Effect of omeprazole administration on the pharmacokinetics of oral extended-release nifedepine: physiologically based pharmacokinetic modeling

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PURPOSE

Proton pump inhibitors (PPIs) can affect the release of drugs from their dosage forms in vivo by elevating the gastric pH. Our recent clinical study has demonstrated that drug-drug interactions (DDIs) exist between a PPI, omeprazole, and nifedipine extended-release (ER) formulations, where systemic exposure of nifedipine was increased in subjects after multiple-dose pretreatment of omeprazole[1]. However, the mechanism of the observed DDIs between omeprazole and nifedipine has not been well understood, as the DDI may also be mediated through CYP3A4 enzyme inhibition in addition to the elevated gastric pH caused by omeprazole. This study used physiologically-based pharmacokinetic (PBPK) modeling to understand the effect of omeprazole on nifedipine PK while dosing with two nifedipine ER formulations (pH-dependent and pH-independent release).

OBJECTIVE(S)

Employ PBPK modeling approach to quantitatively investigate the DDI mechanism for two different ER formulations of nifedipine with omeprazole and the potential formulation effect on the DDI.

METHOD(S)

- PBPK modeling and simulations were conducted using the population based PBPK software SimCYP (V.17, SimCYP, Sheffield, UK) in healthy subjects (520 subjects for each simulation, average age and sex matched to the clinical study design[1])
- Omeprazole PBPK model and nifedipine PBPK base model in immediate-release (IR) formulation were previously constructed and verified by simulating DDIs[2]
- A two-stage dissolution study was performed on PROCARDIA XL® and Valeant nifedipine ER 60 mg tablets to evaluate the effects of different pH dissolution media (i.e., pH 1.2, pH 4.5 and pH 6.8) on drug release
- Nifedipine PBPK models in ER formulations were constructed based on the verified nifedipine IR models[2] and the in-house measured dissolution profiles
- The effect of omeprazole on nifedipine PK was simulated by changing the gastric pH and/or the Vmax, maximum rate of metabolite formation by CYP3A4 enzyme

RESULT(S)

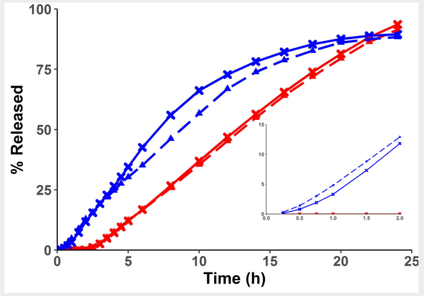

Figure 1: Two-stage in vitro dissolution profiles of PROCARDIA XL® (red) and Valeant (blue) formulations. The symbols represent averages of six samples for each point: ▲ represents 2 hrs in pH 1.2 then 22 hrs in pH 6.8, while **x** represent 2 hrs in pH 4.5 then 22 hrs in pH 6.8. Dissolution testing was done using USP apparatus 2 at 50 rpm in 900 mL dissolution media.

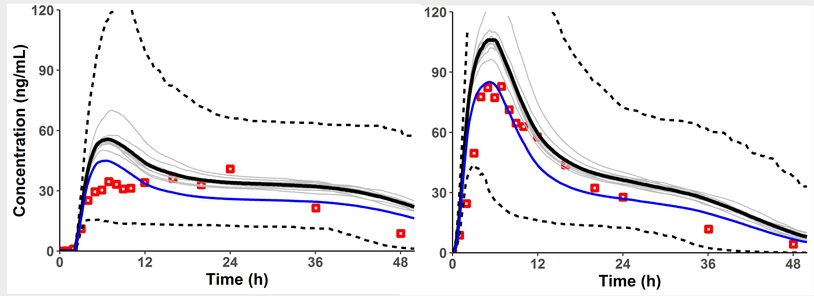

Figure 2: The simulated drug plasma concentration-time profiles in healthy populations of single dose 60 mg nifedipine ER tablet with pH-independent (left, using PROCARDIA XL® dissolution data) and pH-dependent (right, using Valeant dissolution data) formulations, with daily omeprazole treatment for 7 days prior to the nifedipine administration inducing a change in CYP3A4 V_{max}=60%: the solid black line is the simulated mean value, dotted lines are the 5th and 95th percentiles and grey lines are simulated PK profiles from different trials. The blue line is the simulated mean value assuming a change in CYP3A4 V_{max}=78%. Data points are clinically observed values[1].

Table 1. Simulated PK parameters of single dose 60 mg nifedipine pH-independent and pH-dependent ER tablets following placebo and multiple dose treatment of omeprazole in healthy subjects, compared with the observed values

		Observed[1]				Simulated			
		C_{max} (ng/mL)	AUC (ng·h/mL)	AUCR		C_{max} (ng/mL)	AUC (ng·h/mL)	AUCR
pH-independent ER tablet	NIF	40.5	958.6		NIF pH=1.5/V_{max}=100%	38.59	900.3	
					NIF pH=4.5/V_{max}=100%	38.59	901.4	1
	NIF + OMP	49.6	1155.9	1.21	NIF pH=4.5/V_{max}=78%	48.24	1163.2	1.29
					NIF pH=4.5/V_{max}=60%	59.90	1512.9	1.68
pH-dependent ER tablet	NIF	86.2	1059.0		NIF pH=1.5/V_{max}=100%	61.97	1025.9	
					NIF pH=4.5/V_{max}=100%	71.84	1050.9	1.02
	NIF + OMP	97.2	1403.8	1.33	NIF pH=4.5/V^{max}=78%	90.70	1377.9	1.34
					NIF pH=4.5/V_{max}=60%	113.42	1821.4	1.78

AUCR: AUC ratios between NIF with OMP treatment and NIF only (Observed) or between NIF with pH/V_{max} changes and NIF with pH=1.5/V_{max}=100% (Simulated). NIF: nifedipine. OMP: omeprazole. pH: gastric pH values used in simulations. V_{max}: maximum rate of metabolite formation by CY3A4 enzyme. V_{max}=60%: the activity of CYP3A4 enzyme was reduced to 60% after seven days of 40 mg OMP treatment, as simulated from this study. V_{max}=78%: the activity CYP3A4 enzyme was reduced to 78% after 20 mg OMP treatment[2].

CONCLUSION(S)

- PBPK modeling and simulations suggest that the elevated gastric pH following multiple-dose administrations of omeprazole may have minimal effect on nifedipine PK.
- The CYP3A4 enzyme-mediated DDI plays an important role in the clinically observed nifedipine exposure changes.
- The effect of nifedipine ER formulations (pH-dependent vs. pH-independent) on the nifedipine and omeprazole DDIs is insignificant.
- PBPK modeling provides a mechanistic understanding of the observed DDI of nifedipine ER formulations with a PPI, omeprazole.

REFERENCE

1. Zhao, L. *et al.* Effect of omeprazole administration on the pharmacokinetics of oral extended-release nifedipine: clinical study. Submitted (2023)
2. Le Merdy, M. *et al.* Physiologically based pharmacokinetic modeling approach to identify the drug-drug interaction mechanism of nifedipine and a proton pump inhibitor, omeprazole. *Eur J Drug Metab Pharmacokinet* **46**, 41-51 (2021)

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