Comparison of the Pharmacokinetics of an Ondansetron Solution (8 mg) When Administered Intravenously, Orally, to the Colon, and to the Rectum

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Ondansetron, an antagonist of the serotonin type 3 (5-HT_3) receptor, is indicated for the treatment of chemotherapy-induced emesis. This study compares the pharmacokinetics, especially the bioavailability, of an ondansetron 8-mg solution when administered intravenously, orally, to the colon via nasogastric intubation, and to the rectum using a retention enema. Six healthy, male volunteers received ondansetron infused into the colon during the first treatment period. These subjects then received the remaining three treatments in random order, with a minimum 1-week washout period between treatments. Serial plasma samples were obtained for up to 24 hr after dosing in each treatment period. Absolute bioavailability after the oral dosing, colonic infusion, and rectal administration averaged 71 ± 14, 74 ± 26, and 58 ± 18%, respectively. These values were not significantly different ($P > 0.05$). Values of T_{max} and C_{max} were also not significantly different among the nonparenteral routes. Mean absorption half-lives were 0.66, 1.1, and 0.75 hr after the oral, colonic, and rectal administrations, respectively. These results indicate that ondansetron is well absorbed in the intestinal segments studied including the upper small intestine, the colon, and the rectum and that sustained-release and suppository formulations of ondansetron are feasible.

KEY WORDS: serotonin type 3 inhibitor; intestinal absorption; nasogastric intubation; retention enema.

INTRODUCTION

Currently, there is interest in the development of alternative nonparenteral dosage forms such as sustained-release and suppository formulations of ondansetron, a novel and specific antagonist of the serotonin type 3 receptor (5HT_3), indicated for chemotherapy-induced nausea and vomiting in cancer patients (1,2). The recommended oral dosing regimen of ondansetron for emetogenic neoplastic agents is 8 mg three times a day. Sustained-release formulations may reduce the dosing frequency of ondansetron and, therefore, increase patient's compliance. Suppository formulations are particularly useful for patients who may have difficulty swallowing.

In this study, we evaluated the absorption characteristics of ondansetron when administered as a solution orally, to the colon, and to the rectum. Specifically, ondansetron was administered to the colon by nasogastric infusion in the first treatment period. In addition, ondansetron solution was administered to the rectum by retention enema. Oral and intravenous administrations of ondansetron were also investigated in the same subjects for reference.

MATERIALS AND METHODS

Study Population

Six nonsmoking, male, healthy volunteers aged 19 to 35 and weighing 55.5 to 90.5 kg completed the study. Written informed consent was obtained from each subject after the risks and potential side effects were explained. Volunteer 5 had acute viral labyrinthitis after the first treatment (colonic infusion). He was hospitalized and received clemastine fumarate, meclizine hydrochloride, and amoxicillin/clavulanate potassium for 9 days. Because of the viral infection and concurrent medications, data from volunteer 5 were excluded in the final analysis.

Study Procedure

This study was a four-way crossover and open-label study carried out at the facilities of BioClin Inc. (Richmond, Virginia) after the Institutional Review Board approved the protocol. The subjects received a 8-mg infusion of ondansetron into the colon through a nasogastric tube during the first treatment period. These subjects then received the remaining three treatments in random order, with a minimum 1-week washout period between treatments. The four treatments are as follows.

Treatment A. Subjects abstained from food and water for 6 hr before they were admitted to the clinic. A nasogastric tube was inserted into the stomach and fluoroscopies were performed at different times to confirm the placement of the tube in the vicinity of the cecum. The tube was located in the cecum of subjects 1 and 6, in the ascending colon of subjects 3 and 5, in the proximal transverse colon of subject 2, and in the ileocecal junction of subject 4 as determined by the final fluoroscopy. A solution of 8 mg ondansetron in 50 mL normal saline was infused to each subject via the nasogastric tube over a period of 15 min.

Treatment B. A solution of 8 mg ondansetron in 50 mL normal saline was intravenously infused over a 15-min period to each subject.

Treatment C. Subjects abstained from food and water for 6 hr before the treatment. A solution of 8 mg of ondansetron in 120 mL of water was administered orally to each subject. An additional 116 mL of water was used to wash the dosing cup and was ingested after the dosing solution.

Treatment D. One hour before dosing, the subject emptied his colon by a 1000-mL retention enema composed of

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warm normal saline. Approximately 15 min before dosing, a catheter was prepared with a water-soluble lubricant and inserted through the anus, past the rectal sphincter, and into the rectum. The catheter was inserted up to, but not farther than, 8 in. A volume of 20 mL of air was pushed through a 20-mL syringe to inflate the catheter balloon. Additional air was added if necessary to ensure the occlusion of the bowel. The drug solution (8 mg in 50 mL normal saline) was then administered as a bolus. The catheter was sealed at an external point using a Kelly clamp to prevent the back flow. The catheter was removed after 30 min.

Five milliliters of blood was collected by venipuncture into a prelabeled heparinized blood collection tube (green-top Vacutainer) at the following times after dosing for serial blood sampling: baseline (immediately prior to dosing), 5, 15, 30, 45, 60, 75, and 90 min, and 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, and 24 hr. Within 30 min of collection, each sample was centrifuged at the highest setting of a clinical centrifuge for 30 min (or at >3600*g* for 15 min), and the plasma transferred into prelabeled polypropylene tubes and promptly frozen at −20°C.

Sample Analysis

Plasma concentrations of ondansetron free base were determined using a sensitive HPLC procedure involving robotic solid-phase extraction, separation on a reverse-phase cyano column, and UV detection at 305 nm (3). The limit of quantitation for this assay was 1.0 ng/mL.

Data Analysis

Pharmacokinetic parameters based on noncompartmental model were calculated according to standard methods (4). The input function for treatments A, C, and D were evaluated using the Loo–Riegelman method (5). The postinfusion plasma concentration–time profiles of ondansetron following intravenous administration (treatment B) were analyzed by the method of residuals to obtain initial estimates of two compartment model parameters. The intercepts at zero time following the iv bolus were estimated (4). The biexponential parameters thus obtained were used in performing deconvolution and in calculating two-compartment micro rate constants for Loo–Riegelman method. The resulting input function was then fitted to a first-order absorption model to obtain the absorption half-life ($T_{1/2a}$) value for treatments A, C, and D.

Comparisons of pharmacokinetic parameters between treatments were made using analysis of variance (ANOVA), followed by Duncan's multiple-range test for mean values if appropriate (GLM Procedure, PCSAS Version 6.04, SAS Institute, Cary, NC). The statistical model consisted of treatment, subject, and an error term. A probability value smaller than 0.05 was considered statistically significant. Data are presented at mean ± SD unless otherwise specified.

RESULTS

The ondansetron concentration rose sharply after intravenous infusion and reached maximum concentration at the end of infusion. Thereafter, the concentration decayed in a first-order fashion. After enteral dosing, the ondansetron concentration also rose rapidly and reached maximal concentration in 1 to 1.5 hr on average. The concentration then decreased in a first-order fashion. The mean concentration–time curves of ondansetron after the four dosing routes are presented in Fig. 1.

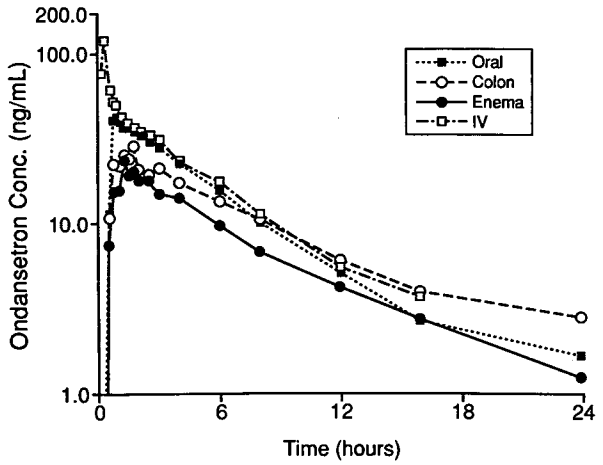

Fig. 1. Mean logarithmic plasma concentration of ondansetron versus time after intravenous infusion (□), oral administration (■), colonic infusion (○), and rectal enema (●).

AUC values after the iv infusion averaged 313 ng * hr/mL, which was comparable with results from earlier studies (6–8). Clearance of ondansetron averaged 26 L/h and volume of distribution averaged 2.2 L/kg, similar to previous results (6–8). AUC values after the oral dose averaged 225 ng * hr/mL, resulting in a mean bioavailability of 71%, which is in the range of 50–70% from the previous studies (6–8). AUC values after the colonic intubation averaged 236 ng * hr/mL, resulting in a bioavailability of 74%, which is not statistically different from that of oral dosing. The mean half-life was statistically different from those of the iv and oral dose. AUC values after the retention enema averaged 157 ng * hr/mL, resulting in a bioavailability of 58%, which did not achieve a statistically significant difference from those values for oral dosing and colonic intubation. The mean half-life was 6.7 hr, which is not different from that of

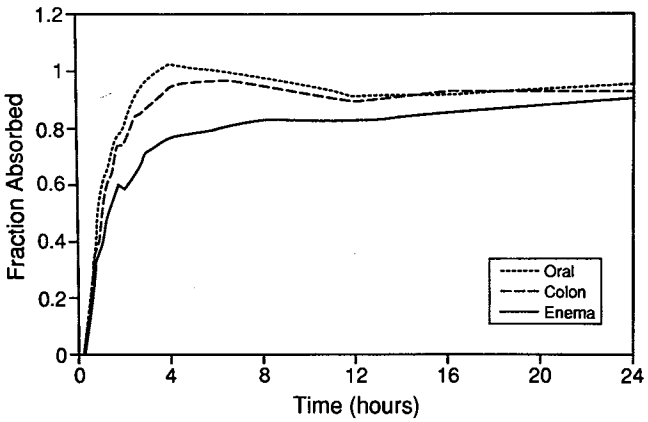

Fig. 2. Fraction absorbed of the amount ultimately absorbed-versus-time plot for ondansetron following treatment A (colonic infusion), treatment C (oral administration), and treatment D (rectal enema).

Table I. Mean Pharmacokinetic Parameters of Ondansetron for Five Subjects[a,*]

Parameter	Route			
	Intravenous	Oral	Colon	Rectal
AUC (ng * hr/mL)	313 ± 50[a]	225 ± 79[b]	236 ± 103[b]	180 ± 64[b]
$T_{1/2}$ (hr)	5.2 ± 1.6[a]	4.9 ± 1.5[a]	6.9 ± 1.4[b]	6.8 ± 0.9[b]
C_{max} (ng/mL)	136 ± 23[a]	40 ± 22[b]	28 ± 13[b]	26 ± 14[b]
T_{max} (hr)	0.26 ± 0.01[a]	1.3 ± 0.7[b]	1.1 ± 0.3[b]	1.3 ± 0.7[b]
Cl (L/hr)	26 ± 4	—	—	—
V_d (L/kg)	2.2 ± 0.8	—	—	—
MRT (hr)	5.8 ± 1.3[a]	6.8 ± 1.4[a]	9.9 ± 1.8[b]	8.8 ± 1.4[c]
F (%)	100[a]	70 ± 14[b]	74 ± 26[b]	58 ± 18[b]
$T_{1/2a}$ (hr)[b]	—	0.66	1.1	0.75

[a] Data are presented as mean ± SD.
[b] Absorption half-life estimated by the Loo–Riegelman method.
* Mean values with the same superscript letter were not significantly different from each other ($P > 0.05$) on the basis of Duncans multiple-range test.

colonic intubation but different from those after iv and oral dosing ($P = 0.02$). AUC values of ondansetron after the iv administration were significantly greater ($P = 0.006$) than those following the nonparenteral routes. No difference in C_{max} and T_{max} was detected among the enteral routes of administration.

Mean residence time (MRT) values after the colonic administration were greater than after the rectal administration ($P = 0.0001$). These values were, in turn, greater than those after the intravenous and oral administrations.

The fraction of the amount ultimately absorbed is plotted against time in Fig. 2 using the Loo–Riegelman method. Absorption half-life from treatments C and D were similar, while for treatment A, it was slightly longer (Table I).

DISCUSSION

The extent of absorption of ondansetron was similar after colonic, rectal, and oral administrations. Although the exact absorption site of oral ondansetron solution cannot be determined from this study, the rapid absorption (absorption half-lives averaging 0.66 hr) suggested that ondansetron was likely absorbed in the upper GI tract, as it usually takes 3–6 hr (9,10) for a drug to reach the colon. Thus, ondansetron appeared to be well absorbed throughout the intestinal segments studied. No statistical difference in bioavailability was observed among the oral dosing, the colonic intubation, and the retention enema regardless of whether or not subject 5 was excluded. This result may suggest that adjustment of the dosing regimen or oral ondansetron in patients who have undergone excision of a segment of the GI tract is not necessary.

The Loo–Riegelman analysis was used to obtain the absorption rate. As ondansetron is stable in physiological pH's (pH 1–8; unpublished data), it can be assumed that the same amount of ondansetron was available for each treatment. The results suggest that the rate of absorption is slightly slower for treatment A. This difference was small, however, and might be due partially to the fact that in treatment A ondansetron was perfused in 15 min as opposed to the bolus for treatments C and D. Different resident time may have also contributed to the observed slower absorption after treatment A. However, resident time was not determined in this study.

Within 4 hr after dosing, greater than 80% of the available drug was absorbed after each administration, suggesting that ondansetron was rapidly absorbed after all enteral administrations. Ondansetron is a fairly lipophilic compound (log$D$ = 2.2 at pH 10.6). Thus, ondansetron may be absorbed principally by transcellular passive diffusion as demonstrated in an *in vitro* transport study of ondansetron in Caco-2 cells (11). It has been suggested that compounds transported transcellularly by passive diffusion tend to have similar rates in different segments of intestine (12).

In summary, there are no physiological or pharmacological reasons to prevent the development of either controlled-release or suppository formulations. Further, the intubation and retention enema techniques employed in this study may be useful approaches to study colonic absorption of new drug candidates prior to initiating extensive development of sustained-release or suppository formulations.

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