1521-0111/12/8202-226–235$25.00
MOLECULAR PHARMACOLOGY
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Mol Pharmacol 82:226–235, 2012

Vol. 82, No. 2
78154/3781922

γ-Hydroxybutyrate (GHB)-Induced Respiratory Depression: Combined Receptor-Transporter Inhibition Therapy for Treatment in GHB Overdose

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Received February 7, 2012; accepted May 4, 2012

ABSTRACT

Overdose of γ-hydroxybutyrate (GHB) frequently causes respiratory depression, occasionally resulting in death; however, little is known about the dose-response relationship or effects of potential overdose treatment strategies on GHB-induced respiratory depression. In these studies, the parameters of respiratory rate, tidal volume, and minute volume were measured using whole-body plethysmography in rats administered GHB. Intravenous doses of 200, 600, and 1500 mg/kg were administered to assess the dose-dependent effects of GHB on respiration.To determine the receptors involved in GHB-induced respiratory depression, a specific $GABA_B$ receptor antagonist, (2*S*)-(+)-5,5-dimethyl-2-morpholineacetic acid (SCH50911), and a specific $GABA_A$ receptor antagonist, bicuculline, were administered before GHB. The potential therapeutic strategies of receptor inhibition and monocarboxylate transporter (MCT) inhibition were assessed by inhibitor administration 5 min after GHB. The primary effect of GHB on respiration was a dose-dependent decrease in respiratory rate, accompanied by an increase in tidal volume, resulting in little change in minute volume. Pretreatment with 150 mg/kg SCH50911 completely prevented the decrease in respiratory rate, indicating agonism at $GABA_B$ receptors to be primarily responsible for GHB-induced respiratory depression. Administration of 50 mg/kg SCH50911 after GHB completely reversed the decrease in respiratory rate; lower doses had partial effects. Administration of the MCT inhibitor L-lactate increased GHB renal and total clearance, also improving respiratory rate. Administration of 5 mg/kg SCH50911 plus L-lactate further improved respiratory rate compared with the same dose of either agent alone, indicating that $GABA_B$ and MCT inhibitors, alone and in combination, represent potential treatment options for GHB-induced respiratory depression.

Introduction

γ-Hydroxybutyate (GHB) is a short-chain fatty acid present endogenously in many human tissues, resulting from production via GABA metabolism (Maitre, 1997). GHB has also recently been identified as a useful therapeutic agent for the treatment of narcolepsy and excessive daytime sleepiness in the form of sodium oxybate (Xyrem; Jazz Pharmaceuticals, Palo Alto, CA). However, GHB has become more popularly known as a drug of abuse. According to reports from the Drug Abuse Warning Network, there have consistently been 1000 to 2000 GHB-related emergency department visits reported annually in the United States over the past several years (Substance Abuse and Mental Health Services Administration, 2011). GHB overdose can result in manifestations including sedation, coma, hypothermia, bradycardia, respiratory depression, and death (Li et al., 1998; Sporer et al., 2003; Caldicott et al., 2004; Galicia et al., 2011). In a recent report of known GHB-associated fatalities, the most common cause of mortality was cardiorespiratory arrest (Zvosec et al., 2011). Respiratory depression with the need for mechanical ventilation is also frequently reported in nonfatal cases of GHB intoxication (Li et al., 1998; Mason and Kerns, 2002; Liechti and Kupferschmidt, 2004).

Although respiratory depression is a common symptom of GHB overdose, neither the dose-dependent effects of GHB on this measure nor the neurotransmitter receptors involved in

This work was supported by the National Institutes of Health National Institute on Drug Abuse [Grant DA023223] and Pfizer Global Research and Development.

This work was previously presented in part as an abstract: Morse B, Uhlander J, and Morris M. Respiratory depression in γ-hydroxybutyrate overdose: interaction with ethanol and treatment using monocarboxylate transporter inhibition, *AAPS Annual Meeting and Exposition*; 2011 Oct 23–27; Washington DC. American Association of Pharmaceutical Sciences, Arlington, VA.

Article, publication date, and citation information can be found at http://molpharm.aspetjournals.org.

http://dx.doi.org/10.1124/mol.112.078154.

ABBREVIATIONS: GHB, γ-hydroxybutyrate; MCT, monocarboxylate transporter; SCH50911, (2*S*)-(+)-5,5-dimethyl-2-morpholineacetic acid; LC, liquid chromatography; MS/MS, mass spectrometry; E_{max}, maximum effect; T_d, duration of effect; AUC, area under the plasma concentration-time

GHB-induced respiratory depression have been investigated. There are several proposed actions of GHB, including 1) direct action at $GABA_B$ receptors (Bernasconi et al., 1992), 2) direct action at its own putative GHB receptor (Maitre, 1997), and 3) indirect action at GABA receptors via GABA production/release (Hechler et al., 1997; Gobaille et al., 1999). Although evidence exists for each of these mechanisms in vitro and/or in vivo, many of the toxicological effects of GHB, including sedation, hypothermia, and fatality, can be attributed to agonism at $GABA_B$ receptors (Carai et al., 2001, 2005; Kaupmann et al., 2003).

Along with a complex pharmacologic profile, the pharmacokinetics of GHB are also notably complicated. In humans, GHB exhibits dose-dependent pharmacokinetics, even at therapeutic concentrations (Palatini et al., 1993). Rats similarly display nonlinear pharmacokinetics, due to several concentration-dependent processes including saturable oral absorption, saturable metabolism, and saturable renal reabsorption (Lettieri and Fung, 1979; Morris et al., 2005). In both humans and rats, GHB metabolism is the predominant route of elimination at low doses, and renal excretion of unchanged drug is minimal (Lettieri and Fung, 1976; Brenneisen et al., 2004). Although limited information exists for supratherapeutic GHB doses in humans, it has been well documented in rats that renal clearance becomes an increasingly important route of elimination as GHB doses are increased (Morris et al., 2005). This nonlinear renal clearance can be attributed to a concentration-dependent transport process, leading to saturable renal reabsorption, demonstrated in our laboratory to involve the group of transporters known as monocarboxylate transporters (MCTs) (Morris et al., 2005; Wang et al., 2006). MCTs are proton-dependent transporters expressed throughout the body, and GHB is an identified substrate for MCTs 1, 2, and 4 (Wang et al., 2006; Wang and Morris, 2007). The ubiquitous expression of these transporters includes that in the intestine, kidney, and brain, regions of interest regarding GHB pharmacokinetics. Because of their role in the renal reabsorption of GHB, inhibition of these transporters represents a potential therapeutic strategy for GHB overdose. This strategy has been demonstrated to translate to in vivo effects on GHB disposition, and administration of MCT inhibitors increases the renal and total clearance in animal models of GHB overdose (Morris et al., 2005; Wang et al., 2008a,b). Likewise, the administration of the MCT inhibitor L-lactate, in combination with osmotic diuresis, increases the renal clearance of GHB in humans, as demonstrated in our pilot clinical study (Morris et al., 2011).

The first aim of this research was to investigate the dose-response relationship of GHB-induced respiratory depression, including the primary neurotransmitter receptors involved in eliciting this effect. The second was to assess potential treatment strategies, including MCT and receptor inhibition, for improving GHB-induced respiratory depression, because the application of these strategies for treating this pharmacodynamic endpoint have not been evaluated previously.

Materials and Methods

Chemicals and Reagents. Sodium GHB used in these studies was provided by the National Institute on Drug Abuse. Deuterated GHB (GHB-d_6) was purchased from Cerilliant Corporation (Round Rock, TX). Sodium L-lactate and bicuculline methiodide were purchased from Tocris Bioscience (Ellisville, MO). High-performance liquid chromatography-grade acetonitrile and acetic acid were purchased from Honeywell Burdick & Jackson (Muskegon, MI).

Animals and Animal Surgery. Male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 270 to 330 g were used for all experiments. Animals were housed under controlled temperature and humidity with an artificial 12-h light/dark cycle, and food was available ad libitum. All animal protocols were approved by the Institutional Animal Care and Use Committee at the University at Buffalo. Animals were allowed to acclimate to their environment for a minimum of 1 week before surgical implantation of jugular and femoral vein cannulae under anesthesia with ketamine-xylazine. Cannulae were flushed daily with 40 IU/ml heparinized saline to maintain patency. Animals were allowed a minimum of 72 h for recovery from surgery before drug administration.

Plethysmography. Measurement of respiration in these studies was performed using a whole-body plethysmograph (model PLY4213; Buxco Research Systems, Wilmington, NC). Plethysmography equipment included unrestrained plethysmography chambers consisting of a main (animal) chamber and reference chamber for buffering changes in atmospheric pressure. The plethysmography chambers were connected to a Rodent Bias Flow Supply (BFL0250) to draw expired CO_2 out of the chambers and provide a smoothed flow of room air at a flow rate of 2.5 l/min per chamber. The plethysmography chambers included ports to which a pressure sensor was connected and led to the MAX 1500 preamplifier. Signals were collected, visualized, and quantitated using BioSystem XA software. Two additional ports were included in the chambers for the insertion of jugular and femoral vein cannulae, allowing for drug administration and blood sampling. Urine was collected at the base of the chamber at intervals by opening an additional port at the base. Calibration of chamber pressure was performed before every experiment by injection of 5 ml of air through the base port. At each recording, signals were collected for six intervals of 10 s each and averaged to represent 1 min of recording. Measurements for the parameters of respiratory frequency (rate), tidal volume, and minute volume (rate · tidal volume) were quantitated for each recording.

Pharmacokinetic/Pharmacodynamic Studies. Rats were placed in plethysmography chambers 1 h before drug administration and allowed to acclimate to the chambers for 45 min before five baseline measurements of 1 min each were collected over 15 min. In all studies, GHB administration was considered time 0, and respiration measurements were recorded at 2.5, 5, 7.5, 10, 15, 20, 25, and 30 min and every 15 min thereafter for 480 min. Blood samples were collected, and collection times were optimized for each GHB dose according to previous studies (Felmlee et al., 2010b, 2011). Urine was collected at intervals up to 480 min. For overlapping pharmacokinetic/pharmacodynamic time points, blood and urine samples were taken directly after the recording of respiratory measurements.

Dose-Dependent Effects of GHB on Respiration. To assess the dose-response relationship of GHB-induced respiratory depression, rats were administered GHB intravenously in doses of 200, 600, and 1500 mg/kg (four to six animals per dose). GHB was injected over 1 to 2 min as a 300 mg/ml solution in sterile water via the jugular vein cannula. A placebo control group received a 5 ml/kg saline bolus.

Neurotransmitter Receptors Involved in GHB-Induced Respiratory Depression. To determine the primary receptors involved in GHB-induced respiratory depression, rats were pretreated with specific receptor antagonists. Bicuculline methiodide (5 mg/kg) was administered for inhibition of $GABA_A$ receptors and SCH50911 (150 mg/kg) for inhibition of $GABA_B$ receptors (three to four animals per group). Inhibitors were administered immediately after the collection of baseline respiratory measurements and 1500 mg/kg GHB was administered 5 min later. Data from dose-dependent experiments were used as the control. Bicuculline methiodide was administered as a 5 mg/ml solution in saline and SCH50911 as a 50 mg/ml

Potential Treatment Strategies. To assess the effect of potential treatment strategies on GHB-induced respiratory depression, treatments were administered intravenously 5 min after 1500 mg/kg GHB. Treatment strategies included SCH50911 (2.5, 5, 10, and 50 mg/kg), the MCT inhibitor L-lactate (66 mg/kg bolus followed by a 302.5 mg/kg/h infusion for 8 h), and combination therapy of 5 mg/kg SCH50911 plus the same dose of L-lactate. Treatment groups included three to five animals per group, and were compared with the 1500 mg/kg control group from dose-dependent experiments to determine the effects of treatment on GHB-induced respiratory depression. The same L-lactate dose was also administered alone at time 0 to assess potential effects of this agent on respiration. In these experiments, SCH50911 was administered as a 2.5, 5, 10, or 50 mg/ml solution in saline via the jugular vein cannula and L-lactate as a 40 mg/ml solution in sterile water via the femoral vein cannula.

Plasma and Urine Sample Analysis. GHB plasma concentrations were determined using an LC-MS/MS method, similar to those published previously (Fung et al., 2008; Felmlee et al., 2010a). Plasma samples were prepared by adding 5 μl of GHB-d_6 (125 μg/ml) to 50 μl of sample. Plasma standards and quality controls were prepared by adding 5 μl of GHB-d_6 and 5 μl of GHB stock solution to 45 μl of blank plasma, and 800 μl of 0.1% formic acid in acetonitrile was added to precipitate the plasma proteins. The samples were vortexed, followed by centrifugation at 10,000*g* for 20 min at 4°C. Then 750 μl of the supernatant was aspirated and evaporated under a stream of nitrogen gas. The samples were reconstituted in 250 μl of aqueous mobile phase.

The LC-MS/MS assay was performed on an Agilent 1100 series high-performance liquid chromatography system with binary pump and autosampler (Agilent Technologies, Santa Clara, CA) connected to a PerkinElmer Sciex API 3000 triple quadrupole tandem mass spectrometer with a TurboIonSpray (Applied Biosystems, Foster City, CA). Chromatographic separation was achieved by injecting 7 μl of sample on an Xterra MS C18 column (250 × 2.1 mm i.d., 5-μm particle size; Waters, Milford, MA). Mobile phase A consisted of 5:95 acetonitrile-water with 0.1% acetic acid and mobile phase B consisted of 95:5 acetonitrile-water with 0.1% acetic acid. The flow rate was 200 μl/min with the following gradient elution profile: 100 to 68% A over 7 min; 68 to 10% A over 3 min; and 10 to 100% over 5 min for a total run time of 15 min. The mass spectrometer was operated in a positive ionization mode with multiple reaction monitoring. Q1/Q3 *m/z* ratios for the parent/product ions of GHB and GHB-d_6 were 105.2/87.2 and 111.1/93.2, respectively. The mass spectrometer parameters were optimized at a declustering potential of 18 V, focusing potential of 100 V, collision energy of 20 V, entrance potential of 10 V, and collision cell exit potential of 5 V. The ion spray voltage was set at 5500 V with temperature at 350°C. Nebulizer and curtain gas flow were set at 10 and 8 ml/min, respectively. The retention time for GHB was 4.15 min. The data were analyzed using Analyst software version 1.4.2 (Applied Biosystems).

Regression analysis of peak area ratios of GHB/GHB-d_6 to GHB concentrations was used to assess linearity of the curve. The intraday and interday precision and accuracy were determined using quality control (QC) samples at 10 μg/ml (low QC), 125 μg/ml (medium QC), and 400 μg/ml (high QC). For determination of the intraday precision and accuracy, quality control samples were analyzed in triplicate on each day, whereas for the interday precision and accuracy, quality control samples were analyzed on three different days. A calibration curve was run on each analysis day along with the quality controls. The precision was determined by the coefficient of variation, and accuracy was measured by comparing the calculated concentration with the known concentration.

Urine samples were prepared and analyzed for GHB using a previously described LC-MS/MS method (Felmlee et al., 2010b). Plasma lactate concentrations were determined using a YSI 1500 Sport Lactate Analyzer (YSI, Inc., Yellow Springs, OH).

Data and Statistical Analysis. Pharmacokinetic parameters 5.2 (Pharsight, Mountain View, CA). The area below the plasma concentration-time curve (AUC) was determined using the trapezoidal method. Total clearance (Cl) was determined as dose/AUC. Renal clearance (Cl_R) was determined as A_e/AUC, where A_e represents the amount excreted in the urine. Percentage of urinary excretion was calculated as A_e/dose. Metabolic or nonrenal clearance (Cl_m) was calculated as $Cl - Cl_R$. The pharmacodynamic descriptors of area below the effect curve (ABEC), maximum effect (E_{max}), time of maximum effect (T_{max}), and duration of effect (T_d) were used to determine the effects of inhibitor administration on GHB-induced respiratory depression. ABEC was calculated using WinNonlin. T_d was determined for each animal as the time to return to its individual baseline respiratory frequency. Statistical analysis was performed using SigmaPlot 10.0 (Systat Software, Inc., San Jose, CA). Differences were considered significant when $p < 0.05$. One-way analysis of variance followed by Dunnett's or Tukey's post hoc tests was used to determine statistically significant differences in mean pharmacokinetic and pharmacodynamic parameters between groups. Paired *t* tests were used to determine statistically significant changes in respiratory parameters compared with baseline. In determining the effects of L-lactate alone on respiration, the average of the last hour of respiratory measurements was compared with the individual average baseline values. Mean steady-state lactate plasma concentrations were calculated as the average of hourly values beginning at 60 min.

Results

Plasma GHB LC-MS/MS Assay. The lower limit of quantification for GHB in plasma was found to be 5 μg/ml with acceptable error in precision and accuracy of less than 20%. The endogenous concentrations of GHB in plasma are negligible compared with GHB concentrations obtained after administration of the lowest dose in our studies (Fung et al., 2004); therefore, the endogenous concentrations were not included in the calculation of GHB concentrations in plasma. The standard curve for GHB ranged from 5 to 500 μg/ml based on regression analysis of peak area ratios of GHB/GHB-d_6 to GHB concentrations with a correlation coefficient (r^2 >0.999). The intraday and inter-

TABLE 1

Intraday and interday accuracy and precision for GHB in rat plasma

Each measured concentration is the mean of triplicate measurements. The analysis was performed over 3 days.

	Nominal Concentration	Measured Concentration	S.D.	Precision	Accuracy
	$\mu g/ml$			*CV%*	*%*
Intraday	10	10.8	0.12	1.07	107.7
	125	121	4.36	3.60	96.8
	400	375	6.93	1.85	93.7
Interday	10	10.5	0.32	3.05	105.2
	125	118	2.96	2.50	94.9
	400	368	6.38	1.73	92.0

CV, coefficient of variation.

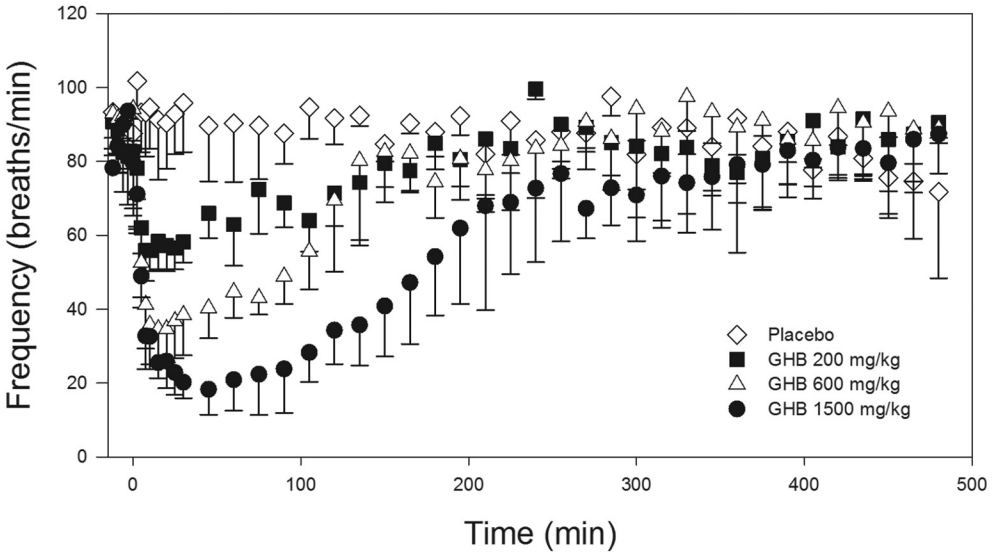
TABLE 2

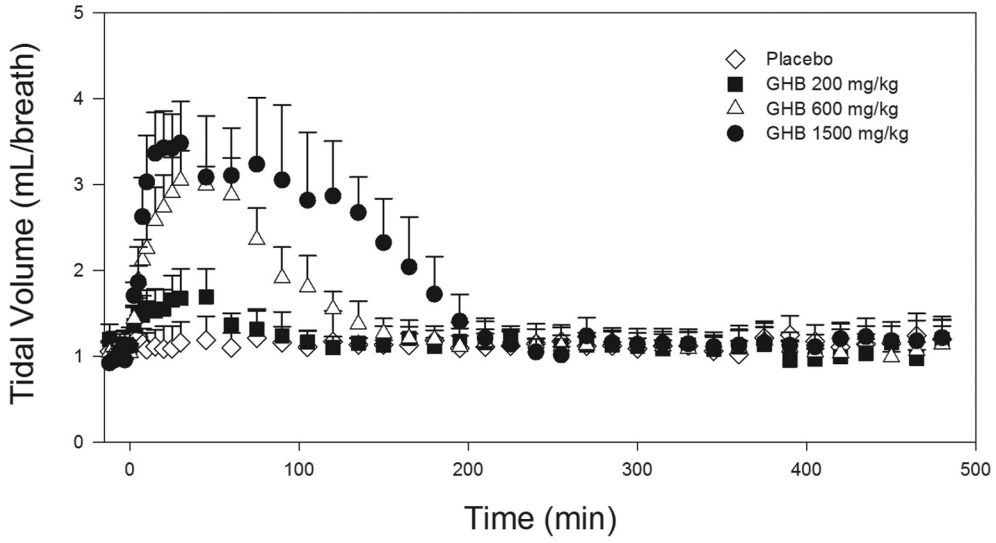
Nonlinear pharmacokinetics of GHB

GHB was administered intravenously. Data are presented as mean (S.D.); n = 4 to 6. One-way analysis of variance followed by Tukey's post hoc test was used to determine statistically significant differences in pharmacokinetic parameters.

	200 mg/kg	600 mg/kg	1500 mg/kg
Cl, ml · kg^{-1} · min^{-1}	7.60 (0.29)	6.00 (0.74)[a]	5.16 (0.70)[a]
Cl_R, ml · kg^{-1} · min^{-1}	0.444 (0.20)	1.68 (0.75)[a]	3.18 (0.66)[a,b]
Urinary excretion, %	6.0 (3)	26.7 (11)[a]	60.1 (7)[a,b]

[a] Significantly different from 200 mg/kg GHB ($P < 0.05$).





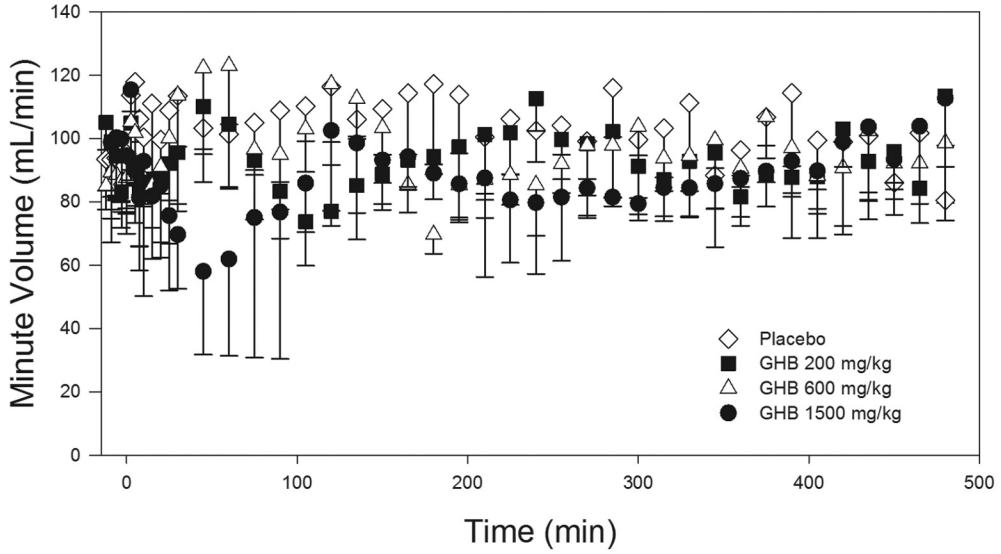


Fig. 1. Dose-dependent effects of GHB on measures of respiration. GHB was administered intravenously at time 0. Data are presented as mean ± S.D.; n = 4 to 6.

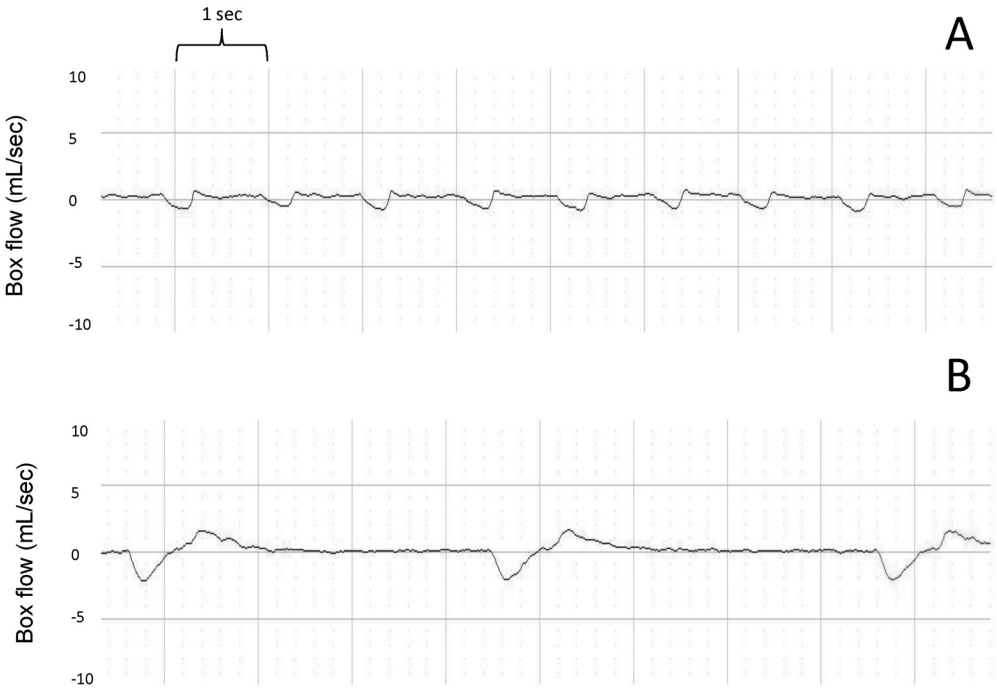


Fig. 2. Effect of GHB administration on respiratory pattern. Displayed are sample 10-s interval plethysmography traces obtained at baseline (A) and 30 min after administration of GHB 1500 mg/kg i.v. (B).

day precision and accuracy of the quality control samples are summarized in Table 1.

Dose Dependence of GHB Pharmacokinetics/Pharmacodynamics. GHB administration in increasing intravenous doses displayed nonlinear pharmacokinetics, as shown in Table 2, similar to previous reports (Lettieri and Fung, 1979; Morris et al., 2005). Renal clearance and the urinary excretion of GHB was almost negligible at the lowest dose of 200 mg/kg but represented the predominant route of elimination at the highest dose of 1500 mg/kg. The pharmacodynamic results of this experiment are shown in Fig. 1. Increasing doses of GHB resulted in a dose-dependent decrease in the parameter of respiratory rate, which was accompanied by a dose-dependent increase in tidal volume. Minute volume was unchanged with the 200 and 600 mg/kg doses but was significantly decreased with the 1500 mg/kg dose (95 ± 18 ml/min at baseline versus E_{max} of 54 ± 24 ml/min; mean ± S.D., $p < 0.05$). Raw plethysmography traces displaying the change in respiratory pattern with GHB administration are shown in Fig. 2. As a result of this experiment, respiratory rate was considered the primary parameter of interest for assessment of receptors involved and potential treatment strategies. It was also determined in this experiment that 1500 mg/kg GHB was the maximal dose that could be administered without causing death; therefore, this dose was used for further investigation.

Neurotransmitter Receptors Involved in GHB-Induced Respiratory Depression. Effects of pretreatment with specific receptor antagonists are given in Table 3. Administration of the $GABA_B$ inhibitor, SCH50911 (150 mg/kg), before GHB, resulted in no significant decrease in respiratory rate nor a change in tidal volume compared with baseline, as displayed in Fig. 3. This inhibitor also increased the nonrenal clearance of GHB, but not the total clearance at this dose. Administration of the $GABA_A$ inhibitor, bicuculline methiodide (5 mg/kg), before GHB, resulted in no change in the respiratory effects compared with those for GHB alone and

TABLE 3

Effects of specific receptor antagonists on the pharmacokinetics/pharmacodynamics of GHB (1500 mg/kg i.v.)

SCH50911 (150 mg/kg) and bicuculline methiodide (5 mg/kg) were administered intravenously 5 min before GHB. Data are presented as mean (S.D.); $n = 3$ to 5. One-way analysis of variance followed by Dunnett's post hoc test was used to determine statistically significant differences in mean pharmacokinetic and pharmacodynamic parameters with inhibitor administration compared with those with GHB alone.

	GHB	GHB + SCH50911	GHB + Bicuculline
Cl, ml · kg^{-1} · min^{-1}	5.16 (0.70)	6.07 (0.47)	5.02 (0.14)
Cl_R, ml · kg^{-1} · min^{-1}	3.18 (0.66)	2.84 (0.32)	2.72 (0.78)
Cl_m, ml · kg^{-1} · min^{-1}	1.99 (0.17)	3.23 (0.78)*	2.30 (0.63)
Frequency ABEC, breaths	10,500 (2700)	—[a]	10,900 (1300)
Frequency E_{max}, breaths/min	17 (7)	—	15 (9)
Frequency T_{max}, min	53.0 (19)	—	67.5 (13)

* Significantly different from GHB alone ($P < 0.05$).

[a] —, no ABEC, E_{max}, or T_{max} values could be calculated because respiration is similar to the baseline values; SCH50911 completely prevented any significant decrease in frequency compared with baseline.

Potential Treatment Strategies. Effects of potential treatment strategies on GHB-induced respiratory depression are given in Table 4. Administration of 50 mg/kg SCH50911 5 min after GHB completely reversed the GHB-induced decrease in respiratory rate, as shown in Fig. 4; there was no significant decrease in respiratory rate compared with baseline after the administration of SCH50911. In fact, a slight, but significant, increase in respiratory rate was observed at early time points in SCH50911-treated animals. Lower doses of 2.5, 5, and 10 mg/kg SCH50911 did not completely reverse GHB-induced respiratory depression, and significant decreases in respiratory rate were still observed after antagonist administration. Administration of 10 mg/kg SCH50911 significantly improved all pharmacodynamic parameters, whereas 5 mg/kg improved only the ABEC and E_{max} and 2.5 mg/kg had no significant effect on any pharmacodynamic parameter compared with that of GHB alone. Administration

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