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Effects of Nifedipine and Diltiazem on Pharmacokinetics of Cefpodoxime Following Its Oral Administration

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We compared the effects of nifedipine and diltiazem on the uptake of cefpodoxime proxetil (CP). The study was aimed at establishing the impact of increased mesenteric blood flow due to calcium channel blockers on passive transport. Twelve volunteers were given CP (200 mg) orally in a crossover design. The absorption, disposition, and elimination parameters of cefpodoxime were compared among the following three treatment groups: CP alone, CP following oral administration of diltiazem (60 mg), or CP following oral administration of nifedipine (20 mg). No statistically significant difference in pharmacokinetic parameters was observed between the three treatment groups.

Two groups of oral beta-lactam antibiotics are available. The first comprises nonester amino beta-lactams, such as amoxicillin and cefixime, which are absorbed via the dipeptide transport system. The second group consists of absorbable esters of parenteral beta-lactams and includes cefpodoxime proxetil (CP), a new broad-spectrum cephalosporin. The carboxyl function on the cephem nucleus of CP is esterified by an isopropyloxycarbonyloxyethyl group to enhance its absorption after oral administration. CP is hydrolyzed during its passage through the intestinal wall, and only cefpodoxime reaches the portal venous blood. The esterases which release cefpodoxime by hydrolysis are also found in the liver and plasma (10). CP is absorbed by diffusion across the enterocyte and has an absolute bioavailability of 45.9% ± 1.5% (12).

Studies with healthy volunteers have indicated that nifedipine increases both the absorption rate and the bioavailability of amoxicillin and cefixime, without modifying their distribution or elimination (5, 15). There are three ways in which nifedipine might increase the absorption of these drugs: (i) by increasing mesenteric blood flow and thereby increasing the rate of passive transport, (ii) by slowing fluid movements through the gut, and (iii) by stimulating the dipeptide transport system, which is mainly responsible for cefixime and amoxicillin absorption in the rat (13). We compared the effects of nifedipine and diltiazem, calcium antagonists which does not affect mesenteric blood flow (6), on CP transport in order to establish (i) the specificity of the interaction between nifedipine and beta-lactams and (ii) the potential part in the interaction played by modifications in mesenteric blood flow.

Twelve healthy male volunteers (mean age, 26.5 ± 3.4 years; mean body weight, 69.8 ± 9.3 kg) were included in the study. All had unremarkable medical histories and normal physical examinations, liver and kidney functions, hematological parameters, and electrocardiograms. None had a known allergy to penicillin or had received any medication for at least 2 weeks before the start of the study. Written informed consent was obtained from each volunteer, and the study was approved by the Ethics Committee of Xavier Bichat University Hospital, Paris, France.

The volunteers were randomly given three treatments according to a crossover design: (i) 200 mg of CP (two CP tablets) alone, (ii) 200 mg of CP 30 min after the administration of a single oral dose of 60 mg of diltiazem (60-mg tablet), or (iii) 200 mg of CP 30 min after the administration of a single oral dose of 20 mg of nifedipine (two 10-mg tablets). The antibiotic was administered at 0800 h after an overnight fast. The volunteers ingested the drugs with 150 ml of water and remained standing for 2 min. A standard breakfast was served 2 h after drug administration, and a standard lunch was served at noon. Caffeine, alcohol, and smoking were prohibited on each study day, and concomitant medications were prohibited throughout the study period. An indwelling catheter was inserted into a forearm vein and was kept open with a dilute solution of heparin. There was a 10-day washout period between treatments. Blood samples were drawn just before dosing and at 15, 30, and 45 min and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h after dosing. Blood was collected into heparinized tubes, and plasma was separated by centrifugation. All samples were frozen (−80°C) until analysis.

A specific high-pressure liquid chromatography method was developed for the determination of cefpodoxime concentrations in plasma (3). Briefly, the sample workup included solid-phase extraction on a C8 cartridge. Cefpodoxime and cefaclor (internal standard) were eluted with methanol and were analyzed on an optimized system composed of a C18 stationary phase and a ternary mobile phase (acetate buffer [0.05 M; pH 3.8], methanol, and acetonitrile; 87, 10, and 3% [vol/vol], respectively) monitored at 235 nm. Between-day coefficients of variation were lower than 13.6% (0.2 μg/ml). The detection limit was 0.05 μg/ml. Individual pharmacokinetic parameters were estimated by using weighted (inverse concentration) least-squares regression (SIPHAR program, version 4.0; Simed Créteil, France). The area under the concentration-time curve from time zero to time t (AUC_{0-t}), with time t being the time of the last detectable concentration of drug in plasma, was calculated by the linear trapezoidal rule. The AUC from time t to infinity was calculated from the last measurable concentration (at time t) divided by the slope of the terminal elimination phase, which was determined by least-squares linear

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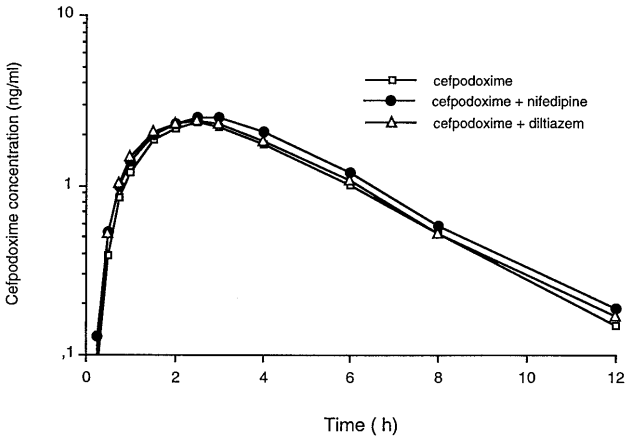

FIG. 1. Mean cefpodoxime concentrations following oral administration of CP (200 mg) alone or in combination with diltiazem (60 mg) or nifedipine (20 mg) administered orally.

regression of at least three points on the log-linear concentration decline. Pharmacokinetic parameters were calculated by standard noncompartmental/compartmental formulae. Absorption rate constants were calculated by the method of Wagner and Nelson (14).

Analysis of variance was used to compare individual parameter estimates. The time to reach the maximum concentration of drug in serum was subjected to the nonparametric Kruskall-Wallis test. In all cases, the level of statistical significance was set at 0.05.

After oral administration, cefpodoxime concentrations declined linearly (Fig. 1), suggesting that a one-compartment model was appropriate for describing cefpodoxime elimination. Table 1 lists the mean pharmacokinetic parameters calculated according to a first-order absorption with a monoexponential elimination.

There was no statistically significant difference in the absorption, disposition, or elimination parameters of cefpodoxime between the three treatment groups.

The three time courses of the cefpodoxime concentrations were similar. Fig. 1 shows the observed mean concentrations in plasma versus time for the three treatment groups.

The pharmacokinetic parameters of cefpodoxime calculated in this study are in agreement with those reported by Tremblay et al. (12).

The CP ester is hydrolyzed in the enterocyte cytoplasm. This is supported by the increase in bioavailability following concomitant food intake (which is known to suppress esterase activity) (7). However, the mechanism of cefpodoxime absorption through the basolateral membrane, via an enterocyte esterase-dependent system, is not known. Inui et al. (8), using Caco2 monolayer cells, found evidence of a specific transport system, located in the basolateral membrane, which is also involved in the efflux of cephadrine. Such a system could exist for cefpodoxime, but it would not be saturated under the conditions of our study, since the first-order model used in this study provided a reasonable fit of the drug's time course. Efflux could also be due to simple diffusion, because cefpodoxime is a zwitterion at physiological pH.

It has been reported that calcium antagonists relax vascular smooth muscle by blocking calcium influx and by preventing calcium release from intracellular stores (6). Calcium antagonists are also known to be potent vasodilators, but relatively little attention has been paid to their effects on intestinal blood flow. Nifedipine binds to dihydropyridine-specific membrane receptors in arterial smooth muscle cells (1) and in intestinal cells (9), resulting in decreased motor activity of some segments of the digestive tract, particularly the esophagus and colon (4). Some parts of the digestive tract may react differently to the blockade of calcium channels in the smooth-muscle fiber. Thus, Gasic et al. (6) showed that diltiazem at therapeutic dosages lowered systolic blood pressure without affecting splanchnic circulation, whereas nifedipine significantly reduced both systemic and splanchnic vascular resistance, producing a 15% increase in the mesenteric blood flow. In another study of fasting healthy volunteers, 30 mg of nifedipine did not modify duodenojejunal motility (11).

Because lipophilic drugs, which passively diffuse across the intestinal epithelium, are apparently dependent on mesenteric blood flow, it is interesting that nifedipine had no effect on the pharmacokinetics of cefpodoxime. The different effects of nifedipine and diltiazem on the motor activity of the digestive tract or splanchnic flow rate did not influence the pharmacokinetics of cefpodoxime. Our results indicate that the cefpodoxime lag time was not modified by nifedipine or diltiazem, which is in agreement with a previous report (2) that these drugs do not affect gastric emptying.

TABLE 1. Pharmacokinetic parameters of cefpodoxime calculated according to a first-order absorption model with monoexponential elimination[a]

Drug(s)	C_{max} (mg · liter^{-1})	T_{max} (h)	Lag time (h)	AUC_{0-t} (h · mg · liter^{-1})	$AUC_{0-\infty}$ (h · mg · liter^{-1})	k_a (h^{-1})	$t_{1/2}$ (h)	CL/F (liters · h^{-1})	V/F (liters)	MRT (h)
Cefpodoxime										
Mean	2.47	2.48	0.54	12.29	12.87	0.95	1.97	16.77	45.28	4.47
SD	0.52	0.43	0.26	2.95	3.43	0.27	0.64	4.91	10.26	0.82
Cefpodoxime diltiazem										
Mean	2.56	2.45	0.44	13.18	13.74	0.92	1.98	15.84	44.14	4.48
SD	0.64	0.49	0.25	3.76	3.94	0.25	0.45	4.72	14.04	0.52
Cefpodoxime nifedipine										
Mean	2.63	2.66	0.36	13.84	14.40	0.80	1.94	14.69	40.10	4.55
SD	0.58	0.39	0.13	3.13	3.32	0.15	0.40	3.60	8.73	0.56

[a] Abbreviations: C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; AUC_{0-t} and $AUC_{0-\infty}$, AUCs from time zero to time t and from time zero to infinity, respectively; k_a, absorption rate constant; $t_{1/2}$, half-life; CL, clearance; F, unknown bioavailability of cefpodoxime; V, volume of distribution; MRT, mean residence time.

Furthermore, our results support the hypothesis that the absorption-promoting effect of nifedipine on antibiotics absorbed by active transport processes, e.g., amoxicillin (15) and cefixime (5), could be due to a direct action on brush-border dipeptide carrier activity rather than to a change in the splanchnic circulation rate.

In conclusion, the calcium channel blockers diltiazem and nifedipine, which have different effects on intestinal motor activity and splanchnic blood flow, do not modify the pharmacokinetics of cefpodoxime. Thus, the previously reported effect of nifedipine on promoting the absorption of some oral amino beta-lactams (5, 15) seems specific to this subclass of beta-lactams and seems to be due to an enhancement of the dipeptide carrier efficiency.

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