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LETTER TO THE EDITORS

Hypotension due to the drug interaction of voriconazole with eplerenone and nifedipine

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Voriconazole, a novel triazole antifungal agent, has a potent activity against a broad spectrum of fungi, including yeasts and moulds. Voriconazole has been reported to improve the survival of patients with invasive aspergillosis as compared with amphotericin-B, and has become the treatment option for invasive aspergillosis [1, 2]. Voriconazole is metabolized by cytochrome P450 (CYP) enzymes, namely CYP 2C9, 2C19, and 3A4 [2]. In vitro studies have demonstrated that voriconazole could be an inhibitor as well as a substrate of these enzymes [3]. Therefore, its drug interaction with a variety of agents metabolized by these enzymes is recognized. We here report the first case of a clinically relevant drug interaction between voriconazole and eplerenone/nifedipine.

A 48-year-old man with myelodysplastic syndrome underwent bone marrow transplantation from an unrelated donor. Cyclosporine A and methylprednisolone were given for the treatment of acute graft-versus-host disease. He had been regularly on candesartan (8 mg/day), nifedipine (40 mg/day), and eplerenone (50 mg/day) for hypertension, and his blood pressure had been maintained in a range of 130~146/70~88 mm Hg. Voriconazole was initiated intravenously for the prophylaxis of fungal infection. The initial two administrations were 6 mg/kg 12 h apart, followed by a maintenance dose of 4 mg/kg every 12 h. His blood pressure began to fall and reached 76/48 mm Hg the next day. The findings of the physical examination and blood tests did not reveal signs of hypovolemia, acute blood loss, or septicemia. All three antihypertensive agents (candesartan, nifedipine, and eplerenone) were discontinued immediately. His blood pressure was restored to 116~124/64~80 mm Hg 1 day after the discontinuation and reached 164~180/80~84 mm Hg 5 days later. Candesartan and nifedipine were started again, with a dose reduction of nifedipine to 20 mg/day, and eplerenone was no longer needed to control hypertension.

Nifedipine, a calcium antagonist, has long been used for hypertension. Eplerenone is a steroid nucleus-based antimineralocorticoid that acts as a competitive and selective aldosterone blocker and has recently been introduced as an antihypertensive agent [4]. Both nifedipine and eplerenone are metabolized by CYP3A4. Because voriconazole acts as an inhibitor as well as a substrate of CYP3A4, its inhibition of the metabolism of nifedipine and eplerenone is plausible. It has been reported that other azoles such as fluconazole interact significantly with nifedipine, but such an interaction has yet to be demonstrated with eplerenone [5, 6].

To the best of our knowledge, there have been no reports showing the drug interaction between voriconazole and nifedipine/eplerenone. In the present case, administration of voriconazole significantly interacted with these two agents, resulting in the marked reduction of blood pressure, including a 70-mm Hg reduction in systolic pressure that could have resulted in serious consequences. Our case indicates that voriconazole inhibits the metabolism of nifedipine and eplerenone, and significantly augments their antihypertensive effects, although the magnitude of the drug interaction with nifedipine and eplerenone may differ.

We conclude that physicians should be aware of the drug interaction of voriconazole with nifedipine and eplerenone,

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and blood pressure should be carefully monitored upon initiating voriconazole in patients who are already on nifedipine and/or eplerenone.

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