Pharmacokinetics of Three Formulations of Ondansetron Hydrochloride in Healthy Volunteers: 24-Mg Oral Tablet, Rectal Suppository, and i.v. Infusion

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Am J Health Syst Pharm. 2000;57(11)

The absolute bioavailability and pharmacokinetics of three formulations of ondansetron hydrochloride 24 mg -- an oral tablet, an intravenous solution, and an extemporaneous rectal suppository -- were studied.

Twelve healthy, nonsmoking volunteers (six men and six women) were given ondansetron in a study with a three-way cross-over design. All subjects received each dosage form on the same day in the following order: oral tablet, rectal suppository, and intravenous infusion. Administrations were separated by one week. Blood sampling times varied, depending on the administration route.

Mean absolute bioavailability for the oral tablet and the rectal suppository differed significantly. Absorption of ondansetron was prolonged when it was administered as the rectal suppository. Absolute bioavailability for the 24-mg tablet was similar to that for other tablet strengths in previous studies. All subjects completed the study without significant adverse effects.

Absorption of ondansetron from the rectal suppository was prolonged compared with the oral tablet and the i.v. infusion. Bioavailability for the 24-mg suppository formulation was considerably lower than for the 24-mg tablet.

The pharmacokinetics of ondansetron have been well studied.[1-3] A variety of administration routes have been evaluated, including intravenous, intramuscular, oral (tablets and solution), colonic, and rectal (retention enema and extemporaneous suppository).[3-5] Ondansetron is well absorbed after colonic administration, and bioavailability is not significantly different from that with oral administration.[5] Additionally, ondansetron is well absorbed after administration as a retention enema and extemporaneous rectal suppository.[4,5] Two 16-mg extemporaneous suppository formulations (Fattibase and Polybase, Paddock Laboratories, Minneapolis, MN) were compared with the 8-mg oral tablet in healthy volunteers, and it was concluded that either formulation would be acceptable for clinical use.[4]

Previous pharmacokinetic studies have used ondansetron doses between 4 and 16 mg (as the hydrochloride salt), with the majority using a standard adult dose of 8 mg.[2-7] Recently, a 24-mg oral tablet was developed. The purpose of this study was to compare the absolute bioavailability and pharmacokinetics of this 24-mg tablet with those of intravenous ondansetron 24 mg and an extemporaneously compounded 24-mg rectal suppository in young, healthy volunteers.

The university's institutional review board approved the study protocol, and informed consent was obtained from each subject.

Twelve nonsmoking healthy volunteers (six men and six women) were selected. The volunteers had no history of cardiovascular, renal, hepatic, neurologic, or gastrointestinal diseases. Each subject had a complete physical examination, ECG, blood tests (liver function tests, electrolytes,

glucose, serum creatinine, blood urea nitrogen [BUN], complete blood count [CBC] with differential), and urinalysis, including serum pregnancy test for females, before study entrance. The laboratory tests were repeated after the study. All physical, ECG, and laboratory results were unremarkable. All subjects were instructed to abstain from caffeine 18 hours before the drug dosing periods and throughout the blood sampling periods. No subjects were taking prescription or nonprescription medications. Female subjects were not taking oral contraceptives before or during the study but used other accepted methods of birth control.

Ondansetron (as the hydrochloride salt) (Zofran) 24-mg tablets (lot A93B85) and 4-mg/mL injection (lot B6758BA) were provided by Glaxo Wellcome, Inc. (Research Triangle Park, NC). Suppositories were compounded using the 24-mg tablets and Polybase.[1] The 24-mg tablets were pulverized, combined with Polybase, and formed into suppositories. After cooling, the suppositories were weighed for uniformity, stored in a plastic container, and refrigerated until use. The procedure for suppository preparation is described elsewhere.[8] Previous studies of stability and studies conducted in rabbits and humans to examine the suppository's absorption profile suggested that this was an appropriate formulation.[4,8]

The study had a three-way crossover design. Placebo comparisons were not used because it was strictly a pharmacokinetic study. All subjects received each dosage form on the same day in the following order: oral tablet, rectal suppository, and intravenous infusion. Administration of each formulation was separated by one week.

Subjects fasted from midnight before drug administration to four hours afterward but were allowed unrestricted water intake. The oral ondansetron tablet was ingested with 8 oz of water. A glycerin suppository was administered 12 hours before the ondansetron suppository to evacuate the bowels. The subjects were instructed to insert the ondansetron suppository with their gloved index finger to the depth of the distal interphalangeal joint and to retain the suppository for at least four hours. The i.v. infusion was prepared by adding ondansetron injection 24 mg (as the hydrochloride salt) to 50 mL of 0.9% sodium chloride injection. The resulting solution was infused over 20 minutes through an indwelling venous catheter. The catheter was then flushed with 5 mL of heparin sodium 10 units/mL.

The blood sampling times varied depending on the administration route. The times were based on the elimination halflife of ondansetron and the possible slower rate of absorption of ondansetron from the suppository.[4] Samples of 5 mL were obtained before and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours after administration of the oral tablet; before and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after administration of the suppository; and before and at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the i.v. infusion.

For all three dosage formulations, blood samples obtained through hour 8 were collected via an indwelling venous catheter (Jelco 4056, Johnson-Johnson, Arlington, TX) placed before drug administration. The catheter was flushed after each sample and every hour with 5 mL of heparin sodium 10 units/mL. The catheter was removed after the eighthour sample was obtained, and the remaining samples were obtained by venipuncture.

Blood samples were collected in evacuated tubes containing heparin sodium. The samples were centrifuged at 3000 rpm for 30 minutes. The plasma was removed and stored at -80 °C until assay.

The plasma samples were assayed for ondansetron by high-performance liquid chromatography (HPLC). The assay method described by Colthup et al.[9] was used without major modifications.

The HPLC system consisted of a silica column (Zorbax Rx-Sil 250 ´ 4.6 mm ´ 5

m particle size, Mac-Mod Analytical, ChaddsFord, PA), an HPLC pump (model 110B, Beckman, San Ramon, CA), an integrator (model 3395, Hewlett Packard, Avondale, PA), an injector (model 7125, Rheodyne, Cotati, CA), and an UV/VIS detector (model 759A absorbance detector, ABI, Foster City, CA). The detector was set at a wave-length of 305 nm. The mobile phase consisted of 7:3 v/v 0.01 M sodium acetate buffer (adjusted to pH 4.7 with glacial acetic acid) and acetonitrile filtered through a 0.45-

m filter (Micro-Separations, Westborough, MA) and was degassed by sonication before use. Calibration standards for ondansetron hydrochloride (working standard, lot AWS332B, Glaxo Wellcome, Inc., Research Triangle Park, NC) were prepared in drug-free human serum (Biological Specialty Corporation, Colmar, PA) over the range of 5-200 ng/mL for the intravenous and oral-tablet studies and 5-100 ng/mL for the rectal-suppository study.

The serum samples were thawed for one hour, each sample was centrifuged, and the supernate carried forward for the assay of ondansetron. Sample preparation was achieved using a solid-phase extraction method. The cyanopropyl cartridges (1 mL, cat. no. 188-0610, J and W Scientific, Folsam, CA) were placed in a vacuum manifold (Vac-Elut, Varian Sample Products, Harbor, CA), and each was conditioned with 2 ´ 1 mL of absolute methanol followed by 2 ´ 1 mL of deionized water. The cartridges were not allowed to dry. A 1-mL volume of serum was added and passed through the cartridge with the aid of a mild vacuum. The cartridge was then dried for 10 minutes under full vacuum and washed with 2 mL of water for an additional 20 minutes. Ondansetron was eluted with 0.1% triethylamine in absolute methanol (10 ´ 200

L). The extract was mixed with mobile phase with the aid of a Vortex mixer. Duplicate 50-

l volumes were injected into the HPLC system at a mobile phase flow rate of 1 mL/min. An external standard was used for this assay. After every 400 injections into the HPLC system, the inlet frit of the silica column had to be replaced because of pressure buildup (>2000 psig).

Linear regression was used to construct a calibration curve from a plot of peak height versus concentration. The slope, intercept, and correlation coefficient were then used to calculate ondansetron concentration in the serum samples. The intraday coefficient of variation (CV) was 2.79% at 10 ng/mL and 2.60% at 100 ng/mL. The interday CV was 3.49% at 10 ng/ mL and 3.02% at 100 ng/mL.

The pharmacokinetics of ondansetron were determined by model-independent methods with nonlinear least-squares regression analysis (WinNonlin, Scientific Consulting, Inc., Cary, NC). The area under the plasma concentration-time curve (AUC) from time zero to the last time point (24 hours for the oral tablet and intravenous infusion or 48 hours for the suppository) was calculated by the trapezoidal rule. AUC was extrapolated to infinity (AUC_{inf}) by dividing the last concentration measured by the elimination rate constant (k). Systemic clearance (CL) for the intravenous route was determined by dividing the dose by AUC_{inf}. The elimination half-life ($t_{1/2}$) was calculated as ln 2/k. The maximum plasma concentration (C_{max}) was the highest plasma concentration measured for each subject. The time to maximum plasma concentration (t_{max}) was the time at which C_{max} occurred. The absolute bioavailability (F) of the oral tablet and

the rectal suppository was calculated as the ratio of AUC_{inf} of the respective formulation to AUC_{inf} of the intravenous formulation.

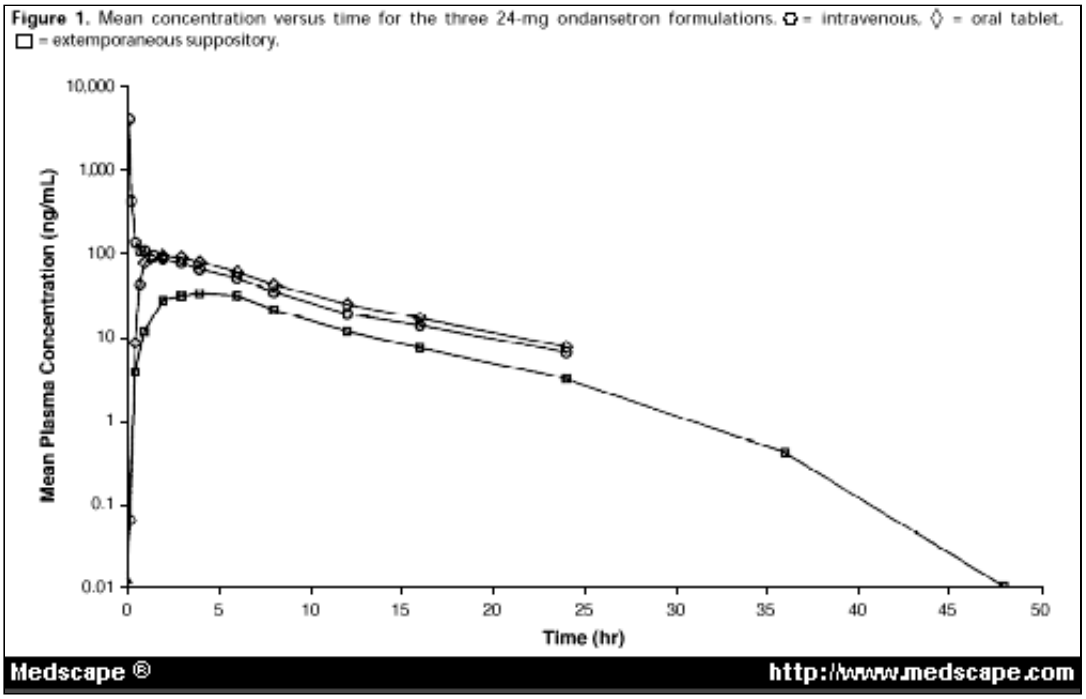
All data were reported as mean ± S.D. Comparisons between the pharmacokinetic values for each formulation were made by a two-way analysis of variance (ANOVA) followed by Scheffe's multiple-range test. The a priori level of significance was set at 0.05.

All 12 subjects completed the study. A summary of the pharmaco-kinetic data for the oral tablet, rectal suppository, and intravenous infusion is presented in Table 1. The mean absolute bioavailability (F) of the oral tablet differed significantly from that of the rectal suppository (0.65 ± 0.26 and 0.29 ± 0.12, respectively; $F = 23.986$, d.f. = 11, $p < 0.001$).

Mild headache was reported by three subjects during the oral tablet study, six subjects during the suppository study, and two subjects during the i.v. infusion study. Three subjects were allowed single doses of aceta-minophen 650 mg for their headache, which were effective. Drowsiness or sedation was reported by one subject during the oral tablet study, three subjects during the suppository study, and one subject during the i.v. infusion study. The study subjects reported no other adverse effects.

Data on the absolute bioavailability of ondansetron (as the hydrochloride salt) in doses greater than 8 mg are limited. This study provided data on a new 24-mg oral tablet and a 24-mg extemporaneous rectal suppository formulation. Like other studies, this study showed wide interpatient variability in plasma ondansetron concentrations. The following discussion focuses on the differences observed among the three formulations.

Prolonged absorption (up to three hours) has been reported when ondansetron is administered as an extemporaneous rectal suppository. [4,7] Prolonged absorption of ondansetron from the rectal suppository was observed in this study (mean ± S.D. t_{max}= 4.42 ± 1.56); however, C_{max}remained relatively low compared with intravenous and oral administration. Plasma levels of ondansetron were minimal at 36 hours and undetectable at 48 hours after rectal administration. After the six-hour time point, plasma drug concentrations for the suppository formulation declined at a steady rate resembling those of the other two administration routes (Figure 1).



. Mean concentration versus time for the three 24-mg ondansetron formulations.

The mean bioavailability of the oral 8-mg tablet ranges from 56% to 69%.[2] The calculated mean bioavailability of the 24-mg tablet in this study was 65%. The absolute bioavailability of ondansetron solution after oral administration (71% ± 14%) and rectal administration (retention enema, 58% ± 18%) is not significantly different.[5] In this study, the mean ± S.D. absolute bioavailability of the 24-mg rectal suppository (0.29 ± 0.03) was significantly lower than that of the oral tablet (0.65 ± 0.06). The t_{max}after suppository administration was consistent with the reported retention time, suggesting that evacuation of the bowels may have limited the extent of absorption. Study participants were asked to retain the suppository for a minimum of four hours to allow for absorption (range, four to six hours). Retention of the suppository for a longer time may further delay $t_{max}$and could increase the calculated bioavailability.

As expected, the highest C_{max}values were associated with intravenous administration; however, $C_{max}$for the 24-mg intravenous infusion was disproportionately higher after dosage adjustment than C_{max}in other studies.[5,9,10] One possible explanation of the higher C_{max}observed in this study is that residual drug may have been present in the catheter at the first postinfusion sample time. The same intravenous catheter was used for drug administration and sample collection. Even though the catheter was flushed with heparin, residual ondansetron may have been present in the catheter. The subjects did not report significant adverse effects temporally related to the $C_{max}$of the intravenous infusion. Plasma levels of ondansetron after intravenous administration quickly declined to parallel plasma levels measured after oral administration (Figure 1). By the two-hour time period, plasma ondansetron concentrations for the oral-tablet and the intravenous-infusion studies declined in a parallel manner. AUC values for the 24-mg intravenous infusion corresponded to dose-adjusted values from previous studies.[2]

The half-lives calculated for the three formulations were consistent (6.2-6.5 hours). The mean half-life is slightly longer than in previous studies of oral and intravenous administration of ondansetron 8 mg.[2] The small difference in half-life is difficult to explain; however, it may be

related to large interpatient variability resulting from differences in metabolism. Ondansetron is metabolized by cytochrome P-450 isozymes 1A2, 2D6, and 3A4. [11] Therefore, differences in half-life and interpatient variability may be explained by differences in cytochrome P-450 isozyme activity. Nonsmoking subjects were chosen and caffeine intake was prohibited to minimize alterations in isozyme activity.

Although this study was not specifically designed to monitor adverse events, all subjects completed the study without significant adverse effects. Only minor adverse effects (mild headache and sedation) were reported. The highest rate of headache (50%) occurred with the suppository formulation. Since the C_{max} of ondansetron was significantly lower with the suppository than with either the intravenous infusion or the oral tablet, and the reported time of the headaches did not coincide with the t_{max}, it is likely that the headaches were not strictly related to the drug. The frequency of headache and sedation after intravenous and oral administration in this study was slightly higher than reported in the literature.[12] Like the extemporaneous suppository, these events did not coincide with the drug's C_{max} or t_{max} and may be due to the higher dosage used. Finally, headache and sedation may also be related to study methods, such as dysregulation of the sleep wake cycle, fasting, and avoidance of caffeine intake.

Absorption of ondansetron from the rectal suppository was prolonged compared with the oral tablet and the i.v. infusion. Bioavailability for the 24-mg extemporaneous suppository was considerably lower than that for the 24-mg tablet.

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Funding information

This project was supported by a grant-in-aid from Glaxo Wellcome.

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Am J Health Syst Pharm. 2000;57(11)