Case Report

# Recurrence of atrial fibrillation after switching from brand to generic atenolol

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## ABSTRACT

Beta blockers are the initial treatment for rate control of supraventricular tachyarrhythmia in patients without a history of myocardial infarction or left ventricular dysfunction. In this article we report the recurrence of atrial fibrillation after switching to the generic formulation of atenolol.

**Key words:** Atenolol, atrial fibrillation, brand drug, clinical ineffectiveness, generic drug

## INTRODUCTION

Supraventricular arrhythmias are common. They are more common in women than in men.[1,2]

Often β-adrenoceptor antagonists (β-blockers) are able to control the ventricular rate by slowing the atrioventricular conduction.[3]

Several years ago, generic drugs were introduced in Italy in agreement with the Finance Law of 1996 (Law n. 549/1995 in G.U. n. 302 of 29.12.1995). These formulations are equivalent to brand one if they have the same active substance (with a difference of ± 5%), the same pharmaceutical form, the same therapeutic indications, and a similar bioequivalence (±20%) with the reference medicinal product (Law n. 425/1996 in G.U. n. 208 of 05.09.1996; Legislative Decree No. 219/06). In this article we report recurrence of atrial fibrillation after changing from the brand to the generic formulation of atenolol.

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## CASE REPORT

A 63-year-old woman, with a past medical history of paroxysmal atrial fibrillation, was in sinus rhythm, on maintenance beta blocker (Tenormin) therapy. She presented with symptomatic palpitations, nausea, weakness, and dizziness. Clinical evaluation revealed the presence of tachycardia (heart rate of 130 heart beats and atrial fibrillation by electrocardiography). Her blood pressure was 130/80 mmHg, without clinical or laboratory features of heart failure.

History revealed that about 18 years ago (age of 45 years), she was treated for hypertension and hyperthyroidism and at the time of this presentation the patient was treated with telmisartan (Micardis®, 40 mg/day), amlodipine (Norvasc®, 5 mg/day), and tapazole (Tiamazole®, 5 mg/day). Moreover, in 2002, she started atenolol (Tenormin® 50 mg bid) for the development of tachycardia, with a good control of heart symptoms. In-depth evaluation revealed that in March 2013, the pharmacist switched the medication from the brand

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formulation of atenolol (Tenormin® 50 mg bid) to the generic one (atenolol Almus generics® 50 mg bid). About 14 days later the patient developed palpitations, and in November 2013, she was admitted to the Medicine Interne Operative Unit, with a diagnosis of atrial fibrillation. Both blood and urinary chemical analyses, to evaluate the activity of the kidney, liver, and thyroid, were negative. Similarly, the urinary catecholamine levels were normal. The drug levels were checked and it was demonstrated that her plasma levels of atenolol (45 ng/mL; normal range 50–70 ng/mL) were subtherapeutic. Given this temporal relationship of changing the Tenormin®–based therapy to the generic type of atenolol therapy could have led to the subtherapeutic beta-blocker levels, resulting in recurrence of atrial fibrillation, although this may be a causal relationship. The Naranjo probability scale[4] documented a possible association between generic atenolol and heart symptoms, therefore, generic atenolol was switched to the brand formulation (Tenormin® 50 mg bid), with an initial improvement of symptoms in about three days and with complete control of symptoms in about 14 days (atenolol plasma levels: 57 ng/mL). The patient was also treated with dabigatran (Pradaxa®, 150 mg bid). During this time, the dosages of other medications, such as, tapazole and telmisartan, remained unchanged.

## DISCUSSION

Beta blockers represent the initial treatment for rate control as well as maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation.[5] We have reported a case of recurrence of atrial fibrillation after a switch from the chronic treatment with Tenormin® to generic atenolol.

Several factors may be involved in the genesis of atrial fibrillation,[6-9] however, in our patient clinical manifestation and laboratory findings excluded a suggestion that atrial fibrillation was related to other cardiac or systemic diseases.

Previously, we described that dispensing error may be involved in the development of side effects or in the lack of efficacy.[10,11] In our patient, we can exclude an error in the timing of drug administration or in the drug used, as referred by the patient and his parents.

As it has been reported that drug–drug interaction may be able to induce clinical ineffectiveness,[12] pharmacological evaluation has excluded that these could have played a role in the development of atrial fibrillation in our patient.

Using the Naranjo probability scale, we documented an association between the generic drug and the development of atrial fibrillation, and we demonstrated in this case that a switch from the generic formulation of atenolol to the Tenormin®-based therapy resulted in the improvement of symptoms, with an increase in plasma atenolol values. As other articles have suggested a difference in the clinical efficacy of the generic drug with respect to the brand formulations,[13-16] in recent times, a retrospective study performed in Italy has reported that off-patent generic drugs have the same efficacy as the brand formulation.[17]

**Table 1: Differences in excipients between the brand (Tenormin®) and generic (Atenolol Almus®) formulations of atenolol**

| Tenormin® | Atenolol Almus® |
|---|---|
| Heavy magnesium carbonate | Heavy magnesium carbonate |
| Corn starch | Corn starch |
| Sodium lauryl sulfate | Sodium lauryl sulfate |
| Gelatin | Magnesium stearate |
| Magnesium stearate | |

Some factors such as differences in bioequivalence, excipients, and impurity may be involved in the difference of clinical efficacy between brand and generic formulations.[15,16,18,19] However, in the present case we can exclude the role of excipients, because the generic formulation shows excipients similar to those in the brand formulation [Table 1].

In conclusion, as this is only a case report, we suggest that treatment must not be changed from a brand formulation to a generic one when the patient is chronically treated, or if it is necessary we suggest performing a plasma pharmacological evaluation of the drug concentration in order to avoid possible clinical ineffectiveness.

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