Influence of Cisapride on the Pharmacokinetics and Antihypertensive Effect of Sustained-Release Nifedipine

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To investigate the clinical significance of interactions between cisapride and sustained-release nifedipine, we compared the plasma nifedipine concentration and blood pressure after administration of nifedipine alone (20 mg) with those obtained after administration of nifedipine with cisapride (2.5 mg) in 20 patients with hypertension. The plasma nifedipine level was not altered by cisapride at one hour after administration, but was significantly increased at two (p<0.01), three (p<0.01), and four (p<0.05) hours when compared with the level measured after nifedipine alone. Cisapride significantly decreased the mean blood pressure at three hours (p<0.05) after administration of nifedipine. The acetaminophen method was used to determine gastric emptying time. The plasma concentration of acetaminophen at 45 minutes after administration was significantly increased by cisapride, suggesting that enhanced gastrointestinal motility might be the basis for the increase in the plasma nifedipine concentration. These results suggest that enhancement of the antihypertensive effect of nifedipine can occur when the drug is prescribed with cisapride, and that caution is needed when using such a combination therapy.

(Key words: drug interaction, plasma concentration, gastrointestinal motility, pharmacokinetics)

Introduction

Many middle-aged to elderly patients with hypertension have other diseases and it is thus common for such individuals to receive antihypertensive therapy concurrently with other agents. Drugs for the treatment of various gastrointestinal diseases can affect the absorption of antihypertensive agents and those are often prescribed with antihypertensive agents. Most antihypertensive agents are absorbed through the small intestine and show a pharmacological effect after a sufficient increase in their blood concentration (1). Although gastrointestinal drugs have the potential to produce significant interactions with antihypertensive agents, few studies on the concurrent administration of these two types of drugs have been performed. Because one of the most commonly used classes of antihypertensive agents is calcium antagonists such as nifedipine, nicardipine, or diltiazem (2), it is important to examine possible interactions between calcium antagonists and gastrointestinal agents.

Cisapride (Risamol(R)) is a gastrointestinal agent that increases gastrointestinal motility from the esophagus to the large intestine by facilitating the release of acetylcholine in the myenteric plexus, especially in the small intestine where many antihypertensive agents are absorbed (3). Therefore, cisapride can alter the pharmacokinetics of antihypertensive agents and thus modulate their antihypertensive effect. Although the interactions between cisapride and other drugs (e.g. cimetidine, diazepam, and digoxin) have been investigated (4-6), concomitant administration of cisapride with antihypertensive agents has not been studied previously.

In the present study, we investigated the influence of cisapride on the plasma concentration and the antihypertensive effect of a commonly prescribed calcium antagonist, sustained-release nifedipine (Adalat-L(R)), in patients with essential hypertension. We found that cisapride had a significant effect on the plasma concentration and the blood pressure-lowering ability of nifedipine which suggested the need for caution in the concomitant use of these agents.
Methods

Subjects

Twenty inpatients [15 men and 5 women aged 65.8±2.8 years (mean±S.E.M.)] with essential hypertension [mild to moderate hypertension (7)], who were treated at The Jikei University School of Medicine or affiliated institutions, were enrolled in this study. Patients with secondary hypertension, a history of abdominal surgery, serious gastrointestinal disease or severe cardiovascular complications were excluded. The details of this study were explained to the patients and informed consent was obtained.

Other agents which might affect blood pressure or gastrointestinal motility were not administered to the patients. In addition, strenuous physical exercise was prohibited during the study period.

Drug administration

All antihypertensive agents were discontinued one week prior to the study. On the day of the study, a 20-mg sustained-release nifedipine tablet was ingested after breakfast (8:30 AM). Plasma nifedipine concentration and blood pressure were determined at the specified times. After the administration of nifedipine alone, a washout period of at least four days was allowed. On the day of the second phase of the study, a 2.5-mg cisapride tablet was administered 30 minutes before breakfast and nifedipine was administered at the same time as in the first phase of the study. The plasma nifedipine level and blood pressure were then monitored.

Measurement of plasma nifedipine and blood pressure

Before and at 1, 2, 3, and 4 hours after nifedipine administration, blood samples were obtained from an indwelling cannula with a heparin lock, which was inserted into an antecubital vein. The nifedipine concentration was determined by high performance liquid chromatography (8). Blood pressure was measured in the supine position before and at 1, 2, 3 and 4 hours after the administration of nifedipine.

Assessment of gastrointestinal motility

The acetaminophen method was used to determine gastric emptying time (9). Harasawa et al (1979) reported that the 45-minute blood concentration of acetaminophen could be used as an index of gastric emptying, because they found the peak concentration of acetaminophen occurred at 45 minutes after administration in patients with duodenal ulcer, whose gastric emptying is thought to be accelerated (10). It has also been reported that the rate of gastric emptying is related to both the time of the peak plasma concentration and the maximum concentration of acetaminophen, since more rapid gastric emptying causes an earlier peak plasma concentration and a higher maximum concentration (9). Therefore, we measured the 45-minute plasma acetaminophen concentration when nifedipine was given alone or in combination with cisapride, and used it to compare the rate of gastric emptying. A 1.5-g dose of acetaminophen was administered at the same time as nifedipine (with or without cisapride), and the blood level of acetaminophen was determined at 45 minutes after administration.

Statistical analysis

Differences between data obtained after the administration of nifedipine alone and after nifedipine plus cisapride were assessed using paired r-test and p<0.05 was taken to indicate statistical significance. Results are shown as the mean±S.E.M.

Results

In the course of this study, subjects had no adverse effects of nifedipine such as flushing, palpitation or headache. Laboratory findings revealed no significant changes in the biochemical data.

Plasma nifedipine concentration (Fig. 1)

When nifedipine was administered alone, its plasma concentration increased at a relatively constant rate until 4 hours after administration. When cisapride was administered with nifedipine, the plasma nifedipine concentration at 1 hour after administration was similar to that obtained with nifedipine monotherapy (83.8±27.2 nmol/l for nifedipine alone and 87.1±26.8 nmol/l for nifedipine plus cisapride, p>0.05). However, from 2 hours onwards, the plasma nifedipine concentration was significantly increased by cisapride administration. The blood level of nifedipine was increased by cisapride at 2 hours (from 122.1±36.9 to 235.1±37.7 nmol/l, p<0.01), at 3 hours (from 133.8±34.4 to 276.9±42.1 nmol/l, p<0.01), and at
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Figure 2. Effect of cisapride on the antihypertensive effect of nifedipine. Percent changes in mean blood pressure (MBP) were determined after nifedipine alone (○) and nifedipine plus cisapride (●). Symbols show the mean ± S.E.M. values for 20 patients. A significant difference in MBP was noted at 3 hours. *p<0.05.

Figure 3. Effect of cisapride on plasma acetaminophen concentration. Plasma acetaminophen concentration was measured at 45 minutes after the administration of 1.5-g of acetaminophen with nifedipine alone (left column) or nifedipine plus cisapride (right column). Each column shows the mean value for 20 patients and the error bars show the S.E.M. (from 176.7±44.0 to 282.6±39.3 nmol/l, p<0.05) after administration.

Antihypertensive effect of nifedipine (Fig. 2)
Baseline mean blood pressure (MBP) was determined before drug administration in both phases of the study and there were no statistically significant differences between the baseline levels measured in the two phases [114.0±2.8 mmHg for nifedipine alone and 112.3±2.8 mmHg for nifedipine plus cisapride (p>0.05)]. To compare the changes in the MBP between nifedipine alone and nifedipine with cisapride, the change in the MBP was normalized with the baseline blood pressure and was expressed as percentage.

One hour after the administration of nifedipine alone, MBP was significantly decreased by 13.4±2.9%. However, there was no further significant decrease thereafter. When cisapride was administered with nifedipine, MBP decreased by 14.5±2.6% at 1 hour after administration. This value was not significantly different from the value obtained at 1 hour after nifedipine alone (p>0.05). However, there were significant decreases in MBP at 2 and 3 hours after administration, and the 3-hour MBP was significantly lower with combined therapy than with nifedipine alone (12.6±3.7% vs 22.5±2.9%, p<0.05). A similar difference between combined therapy and nifedipine alone was seen at 4 hours although no significant difference was observed (14.2±3.1% vs 18.7±3.4%, p>0.05) (Fig. 2).

Gastric emptying (Fig. 3)
The plasma acetaminophen concentration at 45 minutes after administration was significantly higher after cisapride plus nifedipine than after nifedipine alone (72.8±11.4 vs 41.3±6.7 nmol/l, p<0.01) (Fig. 3). This result indicated that cisapride accelerated gastric emptying (9, 10).

Discussion
The pharmacokinetics and metabolism of nifedipine have been described previously (11). It is known that the blood concentration of nifedipine is closely related to the blood pressure (12). There have also been a few reports on the interactions between sustained-release nifedipine and other cardiovascular agents (13–17). It was reported that nifedipine increased the plasma concentration of digoxin by 45% in 9 of 12 volunteers by an unknown mechanism (13), whereas others reported no significant changes in the serum digoxin levels by the concurrent use of nifedipine (14, 15). One possible mechanism for the increase in the serum digoxin levels is an inhibition of the clearance of digoxin as suggested for the interaction between digoxin and verapamil (18). It was also observed that excessive hypotension or left ventricular depression developed when nifedipine was administered with alpha- or beta-adrenoceptor blockers (16, 17).

The only studies on the concomitant administration of nifedipine with gastrointestinal agents are related to histamine H2 blockers (19). Cimetidine and ranitidine have been shown to inhibit the hepatic metabolism of nifedipine and to reduce...
gastric acid secretion, resulting in an increased gastrointestinal pH and an enhanced bioavailability of nifedipine (19). Unlike nifedipine capsules, sustained-release nifedipine is reported to show pH-independent dissolution (20), suggesting that its absorption would be largely influenced by changes in gastrointestinal motility. The effect of food intake on pharmacokinetics of sustained-release nifedipine has been assessed previously (21). When a 20-mg tablet of sustained-release nifedipine was administered under fasting conditions, the peak blood concentration was seen at 2–3 hours and the half-life was approximately 4 hours. In contrast, when the same nifedipine tablet was ingested after food, absorption of the drug was delayed and the peak blood concentration was increased (21).

Cisapride selectively stimulates the myenteric plexus and thus increases gastrointestinal motility (3). Therefore, gastric absorption might be decreased and absorption from the small intestine would be enhanced by cisapride (3). Interactions between cisapride and cimetidine, diazepam, and digoxin have been investigated previously (4–6). Cisapride shortened the time to peak plasma concentration and enhanced the gastrointestinal absorption of cimetidine (4). Cisapride also increased the initial rate of absorption of diazepam by enhancing gastric emptying (5). However, the gastrointestinal absorption of digoxin was reduced by cisapride, although the time required to reach the peak plasma concentration was not altered (6).

In the present study, plasma nifedipine concentration was increased by the concurrent administration of cisapride, while MBP was lower with combined administration compared with nifedipine monotherapy. These results suggest that the concurrent administration of cisapride increases the blood level of nifedipine and enhances its antihypertensive effect, and that a marked decrease in blood pressure may occur when these two agents are used concomitantly. Therefore, caution is needed in the case of such a combined therapy.

We monitored the plasma concentration of nifedipine and blood pressure for only a few hours in the present study. However, excessive hypotension soon after the administration of antihypertensive agents can cause various adverse effects, such as headache, dizziness, and reflex tachycardia (22). Recently, it was reported that treatment with short-acting calcium antagonists, such as nifedipine capsules, could worsen the prognosis of patients with coronary artery disease (23). Because patients with hypertension often have coronary artery disease and the rapid onset of hypotension is one of the important features of preparations such as nifedipine capsules (21), enhancement of the hypotensive effect of sustained-release nifedipine may cause similar adverse effects.

The influence of cisapride on the steady-state effect of sustained-release nifedipine should be determined in the future. The effect of cisapride on hepatic drug metabolizing enzymes also needs to be investigated because the elimination of nifedipine is known to be a result of hepatic metabolism (11).

In the present study, we chose middle-aged to elderly people with hypertension as subjects, because sustained-release nifedipine is used safely in this age group and many patients who receive antihypertensive agents belong to this age group. Since this interaction between nifedipine and cisapride possibly occur in all age groups with hypertension, it is important to clarify this possibility in the future.

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References

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