R_x only

Xyrem® (sodium oxybate) oral solution

CIII

!WARNING: Central nervous system depressant with abuse potential.
Should not be used with alcohol or other CNS depressants.

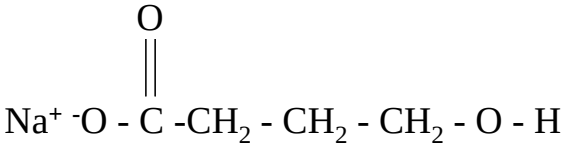
Sodium oxybate is GHB, a known drug of abuse. Abuse has been associated with some important central nervous system (CNS) adverse events (including death). Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all of the patients who received sodium oxybate during clinical trials were receiving CNS stimulants.

Important CNS adverse events associated with abuse of GHB include seizure, respiratory depression and profound decreases in level of consciousness, with instances of coma and death. For events that occurred outside of clinical trials, in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (e.g., dose of GHB taken, the nature and amount of alcohol or any concomitant drugs).

Xyrem is available through the Xyrem Success Program, using a centralized pharmacy 1-866-XYREM88® (1-866-997-3688). The Success Program provides educational materials to the prescriber and the patient explaining the risks and proper use of sodium oxybate, and the required prescription form. Once it is documented that the patient has read and/or understood the materials, the drug will be shipped to the patient. The Xyrem Success Program also recommends patient follow-up every 3 months. Physicians are expected to report all serious adverse events to the manufacturer. (See WARNINGS).

DESCRIPTION

Xyrem (sodium oxybate) is a central nervous system depressant that reduces excessive daytime sleepiness and cataplexy in patients with narcolepsy. Sodium oxybate is intended for oral administration. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$ and the molecular weight is 126.09 grams/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Xyrem oral solution contains 500 mg of sodium oxybate per milliliter of USP Purified Water, neutralized to pH 7.5 with malic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action

The precise mechanism by which sodium oxybate produces an effect on cataplexy is unknown.

Pharmacokinetics

Sodium oxybate is rapidly but incompletely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5 to 1 hour. Pharmacokinetics are nonlinear with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 grams (g). The pharmacokinetics are not altered with repeat dosing.

Absorption

Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 25%. The average peak plasma concentrations (1^{st} and 2^{nd} peak) following administration of a 9 g daily dose divided into two equivalent doses given four hours apart were 78 and 142 micrograms/milliliter (mcg/mL), respectively. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours in eight pharmacokinetic studies. Following oral administration, the plasma levels of sodium oxybate increase more than proportionally with increasing dose. Single doses greater than 4.5 g have not been studied. Administration of sodium oxybate immediately after a high fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2.0 hr) and a reduction in peak plasma level (C_{max}) by a mean of 58% and of systemic exposure (AUC) by 37%.

Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190-384 mL/kg. At sodium oxybate concentrations ranging from 3 to 300 mcg/mL, less than 1% is bound to plasma proteins.

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, that catalyses the conversion of sodium oxybate to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A

second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyses the conversion to succinic semialdehyde in the presence of α-ketoglutarate. An alternate pathway of biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 mcg/mL). These levels are considerably higher than levels achieved with therapeutic doses.

Elimination

The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible.

Special Populations

Geriatric

The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied.

Pediatric

The pharmacokinetics of sodium oxybate in patients under the age of 18 years have not been studied.

Gender

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate following a single oral dose of 4.5 g.

Race

There are insufficient data to evaluate any pharmacokinetic differences among races.

Renal Disease

Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected.

Hepatic Disease

Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. The kinetics of sodium oxybate in 16 cirrhotic patients, half without ascites, (Child's Class A) and half with ascites (Child's Class C) were compared to the kinetics in 8 healthy adults after a single oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control subjects (mean $t_{1/2}$ of 59 and 32 versus 22 minutes). It is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction (see Dosage and Administration).

Drug-Drug Interaction

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics.

CLINICAL TRIALS

Cataplexy

The effectiveness of sodium oxybate in the treatment of cataplexy was established in two randomized, double-blind, placebo-controlled trials (Trials 1 and 2) in patients with narcolepsy, 85% and 80%, respectively, of whom were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of Xyrem® independent of stimulant use. In each trial, the treatment period was 4 weeks and the total daily doses ranged from 3 to 9 g, with the daily dose divided into two equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing.

Trial 1 was a multi-center, double-blind, placebo-controlled, parallel-group trial that enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomized to receive placebo, sodium oxybate 3 g/night, sodium oxybate 6 g/night, or sodium oxybate 9 g/night.

Trial 2 was a multi-center, double-blind, placebo-controlled, parallel-group, randomized withdrawal trial that enrolled 55 narcoleptic patients who had been taking open-label sodium oxybate for 7 to 44 months. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomized to continued treatment with sodium oxybate at their stable dose or to placebo. Trial 2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use.

The primary efficacy measure in Trials 1 and 2 was the frequency of cataplexy attacks.

Table 1
Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Trial/ Dosage Group (n)	Baseline	Median Change From Baseline	Comparison to Placebo p-value
CATAPLEXY ATTACKS			
	Trial 1		
		(median attacks/week)	
Placebo (33)	20.5	-4	—
6.0 g/night (31)	23.0	-10	0.0451
9.0 g/night (33)	23.5	-16	0.0016
	Trial 2		
		(median attacks/two weeks)	
Placebo (29)	4.0	21.0	-
Sodium oxybate (26)	1.9	0	<0.001

In Trial 1, both the 6 g/night and 9 g/night doses gave statistically significant reductions in the frequency of cataplexy attacks. The 3 g/night dose had little effect. In Trial 2, following the discontinuation of long-term open-label sodium oxybate therapy, patients randomized to placebo experienced a significant increase in cataplexy ($p < 0.001$), providing evidence of long-term efficacy of sodium oxybate. In Trial 2, the response was numerically similar for patients treated with doses of 6 to 9 g/night, but there was no effect seen in patients treated with doses less than 6 g/night, suggesting little effect at these doses.

Excessive Daytime Sleepiness

The effectiveness of sodium oxybate in the treatment of excessive daytime sleepiness in narcolepsy was established in two randomized, double-blind, placebo-controlled trials (Trials 3 and 4) in patients with narcolepsy. Seventy-eight percent of patients in Trial 3 were also being treated with CNS stimulants.

Trial 3 was a multi-center randomized, double-blind, placebo-controlled, parallel-arm trial that evaluated 228 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale (see below) score of 18, and Maintenance of Wakefulness Test (see below) score of 8.25 minutes. These patients were randomized to one of 4 treatment groups: placebo; sodium oxybate 4.5 g/night; sodium oxybate 6 g/night; and sodium oxybate 9 g/night. The period of double-blind treatment in this trial was 8 weeks. Antidepressants were withdrawn prior to randomization; stimulants were continued at stable doses.

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