Effects of Ranitidine and Sucralfate on Ketoconazole Bioavailability

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Ketoconazole is an oral imidazole antifungal agent useful in the treatment of opportunistic fungal infections. Gastrointestinal absorption of this agent is variable and dependent on the presence of gastric acid. This study compared the effects of concomitant sucralfate administration with ranitidine administration on the pharmacokinetic disposition of a 400-mg ketoconazole dose. Six healthy male volunteers were randomized to receive 400 mg of ketoconazole alone, 1.0 g of sucralfate concomitantly with a 400-mg ketoconazole dose, or ranitidine, administered 2 h prior to a 400-mg ketoconazole dose to titrate to a gastric pH of 6. All subjects received all three regimens in crossover fashion. Gastric pH was measured continuously for 4 h after ketoconazole administration in all subjects by using a Heidelberg radiotelemetry pH capsule. Relative ketoconazole bioavailability was compared between treatments. With sucralfate, five of six subjects demonstrated a decrease in the peak drug concentration in serum as well as an increase in the time to peak concentration, indicating a delay in ketoconazole absorption. The mean area under the concentration-time curve from 0 to 12 h for ketoconazole following gastric alkalinization was significantly different from that of either ketoconazole alone or ketoconazole with sucralfate ($P < 0.01$). Continuous gastric pH monitoring allowed correlation between the decrease in ketoconazole bioavailability observed with ranitidine and the increase in gastric pH. The apparent decrease in ketoconazole bioavailability observed with sucralfate appears to be caused by an alternative mechanism since a change in gastric pH was not observed. On the basis of these findings, separating the administration of ketoconazole and sucralfate should be considered to decrease the potential for interaction of sucralfate on ketoconazole bioavailability.

Ketoconazole is an oral antifungal agent of the imidazole class. It is used for the treatment of systemic opportunistic fungal infections which commonly occur in oncology patients undergoing radiation or chemotherapy and in other immunocompromised hosts (1, 6, 10, 12). Although a clinical correlation has not been demonstrated, it is assumed that successful treatment requires ketoconazole concentrations exceeding the MIC for the organism. Antifungal efficacy, like antibacterial efficacy, is theoretically dependent on the area under the concentration-time curve (AUC) of the antifungal agent above MIC and on the duration of time the serum antifungal concentrations remain above the MIC at the site of infection. Comparing the AUCs achieved under differing dosing conditions is appropriate to assess changes in relative bioavailability and, in turn, presumed antifungal efficacy.

Studies assessing the bioavailability of ketoconazole have documented that absorption is variable and pH dependent, with highest concentrations in serum achieved at low gastric pH (25). Therefore, to ensure maximum effectiveness, ketoconazole should not be administered concomitantly with agents that increase gastric pH such as antacids and H_2 antagonists (14).

Treatment of the cancer patient may lead to mucositis and esophagitis due to desquamation of the alimentary tract (13). In addition to proof of safety and efficacy in the treatment of peptic ulcer disease, sucralfate has been reported to improve healing and relieve pain associated with mucositis (7, 21).

Sucralfate may also reduce the likelihood of alimentary tract colonization with potential pathogens (20). Presumably, many of the same patients requiring ketoconazole may also benefit from concomitant sucralfate therapy when these complications arise.

Sucralfate is a complex of sulfated sucrose and aluminum hydroxide. Administration of this agent has been shown to lower concentrations of norfloxacin and phenytoin, but neither prednisone nor erythromycin, in plasma (8, 11, 16, 18). Since sucralfate has not been reported to alter gastric acidity, these interactions are thought to result from binding of the affected drug to either the aluminum or sulfated sucrose moiety and not from changes in gastric pH (15, 17).

In this study, gastric pH was monitored to aid in assessing the mechanistic role of pH on any observed effects of sucralfate and the H_2 antagonist ranitidine on ketoconazole pharmacokinetics.

MATERIALS AND METHODS

Six healthy male volunteers between the ages of 18 and 30 participated in this study. The study was approved by the Millard Fillmore Hospital Human Research Committee, and written informed consent was obtained from all subjects. Health status was assessed by medical history, laboratory profiles, and physical exam. Subjects were required to be nonsmokers and were not permitted to take any other medications for 48 h before and during all study treatments.

Subjects were randomized to a treatment sequence which was administered in a three-way crossover, Latin square design to control for order of treatment effects. Each study treatment was separated by 1 week. Treatment I consisted of a single oral 400-mg dose of ketoconazole (lot 98H130;

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TABLE 1. Serum ketoconazole concentration data

Treatment[a]	Subject no.	AUC_{0-12} (mg · h/liter)	C_{max} (µg/ml)	T_{max} (h)	K_{el} (h^{-1})	Relative bioavailability (AUC_{0-12}) (mg · h/liter)	Median 4-h pH
I	001	28.35	6.35	2.00	0.407	1.00	2.36
	002	48.99	9.04	2.50	0.461	1.00	1.84
	003	38.76	11.78	1.00	0.244	1.00	4.21
	004	47.42	8.42	3.00	0.405	1.00	3.25
	005	27.35	7.59	0.50	0.312	1.00	1.63
	006	31.41	6.03	1.50	0.512	1.00	4.38
Mean		37.05	8.20	1.75	0.390	1.00	2.95
SD		9.54	2.10	0.94	0.089	0.00	1.19
II	001	31.85	6.62	2.50	0.645	0.123	2.09
	002	38.91	6.25	4.00	0.445	0.794	1.89
	003	26.39	5.59	3.00	0.358	0.681	1.59
	004	36.33	6.17	3.00	0.364	0.766	3.24
	005	21.03	5.28	2.00	0.390	0.769	1.73
	006	20.53	2.41	6.00	0.177	0.654	1.27
Mean		29.17	5.39	3.42	0.396	0.798	1.97
SD		7.77	1.54	1.43	0.138	0.170	0.68
III	001	1.23	0.43	4.00	ND[b]	0.043	6.20
	002	0.29	0.25	1.50	ND	0.006	7.35
	003	2.49	0.96	4.00	ND	0.064	7.31
	004	0.32	0.28	2.00	ND	0.007	6.36
	005	5.44	1.51	2.50	ND	0.199	5.79
	006	0.06	0.24	1.50	ND	0.002	6.79
Mean		1.64	0.61	2.58	ND	0.050	6.72
SD		2.07	0.52	1.16	ND	0.080	0.66

[a] Treatment I, ketoconazole (400 mg); treatment II, ketoconazole (400 mg) plus sucralfate (1 g); treatment III, ketoconazole (400 mg) plus ranitidine (150 mg).
[b] ND, not done.

Janssen Pharmaceutica). For treatment II, subjects received 1.0 g of oral sucralfate (lot H9507; Marion Laboratories) four times daily for 2 days prior to ketoconazole administration, and then an extemporaneously compounded sucralfate suspension (1.0 g in 30 ml of water) was administered 5 min before the 400-mg oral ketoconazole dose. Sucralfate was administered in suspension to simulate the regimen reported to provide symptomatic relief of stomatitis in cancer patients (7, 21). During treatment III, subjects received 150 mg of ranitidine (lot Z10989FP; Glaxo) orally every 12 h for 2 days prior to ketoconazole administration, and then 150 mg was administered orally 2 h before the 400-mg oral ketoconazole
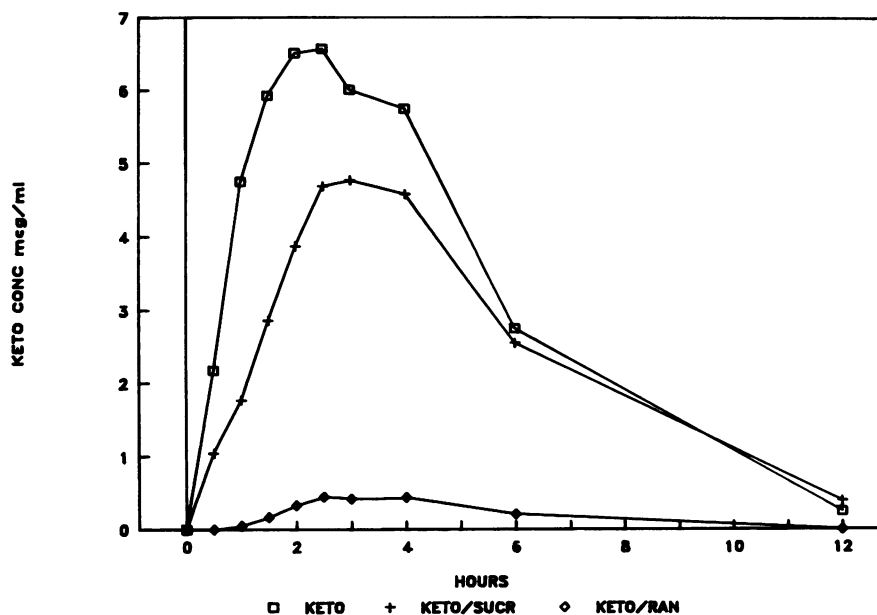

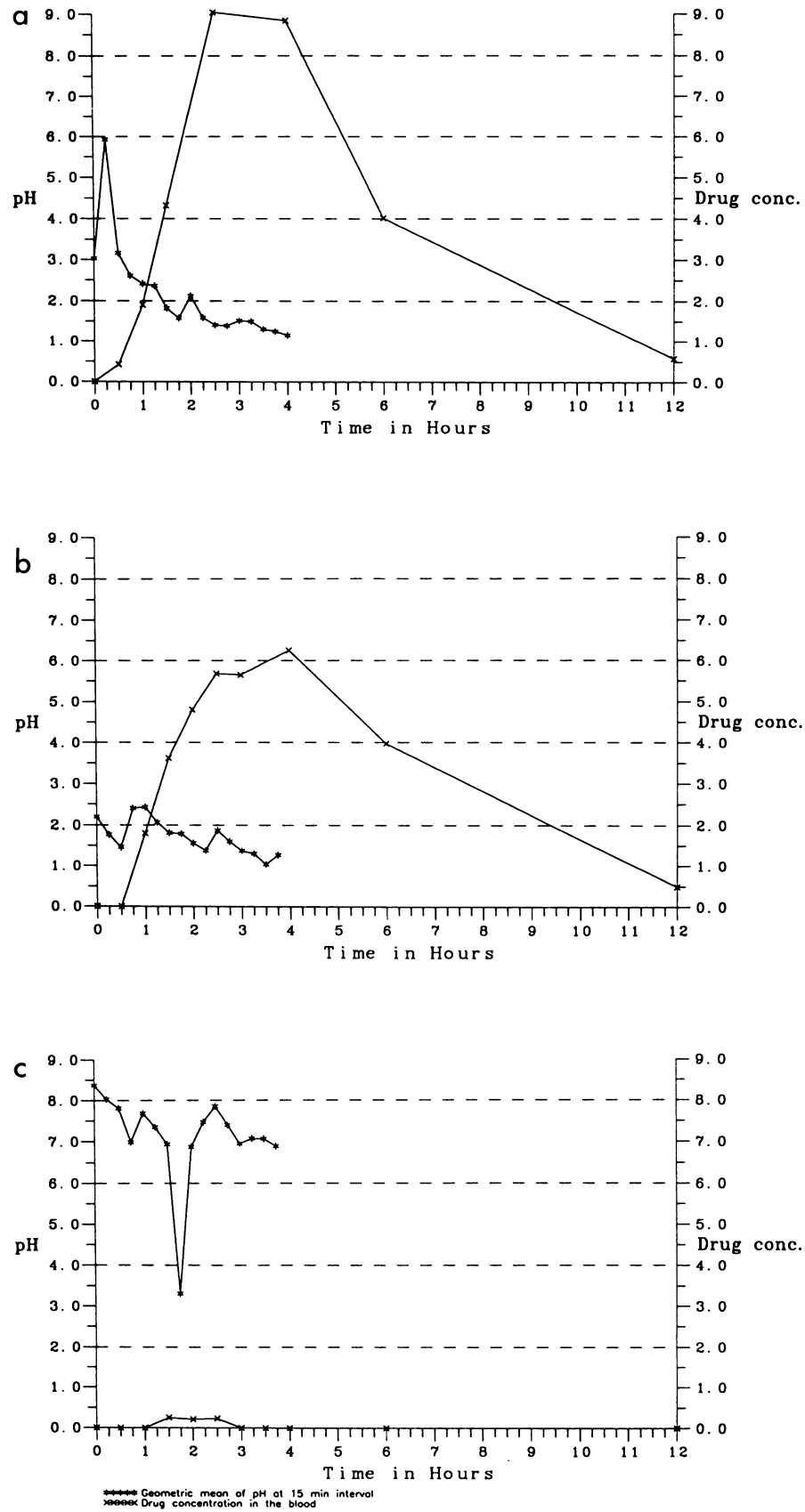FIG. 1. Mean ketoconazole serum concentration for each study phase.

FIG. 2. Serum ketoconazole concentration versus time for ketoconazole alone (treatment I) (a), ketoconazole with sucralfate (treatment II) (b), and ketoconazole with ranitidine (treatment III) (c) for subject 002. Four-hour gastric pH recording is also illustrated.

dose. During treatment III, a 50-mg intravenous dose of ranitidine (lot B6049Ca; Glaxo) was allowed if gastric pH fell below 6.0 at any time in the 4-h period after ketoconazole administration. A maximum of two doses of intravenous ranitidine was permitted. Additional doses were necessary for subjects 2 and 3, who required one 50-mg ranitidine injection, and subjects 1, 4, and 5, who required two 50-mg injections, to maintain a gastric pH greater than 6 during the monitoring period.

Subjects fasted for 8 h before each study day and abstained from alcohol for at least 48 h before taking study medications. Compliance was assessed by subject interview on each study day.

The subjects' gastric pH was monitored continuously for 4 h after ketoconazole administration in each study treatment by using an ingestible Heidelberg pH transmitting radiotelemetry capsule. The Heidelberg capsule was suspended in the stomach by using sterile suture material. The free end of the string was secured to the outside of the subject's cheek to prevent passage of the capsule from the stomach. Correct positioning of the Heidelberg capsule was verified by the observed pH data and a radio-locating (signal peaking) technique. The pH was monitored continuously by a belt antenna worn by each subject. The antenna was connected to a Clinical Pharmacokinetics Laboratory-designed TE-2000 receiver to convert the capsule signal to a pH value and measure received signal strength and quality. The receivers were connected to an IBM-PC XT computer with software designed to calculate a 5-min geometric mean pH by using 60 samplings per subject taken during that period. The program also allowed the operator to enter comments regarding adverse effects, time of dose, and ingestion of water, etc. A description of the Heidelberg capsule and the Clinical Pharmacokinetics Laboratory TE-2000 receiving system has been published (4, 23, 24, 26).

Blood samples were obtained from an indwelling venous catheter at 5 min prior to ketoconazole dosing and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, and 12 h postdosing. Twenty-four-hour samples were obtained by direct venipuncture. Approximately 5 ml of blood was collected per sample in Vacutainer tubes (Becton Dickinson Vacutainer Systems, Rutherford, N.J.), allowed to clot, and then centrifuged. Serum was separated and immediately frozen at −20°C until analyzed.

Ketoconazole assay. Ketoconazole concentrations in serum were assayed at The Clinical Pharmacokinetics Laboratory by using reverse-phase high-performance liquid chromatography using a modification of the method described by Riley and James (19). Equipment consisted of a high-performance liquid chromatography pump (model 6000A; Waters, Inc.), an autosampler (model SP8780; Spectra-Physics), an integrator (model SP4270; Spectra-Physics), and a UV detector (model 757; Kratos Spectroflow) set at 254 nm. The analytical column used was a Waters Novopak C18 (3.9 mm by 15 cm). The mobile phase, which consisted of 300 ml of methanol, 300 ml of acetonitrile, and 350 ml of 0.02 M monobasic potassium phosphate, was adjusted to pH 6.8, filtered, and degassed before use at a flow rate of 2.0 ml/min. Retention times of ketoconazole and clotrimazole, the internal standard, were 4.3 and 7.0 min, respectively. Serum samples were thawed at room temperature, and a 1.0-ml aliquot was prepared over a C18 solid-phase extraction column (part 607303; Analytichem).

Serum standard curves were linear over a concentration range of 0.2 to 12 μg/ml. Concentrations below 0.2 μg/ml were reported as not detectable. The overall precision

(percent coefficient of variation) of the study standard curves was 2.54%. The overall precisions of the seeded quality controls at concentrations 30.0, 10.0, 3.00, and 0.60 μg/ml were 4.25, 2.49, 0.80, and 3.46%, respectively.

Pharmacokinetic analysis. Serum concentration-versus-time data were fit by using PCNONLIN (22). Data were fit to a one-compartment model with first-order absorption and first-order elimination to estimate the elimination rate constant (k_{el}). The AUC was estimated by using the linear trapezoidal rule from 0 to 12 h, and for treatments I and II, addition of the area approximated by the last measurable concentration-time point/K_{el} was used to extrapolate the AUC to infinity (9). As there were few measurable concentrations in serum during the ranitidine treatment of the study, estimation of the terminal K_{el} was not possible; hence, it was not possible to assess total body clearance and noncompartmental parameters which are dependent on an accurate estimation of K_{el}.

Statistical analysis. Single-factor analysis of variance for repeated measures was used to test whether significant differences in ketoconazole bioavailability (AUC) existed between treatments. Tukey's multiple comparison test was performed when a difference was noted. An alpha value of 0.05 was determined a priori.

RESULTS

All six subjects completed the study. Adverse effects which occurred during the study were minor. Two subjects had complaints of mild nausea, and one subject reported a headache; all resolved without treatment. Evaluation of post-study laboratory tests revealed that one subject had an elevated serum creatinine concentration which was not thought to be medication related and was noted to be normal on follow-up.

Mean serum ketoconazole concentration data collected for each subject during each treatment of the study are summarized in Table 1 and include the AUC from 0 to 12 h (AUC_{0-12}), peak drug concentration in serum (C_{max}), time to peak concentration (T_{max}), K_{el} (treatments I and II), and relative bioavailability for each treatment compared with the AUC achieved during the control treatment. A decrease in C_{max} was observed in five subjects during the sucralfate treatment compared with the control treatment, while a nominal increase was observed in one subject. An increase in T_{max} was observed in five subjects whereas one subject exhibited no change during the concomitant treatment with sucralfate. During the ranitidine treatment, a large decrease in C_{max} was observed in all subjects while only three of six subjects showed an increase in T_{max}.

The mean AUCs for the three treatments are shown in Fig. 1. Only subject 1 had a higher ketoconazole AUC_{0-12} after concomitant administration of sucralfate than at baseline (Table 1). All subjects had a lower AUC_{0-12} during the ranitidine treatment than during the other two treatments. For the ranitidine treatment, all of the 12- and 24-h samples as well as the majority of the other samples had concentrations below the minimum detectable concentration of the assay. This observation leads us to conclude the difference in ketoconazole bioavailability was not due to delayed absorption; rather, it was likely due to decreased ketoconazole dissolution. Relative to the control, the average bioavailability for ketoconazole was 80% when administered with sucralfate and 5% with ranitidine.

The differences in AUC_{0-12} observed between treatments I and III and between treatments II and III were statistically
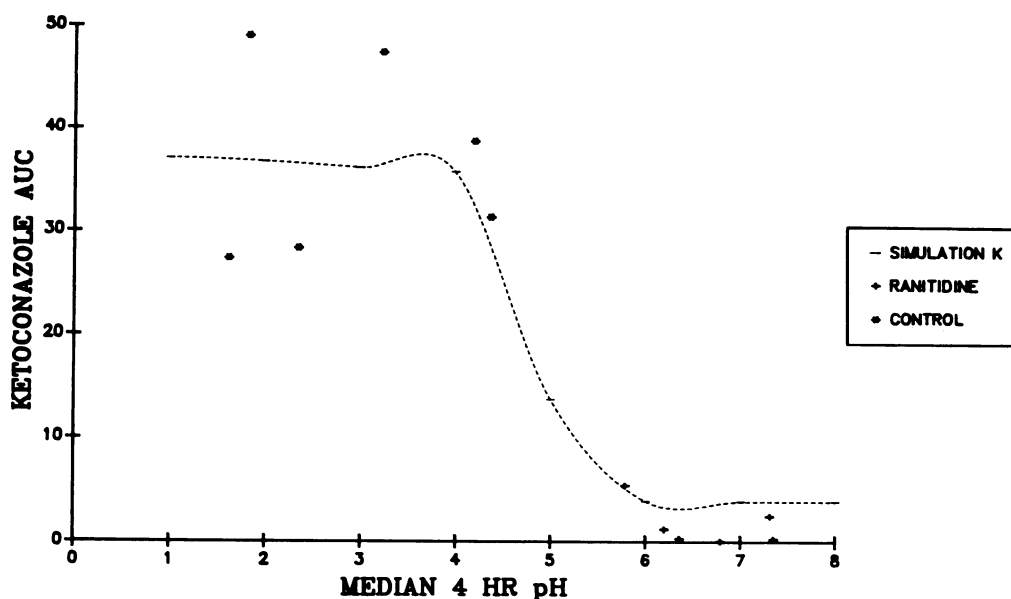
FIG. 3. Simulated ketoconazole bioavailability at different gastric pHs (– – –) based on in vitro dissolution data compared with actual patient data during control and ranitidine treatments.

significant ($P < 0.01$). However, a 20.2% mean decrease in AUC_{0-12} noted between ketoconazole treatment alone and its concomitant administration with sucralfate was not statistically significant, and failure to detect such a difference may be due to a combination of small sample size and large variability in ketoconazole absorption. A sample size calculation performed prior to study initiation indicated that a 94% difference in bioavailability would be detectable with alpha = 0.05, beta = 0.1, power = 0.9, and a variance of 13% of the mean. This difference was detected for treatment with ranitidine.

The mean 15-min pH versus concentration versus time graphs are shown in Fig. 2 for a representative subject (subject 002). During treatment III (Fig. 2c), the low AUC_{0-12} for ketoconazole was associated with a consistently elevated gastric pH in all subjects during the 4-h period following ketoconazole administration. This elevation is best represented by the median 4-h gastric pH data provided in Table 1 (pH 7.35 for subject 002). With concomitant sucralfate administration, there appears to be a decrease in ketoconazole bioavailability although there was no difference in median 4-h pH compared with that for the control treatment (Fig. 2a and b, respectively), with median 4-h pHs of 1.89 in treatment II and 1.84 in treatment I for subject 002.

DISCUSSION

This study confirms that significant reduction in bioavailability of ketoconazole is associated with an increase in gastric pH. When gastric pH was titrated above 6.0, the AUC_{0-12} for ketoconazole was reduced by 95%.

The most plausible explanation for the changes in ketoconazole absorption observed during the ranitidine treatment of this study is decreased ketoconazole dissolution at pH >5. This is consistent with in vitro work reported by Carlson and coworkers which demonstrated that dissolution of ketoconazole is rapid and complete (>90%) at pH <4 (3). However, at pHs of 5 and 6, in vitro ketoconazole dissolu-

tion is delayed and incomplete. Figure 3 represents ketoconazole AUC (in milligrams · hours per liter) versus median 4-h pH for the ketoconazole (control) and ranitidine treatments which provides a strong correlation between bioavailability and pH-dependent dissolution. The line superimposed on this plot represents a simulation of the AUC which would be expected by administration of the same oral dose at different gastric pHs, based on percent ketoconazole dissolution from the in vitro data. The initial AUC for the simulation represents the mean treatment I AUC_{0-12} (37.05 mg · h/liter). This simulation assumes that at pH 1 there is 100% dissolution and 100% absorption and that absorption is proportional to percent dissolution at every pH. The percent dissolution at each pH value was estimated by using the in vitro dissolution data provided by Carlson and coworkers and plotted at pH 2, pH 3, pH 4, pH 5, pH 6, and pH 7 (3). This figure represents the fraction dissolved multiplied by the mean treatment I AUC. As indicated by the simulation curve, there appears to be a sharp decrease in ketoconazole dissolution between pH 4 and 5, resulting in a sharp decrease in bioavailability. Our results fit this simulation well. Figure 4 also represents the relationship between the fraction of AUC for each treatment compared to baseline versus median 4-h pHs. Again, a trend indicating decreased fraction absorbed with increasing gastric pH is observed.

The concomitant administration of ketoconazole with sucralfate resulted in a 20.2% mean decrease in ketoconazole bioavailability. In contrast to the result for ranitidine, elevation of gastric pH does not explain this change. Sucralfate appeared to delay the absorption of ketoconazole as evidenced by a mean increase in the T_{max} of 1.67 h. Results for all subjects showed an increase in this parameter, except one that demonstrated no change. This is consistent with the effects of sucralfate administration reported for other medications such as naproxen and prednisone (2, 8).

Previous authors have noted the lack of effect of sucralfate on gastric pH (15, 17). This study supports these observations but gives no definitive explanation for the apparent
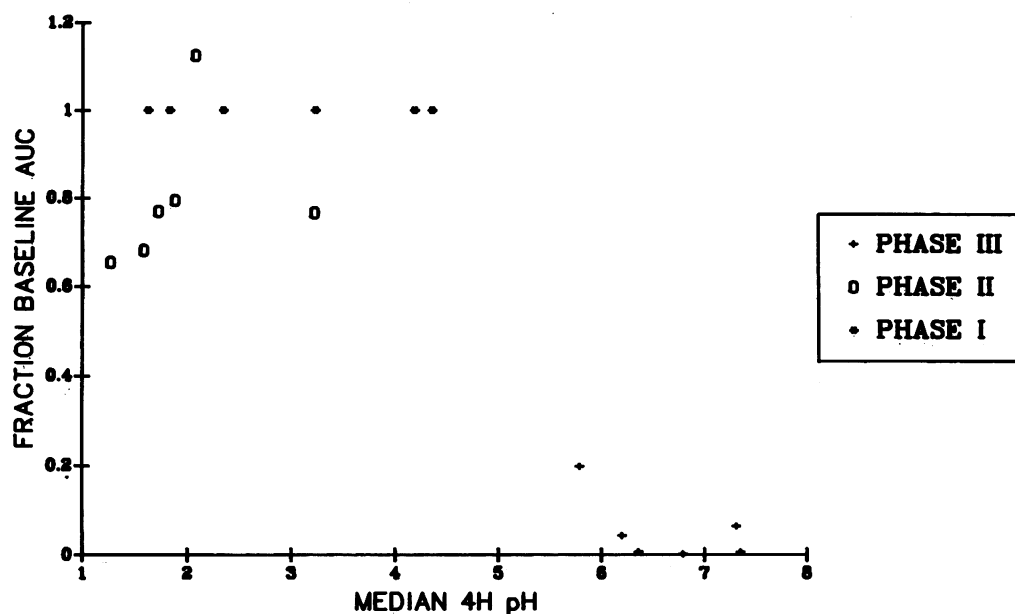
FIG. 4. Fraction of AUC achieved in treatments II and III compared with treatment I versus median 4-h (4H) gastric pH.

decrease in ketoconazole AUC_{0-12} in five of six subjects after concomitant sucralfate administration.

The Heidelberg capsule technology used in this study proved to be valuable in assessing drug-drug interaction mechanisms with regard to the effect of pH. As no change in pH was noted between treatments I and II, binding of ketoconazole to sucralfate in the gastrointestinal tract remains a strong possible explanation for the observed 20% decrease in bioavailability but is not proven by this study.

A statistically significant decrease in ketoconazole bioavailability was not associated with sucralfate administration even though bioavailability decreased 20.2%. Since the in vitro MICs of ketoconazole for various fungal organisms exhibit an extremely wide range, are method dependent, and do not necessarily correlate well to in vivo efficacy, this potential decrease in ketoconazole bioavailability (AUC_{0-12}) associated with concomitant sucralfate administration may be clinically significant (5). However, this potential decrease in relative ketoconazole bioavailability after concomitant sucralfate administration was highly variable as measured by AUC_{0-12} and ranged from a 12.3% increase in subject 001 to a 31.9% decrease in subject 003. Therefore, the data here do not preclude the concomitant use of sucralfate and ketoconazole, although this wide variability suggests that in some patients, clinical failure could be associated with concomitant administration of these two agents. Separating the administration of the two agents would possibly decrease the potential interaction of sucralfate on ketoconazole bioavailability. On this basis, and until further studies assessing effects at different administration times are performed, reasonable alternative regimens to consider are ketoconazole administration at least 2 h before sucralfate or use of a dosage of 2.0 g of sucralfate every 12 h, which would result in a maximum 6-h separation of the two agents. The decision to separate the two drugs should be based on the clinical situation.

In summary, this study demonstrates that continuous gastric pH monitoring and pH control are essential for determining possible mechanisms of changes in oral keto-

conazole absorption observed with ranitidine and sucralfate administration. In addition, using the Heidelberg capsule allowed for a decrease in the sample size required to conduct this study. Control of pH to a specified target range allowed precise determination of the impact of alkaline pH in a setting where baseline gastric pH was variable. This pH control, therefore, improved the assessment of the associations between gastric pH and ketoconazole bioavailability.

Many questions remain for further study. An avenue for further study would be an in vitro evaluation of a possible interaction between ketoconazole and sucralfate by the formation of chelates. Clearly, the concurrent administration of agents which increase gastric pH should be avoided in patients treated with ketoconazole therapy.

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