

# BPB Reports

## Report

### Effect of Fluconazole on Blood Pressure in Patients Treated with Dihydropyridine Calcium Channel Blockers: A Retrospective Study

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Fluconazole and dihydropyridine calcium channel blockers (DCCBs) are simultaneously used in clinical practice. Although fluconazole can increase the blood levels of DCCBs by inhibiting CYP3A4, there are only a few reports regarding the effects of interaction of these drugs on blood pressure. Based on electronic medical records, we conducted a retrospective study of blood pressure in hospitalized patients treated with fluconazole while receiving amlodipine and nifedipine. The mean blood pressure over 3 days, specifically 2 days before starting fluconazole treatment and the first day of fluconazole treatment (day 1), was used as the reference value to compare the mean blood pressure calculated every 3 days after day 1 until day 13. Most of the 26 patients included in the study had underlying hematologic malignancies. The average age of patients was 71.8 years. Twenty-one patients received amlodipine and five received nifedipine. The combination of DCCBs and fluconazole was associated with a significant decrease in blood pressure on day 11–13 ( $p < 0.01$ ). The mean difference in overall systolic blood pressure was  $-15.8$  mmHg (95% CI:  $-21.1$  to  $-10.4$ ). Therefore, the combination of fluconazole and DCCBs might potentiate the antihypertensive effect of DCCBs, and caution should be exercised when using them for lowering blood pressure.

**Key words** fluconazole, calcium channel blocker, blood pressure

## INTRODUCTION

Dihydropyridine calcium channel blockers (DCCBs) can be used to treat high blood pressure because of their rapid and potent antihypertensive effects. Fluconazole, a triazole antifungal agent, is active against *Candida* and *Cryptococcus* species and is often used to treat and prevent fungal infections. Fluconazole inhibits cytochrome P-450 3A4 (CYP3A4) and increases the blood levels of CYP3A4 substrates; though, this inhibitory effect is less pronounced than that of ketoconazole and itraconazole. Additionally, ketoconazole and itraconazole have been reported to increase the area under the blood concentration time curve (AUC) of triazolam, a CYP3A4 substrate, by 22.4- and 27.1-fold, respectively, whereas fluconazole increased the AUC by 4.4-fold.<sup>1,2)</sup> Therefore, fluconazole is often prescribed simultaneously with DCCBs in clinical practice.

As DCCBs are mainly metabolized by CYP3A4, their concomitant use with drugs that inhibit CYP3A4, such as fluconazole, might increase their blood concentrations and enhance their antihypertensive effects. Furthermore the drug-drug interaction between DCCBs and fluconazole is well known, but there is only one report of an actual decrease in clinical blood pressure.<sup>3)</sup> Further, this needs to be analyzed in a larger number of patients.

We conducted a retrospective study on patients for whom fluconazole therapy was initiated while they were receiving amlodipine and nifedipine to evaluate the effect of fluconazole–DCCB interactions on the antihypertensive effect of amlodipine and nifedipine.

## MATERIALS AND METHODS

**Study Design and Target Patients** This was a single-center, backward-looking, observational study conducted at Akita City Hospital from April 2016 to March 2021. The inclusion criteria were as follows: 1) patients who had received the same dose of DCCBs for at least 1 month, 2) patients who initiated fluconazole therapy after admission, and 3) patients whose blood pressure was measured at least twice per day. The exclusion criteria were as follows: 1) patients receiving drugs other than fluconazole that have been reported to be potent inhibitors of CYP3A4 (e.g., voriconazole, itraconazole, clarithromycin, erythromycin, diltiazem, verapamil, grapefruit juice),<sup>4)</sup> 2) patients receiving drugs that have been reported to induce CYP3A4 (e.g., rifampicin, phenytoin, carbamazepine, efavirenz and Saint John's wort),<sup>5)</sup> 3) patients who were diagnosed with sepsis or any infections and initiated antimicrobial therapy during the study period, 4) patients with a body temperature of 37.8°C or higher, 5) patients with bleeding disorders, and 6) patients diagnosed with acute kidney injury.

**Survey Items** The primary endpoint was the change in mean systolic blood pressure. The systolic and diastolic blood pressures were recorded for 15 days, from 2 days before to 13 days after the start of fluconazole treatment. Sex, age, body weight, body mass index, underlying medical conditions, DCCB and fluconazole doses, and concomitant drugs were investigated as patient background parameters. These data were recorded by retrospectively examining the patients' electronic medical records.

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**Table 1.** Characteristics of Patients

Number of patients, n	26
Sex, Male/Female	14 / 12
Age, years	71.8 (7.5)
Body weight, kg	57.8 (10.9)
BMI	23.1 (3.4)
Underlying disease, n	
Hematologic malignancy	19
Diabetes	9
Cardiovascular disease	7
Chronic kidney disease	4
Solid cancer	1
Calcium channel blocker	
Amlodipine, n	21
10 mg/d	15
5 mg/d	6
Nifedipine, n	5
40 mg/d	3
20 mg/d	2
Fluconazole, n	
100 mg/d	26
Concomitant drug, n	
Angiotensin receptor antagonist	12
Olmesartan	4
Azilsartan	3
Candesartan	3
Valsartan	2
Loop diuretic	4
Furosemide	3
Azosemide	1
Beta blocker	3
Bisoprolol	3
Alpha blocker	1
Doxazosin	1
Chemotherapy	
R-CHOP	6
BR	6
High-dose corticosteroid pulse	3

Continuous variables are presented as mean (standard deviation).

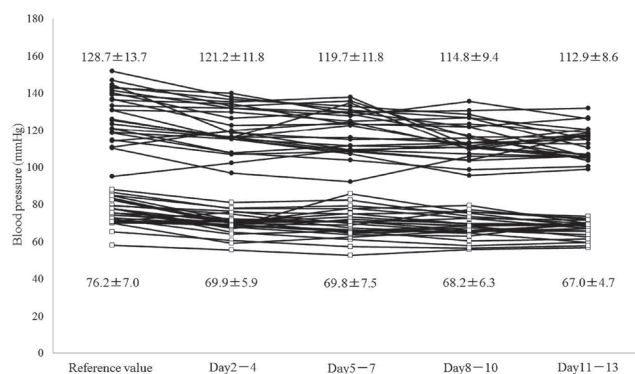
BMI: body mass index, R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, BR: bendamustine plus rituximab.

**Statistical Analysis** For each patient, the mean systolic and diastolic blood pressure over 3 days, specifically 2 days before starting fluconazole treatment and the first day of fluconazole treatment (day 1), was used as the reference value to compare the mean systolic and diastolic blood pressure calculated every 3 days after day 1 until day 13. Paired t-tests were used for the comparison of reference values and day 11 to day 13. Statistical significance was set at  $p < 0.05$ . EZR ver. 1.36 was used for statistical analysis.

**Ethical Considerations** This study was conducted in accordance with the “Ethical Guidelines for Life Science and Medical Research Involving Human Subjects” and was approved by the Ethics Committee of Akita City Hospital (Reception No. 21–24).

## RESULTS

During the study period, 31 patients received DCCBs and fluconazole. Of these, one patient on clarithromycin, one patient on carbamazepine, one patient on antimicrobial agents due to infection, and two patients with a body temperature of 37.8°C or higher were excluded, leaving 26 patients for the final study. The background of patients included in the study is shown in

**Fig. 1.** Change in Mean Systolic and Diastolic Blood Pressure

Circles: systolic pressure, Squares: diastolic pressure. Each point represents data from an individual patient. The mean blood pressure over 3 days, specifically 2 days before starting fluconazole treatment and the first day of fluconazole treatment (day 1), was used as the reference value to compare the mean blood pressure calculated every 3 days after day 1 until day 13. Data are presented as mean ± standard deviation.

**Table 2.** Mean Difference in Systolic Blood Pressure (mmHg)

	All patients (n = 26)	Treatment with amlodipine (n = 21)	Treatment with nifedipine (n = 5)
Reference value	128.7 ± 13.7	129.9 ± 14.2	123.7 ± 19.0
Day 11–13	112.9 ± 8.6	113.7 ± 8.7	109.8 ± 8.4
Mean of the differences	-15.8	-16.2	-13.9
(95% CI)	(-21.1 to -10.4)	(-21.8 to -10.6)	(-36.9 to 9.1)
<i>p</i> value	< 0.01	< 0.01	0.17

Data are presented as the mean ± standard deviation. *p* values were calculated using paired t-test. 95%CI: 95% confidence interval.

Table 1. Most patients were elderly and had underlying hematologic malignancies. Amlodipine and nifedipine were the first and second most commonly administered DCCBs, respectively. Fluconazole (100 mg/d) was administered to all patients.

Angiotensin II receptor antagonists (ARBs) are the generally used antihypertensive drugs, followed by loop diuretics. No new antihypertensive drugs (ARBs or DCCBs) were administered during the study period. A total of 12 patients received several antineoplastic drugs for the treatment of hematologic malignancies. The doses of amlodipine and nifedipine were reduced from 5 mg/d to 2.5 mg/d and from 40 mg/d to 20 mg/d, respectively, in two patients owing to a decrease in blood pressure.

Changes in blood pressure are shown in Fig. 1. Based on the predefined reference value, a decrease in the mean blood pressure was observed from day 2 to day 13 of the fluconazole treatment period. The mean difference between the reference values and the systolic blood pressure from day 11 to day 13 is shown in Table 2. In all patients, the systolic blood pressure from day 11 to day 13 was significantly lower than the reference value ( $p < 0.01$ ). The difference between the reference value and the systolic blood pressure in all patients and in the group of patients treated with amlodipine was -15.8 mmHg (95% CI: -21.1 to -10.4) and -16.2 mmHg (95% CI: -21.8 to -10.6), respectively. Similarly, the difference of systolic blood pressure in the patients treated with nifedipine was -13.9 mmHg, although there was no statistical significance.

## DISCUSSION

In the present study, we investigated the effect of the interaction between DCCBs and fluconazole on the antihypertensive activity of DCCBs. The results showed that the mean blood pressure decreased when fluconazole was administered to patients receiving DCCBs.

Most patients enrolled in this study were receiving treatment for hematologic malignancies. The treatment included a regimen of corticosteroids, which may have influenced the changes in blood pressure in this study. As oral fluconazole effectively prevents fungal infections in neutropenic patients, the reason for administering fluconazole might be to avoid infections caused by *Candida*.<sup>6)</sup> As some patients were treated with high-dose corticosteroids, occurrences of blood pressure elevation, possibly due to corticosteroid use, have been reported. In addition to DCCBs, many patients were concomitantly treated with ARBs. The involvement of CYP in the metabolism of ARBs is minimal; hence, the inhibition of CYP by fluconazole would not alter the effect of ARBs. Non-pharmacological factors which can decrease blood pressure comprising dehydration, hemorrhage, and sepsis were excluded. Accordingly, the decrease in blood pressure might be due to the interaction between DCCBs and fluconazole.

Some DCCBs are increased by inhibiting hepatic and intestinal CYP3A4 mediated by grapefruit juice and CYP3A4 inhibitor.<sup>7,8)</sup> In the present study, a significant decrease of blood pressure was observed after the start of the administration of fluconazole. In other words, hepatic CYP3A4 was inhibited instantaneously after initiating fluconazole treatment, which increased the blood concentration of DCCBs and enhanced their antihypertensive effect. The previously reported effect of the interaction between nifedipine and fluconazole on blood pressure was observed quickly, and the change in blood pressure was more than 10 mmHg, which was consistent with the results of this study.<sup>3)</sup> We speculate that the lack of significant blood pressure reduction in the group of patients treated with nifedipine in this study was owing to the limited number of patients. Most of the patients included in this study were administered amlodipine, which is less susceptible to the inhibition of intestinal CYP3A4 by grapefruit juice.<sup>9)</sup> However, an increase of more than 1.5-fold in the AUC of amlodipine was observed when administered in combination with diltiazem, which inhibited hepatic CYP3A4.<sup>10)</sup> The hypotensive effect of amlodipine might be also enhanced owing to its interaction with fluconazole. This is the first paper on the interactions between amlodipine and fluconazole to date.

Conversely, this study has several limitations. First, it was

a single-center, retrospective, observational study with few patients. Second, the number and duration of blood pressure measurements differed between patients; therefore, various biases might have occurred in the study. Third, we did not measure blood concentrations of DCCBs. Fourth, several patients were treated for hematologic malignancies, but these biases have not been excluded. To overcome these limitations, prospective studies that measure the blood levels of DCCBs before and after drug interactions and regular blood pressure measurements are needed.

The reason underlying the decrease in blood pressure in response to the combination of DCCBs and fluconazole is unclear, owing to the limitations mentioned. Therefore, caution should be exercised with the concomitant use of these drugs.

**Conflict of interest** The authors declare no conflict of interest.

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