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Side Effects of Antihypertensives Induced by Switching to Different Generic Medications: Case Reports

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Abstract: Generic medication is a product that contains the same active substance and pharmaceutical characteristics as brand-name medications. Generic medications are cost-effective and comparable to brand-name medications in terms of clinical endpoints. However, the use of generic medications instead of brand-name medications is a debatable issue among patients and healthcare providers. Two patients with essential hypertension experienced side effects after switching to different generic antihypertensives (one generic medication to another generic medication). Adverse drug reactions, including, hypersensitivity, side effects, and intolerance, should be identified through present and past medical history and clinical characteristics. The adverse drug reactions in both patients were more likely to be side effects of the medications after switching to different generic antihypertensives produced by different companies (patient 1: enalapril and patient 2: amlodipine). The side effects were possibly caused by the different inactive ingredients or excipients. These two case reports emphasise the importance of monitoring adverse drug reactions throughout the course of treatment and communicating with patients prior to switching to a new generic medication.

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Introduction

Generic medication is defined as a product that contains the same active substance (with a difference of ± 5%) and has the same pharmaceutical characteristics as brand-name counterparts and exhibits bioequivalence (with a difference of ± 20%) (Gallelli et al., 2016; Desai et al., 2019). A major benefit of generic medications is that they are usually much cheaper than corresponding brand-name medications. In a study that included more than 2.2 million matched pairs of patients in the USA, generic medications were comparable to brand-name medications in terms of clinical endpoints (Desai et al., 2019). Notably however, serious adverse drug reactions (ADRs) due to switching from brand-name medications to generic medications have been reported (Gallelli et al., 2016). The prescription and use of generic medications instead of brand-name medications is a debatable issue among patients and healthcare providers. Many healthcare providers are concerned about the efficacy and safety of generic medications produced by different companies. Herein we describe the cases of two patients with primary hypertension treated at a family medicine clinic who had non-severe side effects after switching to different generic hypertensive medications. The treatments were adjusted to resolve the side effects.

Case reports

Patient 1

Patient 1 was a 62-year-old man with a history of primary hypertension, dyslipidaemia, and benign prostate hyperplasia. His medications were amlodipine 10 mg daily, simvastatin 20 mg daily, and doxazosin 2 mg daily. In July 2020, enalapril 5 mg (a generic medication) was added due to uncontrolled blood pressure. He was diagnosed with rotator cuff syndrome and carpal tunnel syndrome in December 2020, and treated with meloxicam, tolperisone, and gabapentin.

In January 2021, his blood pressure was under control and other examinations were unremarkable. Ten days later he developed dysuria and was diagnosed with a urinary tract infection (UTI). The initial treatment for the UTI was oral ciprofloxacin for 7 days followed by intravenous ceftriaxone. Renal caliculi were subsequently diagnosed via ultrasonography.

Two days after the intravenous antibiotic he presented at the family medicine clinic due to a dry cough. He noted that the cough had developed since he took a “new medication”. At the previous family medicine clinic visit, he had received 5 mg enalapril as a generic formulation produced by a different company. The cough developed prior to the treatment for the UTI.

The family physician advised him to discontinue enalapril and prescribed 50 mg oral losartan as a replacement. A follow-up appointment was scheduled for 3 weeks’ time, to assess any side effects of the antihypertensive medication. The patient reported no abnormal symptoms after discontinuing the second generic enalapril.

Patient 2

Patient 2 was a 40-year-old woman with primary hypertension. Her blood pressure had reached the treatment goal via administration of amlodipine 5 mg daily (generic medication produced by company A), and it had been maintained at that level for almost 2 years (since December 2018). After a family medicine clinic visit in September 2020, she noticed that a new antihypertensive medication (5 mg amlodipine, product of company B) had been prescribed. The patient had experienced a cramp in her right arm. She decided to stop her current medication and bought her previous medication (5 mg amlodipine, product of company A) from a pharmacy. The cramp in her arm recovered. Thereafter, she continued with the medication bought from the pharmacy.

At the next visit in February 2021, she informed her physician about the change in medications and the side effect. The physician revealed that both medications were generic medications (5 mg amlodipine) from different companies. The patient discussed the suspected side effect with her physician. The physician did not confirm that the arm cramp was a side effect of the medication and reassured the patient that she could take the currently prescribed amlodipine (product of company B). The physician also advised the patient to discontinue the medication if there were any abnormal symptoms or evidence of ADRs.

After that consultation, the patient tried the product from company B again. She again experienced a cramp in her right arm and stopped the medication as the suggestion of her physician. She resumed taking her initial form of amlodipine (product of company A), and no recurrence of the arm cramp had been reported.

Discussion

The two above-described patients noticed side effects after switching to different generic antihypertensives. A term "side effect" is a subset of an umbrella term, "adverse drug reaction (ADR)" which is a harmful reaction to a drug. The three main types of ADRs are allergy or hypersensitivity (immunological mechanism), side effects (pharmacological mechanism), and intolerance or sensitivity (pharmacological mechanism and susceptibility to a medication) (Smith, 2013). For example, enalapril can possibly cause various features of ADRs such as skin rash (allergy), dry cough (side effect), and hypotension (intolerance) (Smith, 2013). Another ADR classification system by World Health Organization (WHO) defines six types of reactions: type A (dose-related or "augmented"), type B (non-dose-related or "bizarre"), type C (dose-related and time-related or "chronic"), type D (time-related or "delayed"), type E (withdrawal or "end of use"), and type F (unexpected failure of therapy or "failure") (Edwards and Aronson, 2000).

In the current cases, the side effects were reported after switching one generic medication (patient 1: enalapril and patient 2: amlodipine) to another generic medication. These two cases raise a question as to why the patients experienced the

ADRs after the long-term use of medications. Type 4 hypersensitivity (cell mediated or delayed type), of which rash, angioedema, and anaphylaxis are common clinical features, should be differentiated. However, the ADRs described in both patients were more likely to be side effects of the medications than allergic reactions. Dry cough is a common side effect of enalapril, whereas muscle cramp is a less common side effect of amlodipine (Gibson, 1989; Yajnik et al., 1995). The ADRs in these two cases were defined as type A (dose-related or "augmented") according to the WHO classification, which related to the pharmacological actions of the drugs and predictable (Edwards and Aronson, 2000).

With respect to why the side effects occurred, one possible reason is that the two different generic medications produced by different companies contained some different ingredients. Oral forms of medication generally contain both active pharmaceutical ingredients and a mixture of inactive ingredients called excipients (Reker et al., 2019). Excipients are combined with the active pharmaceutical ingredient to control drug stability, preservation, tonicity, and delivery (Ionova and Wilson, 2020). Different excipients can cause a variety of ADRs via different mechanisms (Ionova and Wilson, 2020; Pottel et al., 2020). The side effects in the two current patients were possibly caused by the different excipients in the medications produced by different companies.

Medication side effects are a factor associated with poor treatment adherence in patients with chronic illnesses (Lemay et al., 2018). Managing side effects of medications in patients with chronic medical conditions is a challenge among primary care physicians (Sellappans et al., 2015). Within primary care settings, a recent systematic review and meta-analysis reported that the prevalence of ADRs was 8.32% (7.82–8.83%), and nearly a quarter (22.96%; 7.82–38.09%) of those ADRs were preventable (Insani et al., 2021).

Conclusion

The above-described case reports emphasise some lessons for physicians and healthcare providers. One is that ADRs associated with medications for chronic conditions should be monitored throughout the course of treatment. Another is that classifying ADRs into specific mechanisms (allergy, side effect, and intolerance) can help to identify the associated causes, which may be either active pharmaceutical ingredients or inactive ingredients (excipients). Lastly, there is a need to communicate with patients prior to switching to a new generic medication because its excipients may cause ADRs.

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