QTc Prolongation During Concurrent Treatment with Depot Antipsychotics and High-dose Amisulpride: A Report of 2 Cases

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Abstract

Antipsychotic drugs may cause prolongation of the heart rate-corrected QT interval (QTc). Amisulpride, a relatively new atypical antipsychotic drug, has been considered to have few cardiac adverse effects, except in cases of overdose. We report 2 schizophrenic patients with no history of cardiac disease who developed significant QTc prolongation after concurrent use of intramuscular depot injections of typical antipsychotics and high-dose amisulpride. A 37 year-old woman, had no known history of arrhythmia. Previous exposure to flupenthixol decanoate had not resulted in cardiotoxicity. She was treated with weekly depot injections of flupenthixol and with amisulpride 1400mg/day, after which QTc prolongation was noted. The electrolytes were normal. The ECG normalized when we switched from amisulpride to another antipsychotic medication. Another patient was a 38 year-old woman who had a cardiac arrest after 7 days of concurrent use of haloperidol decanoate 50mg and amisulpride 1400mg/day. She was resuscitated but was seen to have QTc prolongation on subsequent ECGs. This abnormality resolved within 3 days after amisulpride was discontinued. In both cases, it was only the simultaneous administration of 2 drugs that was associated with the adverse effect. It is possible that the combination had an additive effect on the human Ether-a-go-go Related Gene (hERG) potassium channel.（J Intern Med Taiwan 2009; 20: 544-549）

Key Words：Amisulpride, Depot antipsychotics, QTc prolongation, Cardiotoxicity

Introduction

Antipsychotic drugs have a central role in treating schizophrenia, but they are associated with a variety of side effects. One of the most dangerous adverse effects of these agents is prolongation of the heart rate-corrected QT interval (QTc).[1-3] QTc prolongation is associated with the occurrence of torsades de pointes, a polymorphic ventricular tachycardia which may precipitate lethal ventricular fibrillation and sudden death. Although there may be less similar observations with long-acting depot antipsychotics, QTc prolongation has still been reported, including cases involving flupenthixol decanoate[4], as well as many of the other typical and

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atypical antipsychotics.

Amisulpride, a substituted benzamide used in the treatment of schizophrenia, is generally well tolerated over a range of doses (200 to 1200 mg)[5,6]. A pilot study in Taiwan indicated that amisulpride was well tolerated; no serious adverse cardiovascular effects with the drug for 6 weeks[7]. Here we report 2 patients who developed significant QTc prolongation during concurrent treatment with a depot antipsychotic drug and high dose amisulpride.

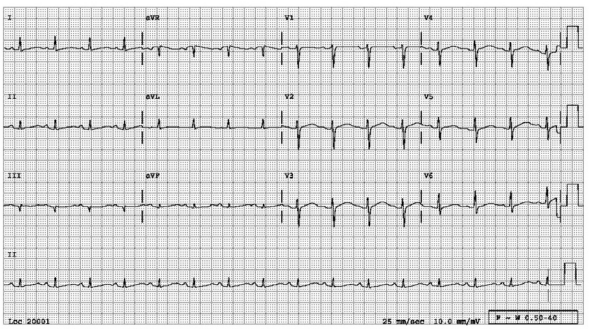
Case Reports

Patient 1

A 37-year-old woman had been diagnosed with schizophrenia 7 years previously. She also had hypertension and diabetes mellitus, treated with amlodipine, irbesartan, gliclazide, and pioglitazone. There was no family history of significant cardiovascular disease. In May 2005, after an exacerbation of psychosis characterized by mutism and social withdrawal, she was treated with intramuscular depot flupenthixol 40 mg monthly and oral flupenthixol 9 mg/day. Her psychotic symptoms were controlled on this regimen. An electrocardiogram (ECG) showed normal sinus rhythm with a QTc interval of 423ms on November 14, 2005. However, she had significant weight gain to 125 kg, so the flupenthixol was discontinued and she was given amisulpride 1000 mg/day beginning in December 2005. She was able to maintain a job and her weight dropped to 103 kg by June 2007. Because of a relapse of symptoms at that point, the amisulpride dose was increased to 1200 mg/day and a weekly 20 mg injection of depot flupenthixol was added. On July 20, 2007, she was hospitalized for psychotic symptoms, and a 20-mg depot flupenthixol injection was given. On July 26, the dose of amisulpride was titrated up to 1400 mg/day. Five days later (July 31), an ECG showed a QTc of 510 ms (Fig. 1). The patient had no cardiac complaints or abnormal findings on physical examination. Her blood pressure was well controlled on her usual medications, and the results of routine laboratory tests were normal except for hyperglycemia and hypertriglyceridemia. On September 4, she received another dose of intramuscular depot flupenthixol. Although she did not have any documented arrhythmias, the QTc prolongation was of concern. Therefore, the amisulpride was stopped and risperidone 4.5 mg/day was begun. The ECG on September 11 was normal, with a QTc of 430 ms.

Patient 2

A 38-year-old woman with schizophrenia had been treated with antipsychotics for about 10 years. Chronic renal insufficiency had been



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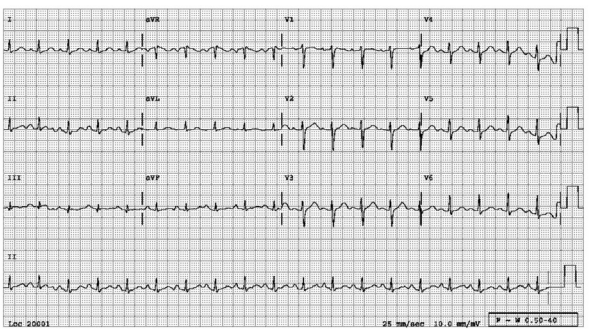
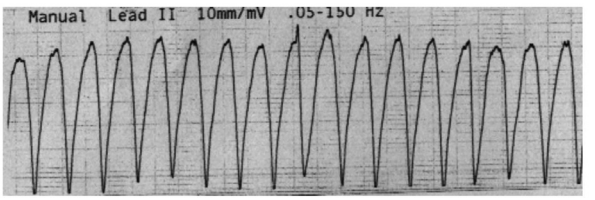


(b)

Fig.1 The electrocardiogram of patient 1, (a) QTc prolongation was present after higher amisulpride dose was administered. (b) The ECG returned to normal after amisulpride was discontinued and another atypical antipsychotic begun.

present for 3 years. She had hypertension but no other apparent cardiac disease. She was admitted to the psychiatric ward with a relapse of symptoms attributed to poor drug adherence. Her blood urea nitrogen was 26 mg/dL and creatinine 2.3 mg/dL. The levels of electrolytes were within normal limits. A routine ECG showed a sinus rhythm and a normal QTc interval (446 ms). Risperidone, 3 to 6 mg, was given for 3 weeks, but her symptoms did not respond. We therefore switched to amisulpride, which was gradually titrated up to 1400 mg/day within 4 weeks. There was some improvement in both positive and negative symptoms, and her discharge was planned. There was still some concern about compliance, so 50 mg of haloperidol decanoate was injected intramuscularly. However, 7 days later, the patient had a sudden cardiac arrest. ECG monitoring showed ventricular tachycardia and ventricular fibrillation. The patient's plasma sodium concentration was 142 mmol/L, potassium 3.4 mmol/L, chloride 106 mmol/L, calcium 9.3 mg/dL, and free calcium 1.23 mmol/L. Cardiopulmonary resuscitation was initiated, and sinus rhythm with a QTc of 457 ms was restored after intravenous atropine and epinephrine and direct current cardioversion. She was temporarily intubated and mechanically ventilated. Serial cardiac enzyme and electrolyte levels were within normal limits. Serial ECGs showed sinus rhythm with a prolonged QTc interval of 507ms (Fig.2). Amisulpride was discontinued, and the QTc interval gradually normalized over the next 3 days. Cardiac sonography did not reveal any structural abnormality. The patient eventually had a partial neurologic recovery with cognitive deficits.



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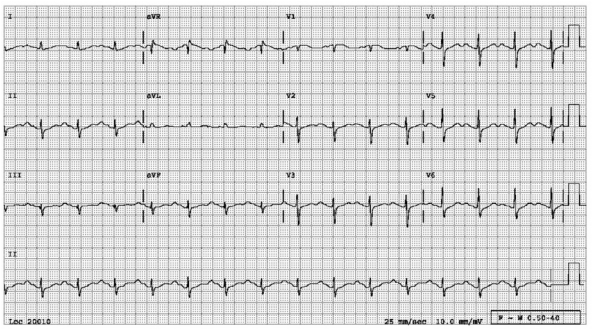

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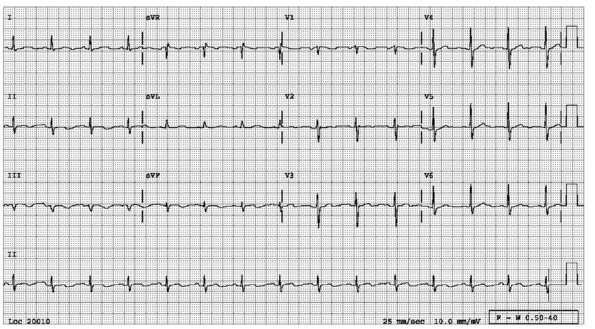

(c)

Fig.2 The electrocardiogram of patient 2 showing (a) ventricular tachycardia after concurrent treatment with haloperidol decanoate and high dose amisulpride (b) QTc prolongation 12 hours after resuscitation. The QTc prolongation persisted during the next 3 days. (c) The normalized ECG 3 days after discontinuation of amisulpride.

Discussion

These 2 cases suggest that the combination of amisulpride with depot antipsychotics may be associated with significant QTc prolongation, despite the apparent safety of amisulpride as a single agent. A study in Taiwan suggested that women were at greater risk than men for developing QTc prolongation[9]. It is interesting that both our patients were women. There have been reports of amisulpride associated with QTc prolongation or torsades de pointes. However, in all cases except one[8], the cardiotoxicity was associated with overdose of the medication[9-14]. Both our patients received doses of amisulpride slightly over the

recommended amounts because of their refractory psychotic symptoms. However, throughout the period in which the dose was titrated upwards, the women had no symptoms suggestive of cardiac toxicity. The first patient had been on combined oral and depot flupenthixol previously without QTc prolongation. It was only when depot flupenthixol was combined with amisulpride that the abnormality appeared; the QTc was then normal after amisulpride was discontinued and another atypical antipsychotic begun. Flupenthixol decanoate had been given again one week before the QTc normalized. Since the peak concentration after intramuscular injection occurs at 7 to 10 days, it must have been the discontinuation of the amisulpride that resulted in the normalization of the ECG. It therefore appears that it was the concurrent use of high-dose amisulpride along with flupenthixol decanoate that was responsible for the QTc prolongation.

The second patient had had normal routine ECGs before medication was begun. There were no apparent cardiac effects as the dose of amisulpride was titrated up, although because the patient was mute, we can not be certain she was completely asymptomatic. There was, however, no known history of syncope. It seems likely that her cardiac arrest was related to the combination of haloperidol and amisulpride. Although the initial ECG immediately after resuscitation had a normal QTc interval, this may have been due to atropine and other agents used during the resuscitation. Once she had stabilized, however, the QTc was definitely prolonged and remained so for 3 days after the amisulpride was stopped. Normally, the abnormality would not be expected to persist for so long if amisulpride were responsible, as the drug has a half life of only 14.5 to 17.3 hours. However, it is excreted primarily through kidney (70% as unchanged drug)[12]. This patient had compromised renal function, which might have resulted in higher than expected plasma levels as well as delayed excretion of the drug after it was discontinued. In theory, toxic levels of the drug might have been accumulating as the dose of amisulpride was titrated upwards over 4 weeks, but there was no apparent cardiotoxicity during that period. It was only after the depot haloperidol was given that she experienced a life-threatening arrhythmia.

Polypharmacy is a risk factor for cardiotoxicity[2,3] or any other adverse drug effect for that matter. A common drug-drug interaction problem arises from the effects of one drug on the hepatic cytochrome P450 enzymes which may influence clearance of a second drug. Amisulpride has been thought to be relatively safe in this respect, as it has little effect on the hepatic enzymes and therefore reportedly has few drug interactions[5].

Most antipsychotic drugs block the potassium rapid delayed rectifier (Kr) channel, encoded by the human Ether-a-go-go Related Gene (hERG). This effect interferes with cardiac repolarization[15,16]. It is this blockade of hERG potassium channels that is thought to be the primary mechanism of antipsychotic-induced QTc prolongation. Again, amisulpride was thought to have a relatively low, albeit dose-related, effect on the channel[16] and was thus considered to have little cardiotoxicity if the blood level is within the therapeutic range[6]. However, our 2 cases raise the possibility of an additive toxic effect of the combination of amisulpride with another antipsychotic, resulting in blockade of the hERG channels even though neither drug alone would have done so in the doses given. In both cases, once the amisulpride was stopped, the QTc returned to and remained normal.

In conclusion, these 2 cases suggest that, just as with other antipsychotics known to affect the QTc interval, amisulpride should be used with caution, with careful ECG monitoring. This is especially true in a patient with compromised renal function or in whom very high doses of the

drug are required for symptom control. Monitoring appears to be of even greater importance if another antipsychotic is also being used, particularly a depot preparation. Regardless of which drug is introduced first, if apparently synergistic adverse effects occur, the drug with the shortest half-life must be stopped. Further investigation of the arrhythmogenic properties of antipsychotics, particularly their effects on ion channels, may clarify whether some combinations are safer than others.

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高劑量amisulpride與長效抗精神病針劑所造成之心電圖QTc間隔延長：二例報告及文獻回顧

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摘 要

心電圖QTc間隔的延長，爲抗精神病藥之重要副作用之一。Amisulpride爲一被認爲對心電圖相對安全之抗精神病藥物，造成心臟問題之報告較少。吾人在此報告二例無心臟病史之患者，因注射皮下長效抗精神病藥物與amisulpride高劑量使用而發生QTc的延長。病患一爲37歲女性，之前無心律不整病史。之前使用長效flupenthixol decanoate也未有心臟方面影響。其在同時使用每週長效之flupenthixol 注射及每日口服amisulpride 1400mg後，發生了QTc的延長。此一心電圖之變化在病患將口服藥物更換後恢復正常。病患二是38歲女性，在同時使用haloperidol decanoate 50mg長效針劑注射一次與每日amisulpride 1400mg使用七天之後發生了致命性心律不整。經過急救之後的心電圖發現有QTc的延長，此情形在停用amisulpride三天後得到緩解。兩例都僅在兩藥同時使用時產生此一副作用，可能與對human Ether-a-go-go Related Gene (hERG)鉀離子通道之加成作用有關。