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Case Report Open Access

Arrhythmic Side Effect of Itraconazole Monotherapy: A Case Report

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Abstract

A 39-year-old woman treated with itraconazole for onychomycosis developed palpitation and dizziness during her treatment. Premature ventricular contractions (PVC) were detected during monitoring in the emergency room. Twenty-four hour holter electrocardiogram revealed aberrant premature atrial contractions (PACs) and PVCs. Corrected QT interval was in normal limits. After discontinuing the therapy, her complaints disappeared couple of days later. Her 24-h holter ECG displayed no PACs or PVCs. In this case the etiology of extra systoles is not well-known. She did not have any other infection or used any other medication which may interfere with the metabolism of itraconazole. Enhanced cardiac automaticity may be a probable mechanism instead of more commonly encountered QT prolongation. Cardiac side-effects of itraconazole is rare but may be life threatening. Arrhythmic side effects should be monitored carefully even in otherwise healthy patients.

Keywords: Drug toxicity; Enhanced automaticity; Extra systoles; Itraconazole

Introduction

Itraconazole-a fungal cytochrome P450 inhibitor is a widely used antifungal agent in treating onychomycosis. Arrhythmic side effects of itraconazole are reported in literature. We present an otherwise healthy woman who experienced premature atrial contractions (PACs) and premature ventricular contractions (PVCs) during itraconazole treatment for onychomycosis.

Case Report

A 39-year-old woman has been treated with itraconazole for onychomycosis by pulse therapy protocol, as 3 cycles including 400 mg/day for a week and then 3-week pause interval. She developed palpitation and dizziness on the ninth day of her treatment when she was in the second day of the first 3-week pause interval.

She was consulted to cardiology. On her physical examination, blood pressure was 90/60 mmHg; heart rate was 66/min and arrhythmic with rare premature beats. She did not have any other infection or used any other medication which may interfere with the metabolism of itraconazole. Her PVCs were detected during monitoring in the emergency room, but not recorded. Corrected QT interval was supposed to be in normal limits as calculated 396 ms in twelve-lead electrocardiography (ECG) and revealed no other pathological finding. Her echocardiography was in normal limits as no wall motion abnormality, valvular regurgitation or pericardial effusion detected.

Twenty-four hour holter ECG revealed rare aberrant PACs and PVCs (12 and 75 times respectively) (Figure 1) and rare bigeminal aberrant PACs (8 times) (Figure 2). Corrected QT interval was calculated by Fridericia formula and was 400 msec.

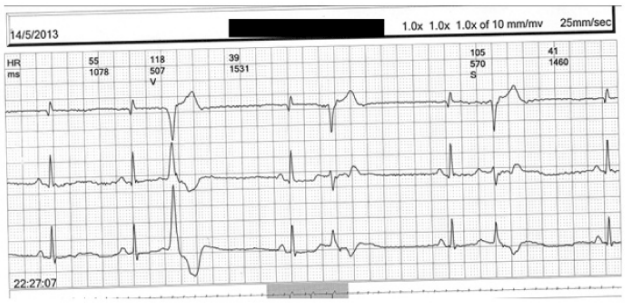

Figure 1: Premature ventricular and aberrant premature atrial contractions on 24 hr Holter Electrocardiogram.

V: Premature ventricular contraction, S: Premature atrial contraction

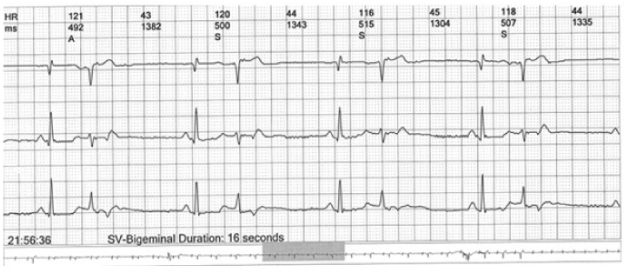

Figure 2: Bigeminal aberrant premature atrial contractions on 24 hr Holter Electrocardiogram.

S: Premature atrial contraction

Heart rate variability was counted up by 24-h holter ECG. The standard deviation of the normal-to-normal interval (SDNN, ms) and the standard deviation of the average normal-to-normal interval (SDANN, ms) were calculated. SDNN was 159 ms and SDANN was 148 ms.

After cessation of the therapy, her complaints disappeared couple of days later. Her 24-h holter ECG displayed no PACs or PVCs.

Discussion

Rare PVCs and PACs were demonstrated by Holter ECG in an otherwise healthy woman treated with itraconazole. Disappearance of the extra systoles with discontinuation of the therapy is sufficient enough to support the proarrhytmic effect of itraconazole.

In literature, cardiac side effect of itraconazole is mostly due to QT prolongation in ECG when used with – one of the antihistaminic drugs– terfanadine [1,2]. Itraconazole acts on fungus by suppressing cytochrome P450 and interfering with cell membrane formation, meanwhile it minimally influences mammalian cell membranes [3]. As it's a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, it may increase plasma concentrations of drugs metabolized by this pathway and augment their side effects. Serious ventricular arrhythmias may occur due to QT prolongation. But our patient did not use any other medication together with itraconazole. Okamoto et al. reported a case similar to ours' in which itraconazole monotherapy, induced PACs and PVCs. Additionally their patient also developed a short run of ventricular tachycardia with four beats [4].

Premature contractions may also be noticed in electrolyte imbalance, thyroid dysfunction, myocarditis, ischemic heart disease but in this case biochemical and hormonal blood tests, 12- lead ECG and echocardiogram were all in normal limits.

The age of the patient may also increase the probability of PVCs. It is documented by Simpson et al. that for women the prevalence approximately doubles and for men triples from age 45 to 65 years in normal population [5]. As our patient was relatively younger the influence of age may be ignored.

In our case the etiology of PVCs and PACs is not well-known. Enhanced cardiac automaticity may be a probable mechanism instead of more commonly encountered QT prolongation. Existence of both atrial and ventricular premature contractions may suggest this mechanism in this patient.

Conclusion

Cardiac side-effects of itraconazole is rare but may be life threatening. Atrial and ventricular arrhythmias may occur not only due to QT prolongation or any drug interaction but also due to enhanced automaticity caused by drug itself. So arrhythmic side effects should be monitored carefully especially in advanced age even they are on itraconazole monotherapy and even do not have QT prolongation in ECG.

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