The Influence of Gender and Food on the Pharmacokinetics of Sodium Oxybate Oral Solution in Healthy Subjects

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Sodium oxybate (Xyrem®; gamma-hydroxybutyrate) oral solution was recently approved in the United States for the treatment of cataplexy in patients with narcolepsy. Two single-center, randomized, open-label studies in healthy volunteers receiving single oral 4.5-g doses of sodium oxybate evaluated effects of (1) gender on oxybate pharmacokinetics and (2) food on its oral bioavailability. In the latter study, one dose was administered after an overnight fast, another after a high-fat meal; 1 week separated treatments. Sodium oxybate pharmacokinetics was not significantly different between sexes. However, food significantly altered the bioavailability of oxybate by decreasing mean peak plasma concentration, increasing median time-to-peak concentration, and decreasing the area under the plasma concentration-time curve. Food did not affect elimination and urinary excretion of unchanged drug. No dose adjustment of sodium oxybate based on sex is indicated. Although significant food effects were observed, these are minimized in patients by the nocturnal dosing of sodium oxybate hours after the evening meal at a consistent time interval following food ingestion.

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Sodium oxybate (gamma-hydroxybutyrate) oral solution represents a novel approach to the pharmacotherapy of narcolepsy, a debilitating sleep disorder characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic hallucinations, and the disruption of normal sleep patterns.[1] Sodium oxybate differs from other symptomatic treatments presently used for narcolepsy such as antidepressants and stimulants in that it appears to act more directly on the disrupted sleep architecture characteristic of this disorder.[2,3] Thus, although sodium oxybate does not fully normalize nocturnal sleep in narcoleptic patients, it has shown significant beneficial effects on both daytime and nighttime symptoms of narcolepsy, particularly the symptom of cataplexy.[3-11] In July 2002, the U.S. Food and Drug Administration approved sodium oxybate (as Xyrem® oral solution marketed by Orphan Medical, Inc.) for the treatment of cataplexy in narcoleptic patients. Used as an approved medication, gamma-hydroxybutyrate is a Schedule III drug; however, when used for illicit, nonmedical use (as GHB or its chemical analogs), it is classified as a Schedule I controlled substance.

The oral pharmacokinetics of sodium oxybate has been assessed previously in healthy volunteers[12] and in patients with narcolepsy[13] as well as alcohol-dependent patients[14] and patients with moderate or severe liver dysfunction.[15] Overall, these studies have shown that the pharmacokinetics of oxybate in patients with narcolepsy is comparable to those in healthy subjects and in alcohol-dependent patients.[12,13,16] While cirrhosis modified the disposition kinetics of oxybate, it did not alter tolerability to the drug.[14] These studies also indicated that oxybate is rapidly absorbed and has a half-life of approximately 1 hour.

This short half-life of oxybate supports the proposal that the effects of sodium oxybate on daytime symptoms are the result of the consolidation of nocturnal sleep.[11] It also provides a pharmacokinetic basis for the

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clinical finding that a divided dosing schedule, with total doses of 3 to 9 g sodium oxybate given in two portions at bedtime and 2.5 to 4 hours later, is most effective in the treatment of narcolepsy.[6,8,10,11] The development of the sodium oxybate oral solution formulation recognized the need for individualized dosing titration provided by a convenient liquid dosage form for the drug. The present studies were undertaken to describe the plasma pharmacokinetics of sodium oxybate oral solution in healthy males and females and to determine the effects of food on its oral bioavailability.

METHODS

Two randomized, open-label studies were conducted in healthy volunteers. One study evaluated the pharmacokinetics of a single dose of sodium oxybate oral solution in males and females; the other evaluated the oral bioavailability of sodium oxybate oral solution after an overnight fast and after a high-fat meal in a two-period, two-sequence, crossover design. The dose of sodium oxybate used in both studies was 4.5 g, which was chosen because it represents the maximum dose that is given in a single administration to patients with narcolepsy. Both studies were conducted at Bio-Kinetic Clinical Applications (Springfield, MO) after approval of the protocols and informed consent forms by the affiliated institutional review board.

Subjects

For both studies, eligible subjects were nonsmoking male or female volunteers ages 18 to 55 years who were within 15% of their ideal body weight (according to 1983 Metropolitan Life Insurance tables). They were deemed healthy based on physical examination, medical history, 12-lead electrocardiogram, and clinical laboratory evaluations (hematology, serum chemistry, urinalysis, serum pregnancy test for females, and urine drug screen) performed at screening. Subjects were excluded if they had known or suspected illicit drug use, hypersensitivity to sodium oxybate or related compounds, or any disease or condition that could affect absorption, distribution, metabolism, or elimination of sodium oxybate. Pregnant or nursing females were not admitted to either study, and women of childbearing potential were required to use adequate contraception. Subjects were required to have not used tobacco products for 1 year, given blood or used investigational drugs within 30 days, given plasma within 14 days, or used any prescription or over-the-counter medication (excluding oral contraceptives) or alcohol within 48 hours of dosing. All subjects gave written informed consent prior to participation in the studies.

Study Designs and Procedures

Gender study. Eighteen males and 18 females were chosen for the study; weight was matched as closely as possible (within ± 3 kg) between sexes. Subjects were required to enter the clinical research facility in the evening, approximately 3 hours before dosing with 4.5 g sodium oxybate oral solution (500 mg/mL; Orphan Medical, Inc.). Blood samples (5 mL) were collected before dosing (0 hour); at 10, 20, 30, 45, and 60 minutes after dosing; and at 30-minute intervals thereafter until 8 hours after dosing. A 25-mL urine aliquot was collected during the hour before dosing, and all urine was collected in the 8-hour period after dosing. Subjects received a light meal approximately 2 hours prior to dosing; thereafter, they did not receive any food until the 8-hour blood collection was completed or water or other fluids until 2 hours after dosing. Subjects remained in the study facility until 3 hours after the final 8-hour blood sample was obtained.

Food Study. Eligible subjects were randomized to one of two treatment sequences. In one sequence, subjects received a 4.5-g sodium oxybate oral dosage after an overnight fast; after a 7-day washout, they received the same study medication 30 minutes after a standardized high-fat meal. The standard meal consisted of 2 fried eggs, 2 pieces of bacon, 4 ounces of hash brown potatoes, 2 slices of buttered toast, 8 ounces of whole milk, and 8 ounces of orange juice. This meal represents approximately 150 protein calories, 250 carbohydrate calories, and 500 fat calories. In the other sequence, subjects received the 4.5-g dose of sodium oxybate in the opposite order, first after the high-fat meal and then after an overnight fast.

Each dose of sodium oxybate was administered at approximately 7 a.m. In each treatment period, 18 subjects received the study medication after an overnight fast and 18 after a high-fat meal. Blood (5 mL) was collected before dosing (0 hour); at 10, 20, 30, 45, and 60 minutes after dosing; at 30-minute intervals thereafter until 8 hours after dosing; and at 9 and 10 hours after dosing. A 25-mL urine aliquot was collected during the hour before dosing, and all urine was collected in 2-hour segments during the 10-hour period after dosing. In each treatment phase, subjects were required to enter the research facility on the evening before dosing and remain there until after the final blood and urine collection (10 h after dosing). Subjects received a light meal in the evening; thereafter, they did not receive any food (apart from the high-fat breakfast if appropriate)

until after the 4-hour blood sample was collected or water or other fluids in the 2-hour periods before and after dosing.

Safety was assessed in both studies by monitoring vital signs and occurrence of adverse events throughout the study.

Analysis of Plasma and Urine Samples

Whole blood was centrifuged at 4°C for 10 minutes at 3000 rpm within 15 minutes of collection into heparinized Vaccutainers. Plasma was pipetted into polypropylene tubes and frozen at –20°C. Urine was stored refrigerated or on wet ice until the collection interval was complete; then it was mixed, the volume was recorded, and a 25-mL aliquot was stored frozen at –20°C. Plasma and urine samples were shipped on dry ice to Covance Laboratories, Inc. (Madison, WI), where concentrations of oxybate were determined. For the assay, 2.0 mL water was added to plasma or urine samples (0.1-mL aliquots), and sodium oxybate and the internal standard (2-hydroxyvalerate; Aldrich) were extracted with methanol. Oxybate was determined by a validated liquid chromatography atmospheric pressure ionization tandem mass spectrometry (LC/MS/MS) assay with a limit of quantification (LOQ) of 5 µg/mL. The calibration curve was linear ($r = 0.9952$) over the relevant concentration range of 5 to 200 µg/mL.

Pharmacokinetic Parameters

Noncompartmental methods (WinNonlin, version 1.1) were used in the determination of pharmacokinetic parameters, which were assessed from each subject's plasma oxybate concentration versus time data for each dose. Pharmacokinetic endpoints were peak plasma concentration of oxybate (C_{max}), time from dosing to when C_{max} was reached (t_{max}), area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), elimination rate constant (λ_z), apparent elimination half-life ($t_{1/2}$), plasma clearance (CL/F), renal clearance (CL_R), and apparent volume of distribution (V_z/F).

The C_{max} and t_{max} were observed values, λ_z was calculated by log-linear regression analysis of the terminal phase of the plasma oxybate concentration versus time decay curve, and $t_{1/2}$ was calculated as $0.693/\lambda_z$. $AUC_{0-\infty}$ was obtained through summation of AUC_{last} (area under the curve from time 0 to last measurable concentration, calculated by the linear trapezoidal rule) and AUC_{ext} (estimated by taking the ratio of the last measurable concentration and λ_z). CL/F was determined from the ratio of dose and $AUC_{0-\infty}$, CL_R was computed from the ratio of the total amount excreted unchanged to $AUC_{0-\infty}$, and V_z/F was calculated from dose divided by $AUC_{0-\infty} \bullet \lambda_z$.

Table I Demographic Characteristics of Study Populations

Parameter	Gender Study ($n = 36$)		Food Study ($n = 36$)
Sex (male/female)	18/0	0/18	0/36
Race (C/B/H/O)[a]	16/0/1/1	16/0/1/1	34/0/2/0
Mean age (years)	27	34	30
Mean weight (kg)	75	73	66

a. C, Caucasian; B, Black; H, Hispanic; O, Other.

Statistical Analysis

Pharmacokinetic data are presented as mean (median for t_{max}) and standard deviation (*SD*). The effect of gender on sodium oxybate pharmacokinetics was determined by an unpaired *t*-test of the log-transformed $AUC_{0-\infty}$, log-transformed C_{max}, CL/F, $t_{1/2}$, the percentages of the dose recovered unchanged in urine, and CL_R. The Wilcoxon rank-sum test (a nonparametric analysis) was performed on t_{max}.

The effect of food on sodium oxybate pharmacokinetics was determined by an analysis of variance (ANOVA), including effects for sequence, subject within sequence, treatment, and period, of the $AUC_{0-\infty}$ and C_{max} after logarithmic transformation and computation of the 90% confidence interval (CI). The CIs were compared to the reference intervals of 0.80 to 1.25 for $AUC_{0-\infty}$ and 0.70 to 1.43 for C_{max} for description of the effect of administration with food on the bioavailability of sodium oxybate. In addition, t_{max}, λ_z, and $t_{1/2}$ were analyzed for significant effects of food. After the treatments, t_{max} was also compared by a nonparametric analysis.

RESULTS

Study Populations

Demographic information regarding subjects in each of the studies is summarized in Table I. Data from all 36 subjects (18 males, 18 females; 18 to 55 years old and weighing 57 to 96 kg) who entered the gender study were included in the safety analysis and in the pharmacokinetic statistics. Two of the 36 subjects (both 29-year-old females) who entered the food study did not complete the study, and data from these subjects were not included in the pharmacokinetic analysis.

Table II Pharmacokinetics of Sodium Oxybate in Healthy Males and Females

Parameter	Male (n = 18)		Female (n = 18)	
$AUC_{0-\infty}$ (μg•h/mL)	241	(81.7)	233	(81.5)
C_{max} (μg/mL)	88.3	(21.4)	83.0	(18.7)
t_{max} [a] (h)	1.00		1.00	
$t_{1/2}$ (h)	0.65	(0.23)	0.61	(0.12)
CL/F (mL/min/kg)	3.8	(1.3)	4.2	(1.6)
V_z/F (mL/kg)	202	(61.4)	218	(86.6)
Urinary recovery (%)	3.1	(1.3)	3.1	(1.8)
CL_R (mL/h)	484	(185)	510	(276)

Data presented as mean ± standard deviation.
a. Median.

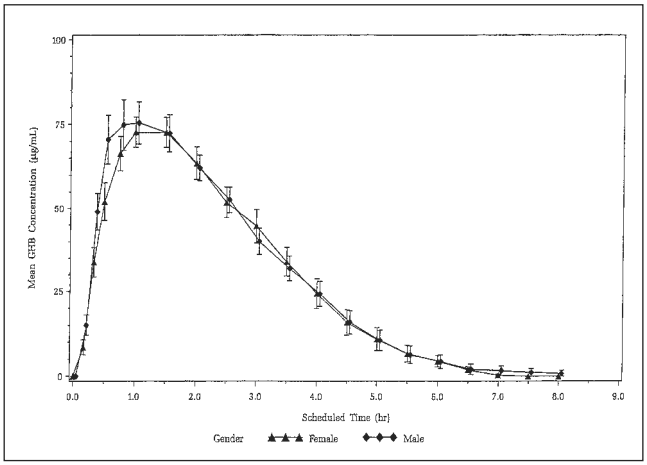

Figure 1. Mean (± SEM) plasma oxybate (GHB) concentration-time profiles in healthy adult males (n = 18) and females (n = 18) following a single oral dose of 4.5 g sodium oxybate oral solution.

One subject did not return for the second treatment period because of adverse events experienced during the first treatment period; the other did not return because of reasons unrelated to the study. Data from all 36 subjects in the food study were included in the safety analysis.

Pharmacokinetics of Sodium Oxybate in Healthy Males and Females

Plasma concentration versus times curves for oxybate in males and females are shown in Figure 1, and pharmacokinetic parameters are summarized in Table II. There was no difference in the systemic exposure to oxybate between male and female subjects, and there was no significant difference ($p > 0.05$) between male and female volunteers for any of the pharmacokinetic parameters assessed.

Oxybate was rapidly absorbed and quickly eliminated. Concentrations above 5 μg/mL (the assay LOQ) were observed at the first sampling time (10 min), and concentrations were below 5 μg/mL by 4 hours after dosing in most subjects. Mean plasma oxybate concentrations in males and females were superimposable between 1 and 8 hours after dosing (Figure 1), and the mean pharmacokinetic parameters related to the rate of absorption (C_{max}, t_{max}) were similar between the sexes (Table II). Plasma concentrations of oxybate climbed rapidly, peaking at an average of 1.25 hours and 1.14 hours in males and females, respectively, and then declined in a multiphasic manner (Figure 1). The convex nature of the log-concentration versus time data observed when the dose was administered after an overnight fast indicated the presence of a saturable process in the elimination of oxybate. The mean elimination half-life (estimated from the last three concentrations above the assay LOQ and observed over an interval of 1 h) was 0.65 hours in males and 0.61 hours in females. $AUC_{0-\infty}$, estimates of plasma oral clearance, and mean apparent volumes of distribution (Table II) were not different between males and females.

Urinary excretion of unchanged oxybate was a minor elimination pathway in both sexes. For both men and women, the average urinary recovery of unchanged drug was about 3% in the 8-hour period following dosing. Urinary excretion ranged from 1% to 7% among the 36 subjects.

Effect of Food on the Bioavailability of Sodium Oxybate

Plasma concentration versus times curves for oxybate after an overnight fast and after a high-fat meal are shown in Figure 2, and pharmacokinetic parameters are summarized in Table III. Food significantly affected systemic exposure to oxybate. By 1 hour after dosing with sodium oxybate, plasma concentrations of oxybate were twice as high in subjects who received the drug after an overnight fast than in those who received it after a high-fat meal (Figure 2). Absorption was slower and peak plasma concentrations were observed later when sodium oxybate was dosed after a high-fat meal.

Peak plasma concentrations of oxybate were lower in all 34 evaluable subjects in the fed state. The mean C_{max} values were significantly decreased more than twofold in the fed condition as compared to the fasted state ($p < 0.05$). Mean $AUC_{0-\infty}$ values were likewise significantly higher in the fasted versus fed state ($p <$

Table III Effect of Food on the Pharmacokinetics of Sodium Oxybate

Parameter	Fasted State (n = 34)	Fed State (n = 34)
$AUC_{0-\infty}$ (µg•h/mL)	289 (109)	188* (80.0)
C_{max} (ng/mL)	142 (34.2)	60.1* (20.1)
t_{max} [a] (h)	0.75	2.00**
$t_{1/2}$ (h)	0.57 (0.30)	0.68 (0.22)
CL/F (mL/min/kg)	3.7 (1.4)	6.2 (3.2)
V_z/F (mL/kg)	192 (193)	384 (324)
Urinary recovery (%)	3.8 (2.0)	3.5 (1.8)
CL_R (mL/h)	490 (251)	826 (462)

Data presented as mean ± standard deviation.
a. Median.
*$p < 0.05$. **$p = 0.001$.

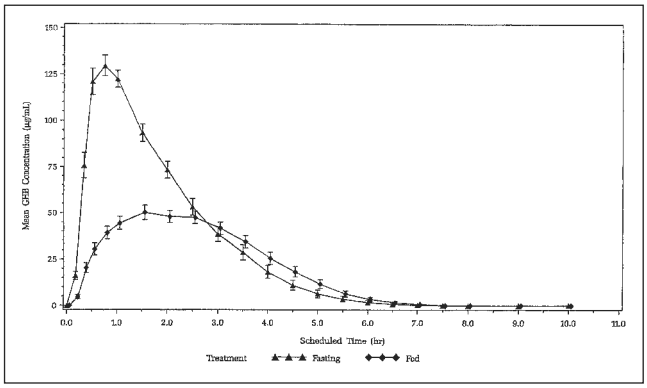

Figure 2. Mean (± SEM) plasma oxybate (GHB) concentration-time profiles in healthy adult females (n = 34) following a single oral dose of 4.5 g sodium oxybate oral solution under fasted and fed conditions.

0.05). The median t_{max} of 2.00 hours in the fed state was significantly later than the median t_{max} of 0.75 hours in the fasted state ($p = 0.0001$).

Based on the logarithmic transformations of C_{max} and $AUC_{0-\infty}$, the mean (90% CI) ratio of fed/fasted for C_{max} was 0.41 (0.37-0.46) and for $AUC_{0-\infty}$ was 0.63 (0.57-0.69). The 90% CIs for both parameters were outside the reference ranges that indicate equivalence (0.70-1.43 for C_{max} and 0.80-1.25 for $AUC_{0-\infty}$).

In both the fed and fasted conditions, decline in plasma concentrations of oxybate proceeded in a multiphasic manner (Figure 2). The mean elimination half-life was 0.68 hours when the dose was administered after a high-fat meal and 0.57 hours when the dose was administered after an overnight fast, a nonsignificant difference. Estimates of plasma oral clearance, mean apparent volumes of distribution, and renal clearance were not significantly different between the fed and fasted states.

Urinary excretion of unchanged oxybate was a minor elimination pathway in both conditions. Urinary recovery of unchanged oxybate over the 10-hour postdose period averaged 3.5% (range = 1.2%-8.8%) for fasted subjects and 3.8% (range = 0.6%-11.0%) for fed subjects. Most of the urinary excretion occurred in the first 6 hours after dosing. Although the fraction excreted unchanged was unaffected by the treatments, renal clearance tended to be slightly higher when the dose was administered after a high-fat meal (Table III).

Safety

A total of 10 adverse events, including nausea, headaches, hot flash, and itching, were reported by 8 of the 36 volunteers during the gender study; most (70%) were experienced by females. A total of 86 adverse events, most commonly vomiting, nausea, and various CNS symptoms, were reported by 31 of the 36 female volunteers in the food effect study; most (79%) were reported when sodium oxybate was administered after an overnight fast. None of the adverse experiences in either study was classified as serious. One subject discontinued the food effect study prematurely because of multiple nonserious adverse events experienced during the first treatment period in which she had received the drug after an overnight fast.

Vital signs including measurements of blood pressure, heart rate, and respiratory rate were recorded within 1 hour before dosing and at 2, 6, and 10 hours after the dose in each treatment period. No clinically significant changes in vital signs from baseline values were observed during either study.

DISCUSSION

Sodium oxybate oral solution is the first drug approved in the United States for the treatment of cataplexy in patients with narcolepsy. The maximum recommended daily dose is 9 g, in divided portions of 4.5 g given at bedtime and 2.5 to 4 hours later. This unusual dose regimen is based empirically on several early narcolepsy clinical trials conducted in Canada, the Netherlands, and the United States.[4,6,8,9] From a pharmacokinetic perspective, dividing the nightly sodium oxybate dose is rational because the elimination half-life of oxybate in narcoleptic patients is less than 1 hour.[13] The studies presented herein confirm the rapid elimination of oxybate after ingestion of the maximum recommended 4.5-g dose portion of sodium oxybate oral solution. Also, these studies extend findings from

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