6. Protocol OMC-SXB-11: Effect of Food on the Pharmacokinetics of GHB.

Title:

A Study to Examine the Effect of Food on the Bioavailability of Xyrem Oral Solution in Healthy Volunteers.

Objective:

The main purpose of this study was to describe the plasma pharmacokinetics of gamma-hydroxybutyrate (using an [redacted] assay) following a 4.5 g dose of Xyrem oral solution administered after a standardized high fat meal and after an overnight fast. In addition, the safety and tolerability of the drug were evaluated.

Study Design and Methods:

This study utilized a single-center, single-dose, open-label, two-period, two-treatment, crossover, randomized design. After qualifying for the study, each subject was randomized to one of two treatment sequences. All subjects spent the night before dosing at the study facility. During the morning of period 1, half the subjects ingested 4.5 g of the study drug following a standardized high fat breakfast served half an hour before dosing; the other subjects ingested an equivalent dose of the study drug in a fasting state. There was a 7-day washout between periods 1 and 2. During period 2, individual subjects crossed over to the other treatment. Serial plasma samples were collected pre-dose and up to 10 hours following Xyrem dosing for the determination of pertinent pharmacokinetic parameters and evaluation of the effect of administration with food. All urine voided was collected in two-hour increments up to 10 hours post-dose. Throughout the treatment phase, each volunteer was monitored for the occurrence of adverse events (AEs) and changes in vital signs.

Subjects:

Thirty-six healthy female volunteers (34 Caucasian and 2 Hispanic; 18 to 55 years of age; 52 to 84 kg in weight) enrolled in the study and 34 completed the study. If a female subject was of childbearing potential, a negative serum pregnancy test was required prior to study entry. One subject did not return for period 2 because of AEs in period 1 consisting of dizziness, nausea, vomiting, apnea, hypoventilation and involuntary defecation. Another subject did not return for period 2 because of an illness (not related to study drug administration).

Test Product, Dose and Mode of Administration:

Xyrem was supplied as an oral solution containing 500 mg sodium oxybate per milliliter. It was supplied by Orphan Medical in bottles of 180 ml. (Lot No: EH75).

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{inf}), oral plasma clearance (CL/F), elimination half-life ($t_{1/2}$), percentage of dose excreted unchanged in urine and renal clearance (CL_r). Non-compartmental methods were used in the determination of various pertinent pharmacokinetic parameters. The effect of food was determined by ANOVA of logarithmically transformed AUC_{inf} and C_{max} and computation

of the 90% confidence interval about the ratio of the mean results observed after a high fat meal and after an overnight fast. A non-parametric comparison (Wilcoxon rank sum test) was used in the comparison of fed and fasting t_{max} values.

Assay Validation:

The assay used to quantitate GHB was an ——— assay. For both plasma and urine, the calibration curve was linear for the concentration range from with a lower limit of quantitation (LLOQ) of ——— The between day variability did not exceed 10% for the QC samples of 15, 75, 150, and 400 µg/ml. For the accuracy of the method, the deviations from the mean were –7.1% for the low QC sample, -5.7% for the intermediate QC sample, -3.2% for the high QC sample, and 0.9% for the over the curve QC sample. Comparatively for urine, the deviations from the mean were –1% for the low QC sample, -8.8% for the intermediate QC sample, and -3.4% for the high QC sample.

Results:

Figure 6. Effect of Food on the Plasma Concentrations of GHB Following a 4.5 g oral dose.

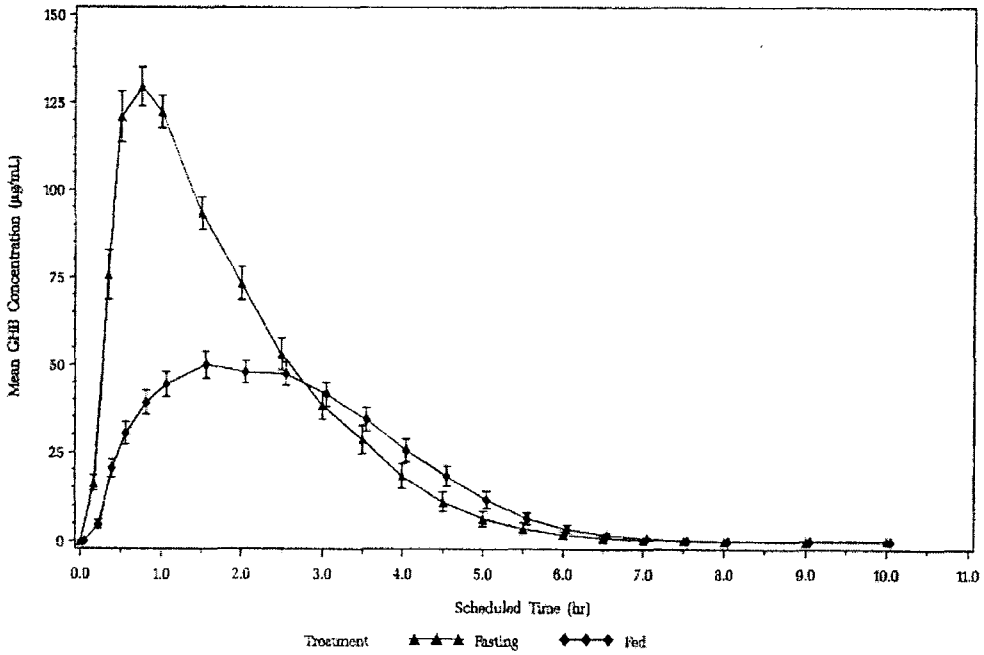

Figure 7. Cumulative Renal Excretion of GHB Following an oral dose of 4.5 g.

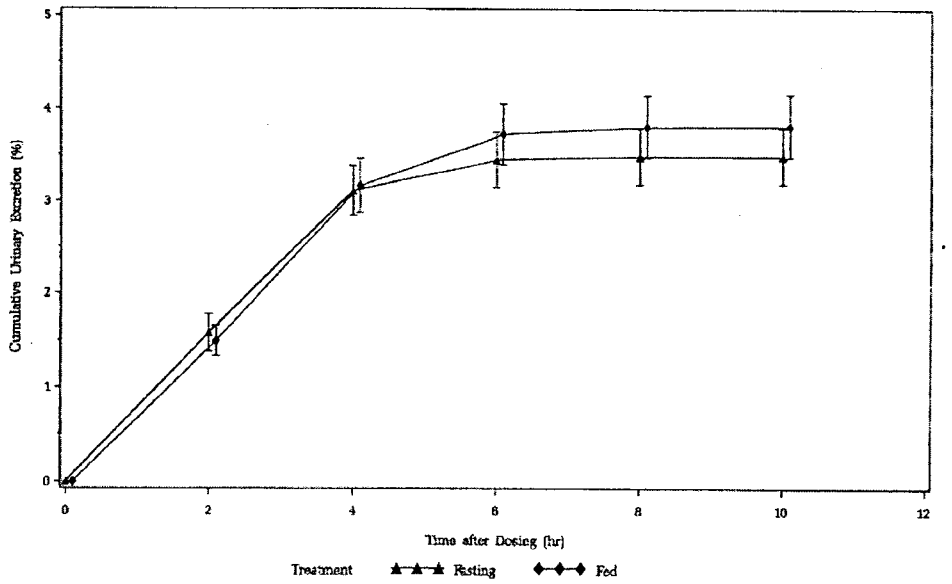

Table 16: GHB Pharmacokinetic Parameters

[Arithmetic Mean (±SD)**]

Parameter (units)	Fed (n=34)	Fasting (n=34)
C_{max} (µg/mL)	60.1* (20.1)	142 (34.2)
T_{max} (hr)	2.00 *	0.75
$T_{1/2}$ (hr)	0.68 (0.22)	0.57 (0.30)
AUC_{inf} (µg.hr/mL)	188* (80.0)	289 (109)
CL/F (mL/min/kg)	6.2 (3.2)	3.7 (1.4)
V_z/F (mL/kg)	384 (324)	192 (193)
Urinary Recovery (%)	3.8 (2.0)	3.5 (1.8)
CL_r (mL/hr)	826 (462)	490 (251)

*Statistically significant at $p < 0.05$.
**Median is reported for t_{max}.

Table 17: Gamma-Hydroxybutyrate Pharmacokinetic Parameters: Effect of Food (90% Confidence Intervals)

Parameter (units)	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval
	Fed (n=34)	Fasting (n=34)		
C_{max} (µg/ml)	56.5	137.9	0.41	0.37 – 0.46
AUC_{inf} (µg-hr/ml)	168.7	269.4	0.63	0.57 – 0.69

On average C_{max} decreased by 59% and AUC_{inf} decreased by 37%. The 90% confidence intervals were outside the reference ranges (0.80 – 1.25 for both C_{max} and AUC_{inf}) that indicate bioequivalence. Absorption of sodium oxybate appeared to be slower following food consumption, resulting in a later t_{max} of 2 hr compared to 0.75 hr. The t_{max} values for fed and fasting states were significantly different (p=0.0001). The apparent half-life of GHB was less than 1 h for both dosing conditions. Urinary excretion of unchanged drug was a minor elimination pathway and unaffected by the treatment conditions (means were 3.5% [fasting] and 3.8% [fed]). More adverse events were experienced when Xyrem was administered after an overnight fast than when it was administered after a high fat meal, probably as a result of the higher plasma concentrations of drug observed when Xyrem was administered after a fast. According to the sponsor, all of the adverse events were well tolerated by healthy adult volunteers and resolved without sequelae.

Conclusion:

Food decreased the systemic exposure of gamma-hydroxybutyrate with decreases in C_{max} and AUC of 59% and 37%, respectively. In addition, the data showed that considerable absorption occurred up to 4 h following administration of the drug. This pronounced effect of food on the bioavailability of GHB suggests that timing of food intake relative to administration is crucial in obtaining the maximum bioavailability of the drug. Therefore, Xyrem should be taken in the fasted state.

7. Effect of Hepatic Impairment on the Pharmacokinetics of GHB.

Title: Effect of moderate or severe liver dysfunction on the pharmacokinetics of γ-hydroxybutyric acid.

Objective:

Since GHB is primarily metabolized by the liver, a hepatic impairment study would be warranted. The sponsor has submitted a previously published study (Ferrara et al, 1996) to support labeling recommendations in this special population. The main

purpose of this study was to assess the effect of moderate or severe liver dysfunction on the pharmacokinetics of γ-hydroxybutyric acid.

Subjects:

Sixteen male patients with biopsy-proven liver cirrhosis (8 with ascites and 8 without ascites) were studied (mean age; 55 and 60 yrs.). All nonascitic patients were categorized as Child's Pugh class A (score of 5), whereas ascitic patients were Child's class C (score of 15). Exclusion criteria included a history of hypersensitivity to the administered drugs, recent history of GI bleeding, severe encephalopathy, a $CL_{CR} < 50$ ml/min, and presence of any other disease. None of the patients were heavy smokers. All of the patients abstained from alcohol and other drugs two weeks prior to the study, apart from those used to treat cirrhosis: diuretics, H2-blockers, and vitamin supplements.

Study Design and Methods.

A liver metabolic function of each patient was evaluated by measuring antipyrine clearance and the formation rate of lidocaine metabolite, monoethylglycinexylidide (MEGX). GHB, lidocaine, and antipyrine were administered at 8 a.m. following an overnight fast. On day 1, each patient underwent a MEGX liver function test. Lidocaine was infused over 2 min. and serial blood samples were collected up to 1 h. On day 3, antipyrine was administered orally at a dose of 10 mg/kg. Subsequently, blood samples were collected over 48 h. On day 8, GHB, dissolved in black cherry syrup was administered orally at a dose of 25 mg/kg (1.75 g). Blood samples were collected at serial time points up to 6 h. In addition, urine was collected before and up to 24 h following administration of the drug.

Analytical Methods.

GHB was quantitated in plasma and urine using a previously described —— assay (Data to support assay validation was not included in the study). The limit of detection for the assay was —— The calibration curve had a correlation coefficient of 0.997 over the relevant concentration range up to 50 μg/ml. The intra- and interassay coefficients of variation were both below 3% at 5 μg/ml and 2% at 50 μg/ml.

Pharmacokinetic Analysis.

Noncompartmental approaches were used to estimate various pharmacokinetic parameters, including the maximum observed plasma concentration (C_{max}), observed time to C_{max} (t_{max}), terminal half-life ($t_{1/2}$), area under the plasma concentration-time curve (AUC), area under the first moment of the plasma concentration-time curve (AUMC), mean residence time (MRT), apparent oral clearance (CL_{po}), renal clearance (CL_r), and apparent volume of distribution following oral administration (V_z/f).

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