INTERNAL MEDICINE

□ CASE REPORT □

Acute Kidney Injury from Excessive Potentiation of Calcium-channel Blocker via Synergistic CYP3A4 Inhibition by Clarithromycin Plus Voriconazole

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Abstract

CYP3A4-inhibitors can potentiate the hypotensive effect of calcium-channel blockers. However, insufficient attention to such drug interactions may result in serious adverse reactions. A 71-year-old hypertensive man prescribed nifedipine was hospitalized for infectious endophthalmitis. Antimicrobial therapy with voriconazole lowered the blood pressure, and then clarithromycin further lowered it through the excessively elevated nifedipine concentration, leading to ischemic acute kidney injury. After the discontinuation of clarithromycin and voriconazole, the blood pressure and renal function were recovered. The combination of CYP3A4-inhibitors such as clarithromycin plus voriconazole can synergistically potentiate calcium-channel blockers. Co-prescription of multiple CYP3A4-inhibitors with calcium-channel blockers increases the risk of hypotension and acute kidney injury.

Key words: acute kidney injury, drug interaction, hypertension, calcium-channel blockers, nifedipine, CYP3A4

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Introduction

Dihydropyridine calcium-channel blockers are a popular class of antihypertensive drugs that are metabolized by cytochrome P450 isoenzyme 3A4 (CYP3A4). Pharmacokinetic studies have shown that CYP3A4-inhibitors such as macrolide antibiotics affect the metabolism of calcium-channel blockers and raise their concentration (1). Thus, CYP3A4-inhibiting medications can potentiate the blood pressure-lowering effect of calcium-channel blockers (2). In clinical settings involving treatment with antibiotics, antifungals and antivirals, multiple medications with CYP3A4-inhibitory effects are occasionally co-prescribed. However, the effects on calcium-channel blockers of a combination of multiple CYP3A4-inhibitors are difficult to predict. In addition, there has been insufficient attention to such drug interactions, which may result in serious adverse reactions.

We herein report a case of an excessive hypotensive effect leading to acute kidney injury due to the synergistic effect of multiple CYP3A4-inhibitors in a patient co-prescribed a calcium-channel blocker, nifedipine.

Case Report

A 71-year-old man was hospitalized to undergo vitreous surgery for the treatment of infectious endophthalmitis. The patient had resistant hypertension and chronic kidney disease (CKD) due to diabetic nephropathy with serum creatinine 3.6 mg/dL and gross proteinuria (6 g/g creatinine). On admission, the blood pressure was 160-180/90-110 mmHg despite receiving a combination of antihypertensive medications including controlled-release nifedipine 40 mg bid, olmesartan 40 mg, furosemide 40 mg, and trichlormethiazide 1 mg per day. The patient had also been prescribed insulin therapy (glulisine 24 units and glargine 4 units per

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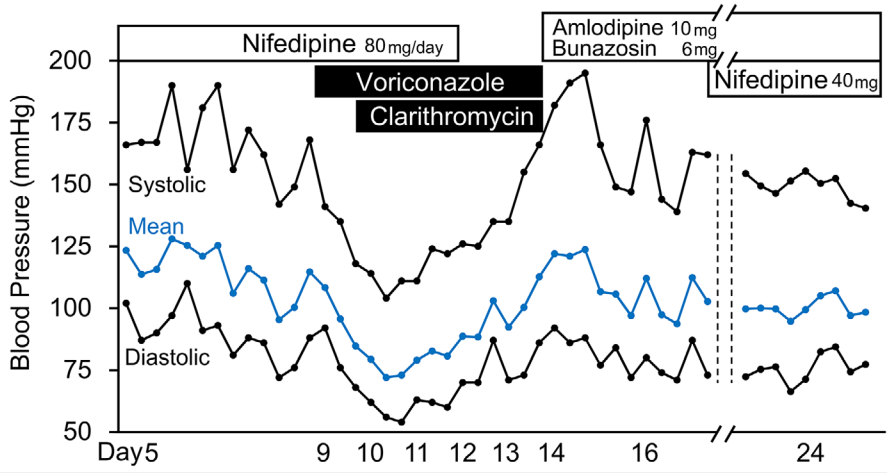

Serum Nifedipine (ng/mL)				189		12		
BW (kg)	70	70	70	72	73	74	72	70
UV (mL/d)			130	450				
sCr (mg/dL)	3.6	3.6			4.9		4.6	3.7
Hb (g/dL)	11.0	9.9			8.6		8.7	9.2

Figure. The course of the blood pressure, serum nifedipine concentration and clinical data. BW: body weight, UV: urine volume, sCr: serum creatinine

day) for glycemic control and febuxostat 20 mg for hyperuricemia. In addition to the surgical treatment for endophthalmitis, empirical antibiotic therapy with oral voriconazole (600 mg/day the first day, then 300 mg/day) was started from Day 9. On the same evening, the blood pressure dropped to 135/70 mmHg (Figure). On the following day, oral clarithromycin 400 mg/day was additionally started. The blood pressure dropped further to 105/56 mmHg and remained below 125/75 mmHg thereafter (Figure), causing dizziness and orthostatic hypotension. Afterward, the patient showed sudden oliguria and increased serum creatinine of 4.9 mg/dL, indicating acute kidney injury (AKI) on CKD (Figure). A urinalysis on Day 14 showed a specific gravity of 1.006, 2+ protein, no hematuria, no red blood cells, no leukocytes, hyaline casts 1-9/HPF, urine Na 80 mEq/L, urine K 12 mEq/L and urine creatinine 25 mg/dL. In this period, the infection was limited to the ophthalmic lesion, and no signs of volume depletion or systemic inflammation were observed (body temperature 36.4℃, white blood cell count [WBC] 4,400/μL, and C-reactive protein < 0.1 mg/dL).

To prevent the persistence of the hypotension, nifedipine was stopped at Day 12. Two days later, the blood pressure rose to 180/90 mmHg, and the urinary volume was promptly recovered (Figure). Measurement of the serum nifedipine concentration showed that it had reached 189 ng/mL on Day 12 (4 hours after the last dose of nifedipine, Figure) and declined to 12 ng/mL on Day 14 (2 days after the last dose). After the discontinuation of clarithromycin and voriconazole, the blood pressure was maintained at 140/70 mmHg by resuming nifedipine 40 mg and adding amlodipine 10 mg and bunazosin 6 mg per day. The serum creatinine returned to the preadmission level of 3.7 mg/dL.

Discussion

In the present case, drug interaction through the combination of clarithromycin plus voriconazole caused an excessive hypotensive effect by nifedipine followed by AKI. Both clarithromycin and voriconazole, a macrolide antibiotic and antifungal triazole, respectively, have potent inhibitory effects on CYP3A4 (3, 4). Their synergistic CYP3A4-inhibitory effects reduced the metabolism of nifedipine, which raised its blood concentration and excessively potentiated its hypotensive effect, resulting in ischemic AKI through renal hypoperfusion.

In the presence of CYP3A4-inhibitors, drugs that are metabolized by CYP3A4 will accumulate, leading to toxicity. Both clarithromycin and voriconazole can potentiate calcium-channel blockers by inhibiting CYP3A4. Co-prescription of clarithromycin and calcium-channel blockers has been associated with the risk of hypotension and AKI (2, 5). Hypotension from co-prescribing voriconazole together with nifedipine has also been reported (6). In the present case, clarithromycin further lowered the blood pressure after it had already been lowered by voriconazole. In addition, the CYP3A4 system has less influence on the metabolism of other co-prescribed antihypertensive medications: olmesartan, furosemide, and trichlormethiazide (7, 8). These findings indicate that the combination of clarithromycin plus voriconazole further raised the nifedipine concentration, inducing hypotension by their synergistic CYP3A4 inhibition. Therefore, co-prescription of multiple CYP3A4-inhibitors exacerbates the risk of hypotension by the excessive potentiation of calcium-channel blockers.

In the present case, the serum nifedipine concentration be-

came far too high (189 ng/mL) when administered with clarithromycin and voriconazole. We did not measure the nifedipine concentration before the addition of clarithromycin and voriconazole. However, a pharmacokinetic study showed that, when controlled-release nifedipine 40 mg bid was repeatedly dosed, the plasma concentration was approximately 80 ng/mL 4 hours after the last dose (9). In our case, the nifedipine concentration became 2.3-fold higher than this reported value. This excessively high nifedipine concentration caused the sudden reduction in the blood pressure despite the patient's resistant hypertension. Salt restriction in the hospital might also have contributed to the marked blood pressure-lowering by the raised nifedipine concentration. Calcium-channel blockers including nifedipine are easily degraded by exposure to light even in plasma samples (10). However, we did not collect the sample under light-shielding condition. Thus, the actual nifedipine concentration in the circulation would likely have been much higher than the level obtained in our case.

Severe hypotension can cause hypoperfusion in kidneys, leading to ischemic AKI. However, the present case showed AKI under a range of systolic blood pressures from 110-125 mmHg without severe hypotension. Although renal perfusion can be maintained by autoregulation with a mean blood pressure as low as 80 mmHg (11), the kidneys are highly vulnerable to moderate hypoperfusion when autoregulation is impaired, which may be seen in elderly patients, those with CKD or those receiving renin-angiotensin system blockers (12). Thus, in such patients, ischemic AKI can result from a sudden drop in the systolic blood pressure to even a low-normal range (11), as in the present case. Although urinary parameters, such as urinary sodium, are often helpful in the differential diagnosis of renal and prerenal AKI, these parameters in AKI can vary according to the underlying renal dysfunction and frequent use of diuretic therapy, as in the present case (13). Thus, a diagnosis of prerenal AKI, including ischemic AKI, requires the consideration of other factors such as pre-existing disease, time frame, and response to interventions (13). In the present case, the elevation of serum creatinine and oliguria were promptly ameliorated after the improvement of renal perfusion by re-elevation of the blood pressure. These findings support the notion that drug interaction-induced transient hypotension was the etiology of AKI under CKD in the present case. During the patient's course, the patient showed no signs of either sepsis, volume depletion, symptomatic arrhythmia or post renal obstruction and did not receive any nephrotoxic agents, including iodine contrasts or nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, voriconazole and clarithromycin themselves do not have direct nephrotoxic effects (14, 15). A urinalysis did not show hematuria or pyuria, although it did show proteinuria, which had been observed since before the onset of AKI. These findings suggest that renal parenchymal diseases such as glomerulonephritis were unlikely to be the cause of the AKI.

In conclusion, the combination of multiple CYP3A4-inhibitors such as clarithromycin plus voriconazole can synergistically potentiate the hypotensive effect of calcium-channel blockers. The present case highlighted the increased risk of adverse drug events in prescribing multiple CYP3A4-inhibitors. Therefore, when multiple CYP3A4-inhibitors are concurrently used, clinicians should be more cautious about the risk of blood pressure changes and AKI in patients already receiving calcium-channel blockers, especially elderly patients with chronic kidney disease.

The authors state that they have no Conflict of Interest (COI).

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