Effect of an Acute Dose of Alcohol on the Pharmacokinetics of Oral Nifedipine in Humans

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Pharmacokinetic and pharmacodynamic interactions of alcohol and nifedipine were assessed in 10 healthy human volunteers. Doses of 20 mg (2 × 10-mg capsules) of nifedipine were administered with either 150 ml of orange juice or 75 ml of alcohol (94%) in 75 ml of orange juice according to a crossover randomized design. Plasma nifedipine levels were monitored for 16 hr after each dosing, along with pulse rate and blood pressure. The relative bioavailability of nifedipine, measured as AUC, was increased by 54% (533 vs 346 ng · hr/ml) after the dose of alcohol ($P < 0.0002$). However, there were no significant differences between treatments in C_{max}, t_{max}, or $t_{1/2}$. Although there was no difference in the systolic and diastolic blood pressure and pulse rate between the two treatment groups, the time to reach peak heart rate was significantly faster in the group treated with alcohol (1.4 vs 2.2 hr). This study shows that ethanol increases the bioavailability of nifedipine and decreases the time for onset of increased heart rate.

KEY WORDS: nifedipine; alcohol interaction; human pharmacokinetics; pharmacodynamics.

INTRODUCTION

Nifedipine, a calcium channel antagonist, is used for the treatment of angina pectoris and hypertension. The usual adult dose is 1 to 3 capsules of 10 mg per day, with a maximum of 120 mg per day. After oral administration, nifedipine is rapidly and almost completely absorbed, with peak plasma concentrations generally being attained within 1 to 3 hr; further, less than 10% of circulating drug is available as unbound drug (1). Nifedipine undergoes extensive first-pass metabolism in man following oral administration (2–4), which results in a systemic bioavailability of about 50%, though some investigators have reported up to 77% of absorption (5). The first-pass metabolism appears to occur mainly in the liver, as patients with liver cirrhosis show reduced systemic clearance with increased bioavailability compared to normal subjects (6). The initial oxidation of this dihydropyridine in rat and human liver has been reported to occur by the cytochrome P-450 system (7). The nitropyridine analogue, a major circulating metabolite, is present at concentrations approaching those of the parent drug after oral but not intravenous dosing (3). In human, the plasma elimination half-life of nifedipine is 3–4 hr, with most drug being eliminated in urine as metabolites and practically no unchanged nifedipine being recovered.

Ethanol-drug interactions are common, because of the prevalence of alcohol use in society (8). These interactions are complex and drug specific and vary with chronic and acute alcohol use. Short-term consumption of alcohol may temporarily decrease the clearance of drugs metabolized by oxidative metabolism. A decrease in oral clearance has been observed in humans with high-hepatic clearance drugs such as chlormethiazole, dextropropoxyphene, chlorpromazine, and triazolam (9). Few studies have been carried out on the interaction of ethanol and calcium channel blockers (10,11). Bailey *et al.* (11) have shown that ethanol alters the hemodynamic effects of felodipine, a dihydropyridine calcium channel antagonist. In the case of nifedipine, *in vitro* (12) and *in vivo* (13–15) drug–drug interactions with ethanol have also been shown to occur. When administered intravenously to rats an increase in half-life and area under the plasma concentration–time curve (AUC) for nifedipine resulted after alcohol ingestion (13–15). These investigators indicated that this effect might be due to a competitive metabolic inhibition of the cytochrome P-450 enzyme system, since both ethanol and nifedipine are dehydrogenated in their metabolic pathways (7,16). If there is metabolic competition between these two agents, one would expect even greater inhibitory effect after oral drug administration, as the drug has to pass through the portal system before it reaches the systemic circulation. As yet there have been no human studies of this interaction to assess the potential clinical impact of concomitant administration of these two agents. The aim of this investigation was to determine the interaction of ethanol and nifedipine in healthy human volunteers after acute administration.

MATERIALS AND METHODS

Materials. Nifedipine and nitrendipine were purchased from Sigma (St. Louis, MO). A sample of the nitropyridine metabolite, dehydronifedipine, was kindly supplied by Miles Laboratories, Toronto, Canada. The dosage form administered was conventional 10-mg capsules of nifedipine (ADALAT, Miles Laboratories, Toronto, Canada).

Internal Standard (IS) Solution. A 100-μl aliquot of nitrendipine solution (0.56 μg/ml) in 5% aqueous methanol was used for spiking the plasma samples.

Subjects. Ten healthy male volunteers (aged 25.7 ± 3.0 years and weighing 72.9 ± 3.4 kg) participated in the study. None of the volunteers had any history of cardiac, hepatic, renal, or gastrointestinal diseases. All had normal physical, electrocardiogram and biochemical/hematological profiles. They were instructed to abstain from their usual/casual alcohol use for at least 10 days prior to the study day and received no other drug for at least 1 month before the study.

Experimental Protocol. The study protocol was approved by the institutional Human Ethics Committee (Hospital Maisonneuve, Rosemont, Montreal) and volunteers gave informed consent for their participation. The study was conducted as a double-blind, placebo-controlled, random-

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ized trial. All volunteers received a single 20-mg oral dose of nifedipine (2× Adalat 10-mg capsules) on separate occasions, with a 1-week interval between treatments, once in the alcohol-free (control) phase and again with alcohol (treatment phase) administration following an overnight fast. The capsules were administered with either 150 ml of orange juice or 75 ml of orange juice containing 75 ml of alcohol (94%). The total volume of fluid was 150 ml and it was consumed over a 10-min period.

Systolic and diastolic blood pressure and pulse rate were recorded just before drug administration (0 time), at every hour for 6 hr, and at 9, 12, and 16 hr after drug administration, using a semiautomated system. All measurements were the mean of three readings.

Venous blood samples (10 ml) were drawn into EDTA-containing tubes immediately prior to the drug administration (0 time) and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 16 hr after drug administration. The blood samples were then centrifuged, plasma was transferred, and the samples were stored frozen at −20°C until analyzed. The blood/plasma samples were adequately protected from light by either covering the container with aluminium foil or working under yellow fluorescent lights.

Drug Analysis. Concentrations of nifedipine in plasma were determined by a gas chromatographic assay with electron capture detection using a modification of the method described by Lutz *et al.* (16) in which chromatographic separation was achieved isothermally at 240°C, rather than by temperature programming. The chromatographic separation was achieved on a HP 5710A (Hewlett Packard, CA) chromatograph equipped with a ^{63}Ni electron capture detector and a DB-5 megabore capillary column (15 m × 0.53-mm I.D., 1.5-μm film thickness) obtained from J&W Scientific, CA. The detector, injector, and oven temperatures were 300, 250, and 240°C, respectively. A 2-μl volume was injected in the splitless mode onto the column by means of an autosampler. Helium was used as carrier gas, having a flow rate of 17 ml/min. The makeup gas was an argon/methane mixture (95:5) maintained at a flow rate of 25 ml/min. The elution times for the pyridine metabolite, nifedipine, and IS were 2.1, 5.0, and 7.8 min, respectively.

Calibration curves were linear over the concentration range (2.5–100 ng/ml), with minimal intercepts and high correlation coefficients (>0.999). Precision (CV) of the method was better than 10% over the calibration range. Samples were analyzed in duplicate, and the average of each pair was used for calculations of the pharmacokinetic parameters.

Data and Statistical Analysis. The AUC_{0-16} for nifedipine in plasma was computed by linear trapezoidal rule. The plasma elimination half-lives ($t_{1/2}$) were estimated from the terminal linear portion of the semilog plot of plasma concentration–time curves by least-squares regression. Pharmacokinetic parameters were determined for individual subjects, and the mean and standard deviation for each parameter were then computed. Statistical evaluations were performed by analysis of variance (ANOVA) for the crossover design using SAS (SAS Institute Inc., Cary, NC).

RESULTS

Analytical Methodology. The chromatographic traces of blank plasma, plasma with added nifedipine, pyridine metabolite, and nitrendipine and a plasma sample from a volunteer at 1 hr are shown in Fig. 1. The method was capable of separating the nifedipine and metabolite and was also free from interference from the endogenous compounds. Metabolite concentrations could not be reliably quantitated because of an interfering peak in the sample.

Pharmacokinetic Parameters. The mean plasma concentration–time profiles of nifedipine are shown in Fig. 2. The plasma nifedipine concentrations following alcohol treatment were higher than those of non-alcohol-treated subjects.

The pharmacokinetic parameters derived in the present investigation are summarized in Table I. A comparison of AUC_{0-16} and $AUC_{0-\infty}$ values revealed that the mean AUC values for the alcohol treatment were 54% greater than that obtained without alcohol. The apparent plasma nifedipine clearance (CL_{oral}) was also decreased (>34%) with the alcohol treatment. Further, intersubject variation, as indicated by the standard deviations (Table I), was smaller in the alcohol-treated group. The time taken to reach peak plasma concentration (T_{max}) was similar with both treatments. The mean peak plasma concentrations (C_{max}) for the two treatments were also not significantly different from each other.

Pharmacodynamic Parameters. The blood pressure and pulse rate profiles for both groups are summarized in Fig. 3. Both systolic and diastolic mean blood pressure values were similar with both treatment phases. However, the time to reach the peak pulse rate value was significantly decreased with alcohol (1.4 vs 2.2 hr; $P < 0.05$).

DISCUSSION

All of the volunteers, except one who experienced confusion related to alcohol, tolerated the dose very well in both phases (control and treatment) without any serious adverse effects. Although high, the dose of alcohol was selected based upon literature reports of the dose used in similar acute dose interaction studies (11,18).

In this study, a 20-mg oral dose of nifedipine alone produced plasma nifedipine profiles and derived pharmacoki-

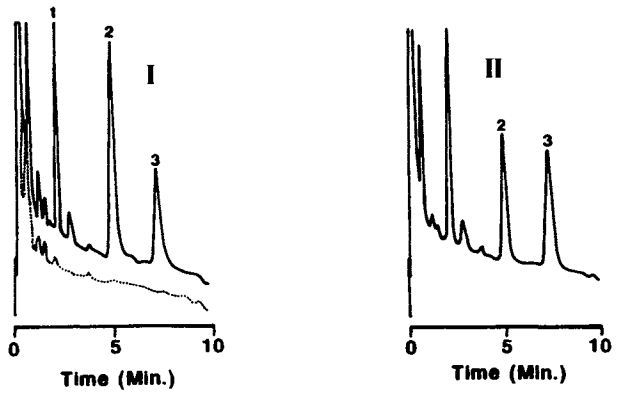

Fig. 1. Chromatographic traces: (I) blank plasma (••••), plasma with added nifedipine (64 ng/ml) and nitropyridine metabolite (30 ng/ml) (——); (II) plasma of a volunteer 1 hr after dosed with nifedipine (20 mg). Peaks: 1, dehydronifedipine (metabolite); 2, nifedipine; 3, nitrendipine (IS).

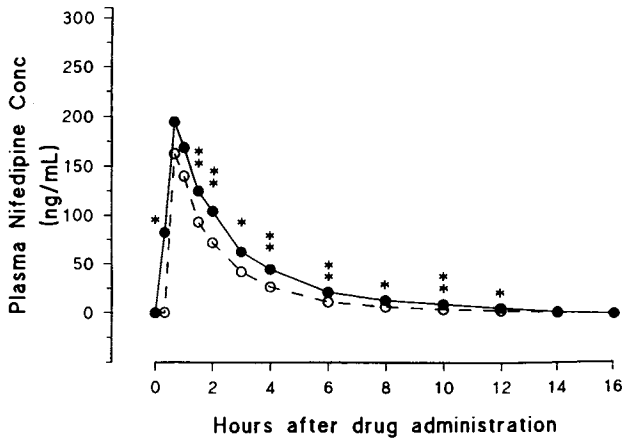

Fig. 2. Mean plasma concentrations of nifedipine vs time after nifedipine only (○---○) or in combination with alcohol (●——●). (*) $P < 0.05$; (**) $P < 0.01$.

netic parameters similar to those reported by others (5). Except at 0.67, 1, 14, and 16 hr, plasma nifedipine levels were significantly ($P < 0.05$) higher with alcohol treatment than with nifedipine alone, which in turn reflected an increase in AUC and a decreased clearance. There were, however, no differences in the C_{max}, t_{max}, and $t_{1/2}$ values (Table I). Nifedipine appeared significantly earlier in the systemic circulation in case of alcohol treatment. Except for one volunteer, plasma nifedipine was detected at 0.33 hr with alcohol (82.8 ± 118.8 vs 0.44 ± 1.4 ng/ml; $P < 0.05$) but, in its absence, only at later sampling times.

From *in vivo* and *in vitro* studies in the literature (12–15), it has been demonstrated that ethanol inhibits the metabolism of nifedipine. Consequently higher plasma nifedipine concentrations and slower rates of elimination would be expected following concurrent administration of ethanol since both nifedipine and alcohol are metabolized by a common pathway (16). In this study, higher plasma nifedipine levels were observed in the presence of alcohol, but with no significant differences in elimination rates. The fact that nifedipine appeared sooner in the circulation in the presence of alcohol with significantly higher concentrations at 0.33 hr, as well as the C_{max} values almost attaining a significant difference ($P = 0.06$), suggests that this coadministration increases the absorption rate of nifedipine. This is possible, as alcohol is known to decrease the stomach emptying rate and could provide a better drug solubility environment. However, with an increased absorption rate alone, higher plasma

Table I. Pharmacokinetic Parameters Obtained After Nifedipine Alone or with Alcohol Administration of 20 mg Nifedipine in 10 Healthy Subjects[a]

	Nifedipine	Nifedipine + alcohol	
$AUC_{0-\infty}$ (ng · hr/ml)	360 ± 100	552 ± 72	($P < 0.0002$)
AUC_{0-16} (ng · hr/ml)	346 ± 95	533 ± 66	($P < 0.0002$)
CL_{oral} (ml/min · kg)	13.5 ± 3.2	8.4 ± 1.0	($P < 0.0002$)
C_{max} (ng/ml)	186 ± 126	223 ± 99	
T_{max} (hr)	0.9 ± 0.4	0.9 ± 0.5	
$t_{1/2}$ (hr)	3.6 ± 1.3	3.1 ± 1.3	

[a] Values are mean ± SD.

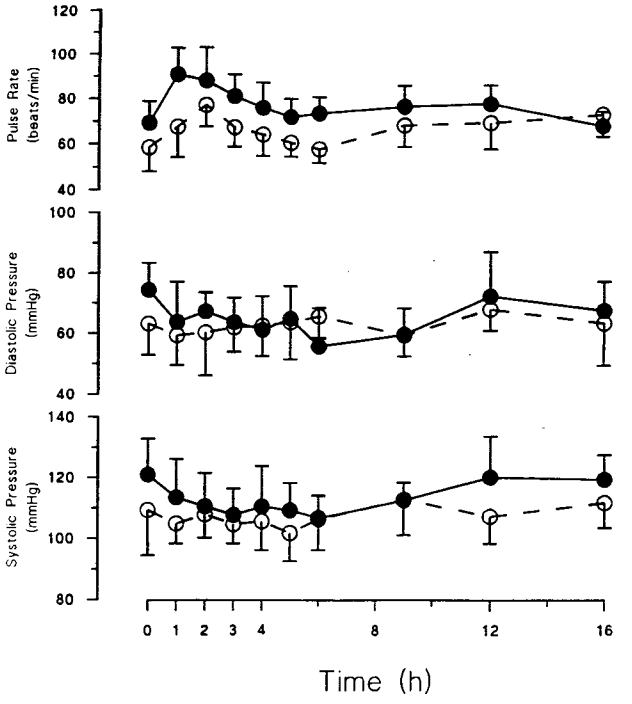

Fig. 3. Time course of systolic pressure, diastolic pressure, and heart rate after nifedipine alone (○---○) or in combination with alcohol (●——●) administration.

concentrations would occur only if the metabolic system in liver were saturated, and this is difficult to assume with high-hepatic extraction drugs such as nifedipine. Further, the increase in AUC cannot be explained solely by an increase in extent of absorption, as it has been reported that nifedipine is almost completely absorbed after oral administration (1). Therefore, it is proposed that both increased absorption and metabolic inhibition might be occurring simultaneously, i.e., initially a faster absorption rate is followed by inhibition and, finally, as ethanol is metabolized, a return to the normal rate of nifedipine metabolism. This assumption explains the earlier appearance of nifedipine in plasma, the higher plasma nifedipine levels, and the higher AUC values following alcohol treatment. A similar situation is described by Bailey *et al.* (18).

Both treatments appear to produce lower blood pressures compared to the initial values. However, no significant difference in change of blood pressure values between treatments was detected. Kleinbloesen *et al.* (6) have shown that pharmacodynamic effects of nifedipine are related to the plasma nifedipine concentrations. Although, alcohol produced significantly higher plasma nifedipine levels at 10 of 14 time points, this was not reflected in a change of blood pressure in the volunteers.

The mean pulse rate increased following ethanol and nifedipine, compared to that obtained with nifedipine alone. However, the percentage changes with respect to the baseline values were similar with both treatments. This lack of difference could be because of the different baseline pulse rate values in two treatment groups, 69 ± 9.5 vs 58 ± 10.4 ($P < 0.05$), with nifedipine and alcohol treatment and with nifedipine only, respectively. Nonetheless, the time to reach

the peak value was shorter with alcohol treatment as compared to nifedipine alone (1.4 vs 2.2 hr; $P < 0.05$). Although in this experiment the effect of alcohol alone was not evaluated, it is known to increase pulse rate. Both agents have been shown to exhibit this effect and there may be synergy, as it took more than 6 hr for the pulse rate to return to the baseline levels.

In conclusion, a drug interaction occurs between alcohol and nifedipine in human volunteers, as previously reported in rats (13–15). This interaction resulted in a 54% increase in relative bioavailability of the drug when administered with alcohol as compared to nifedipine alone. Although this increase in AUC did not produce significant differences in the pharmacological effect, it did cause a reduction in the time of onset of increased pulse rate. Although no major increase in any effect was detected in the healthy volunteers, an adverse effect may occur in patients treated with nifedipine for different indications. Therefore patients should be warned to avoid or reduce alcohol consumption when being treated with nifedipine.

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