematocrit 34%, potassium 3.6 mEq/L, serum creatinine 1.0 mg/dL, and INR of 2.7. A diagnosis of ischemic colitis was established and she was treated conservatively with interruption of anticoagulation and observation. She remained hemodynamically stable and required no blood transfusions. Electrocardiogram (ECG) on hospital day 3 showed sinus rhythm and a QT interval of 400 msec, with a corrected QT interval (QTc) of 460 msec (Figure 1, top panel). Her potassium at the time of that ECG was 3.1 mEq/L. Her hospitalization was complicated by dyspnea, hypoxemia, and bilateral chest infiltrates requiring endotracheal intubation and mechanical ventilation on hospital days 3–6. Bacterial cultures were unrevealing, and diagnostic testing for influenza type A was positive (presumed H1N1 on clinical grounds). She was treated with oseltamivir 75 mg twice daily (hospital days 5–10). Other medications were ceftriaxone 1g Q24H (hospital day 3), vancomycin 1g Q24H (hospital days 4–6), cefepime 1g Q6H (hospital days 4–7), doxycycline 100 mg Q12H (hospital days 5–6), famotidine 20 mg twice a day (throughout hospitalization), furosemide (various doses intermittently), and ondansetron 4mg IV (seven doses over days 2–9). ECG on hospital day 9 (day 4 of oseltamivir) showed a QT of 480 msec and a QTc of 550 msec. The potassium at the time of this ECG was unchanged at 3.1 mEq/L. Her respiratory status improved and anticoagulation was re-instituted. She was discharged home on hospital day 14, but was readmitted within 24 hours for recurrent gastrointestinal bleeding

On hospital day 16 (day 2 of her second admission), she developed typical TdP treated with defibrillation (Figure 1, middle panel). Post-resuscitation ECG showed sinus bradycardia with a QTc of 670 msec (Figure 1, lower panel). The potassium prior to the event was 3.1 mEq/L and 3.0 mEq/L afterwards, similar to values observed the previous week. Sotalol was discontinued and the patient was treated with magnesium, potassium, and transvenous pacing. She had no further disturbances in cardiac rhythm.

Case 2

A 63-year old Caucasian woman was admitted after one week of fever to 102°F, nausea, vomiting, malaise, myalgias, and dry cough. She had a history of nonischemic dilated cardiomyopathy, felt to be secondary to chronic alcohol use that had remarkably improved after a year of abstinence. An echocardiogram performed 1 week prior to admission was significant for a left ventricular ejection fraction of 55% with only trace mitral regurgitation.

She also had a history of paroxysmal AF, had been maintained on a stable dose of sotalol 80 mg twice daily for a year. On admission, she was febrile (99.3°F) and tachycardic (heart rate 116), with oxygen saturations of 96% on room air; the lung examination was normal. A urinalysis was consistent with a urinary tract infection. Serum potassium was 4.1 mEq/L. A few months prior to admission, chronic thyroid replacement therapy was discontinued due to persistently elevated thyroid stimulating hormone level (0.12 mcU/mL (reference range: 0.3–5.0 mcU/mL)) with a free T4 of 1.67 ng/dL (0.5–1.2). Chest x-ray did not demonstrate a focal infiltrate. On admission, her QT interval was 436 ms with a QTc of 506 ms (Figure 1, top panel).

She was treated with ampicillin/sulbactam for pyelonephritis and with empiric oral oseltamivir, 75 mg twice a day for presumed influenza. On hospital day 4, about two hours following her 6th dose of oseltamivir, she was found unresponsive. The initial rhythm was ventricular fibrillation, and with multiple shocks and intravenous magnesium, sinus rhythm was restored. Serum potassium was unchanged (4.1 mEq/L). An ECG performed revealed a QT interval of 460 ms with a QTc of 521 ms (Figure 2, middle panel). Sotalol was discontinued, and a search of the patient's records revealed no other medications with a recognized risk of QT prolongation. That night, now in a setting with continuous cardiac monitoring, the patient developed typical symptomatic TdP on two occasions (Figure 2, bottom panel), responding to intravenous magnesium and external defibrillation. QT interval on a follow-up ECG was 480 ms (rate-corrected 598 ms). Oseltamivir was discontinued. Her QT interval gradually shortened, and there were no further cardiac arrests.

COMMENT

Striking prolongation of the QT interval and the morphologically distinctive polymorphic ventricular tachycardia TdP can occur in up to 1–8% of patients treated with certain antiarrhythmic drugs, including sotalol.^{4–7} This adverse drug reaction also occurs with a range of drugs not used for cardiovascular indications including certain antibiotics, antipsychotics, and antihistamines.⁸ The recent H1N1 pandemic has necessitated treatment of suspected or confirmed cases of H1N1 influenza with oseltamivir. The cases we describe implicate addition of oseltamivir to sotalol as combined triggers for TdP.

To date, no human studies report adverse effects on the QT interval in humans taking oseltamivir. Reports of oseltamivir safety data, including dose escalation studies specifically addressing effects on QT, have not revealed any effect on QT,⁹ and the drug has no reported effect on I_{Kr} , the potassium current whose inhibition underlies most cases of drug-induced TdP. Thus, a direct QT prolonging effect of oseltamivir in the above cases seems unlikely. Both sotalol and oseltamivir are eliminated by glomerular filtration as well as renal secretion. However, oseltamivir is secreted via the probenecid sensitive organic anion transporter while sotalol appears to be secreted via the cimetidine sensitive organic cation transporter,¹⁰ arguing against competitive inhibition of secretion as a potential mechanism. It is also possible that H1N1 infection exerted a direct effect on cardiac repolarization that became manifest in patients receiving sotalol. Thus, the precise mechanism for this drug-drug interaction is not clear.

We cannot invoke a direct drug-drug interaction between oseltamivir and sotalol in Case 1 with the patient developing torsades de pointes many days after the antiviral agent was discontinued. However, it is important to note that the combination of oseltamivir, hypokalemia and sotalol did markedly prolong the QTc interval in this patient. Although the precise trigger for the torsades de pointes in Case 1 is unclear, it is possible that the effects of oseltamivir on sotalol excretion by an undefined mechanism may have persisted for some days after discontinuation

of the drug and the combination of bradycardia and hypokalemia may have precipitated the torsades de pointes.

An important limitation is that these are sick patients with hypokalemia noted in at least case, and we cannot completely eliminate hypokalemia as an important contributing factor. Nevertheless, given the large number of patients expected to receive oseltamivir this winter, it is important to highlight this potentially fatal drug interaction among patients receiving apparently well-tolerated therapy with sotalol and perhaps other drugs known to have QT-prolonging potential.

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Figure 1.

Electrocardiograms recorded from patient one. Top panel: ECG taken on hospital day 3 before initiation of oseltamivir showing a normal QT interval of 400 ms ($QT_c = 460$ ms); middle panel: episode of torsades de pointes recorded after patient was readmitted to hospital with a gastrointestinal bleed and bottom panel: ECG obtained post resuscitation showing marked QT prolongation at 670 msec ($QT_c = 670$ ms).

Figure 2.

Electrocardiograms recorded from patient 2. Top panel: ECG taken on admission showing a QT interval of 436 ms with a QTc of 506 ms; middle panel: ECG performed after resuscitation from ventricular fibrillation arrest revealed a QT interval of 460 ms but the QTc was prolonged (521 ms) and bottom panel: episode of torsades de pointes recorded after successful resuscitation from a VF arrest showing typical short-long-short sequence typical for drug induced long QT syndrome.