Absence of an inhibitory effect of omeprazole and nizatidine on phenytoin disposition, a marker of CYP2C activity

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The effects of omeprazole (40 mg orally per day) and nizatidine (300 mg orally per day) on the disposition of phenytoin (4.5 mg kg⁻¹ p.o. single dose) were studied in 18 healthy, young adult males. Total and unbound plasma concentrations of phenytoin were measured for 48 h after each dose of phenytoin. Neither treatment altered the disposition kinetics of phenytoin, the hydroxylation of which is mediated specifically by cytochromes P450 of the 2C subfamily.

Keywords phenytoin omeprazole nizatidine CYP2C

Introduction

Omeprazole is a substrate for the 2C isoform of cytochrome P450 which hydroxylates S-mephenytoin [1]. In a dose of 40 mg day⁻¹ omeprazole inhibits the hydroxylation of phenytoin in humans by about 15–20% [2, 3]. At a dose of 20 mg day⁻¹ no effect was achieved [4]. Phenytoin is metabolized by CYP2C9, an isoform distinct from mephenytoin hydroxylase [5–7]. Nizatidine is an H₂-receptor blocking agent which, relative to the H₂-receptor antagonist, cimetidine, is poorly bound by human liver microsomes [8], and has been shown not to alter the kinetics of theophylline in patients with chronic obstructive pulmonary disease [9]. Since nizatidine would not be expected to interfere with the disposition of drugs oxidized by the cytochromes P450, and since the effects of omeprazole on phenytoin disposition are equivocal, we compared the effects of omeprazole and nizatidine on CYP2C enzymes using phenytoin kinetics as an index of the rate of its oxidation in order to predict which of these anti-ulcer medications would be least likely to alter the kinetics of drugs that are metabolized by CYP2C.

Methods

Subjects of the study were eighteen healthy male volunteers (age 22.4 ± 2.1; mean ± s.d.). They participated after having given written, informed consent, and the protocol was approved by the Human Subjects Committees of both The University of Toledo and the St Vincent Medical Center. Subjects abstained from ethanol from 48 h before and throughout the study.

Protocol

Subjects were randomized to three groups; control, nizatidine, and omeprazole treatment for treatment period I. Nine doses of nizatidine (Axiid[®]) were given in doses of 150 mg twice daily (08.00 h and 20.00 h). Four doses of omeprazole (Prilosec[®]) were given in doses of 40 mg daily (08.00 h). Phenytoin (Dilantin Infatabs[®]) was given in a dose of 4.5 mg kg⁻¹ 1 h after the third dose of omeprazole, 1 h after the fifth dose of nizatidine, or in the absence of treatment with either nizatidine or omeprazole (control). The doses of phenytoin were taken with 120 ml of tap water after an overnight fast, and food was withheld for an additional 3 h afterwards. The subjects were crossed over in periods II and III with a washout period of 1 week after each successive dose of phenytoin.

Venous blood samples were taken through an indwelling catheter into heparinized tubes prior to and at 1, 2, 4, 6, 8, 12, 24, 36, and 48 h after phenytoin dosage. Plasma was separated and an aliquot stored at -28° C until assay. Additionally, 1 ml plasma was ultrafiltered immediately using an Amicon Centrifree[®] device at room temperature (5000 rev min⁻¹) for 10 min. The ultrafiltrates were frozen immediately and stored at -28° C until assay.

Assays

Phenytoin was measured in plasma and ultrafiltrates by fluorescence polarization immunoassay using a TDx analyzer (Abbott Diagnostics, Irvine, TX) and commercially available reagents. Between-run coefficient

ents of variation were less than 3%, and the minimum detectable concentrations were 0.5 mg l^{-1} and 0.02 mg l^{-1} for total and unbound phenytoin, respectively.

Pharmacokinetic analysis

Values of $C_{\max}$ and $t_{\max}$ were noted directly from the phenytoin data. Total AUC was calculated using the linear trapezoidal rule with extrapolation to infinity using C_{48}/λ_z . Values of λ_z and $t_{1/2}$ were estimated from the terminal phase of the disappearance of phenytoin (or unbound phenytoin) from plasma. Total clearance, CL_0 , was calculated as dose/AUC. The unbound fraction of phenytoin was calculated as the ratio of AUCu/AUC.

Statistical analysis

Differences among means for each pharmacokinetic parameter were examined by analysis of variance (ANOVA). The Friedman two-way ANOVA was used to test for differences between group median $t_{\max}$ values. Differences among group means or medians were considered significant at $P < 0.05$.

Results

Two-way ANOVA revealed no significant differences for any of the mean pharmacokinetic parameters (Table 1). Plasma concentrations of unbound phenytoin after the three treatments are shown in Figure 1. The control unbound fraction was 0.076 ± 0.011 compared with 0.075 ± 0.008 during omeprazole treatment and 0.075 ± 0.010 during nizatidine treatment.

Discussion

We compared the effects of nizatidine and omeprazole, inhibitors of gastric acid secretion, on the kinetics of phenytoin, a substrate for CYP2C9. We did so, because the influence of omeprazole on phenytoin metabolism is

Figure 1 Mean plasma concentrations of unbound phenytoin after a single 4.5 mg kg^{-1} dose in 18 subjects treated with omeprazole (●), nizatidine (▲), or no drug (control (■)). Vertical bars are s.d.s for control treatment only.

equivocal. Others have reported either no inhibitory effects [4] or modest inhibitory effects [2, 3] of omeprazole on phenytoin metabolism. Omeprazole is a CYP2C substrate (mephenytoin hydroxylase), though not a CYP2C9 substrate. Furthermore, nizatidine, on the basis of its lack of interaction with cytochrome P450 would not be expected to interfere with phenytoin metabolism. Our finding was that neither nizatidine (150 mg p.o.) nor omeprazole (40 mg p.o.) treatment altered phenytoin kinetics. Our findings with regard to omeprazole are in accord with the findings of Andersson *et al.* [4] who used a 20 mg dose of omeprazole, but at variance with the modest inhibitory effects demonstrated by Gugler *et al.* [2] and Pritchard *et al.* [3] who report 15–20% decreases using a 40 mg dose.

Our data failed to detect any effect of either omeprazole or nizatidine on the disposition kinetics of phenytoin, and we therefore conclude that neither omeprazole nor nizatidine in therapeutic doses is likely to affect the activity of CYP2C9, or interfere with metabolism of CYP2C9 substrates.

Table 1 Disposition kinetics of plasma total and unbound phenytoin in subjects treated with omeprazole or nizatidine

Treatment	$C_{\max}$ (mg l^{-1})	$t_{\max}$ (h)	$t_{1/2}$ (h)	CL_0 ($\text{l h}^{-1} \text{ kg}^{-1}$)	$C_{u\max}$ (mg l^{-1})	$t_{\max(u)}$ (h)	$t_{1/2(u)}$ (h)	CL_u ($\text{l h}^{-1} \text{ kg}^{-1}$)	fu
Control	4.7 ± 0.9 (4.2–5.1)	12 (4–24)	15.2 ± 9.1 (10.7–19.7)	0.027 ± 0.009 (0.022–0.031)	0.38 ± 0.08 (0.34–0.41)	12 (6–24)	12.8 ± 4.3 (10.7–15)	0.34 ± 0.09 (0.30–0.39)	0.076 ± 0.011
Omeprazole	4.3 ± 1.5 (3.5–5.0)	18 (2–36)	16.5 ± 7.9 (12.6–20.4)	0.027 ± 0.009 (0.022–0.031)	0.33 ± 0.11 (0.28–0.39)	12 (4–36)	15.2 ± 6.8 (11.8–18.6)	0.36 ± 0.11 (0.30–0.41)	0.075 ± 0.008
Nizatidine	4.3 ± 1.4 (3.6–5.0)	12 (4–24)	16.2 ± 9.7 (11.4–21.0)	0.027 ± 0.010 (0.022–0.032)	0.34 ± 0.11 (0.28–0.39)	12 (4–24)	14.7 ± 6.7 (11.4–18.0)	0.36 ± 0.12 (0.31–0.42)	0.075 ± 0.01

Values for all parameters except $t_{\max}$ are given as means $\pm$ s.d. Values for $t_{\max}$ are given as medians with ranges in parentheses. 95% confidence intervals are listed in parentheses below means.

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