Application of Dual Radiotelemetric Technique in Studying Drug–Drug Interaction Between Diclofenac Sodium and Ranitidine HCl in Volunteers

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Drug–drug interaction between a commercial diclofenac sodium enteric-coated tablet (Voltaren; V) and a ranitidine HCl tablet (Zantac; Z) was evaluated using a dual radiotelemetric technique according to a randomized three-way Latin-Square crossover design balanced for carryover effects. V and Z were given either alone or in combination (Treatment V, Z, V/Z), with a 14-day washout period between treatments. Eighteen fasted subjects swallowed a tethered Heidelberg pH capsule to provide continuous gastric pH. Then the assigned treatment drug and another Heidelberg pH capsule were given simultaneously. The free pH capsule provided information regarding gastric residence time (GRT). Serial blood samples were obtained for up to 12 hr after dosing and drug levels were determined by validated HPLC methods. Treatment effects on AUC, C_{max}, T_{max}, T_{lag}, T_{max}–T_{lag}, and $T_{1/2}$ were not significant except C_{max}, which differed slightly for both V and Z when given in combination as compared to alone. Gastric residence times were 46, 33, and 51 min for Treatments V, Z, and V/Z, respectively. Gastric exposure of the enteric-coated tablet of diclofenac was estimated by pH values obtained from the tethered capsule. Median pH values at 3 and 15 min prior to gastric emptying were 3.8 and 4.9 for the combination treatment versus 2.1 and 2.7 for diclofenac alone. The results of this study indicated that there was minimal drug–drug interaction between diclofenac and ranitidine. The gastric pH range resulting from this study did not influence the oral absorption of enteric-coated diclofenac.

KEY WORDS: diclofenac; ranitidine; radiotelemetric technique; Heidelberg capsule; drug–drug interaction.

INTRODUCTION

Diclofenac sodium (Voltaren) is a nonsteroidal antiinflammatory drug (NSAID) indicated for the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Chronic administration of NSAIDs may increase the chances of gastrointestinal damage (1–3), including bleeding, ulceration, and perforation (4–7). Mucosal injury may also result from short-term NSAID therapy (1–3). Patients who suffer from peptic ulceration and arthritic disease have few options for alternative treatment. The addition of histamine (H_2)-receptor antagonists may provide a relatively safe and efficacious treatment option for patients requiring continued NSAID therapy. Ranitidine HCl (Zantac), 150 mg twice daily, has been shown to heal NSAID-associated peptic ulcers effectively (8) and reduce significantly the incidence of duodenal ulceration but not gastric ulceration (9,10). Also, healing with H_2 antagonist appears to be more successful when NSAID treatment is discontinued (8). The potential to develop a combination NSAID and H_2 antagonist product could provide a therapeutic benefit to arthritis patients susceptible to NSAID-induced gastrointestinal side effects.

Radiotelemetric techniques using the Heidelberg capsule have been employed to measure gastric residence time (GRT) and document the onset of diclofenac absorption (11). Simultaneous monitoring of gastric pH and GRT establishes whether drug absorption is affected by pH, gastric emptying, or a combination of both.

The purpose of this study was to determine whether there was a drug–drug interaction between a single 75-mg dose of diclofenac sodium and two doses of 150-mg ranitidine HCl when orally administered alone and in combination and to relate changes in plasma concentrations of the drug with changes in the GRT and pH environment in the gut.

METHODS

Eighteen male subjects were enrolled into this Latin-Square randomized, open-label, three-way crossover study. The study was approved by the Investigational Review Board of the Millard Fillmore Hospital. After giving informed consent and meeting the inclusion criteria, subjects were confirmed to be in good health by physical exam, medical history, and clinical laboratory tests. Subjects with clinically significant illness, a history of gastrointestinal surgery or disease, dyspepsia, or epigastric pain, or hypersensitivity to NSAIDs were excluded. No alcohol was allowed for 72 hr and no concomitant drug treatment was allowed for 14 days prior to, or during, the study.

Each of the 18 subjects was randomly assigned to receive the following treatments on different occasions separated by a 2-week washout period.

- Treatment V: 75-mg diclofenac sodium enteric-coated (EC) tablet.
- Treatment Z: Two doses of 150-mg ranitidine HCl tablet administered as a two-dose sequence given 12 hr apart.
- Treatment VZ: Combination of a single dose of 75-mg diclofenac sodium EC tablet and the second dose of 150-mg ranitidine HCl tablet administered as a two-dose sequence given 12 hr apart.

The night before the drug study day, a control blood sample (predose blank) was obtained. The first dose of ranitidine HCl was given at 8 PM to those subjects assigned to Treatments Z and VZ. All subjects fasted overnight starting at 11 PM and remained fasted until 4 hr after dosing. On each drug study day, all subjects swallowed a calibrated Heidelberg capsule that was tethered to the cheek (suspended pH

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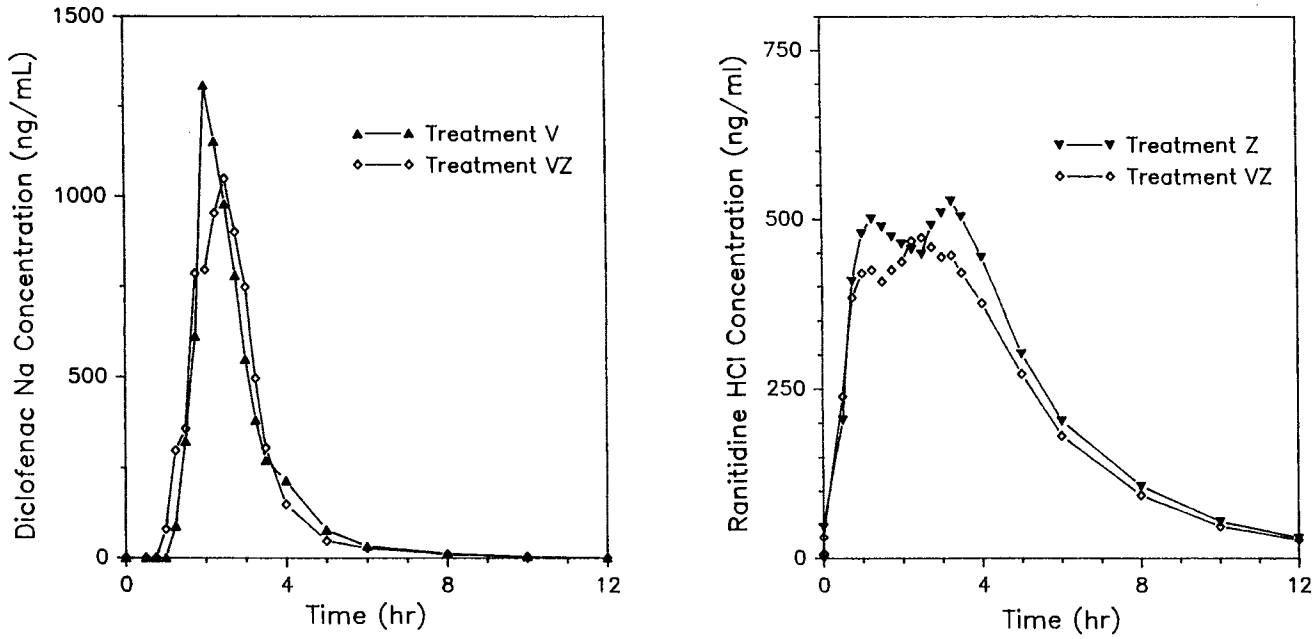

Fig. 1. Mean plasma concentration–time profiles of diclofenac Na and ranitidine HCl.

capsule) to monitor gastric pH. The position of the capsule in the stomach was confirmed by (1) measurement of the tether length from mouth and back throat to stomach, (2) signal strength, and (3) measured pH. At 8 AM the assigned treatment medication(s) and another calibrated Heidelberg capsule (free pH capsule) were administered orally to subjects. All subjects were given standardized meals. Gastric pH was continuously monitored for 4 hr after dosing. Venous blood samples were obtained immediately before dosing (predose) and 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 5, 6, 8, 10, and 12 hr following drug administration. Heparinized blood samples were centrifuged, and the plasma was separated and immediately frozen. Ranitidine HCl and diclofenac sodium were measured in plasma using modified liquid chromatographic methods (12,13). Both methods were validated regarding accuracy, precision, sensitivity, and specificity in the presence of other drugs including drugs of interest in this study.

Standard pharmacokinetic parameters were calculated from the plasma concentration–time data. C_{max} was the highest observed concentration and T_{max} was the time at which C_{max} occurred. T_{lag}, the absorption lag time, was the last time point at which a nondetectable plasma concentration was observed before the onset of absorption. Adjusted T_{max}, the adjusted time to peak, was taken as the difference between T_{max} and T_{lag}. AUC was calculated using the linear trapezoidal rule, with AUC(0–t) being the interval from time 0 to the last measured concentration and AUC(0–inf) being AUC (0–t) plus any residual area, which was calculated from the concentration of the last measured time point divided by the terminal rate constant. The contribution of residual area to the total area was usually small due to the low concentration observed at the last sampling time. The terminal rate constant was determined by linear regression analysis of the log-linear terminal phase of the plasma concentration-time profile.

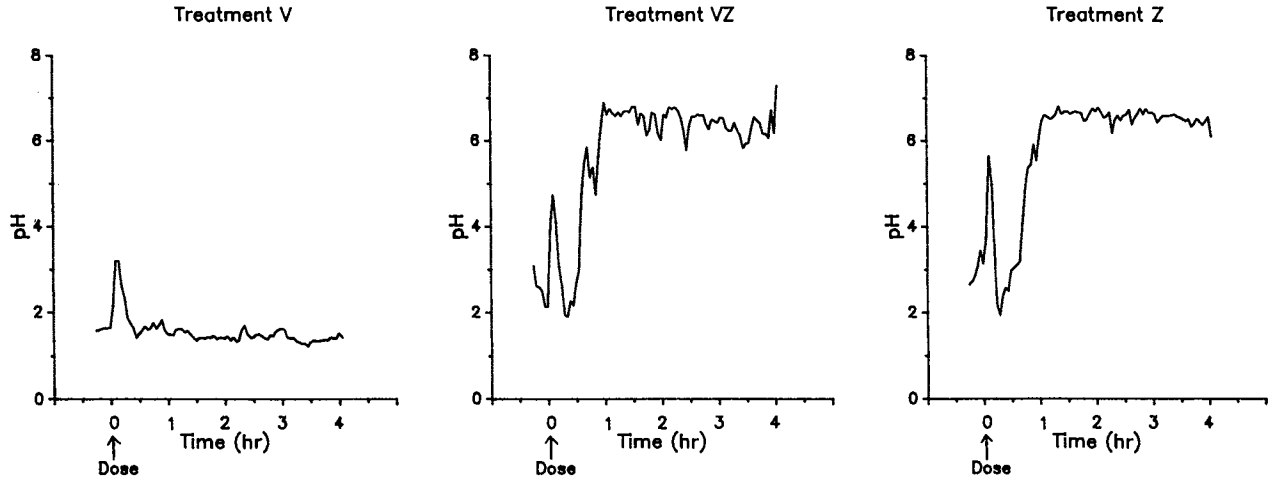

Fig. 2. Median stomach pH–time profiles of suspended pH capsule.

Table I. Summary of Diclofenac Sodium and Ranitidine HCl Pharmacokinetic Parameters and Statistical Analysis After Oral Administration of Voltaren and Zantac Alone and in Combination

Diclofenac sodium						
Mean (SD) parameter	Treatment V	Treatment VZ	VZ/V ratio	Conventional 90% CI		Signed rank
C_{max}, μg/mL	2.30 (0.91)	2.44 (0.72)	1.19 (0.51)	**−10.4%**[a]	**+22.4%**	—
T_{max}, hr	2.25 (1.5–4.0)[b]	2.25 (1.25–3.25)[b]	1.00 (0.29)	−12.1%	+7.3%	N.S.
T_{lag}, hr	1.25 (0.75–2.5)[b]	1.25 (0.75–2.5)[b]	1.04 (0.41)	−11.3%	+9.3%	N.S.
Adj. T_{max}, hr	0.75 (0.5–1.75)[b]	0.75 (0.5–1.5)[b]	1.05 (0.40)	−25.4%	+16.1%	N.S.
AUC(0–t), μg · hr/mL	1.96 (0.32)	1.96 (0.35)	1.00 (0.13)	**−4.2%**	**+3.8%**	—
AUC(0–inf), μg · hr/mL	1.97 (0.32)	1.96 (0.35)	1.00 (0.13)	**−4.2%**	**+3.8%**	—
$T_{1/2}$, hr	1.57 (0.63)	1.54 (0.55)	1.05 (0.21)	**−8.0%**	**+11.5%**	—
Ranitidine HCl						
Mean (SD) parameter	Treatment Z	Treatment VZ	VZ/Z ratio	Conventional 90% CI		Signed rank
C_{max}, μg/mL	0.67 (0.20)	0.60 (0.15)	0.92 (0.19)	**−21.1%**	**−1.2%**	—
T_{max}, hr	2.75 (1.0–4.0)[b]	2.38 (0.75–3.5)[b]	0.93 (0.38)	−27.5%	−0.2%	N.S.
AUC (0–t), μg · hr/mL	2.88 (0.71)	2.58 (0.60)	0.91 (0.14)	**−17.1%**	**−4.0%**	—
AUC(0–inf), μg · hr/mL	2.98 (0.73)	2.67 (0.62)	0.91 (0.14)	**−17.0%**	**−4.0%**	—
$T_{1/2}$, hr	2.22 (0.32)	2.28 (0.26)	1.03 (0.13)	**−3.2%**	**+7.9%**	—

[a] Numbers in boldface indicate primary analysis.
[b] Median (range).

Gastric residence time (GRT) was defined as the residence time of the free pH capsule, which ended when there was a sharp sustained rise of 3 pH units for at least 15 min. The pH values at 3 and 5 min before gastric emptying (GE-3 and GE-15) were estimated using the pH values from the suspended pH capsules and used to estimate the acidic environment of the diclofenac sodium enteric-coated tablet prior to gastric emptying.

An F test and a Fisher's exact test for the comparison between sequences were performed for demographic data (age, weight, height, and race). Fisher's exact test was used for the comparison between sequences for race. Treatment and carryover effects on all parameters were evaluated by ANOVA. Power, Westlake 95% and conventional 90% confidence intervals (CI), and Pitman–Morgan tests were also performed. Wilcoxon signed-rank tests for equality of the treatment effects were performed for T_{max}, T_{lag}, and adjusted T_{max}. The data are presented as mean values ± SD. The significance level was $P < 0.05$ and outside of ± 20% for CI.

RESULTS

The 18 subjects were aged 21 to 42 years (mean, 27.1 ± 6.5 years). Their weights ranged from 64.0 to 84.9 kg (mean, 75.2 ± 7.1 kg), and their heights ranged from 167.6 to 190.5 cm (mean, 178.3 ± 5.6 cm). No significant differences among the sequences were detected with respect to age, weight, height, and race.

Plasma concentration–time curves were similar for diclofenac sodium and ranitidine HCl in Treatment VZ compared to Treatment V and Z (Fig. 1). Median stomach pH's (suspended pH capsule) after treatments, V, VZ, and Z are illustrated in Fig. 2. The pharmacokinetic parameters are summarized in Table I. Environmental pH values of the enteric-coated tablet estimated from the suspended capsule is summarized in Table II.

The primary statistical results (conventional 90% CI for C_{max}, AUC, $T_{1/2}$, and signed rank test for T_{max}, T_{lag}, and adjusted T_{max}) are listed in Table I. No significant differences between the treatments were detected for any of the analyzed pharmacokinetic parameters except for C_{max}, which was barely significant for both V and Z when given in combination as compared to alone. The Power values were very high (>0.90) for all parameter comparisons with the exception of C_{max} (0.52), adjusted T_{max} (0.35) for diclofenac, and T_{max} (0.67) for ranitidine. The average relative bioavailabilities, as determined by the ratios of AUC(0–t) values for diclofenac and ranitidine given alone and together were 1.00 ± 0.13 and 0.91 ± 0.14, respectively. The estimation of ranitidine HCl AUC in Treatment VZ may have been compromised by the observation multiple-peak behavior, which resulted in difficulty in characterizing the whole profile with a fixed and limited plasma sampling schedule.

The mean GRT (SD) values were 45.6 (51.3), 33.2 (14.4),

Table II. Gastric pH Prior to Gastric Emptying (GE)

Treatment	Mean (SD) GRT (min)	Median (SD) pH value at GRT—3 min	GRT—15 min	GRT—30 min
V	45.6 (51.3)	2.1 (0.9)	2.7 (1.8)	3.0 (2.2)
VZ	51.4 (31.0)	3.8 (2.4)	4.9 (2.1)	2.9 (1.7)
Z	33.2 (14.4)	3.1 (1.7)	4.1 (2.7)	2.0 (1.6)

and 51.4 (31.0) min for Treatments V, Z, and VZ, respectively. Large intra- and intersubject variabilities were observed for the pH values obtained in the study. As expected, the median pH values were higher after Treatments VZ and Z as compared to Treatment V, indicating that ranitidine raised the gastric pH in this study (Table II and Fig. 2).

DISCUSSION

Bioavailability of enteric-coated tablet is extremely difficult to determine in humans due to highly variable intra- and intersubject gastric emptying (14,15). Diclofenac sodium presents even greater challenges because of its pharmacokinetic properties. Absorption of this drug is extremely rapid, with peak concentrations reached within 0.5 hr after the onset of absorption (16). Diclofenac is rapidly cleared from plasma, with levels declining to roughly 10% of the peak value within 3 hr (16). The terminal half-life was estimated to be approximately 2 hr (17). These characteristics require frequent blood sampling over an extended time period to define the plasma profile accurately. Without a reliable method for detecting gastric emptying, it would be impossible to obtain reliable estimates for relevant pharmacokinetic parameters, and thus bioavailability assessment can be inaccurate.

Radiotelemetric techniques using Heidelberg pH capsules have been used to detect gastric emptying and the onset of drug absorption from enteric-coated formulations (11,18–23). In this study we added another pH capsule, tethered to the cheek, to monitor the gastric pH continuously and provide an estimate of acidic exposure of the enteric-coated tablet to acid in the stomach.

The potential to combine a H_2-antagonist with a NSAID is attractive, and also a combination product could play an important role in the treatment of patients who are susceptible to NSAID induced gastropathies and also need analgesic therapy. The present study was designed to determine drug–drug interaction of diclofenac sodium and ranitidine HCl. Concomitant ranitidine administration has already been shown not to alter the pharmacokinetics of flurbiprofen (24), ibuprofen (25–28), aspirin (29), indomethacin, and sulindac (30). On the other hand, the influence of gastric pH and GRT on the absorption characteristics of enteric-coated diclofenac sodium tablets cannot be discounted. Both gastric pH and GRT are presumably modulated by the pharmacological effect of ranitidine (31). The results of this study revealed that, after one dose of diclofenac and two doses of ranitidine, there is also no significant difference in the relative bioavailability of diclofenac. Raising the gastric pH with two doses of ranitidine demonstrated no measurable effect on the enteric coating of diclofenac sodium.

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