ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1995, p. 1671–1675 Vol. 39, No. 8
0066-4804/95/$04.00+0

Effects of an Acidic Beverage (Coca-Cola) on Absorption of Ketoconazole

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Received 27 September 1994/Returned for modification 29 January 1995/Accepted 20 May 1995

Absorption of ketoconazole is impaired in patients with achlorhydria. The purpose of this study was to determine the effectiveness of a palatable acidic beverage (Coca-Cola Classic, pH 2.5) in improving the absorption of ketoconazole in the presence of drug-induced achlorhydria. A prospective, randomized, three-way crossover design with a 1-week wash-out period between each treatment was employed. Nine healthy nonsmoking, nonobese volunteers between 22 and 41 years old were studied. Each subject was randomized to receive three treatments: (A) ketoconazole 200-mg tablet with water (control), (B) omeprazole (60 mg) followed by ketoconazole (200 mg) taken with water, and (C) omeprazole (60 mg) followed by ketoconazole (200 mg) taken with 240 ml of Coca-Cola Classic. The pH values of gastric aspirates were checked after omeprazole was administered to confirm attainment of a pH of >6. Multiple serum samples were obtained for measurements of ketoconazole concentrations by high-pressure liquid chromatography. The mean area under the ketoconazole concentration-time curve from zero to infinity for the control treatment (17.9 ± 13.1 mg · h/liter) was significantly greater than that for treatment B (3.5 ± 5.1 mg · h/liter; 16.6% ± 15.0% of control). The mean area under the concentration curve was significantly increased with treatment C (11.2 ± 10.6 mg · h/liter; 64.8% ± 29.7% of control). The mean peak concentration was highest for the control treatment (4.1 ± 1.9 μg/ml), compared with that for treatment B (0.8 ± 1.1 μg/ml) and that for treatment C (2.4 ± 1.7 μg/ml), for which the mean peak concentration showed a significant increase over that for treatment B. The absorption of ketoconazole was reduced in the presence of omeprazole-induced achlorhydria. However, drug absorption was significantly increased, to approximately 65% of the mean for the control treatment, when the drug was taken with an acidic beverage, such as Coca-Cola.

Ketoconazole, an imidazole piperazine compound, has broad-spectrum activity against a wide variety of yeast, dimorphic fungal, and dermatophytic infections (7, 14). It is often used to treat opportunistic mucocutaneous fungal infections that commonly occur in patients with T-lymphocyte immunodeficiencies. For example, patients with AIDS and hematology-oncology patients undergoing bone marrow-suppressive chemotherapy or radiation therapy commonly receive ketoconazole for the treatment of oral thrush or esophageal candidiasis. It has been suggested that ketoconazole-resistant strains of *Candida albicans* have been responsible for causing therapeutic failures with ketoconazole (10, 21). However, recent evidence also suggests that impaired absorption of ketoconazole may play a significant role in the therapeutic failures (15, 16).

Ketoconazole is a weak dibasic compound that is practically insoluble in water, except at a pH below 3 (8). Sufficient gastric acidity is therefore a prerequisite for adequate dissolution and absorption of the drug. The in vitro work of Carlson et al. (5) demonstrated that dissolution of ketoconazole was rapid and complete in 30 min when the pH was less than 3. While only a slight decrease in drug solubility occurred at a pH of 4, there was a significant rapid decline in solubility at pH levels above 5.5. The impairment of ketoconazole absorption secondary to achlorhydria has been documented for both healthy patients and patients with AIDS (1, 16, 17, 19). Histamine H2-receptor antagonists, such as cimetidine or ranitidine, reduce gastric acid secretion and cause significant impairment of ketoconazole absorption (1, 17, 19). Malabsorption of ketoconazole may also occur secondary to the patient's underlying disease. Patients with AIDS have reduced gastric acid secretion as reported by Lake-Bakaar et al. (15), who subsequently demonstrated that AIDS patients indeed have malabsorption of ketoconazole (16). Measures that could circumvent or minimize the absorption problem of ketoconazole include using an alternative effective antifungal agent, such as fluconazole, or administering ketoconazole with dilute (0.1 to 0.2 N) hydrochloric acid (16) or with glutamic acid (17). Although the administration of the drug with an acidic beverage has been proposed, its effectiveness in enhancing ketoconazole absorption has not been studied in a controlled manner.

Our study was therefore conducted to characterize the effects of omeprazole-induced achlorhydria on ketoconazole absorption in healthy subjects and to determine the effectiveness of an acidic beverage in enhancing the absorption of ketoconazole in the presence of achlorhydria. Coca-Cola Classic, which has a pH of 2.5, was selected as the acidic beverage for the study (Table 1).

MATERIALS AND METHODS

Volunteers. Ten healthy, nonsmoking, nonobese volunteers (seven males and three females) between the ages of 22 and 41 years participated in the study after written informed consent was obtained. The study was approved by the St. Michael's Hospital Research Ethics Committee. Each subject underwent a prestudy evaluation to ensure that he or she had no underlying illness, was not currently or recently on any medication, and had normal biochemical and hematological laboratory profiles.

Drug administration. The subjects were randomized to receive three treatment sequences in a three-way crossover design, with a 1-week wash-out period separating each study treatment. Treatment A, which served as the control,

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TABLE 1. pHs of selected commercial beverages

Commercial beverage	pH
Regular	
Coca-Cola Classic	2.5
Pepsi	2.5
7-Up	3.3
Canada Dry Ginger Ale	2.7
Canada Dry Orange Juice	3.7
Diet	
Diet Coca-Cola	3.2
Diet Pepsi	3.2
Diet 7-Up	3.4
Diet Canada Dry Ginger Ale	3.2
Diet Minute Maid Orange Juice	3.0

consisted of 200 mg of ketoconazole (Nizoral; Janssen Pharmaceutica Inc., Mississauga, Ontario, Canada) administered in the morning as a single tablet with 240 ml of water. During treatment B, subjects received 60 mg of omeprazole (Losec; Astra Pharma Inc.) as a total single dose on the night prior to receiving ketoconazole. Six to eight hours later in the morning, 200 mg of ketoconazole was administered with 240 ml of water. Treatment C was similar to treatment B, except that ketoconazole was administered with 240 ml of Coca-Cola Classic. Prior to each treatment, subjects underwent an overnight fast of at least 8 h, which was continued for four more hours after ketoconazole administration.

Gastric pH. To verify that omeprazole effectively inhibited gastric acid secretion, gastric pH was measured 6 to 8 h after omeprazole administration. On the morning of the study day, a nasogastric tube (Radiopaque Levin type [diameter, 5.3 mm-16F; length, 127 cm]; Medi-Craft Ltd., Malton, Ontario, Canada) was inserted into the stomach; the position of the tube was verified by manual auscultation and aspiration. After insertion of the tube, gastric samples (5 to 10 ml) were aspirated every 15 to 30 min. The pHs of the gastric samples were measured by means of a pH meter (Radiometer-Copenhagen; Bach-Simpson). When a pH greater than 6 was attained in at least two consecutive samples, the nasogastric tube was removed and ketoconazole was administered. Gastric pH measurements were performed only with either treatment B or C, whichever one the subject was randomized to receive first. As our subjects were healthy volunteers, it was assumed that if adequate gastric acid inhibition (pH of >6) was produced by omeprazole on one day, the drug would produce similar effects in the same subject on a subsequent day, 1 to 2 weeks later. Thus insertion of the nasogastric tube was performed on only one occasion for each subject.

On each study day, blood samples, 7 ml each, were obtained from an indwelling venous catheter immediately before ketoconazole administration and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 10 h after drug administration. After clotting, the samples were centrifuged and the serum was separated and immediately frozen and kept at −70°C until analyzed.

Ketoconazole assay. Ketoconazole concentrations in serum were measured by high-pressure liquid chromatography at the Pharmacy Quality Control Laboratory, Sunnybrook Health Science Centre, North York, Ontario, Canada. Serum proteins were precipitated from 0.2 ml of serum with 0.5 ml of acetonitrile. Following centrifugation, 0.2 ml of the supernate was directly injected with Waters WISP 710B injector into the liquid chromatographic system. The mobile phase consisted of 40 parts of acetonitrile and 60 parts of 0.05 M phosphoric acid (pH = 2.2) and was pumped with a Waters Scientific pump at 2.0 ml/min through a reverse-phase C_{18}, 5-μm Beckman column (4.6 by 250 mm) and a C_{18}, 1.5-cm precolumn. Column effluent was monitored with a variable wavelength UV detector (Hewlett-Packard 1050) at 207 nm. Chromatograms were recorded on a chromatographic integrator (Spectra Physics 4270) and archived on a computer diskette with an IBM PS/2 computer and the Chromstation/2 software package (Spectra Physics). Standard curves were linear in the range from 0.02 to 10 μg/ml. Values for all serum samples were determined in duplicate. The average error observed (intraday coefficient of variation) for 330 serum samples, ranging in concentration from 0.02 to 8.26 μg/ml, was 5.5%.

Pharmacokinetic analysis. The ketoconazole concentration-time data for serum were analyzed by both noncompartmental and model-dependent methods. NONMEM (version IV 2.1) (2) was used to fit the data to a one-compartment model with first-order absorption and first-order elimination, as previously used by Carver et al. (6). The highest measured drug concentration in serum represented the peak drug concentration (C_{peak}), while T_{peak} was the time for the occurrence of C_{peak}. The area under the serum concentration-time curve from time zero to t (AUC_{0-t}), where t is the time of the last measureable ketoconazole concentration, was determined by the linear trapezoidal method. The AUC was extrapolated to infinity ($AUC_{0-\infty}$) by adding AUC_{0-t} to C_t/k_{el}, where C_t is the last measurable concentration and k_{el} is the elimination rate constant. The best-fit estimation of k_{el} was determined by NONMEM in 26 of the 27 cases. For one case, for which the data could not be accurately modelled, k_{el} was estimated from the terminal linear portion of the serum concentration-time profile by linear regression analysis. The elimination half-life was calculated as $0.693/k_{el}$. The relative bioavailability of ketoconazole in the presence of achlorhydria was determined as the ratio of the $AUC_{0-\infty}$ for treatments B or C, to that for treatment A, which served as the standard for comparison.

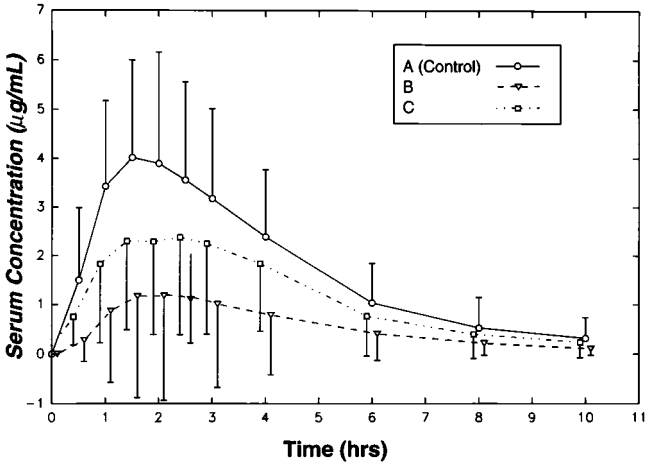

FIG. 1. Comparison of ketoconazole treatments. Mean concentration-time profiles are shown for ketoconazole (200-mg tablet) administered with water (treatment A; control), administered with water in the presence of omeprazole-induced achlorhydria (treatment B), and administered with Coca-Cola in the presence of omeprazole-induced achlorhydria (treatment C). Bars show standard deviations.

Statistical analyses. A prestudy power analysis, with data from the work of Piscitelli et al. (19), indicated that with a sample size of 10 and a power of 90% ($\alpha = 0.05$), a difference greater than 30% could be detected in the AUC of ketoconazole as a result of drug-induced achlorhydria. Similarly, a sample size of nine would provide 90% power to detect a ≥32% difference between AUCs.

A two-way analysis of variance for repeated measurement was applied to assess significant differences in log-transformed $AUC_{0-\infty}$, C_{peak}, and elimination half-life among the three treatments. A logarithmic transformation is generally assumed to produce a normal distribution for pharmacokinetic parameters (9). When a significant difference was detected, Tukey's multiple range test was performed. Friedman's two-way analysis of variance for noncontinuous data was used to assess significant differences in T_{peak} among the treatments. Wilcoxon's signed rank test was then used for pairwise comparisons if statistically significant differences were detected. The difference in relative bioavailability between treatments B and C was assessed by Wilcoxon's signed rank test. The a priori value of significance was set at a P value of less than 0.05. Data are reported as means ± standard deviations unless otherwise indicated.

RESULTS

Nine subjects, seven males and two females, completed the study without any adverse effects. One female subject was excluded from the study because of a lack of demonstrable achlorhydria. The mean age of the nine subjects included for analysis was 28 ± 5.6 years. The median gastric pH induced by omeprazole 6 to 8 h after administration was 6.9, with a range of 6 to 7.6. The pHs of all Coca-Cola drinks used for the study were verified to be 2.5.

The mean serum ketoconazole concentration-time data for the three treatments are depicted in Fig. 1. Ketaconazole concentrations were highest under control conditions (treatment A) and lowest in the presence of achlorhydria (treatment B). The concentrations were increased when ketoconazole was taken with Coca-Cola in the presence of achlorhydria, although they were still not as high as they were during the control treatment. When the log-transformed AUCs for the three treatments were compared, the $AUC_{0-\infty}$ for the control treatment was significantly greater than that for treatment B ($P < 0.05$) (Table 2). The $AUC_{0-\infty}$ for treatment C was also significantly greater than that for treatment B ($P < 0.05$), with

TABLE 2. Effects of drug-induced achlorhydria and consumption of acidic beverage on ketoconazole absorption[a]

Subject	Treatment A			Treatment B				Treatment C				AUC for treatment C/AUC for treatment B
	C_{peak} (μg/ml)	T_{peak} (h)	$AUC_{0-\infty}$ (μg · h/ml)	C_{peak} (μg/ml)	T_{peak} (h)	$AUC_{0-\infty}$ (μg · h/ml)	f[b] (%)	C_{peak} (μg/ml)	T_{peak} (h)	$AUC_{0-\infty}$ (μg · h/ml)	f (%)	
1	3.65	1.5	14.39	0.15	3.0	0.61	4.3	3.82	1.5	16.25	112.9	26.5
2	2.31	1.1	7.04	0.26	4.0	1.40	20.0	1.5	4.0	5.95	84.6	4.2
3	3.56	1.0	12.60	1.71	1.0	5.81	46.2	1.49	2.5	5.56	44.1	1.0
4	1.42	0.95	4.02	0.12	2.5	0.53	13.1	1.43	1.5	3.73	92.8	7.1
5	8.26	2.1	48.58	3.55	1.5	15.96	32.9	6.67	2.0	36.59	75.3	2.3
6	4.70	2.5	21.02	0.58	6.0	1.90	9.1	2.91	2.0	15.31	72.8	8.0
7	2.54	1.5	10.90	0.08	2.5	0.36	3.4	1.30	1.0	3.94	36.1	10.7
8	5.38	1.0	22.22	0.71	4.0	4.31	19.4	1.00	4.0	6.56	29.5	1.5
9	5.31	1.5	20.26	0.05	1.5	0.21	1.1	1.81	1.0	7.05	34.8	33.0
Mean ± SD	4.13 ± 1.95	1.5 ± 0.5	17.89 ± 13.11	0.80 ± 1.09	2.9 ± 1.5	3.46 ± 5.08	16.6 ± 15.0	2.44 ± 1.72	2.2 ± 1.1	11.22 ± 10.57	64.8 ± 29.7	10.5 ± 10.9

[a] Treatment A (control), ketoconazole plus water; treatment B, ketoconazole plus water and omeprazole; treatment C, ketoconazole plus Coca-Cola and omeprazole.
[b] f, relative bioavailability, i.e., ratio of $AUC_{0-\infty}$ for experimental treatment to $AUC_{0-\infty}$ for contol treatment.

an approximately 10-fold mean increase (median increase, 7-fold). The difference in the log-transformed $AUC_{0-\infty}$s for the control treatment and treatment C, however, did not reach statistical significance. Relative to the bioavailability for the control, the mean bioavailability of ketoconazole was 16.6% ± 15.0% with treatment B. This was significantly increased to 64.8% ± 29.7% with the administration of Coca-Cola ($P < 0.05$). However, there was one subject (subject 3) who demonstrated no response to Coca-Cola, while subject 8 showed a relatively small increase (approximately 9%) in the bioavailability of ketoconazole. Although there was a substantial increase in drug absorption for subjects 7 and 9 after the administration of Coca-Cola, the bioavailability was still below 50%, compared with control values in these subjects.

The mean C_{peak}s were significantly different among all treatments ($P \leq 0.01$; Table 2). The highest C_{peak}, 4.1 ± 1.9 μg/ml, was observed during the control treatment, while the lowest, 0.8 ± 1.1 μg/ml, occurred in the presence of achlorhydria during treatment B ($P \leq 0.01$). C_{peak} was significantly increased to 2.4 ± 1.7 μg/ml with Coca-Cola treatment ($P \leq 0.01$). Achlorhydria also significantly prolonged the mean T_{peak} from 1.5 ± 0.5 h (value for control) to 2.9 ± 1.5 h ($P < 0.05$). Coca-Cola shortened the T_{peak} to 2.2 ± 1.1 h, but this was not significantly different from the T_{peak} for either treatment A or B ($P > 0.05$). The elimination half-life of ketoconazole did not differ significantly among the three treatments ($P > 0.05$); the values were 1.56 ± 0.45, 1.91 ± 0.75, and 1.60 ± 0.32 h for treatments A, B, and C, respectively.

DISCUSSION

Our study confirms previous findings that the absorption of ketoconazole is impaired in the presence of achlorhydria. However, our study is the first to demonstrate that an acidic beverage, such as Coca-Cola, may also be used to enhance ketoconazole absorption in the presence of achlorhydria. In addition, our data show that an interaction between ketoconazole and omeprazole occurs.

Patients who have impaired absorption of ketoconazole may include those with disease-induced achlorhydria, such as that induced by AIDS gastropathy (16). Drugs that reduce gastric acidity will also impair ketoconazole absorption and will thus pose a problem for patients who require concomitant treatment with these agents. Cimetidine and ranitidine have been demonstrated to significantly reduce ketoconazole absorption by more than 90% (1, 19). The results of an uncontrolled investigation suggest that antacids reduce ketoconazole absorption (3). Omeprazole is a potent inhibitor of gastric acid secretion (22) and is therefore expected to impair ketoconazole absorption, but there have been no published data on this drug interaction. In our study, omeprazole significantly ($P < 0.05$) reduced the mean bioavailability and C_{peak} of ketoconazole by more than 80% (Table 2). Similarly, reductions in bioavailability greater than 90% have been reported to occur in AIDS patients or in healthy subjects who were given cimetidine or ranitidine (1, 16, 17, 19). The lack of gastric acidity also appears to delay the mean T_{peak}, as shown in our study (Table 2) and previous studies (1, 16, 17, 19). This suggests a decrease in the rate of drug absorption. Although the rate of ketoconazole elimination was not significantly affected, it was most prolonged and variable in the presence of achlorhydria. The serum elimination half-lives are similar to those reported for normal subjects and AIDS patients (8, 16, 17).

Omeprazole was used in our study to induce achlorhydria because it was a more potent inhibitor of gastric acid secretion than the H2-receptor antagonists (22). Single omeprazole

doses of 60 mg or more have been shown to produce >90% inhibition of basal as well as pentagastrin-stimulated acid secretion, while doses of 20 to 40 mg produced inhibition only up to 65% (13, 18). The smaller omeprazole doses were able to produce >90% acid inhibition only after multiple dosings. Previous studies that used H2-receptor antagonists usually required subjects to receive multiple doses prior to study. Thus, in our study, a large single dose of 60 mg of omeprazole was administered in order to produce the desired pH effects after 6 h. This avoided the need for the subjects to receive multiple doses of omeprazole prior to the study.

Different measures have been proposed to minimize or circumvent the absorption problem of ketoconazole. The manufacturer suggests that ketoconazole be administered at least 2 h apart from other medications that reduce gastric acidity (4). This measure may be effective for agents such as antacids or didanosine, which contain alkaline buffers, but it is unlikely to be successful for H2-receptor antagonists or omeprazole, as the latter two produce prolonged and continuous systemic effects on inhibition of gastric secretion. Alternatively, ketoconazole may be taken concurrently with 0.1 to 0.2 N hydrochloric acid as recommended by the manufacturer (4). Recent studies have demonstrated that dilute hydrochloric acid (16) and glutamic acid capsules (17) are effective in enhancing ketoconazole absorption in the presence of achlorhydria. However, the positive response was not uniformly observed, as some subjects showed no response or only a slight response to either agent (16, 17). The availability of glutamic acid capsules (Acidulin) may pose a problem, as the manufacturer, Eli Lilly, no longer markets the drug. The use of dilute hydrochloric acid solution is associated with several drawbacks, including inconvenience, unpalatability, damage to dental enamel, and irritation of the oropharyngeal mucous membranes. Moreover, the acid solution has to be extemporaneously prepared since it is not commercially available.

The use of an acidic beverage, such as Coca-Cola, provides another means of improving ketoconazole absorption in the presence of achlorhydria. The $AUC_{0-\infty}$ of ketoconazole was increased approximately sevenfold (median) when ketoconazole was taken with Coca-Cola (Table 2). Compared with the bioavailability of treatment B, the mean bioavailability was increased significantly, by almost 50%. Absorption was increased by only 9% in one subject, while no increase was demonstrated in another subject. The finding of a relative lack of effect from an acidifying agent in two of our subjects is similar to findings reported by previous investigators (16, 17), and this suggests that other factors, such as gastric emptying rates and the optimal volume of the acidifying agent, may also play roles in influencing drug absorption. The use of an acidifying agent or beverage therefore may not work adequately for every patient. However, the use of Coca-Cola offers advantages, such as palatability and convenience since it is easy to use and can be readily purchased. Pepsi also has a pH of 2.5, and it would be expected to be as effective as Coca-Cola. A survey of selected commercially available beverages showed that the majority have pH levels greater than 3 (Table 1). Although not studied, those drinks with higher pHs may not be as effective as those with a pH of <3 (5), and thus a beverage with a pH of <3 should be selected for use. However, patients such as those with severe odynophagia, active peptic ulcer disease, or diabetes mellitus may not be candidates for the use of an acidifying agent or beverage. Such patients may not be able to tolerate the stimulating effects that caffeine has on gastric acid production or the sugar in and/or caloric contents of these beverages. Some patients may also find it difficult to take an acidic beverage in the early morning. In such cases, the administration of ketoconazole may be scheduled later in the day or afternoon. The use of an acidic beverage may be extended to other drugs that require gastric acidity for optimal absorption, such as itraconazole (12).

Many clinicians currently treat their patients with fluconazole when there is documented or suspected achlorhydria. Although fluconazole is often an appropriate therapeutic alternative to ketoconazole and its absorption is unaffected by a lack of gastric acidity (1), it is relatively more expensive than ketoconazole. A 100-mg capsule of fluconazole ($8.80 [Canadian dollars]) costs approximately five times more than a 200-mg tablet of ketoconazole ($1.80 [Canadian dollars]). Even with the additional cost of a glass or can of an acidic beverage, the daily cost of ketoconazole treatment is still less than that of fluconazole treatment. A significant concern with the routine and widespread use of fluconazole is the emergence of in vitro and clinical resistance of *C. albicans* (7, 11, 20). At present, we limit the use of fluconazole to patients who are intolerant to Coca-Cola or who have suspected or documented fungal resistance to ketoconazole. However, the enhancement of drug absorption by an acidic beverage may not be sufficient for some patients. It is not known how much improvement in drug absorption by an acidic beverage is considered sufficient, as there are inadequate data on the relationship between the MIC of ketoconazole and the clinical response in the treatment of mucocutaneous candidiasis. Thus, if patients with achlorhydria are placed on regimens of ketoconazole and acidic beverages, they must be monitored closely for therapeutic failure since this regimen may not work adequately for every patient or since failure due to fungal resistance to ketoconazole may arise.

In conclusion, our study demonstrated a significant interaction between ketoconazole and omeprazole. The reduced absorption of ketoconazole due to achlorhydria may be counteracted by the use of Coca-Cola or other beverages with similar acidity, such as Pepsi. The clinical efficacy and cost-effectiveness of using ketoconazole with an acidic beverage require further study in a controlled manner. We currently recommend to our AIDS patients who show suboptimal clinical responses to ketoconazole, as well as to itraconazole, or who are suspected to have achlorhydria, that they take ketoconazole with an acidic beverage to enhance absorption prior to switching to an alternative agent.

ACKNOWLEDGMENTS

We most gratefully thank Nicole Lee and Scott Walker from the Department of Pharmacy, Sunnybrook Health Science Centre, for their assistance in both the pharmacokinetic and statistical analyses.

The study was supported in part by a major grant from Janssen Pharmaceutica Inc. and a minor grant from Ontario Branch, Canadian Society of Hospital Pharmacists.

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