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Comparison of the actions of γ-butyrolactone and 1,4-butanediol in Swiss–Webster mice

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Abstract

The abuse of γ-hydroxybutyrate (GHB) and two of its precursors, γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are recognized as a public health concern. Here, we report dose–response and time-course analyses for effects of GBL and 1,4-BD on locomotor activity and body temperature in Swiss–Webster mice. Locomotor activity was measured for 2 h following a single injection of one of four doses of each agent plus a saline vehicle control. At 50 mg/kg, GBL produced an initial depression of locomotor activity which was followed by stimulation of locomotor activity. In contrast, 1,4-BD at 50 mg/kg stimulated locomotor activity without producing any depression of activity. At higher doses, GBL produced primarily a dose-dependent decrease in locomotor activity that returned to baseline within 50 min. In contrast, 1,4-BD produced an initial depression which was followed by stimulation of activity. Body temperature was measured rectally across a 2.5-h time course following injection with either agent. Both drugs produced hypothermia with peak effects occurring at 20 and 30 min for both drugs for the lower and higher dose, respectively. At 150 mg/kg, GBL produced a greater hypothermic response; however, no differences in hypothermic response were observed at 100 mg/kg. These studies demonstrate that the precursor drugs to GHB have some differential actions from each other.

Keywords: γ-Butyrolactone; 1,4-Butanediol; γ-Hydroxybutyrate; Club drugs; Locomotor activity; Hypothermia

1. Introduction

The abuse of γ-hydroxybutyrate (GHB) is recognized as a significant cause for concern in the United States and around the world. Additionally, with GHB being classified as a Schedule 1 compound by the U.S. Food and Drug Administration, the abuse of two precursors of GHB, γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), has emerged as a growing public health concern. Statistics demonstrating the increasing severity of the problem were presented at a June 2000 meeting sponsored by the National Institute on Drug Abuse. Since 1990, there have been more than 7100 overdoses (or law enforcement encounters) with these agents, 65 deaths and 30 GHB-related assaults (Shannon and Quang, 2000). Emergency department mentions of GHB increased from 55 in 1994 to 2973 in 1999 with the largest number of mentions involving young adults (1498, ages 18–25; SAMHSA, 2000).

GHB is a naturally occurring breakdown product of γ-aminobutyric acid (GABA). GABA is enzymatically converted to GHB by succinic semialdehyde reductase. GHB, in turn, is metabolized by GHB dehydrogenase to succinic semialdehyde and eventually enters the Kreb's cycle (Maitre, 1997). At high concentrations, as would be attained during recreational abuse or in vivo study of administered drug, GHB can be converted to GABA (Collier and De Feudis, 1970; Hechler et al., 1997; Vayer et al., 1985). GHB can also be synthesized in vivo from GBL and 1,4-BD.

GBL is rapidly metabolized to GHB by peripheral lactonases or by nonenzymatic hydrolysis. The half-life of conversion of GBL to GHB has been estimated to be less than 1 min (Roth and Giarman, 1966). GBL has a greater lipid solubility than GHB, allowing it a more uniform absorption. Its greater lipophilicity may also result in its absorption into a variety of tissues that may serve as reservoirs increasing the duration of GBL action (Lettieri and Fung, 1978).

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1,4-BD is metabolized to γ-hydroxybutyraldehyde by alcohol dehydrogenase, which is subsequently metabolized to GHB by aldehyde dehydrogenase (Snead et al., 1989). The common pathway of metabolism of 1,4-BD and ethanol (Poldrugo and Snead, 1986) leads to the possibility of interactions between 1,4-BD and ethanol (Poldrugo and Snead, 1984).

GHB-related compounds have been found to have a number of acute and chronic effects. Acute effects include euphoria, ataxia, confusion, hallucinations and loss of consciousness (Shannon and Quang, 2000; Teter and Guthrie, 2001). In animals, these drugs cause alterations in locomotor activity (Cook et al., 2002; Davies, 1978), loss of the righting response (Dudek and Fanelli, 1980), seizures (Snead, 1990) and hyper/hypothermia (Kaufman et al., 1990). Tolerance develops to GHB/precursor effects in rodents (Colombo et al., 1995; Gianutsos and Moore, 1978; Itzhak and Ali, 2002) and a withdrawal syndrome has been seen in humans for each of these drugs (Catalano et al., 2001; Dyer et al., 2001; Zvosec et al., 2001).

Much evidence suggests that both GBL and 1,4-BD act primarily as prodrugs of GHB; that is, GHB is the pharmacologically active species (Carai et al., 2002; Guidotti and Ballotti, 1970; Poldrugo and Snead, 1984; Quang et al., 2002a,b; Roth et al., 1966; Schneidereit et al., 2000; Snead, 1982; Snead et al., 1989). However, the pharmacokinetics of GBL and 1,4-BD, including their initial distribution and rate of conversion to GHB, may influence their pharmacological actions. Hence, GBL and 1,4-BD may not display actions identical to GHB nor to each other. Early studies of these agents support nonidentical time courses of action for these agents which are suggestive of differences in the pharmacokinetics of the agents (for review, see Irwin, 1996). Differences in pharmacokinetics among these agents may affect their abuse potential or patterns of abuse. For other agents, both the rate of onset of drug action as well as the duration of action have been shown to play a role in modulating a drug's reinforcing properties (Winger et al., 2002).

Most of the earlier work described in the preceding paragraph concerning the differential actions of GHB-related compounds was conducted in rats. In the current study, the actions of GBL and 1,4-BD on locomotor activity and body temperature were compared in Swiss–Webster mice, a species more amenable to future pharmacogenetic analyses. The results suggest that these agents produce effects which are quantitatively and qualitatively different from each other.

2. Methods

2.1. Animals

At approximately 8 weeks of age, male Swiss–Webster mice were obtained from Harlan (Indianapolis, IN). All animals were housed in the climate-controlled vivarium at the University of North Texas Health Science Center until tested at approximately 10 weeks of age. Animals were group housed in cages on a 12:12-h light/dark cycle and were allowed free access to laboratory rodent chow (Harlan Teklad; Madison, WI) and water. Use of animals was approved by the Institutional Animal Care and Use Committee of the University of North Texas Health Science Center and all procedures abide by the guidelines set forth in the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Drugs

GBL was obtained from Sigma-Aldrich (St. Louis, MO) and 1,4-BD was obtained from Acros-Fisher (Pittsburgh, PA). Both agents were diluted in physiological saline and were administered by intraperitoneal injection. The volume of injection was 0.01 ml/g body weight.

2.3. Locomotor activity

The general method and apparatus used for measurement of drug-induced changes in locomotor activity have been described previously (Uzbay et al., 2000). An automated apparatus (VersaMax Monitors, Analyzers and software, Accuscan, Columbus, OH) was used that monitors x–y coordinate information from arrays of 16 photocells to measure movement of mice within the horizontal plane of a $40.5 \times 40.5 \times 30.5$ cm clear acrylic test cage. Test cages were housed in sound-attenuating chambers with fans providing background noise and house lights providing dim illumination. Mice received an injection of a single dose of one of the test compounds or saline vehicle and were immediately placed in the testing chambers. Locomotor activity (total horizontal distance traversed) was measured continuously and summarized in 10-min blocks of time for a 120-min testing session.

Dose–response analyses were conducted for locomotor activity in drug-naive, male Swiss–Webster mice. Four doses each of GBL and 1,4-BD were used (25, 50, 100 and 150 mg/kg) and separate groups of mice were tested following injection with vehicle (0.9% saline) for each of the two test drugs. At each dose of each drug or vehicle control, six mice were tested.

2.4. Body temperature

Effects of GBL and 1,4-BD on body temperature were measured in Swiss–Webster mice using a Physitemp (Clifton, NJ) TH-8 temperature monitor and BAT-12 probe. The probe was lubricated with peanut oil and inserted approximately 1.5 cm into the rectal cavity. Immediately following measurement of baseline body temperature, drug-naive mice were injected with a single dose of either GBL or 1,4-BD (100 or 150 mg/kg) and body temperature was measured

periodically across a 150-min period following injection. Between body temperature assessments, animals were singly housed in holding cages and there was a minimum of 30 min between body temperature assessments in a given mouse. Body temperature was expressed as a change from baseline temperature and each animal served as its own control. We have previously used this method (de Fiebre et al., 1992) and have found that data obtained are similar to those in which vehicle-injected animals serve as controls and a single-body temperature measurement is obtained from each animal.

2.5. Statistical analyses

Because both locomotor activity and hypothermia data were obtained at multiple sampling times from the same animals, a repeated-measures analysis of variance (ANOVA) was used to ascertain the main and interactive effects of dose and time for each of the two drugs. Where significant effects were found, data were subjected to a Fisher post hoc test. An ANOVA was performed on transformed data (change from saline) from that dose and time points where significant stimulation of locomotor activity was produced by GBL to compare to the stimulation produced by 1,4-BD.

3. Results

The effects of GBL (left panels) and 1,4-BD (right panels) on the locomotor activity of male Swiss–Webster mice are presented in Fig. 1. Data were analyzed by a

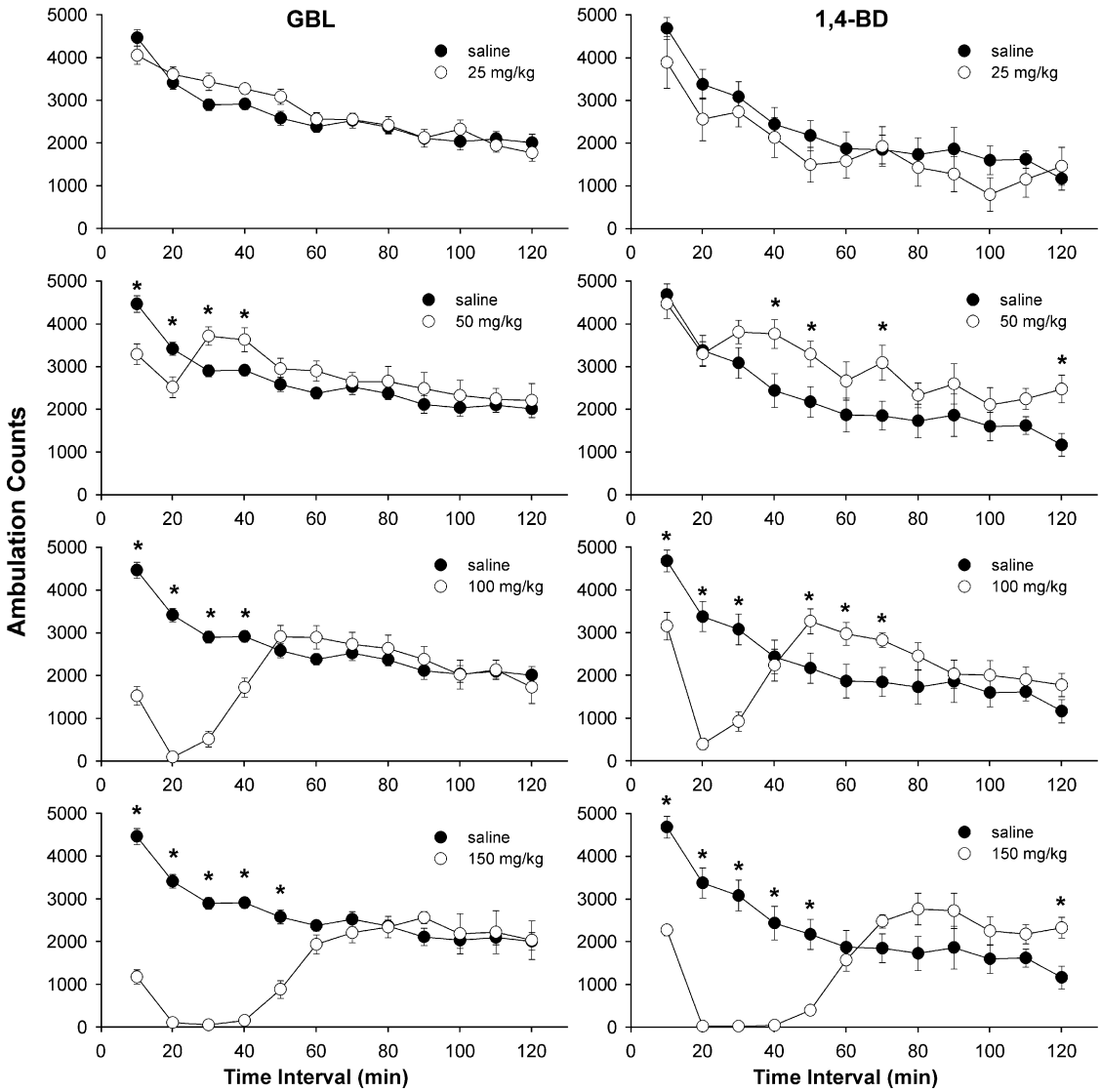

Fig. 1. Effect of GBL (left panels) and 1,4-BD (right panels) on the locomotor activity of male Swiss–Webster mice. Mice received an intraperitoneal injection of either drug or saline vehicle and were immediately placed in an activity monitor. Horizontal activity was monitored for 2 h. Each point represents the mean ± S.E.M. for six to eight mice. * $P < .05$.

mixed-design, repeated-measures ANOVA (both within and between subjects). Both agents produced a dose-dependent decrease in locomotor activity resulting in a significant main effect of dose [GBL: $F(4,42) = 15.371$, $P < .0001$; 1,4-BD: $F(4,35) = 5.082$, $P < .005$]. There was also a main effect of sampling time for each agent [GBL: $F(11,462) = 12.229$, $P < .0001$; 1,4-BD: $F(11,385) = 19.939$, $P < .0001$] as well as a significant Dose × Time interaction [GBL: $F(44,462) = 20.842$, $P < .0001$; 1,4-BD: $F(44,385) = 11.292$, $P < .0001$].

Post hoc analyses which examined the entire 2-h test period revealed that 25 and 50 mg/kg GBL did not differ from saline; however, there was significant depression in locomotion at 100 and 150 mg/kg of GBL. A similar analysis for 1,4-BD revealed that activity at 50 and 150 mg/kg differed significantly from saline; however, at 50 mg/kg, activity was stimulated while at 150 mg/kg, activity was depressed. 1,4-BD at 100 mg/kg clearly had a biphasic effect with locomotor activity depression being followed by stimulation of locomotor activity. This biphasic effect resulted in no significant differences between activity after 100 mg/kg 1,4-BD and saline in post hoc analyses which examined locomotor activity across the entire 2-h testing period.

Individual ANOVAs were conducted to ascertain whether a given dose of drug differed from saline at each 10-min time interval. For GBL (Fig. 1, left panels), a dose of 25 mg/kg had no significant effect on locomotor activity. A dose of 50 mg/kg had a modest, yet significant, depressant effect for the first 20 min followed by modest, yet significant, stimulatory effects for the next 20 min. At GBL doses of 100 and 150 mg/kg, locomotor activity was reduced to zero and was significantly different from saline for the first 40 min of testing at 100 mg/kg and for the first 50 min of testing at 150 mg/kg. At neither of these two higher doses, however, was there any significant stimulation.

For 1,4-BD (Fig. 1, right panels), a dose of 25 mg/kg also had no significant effects on locomotor activity. At 50 mg/kg, stimulation of locomotor activity was seen without any indication of locomotor activity depression. This stimulation was significant from 30 to 50 min after injection and then again from 60 to 70 min and from 110 to 120 min after injection. Doses of both 100 and 150 mg/kg significantly reduced locomotor activity with the extent of activity depression and the time course for recovery from depression of locomotor activity being longer for the higher dose. At 100 mg/kg of 1,4-BD, locomotor activity was depressed for the first 30 min after injection. This was followed by a pronounced stimulation in locomotor activity which was significant from 40 to 70 min. At a dose of 150 mg/kg, locomotor activity was depressed for the first 50 min of testing. Stimulation of locomotor activity was seen after 70 min and was significantly different from saline from 110 to 120 min.

An examination of the data for these two drugs across doses suggested that 1,4-BD had greater stimulatory effects than GBL and that the greatest stimulatory and depressant effects were primarily seen within the first 70 min of testing. Therefore, an ANOVA was conducted to assess whether differences between these two drugs could be detected during the first 70 min. The differential effects of these two drugs on locomotor activity were detected as significant Dose × Drug [$F(4,102) = 3.448$, $P < .05$], Time × Drug [$F(6,612) = 10.003$, $P < .0001$] and Time × Dose × Drug [$F(24,612) = 1.877$, $P < .01$] interactions.

The only times where significant stimulation of locomotor activity by GBL were detected were at the 30- and 40-min time points following a dose of 50 mg/kg. At these times and at this dose, GBL and 1,4-BD were compared after transforming data to a change from saline. The two drugs displayed a similar degree of locomotor stimulatory effects.

Effects of GBL and 1,4-BD on body temperature are depicted in Fig. 2. Data were analyzed by a mixed repeated-measures ANOVA to assess the main and interactive effects

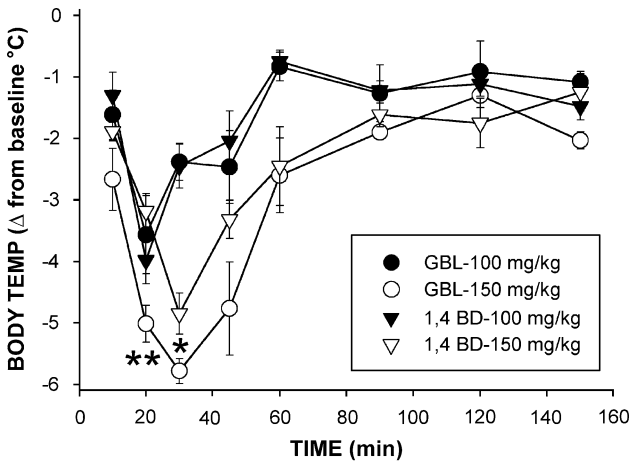

Fig. 2. Effect of GBL and 1,4-BD on the body temperature of male Swiss–Webster mice. Mice received an intraperitoneal injection of either drug and were returned to their home cage. Body temperature was measured rectally no more often than every 30 min for any given mouse. Each point represents the mean ± S.E.M. for six mice. * $P < .05$; ** $P < .005$.

of drug (GBL vs. 1,4-BD), dose and time. The main effect of each was significant [drug: $F(1,19) = 5.032$, $P < .05$; dose: $F(1,19) = 53.167$, $P < .0001$; time $F(7,133) = 36.176$, $P < .0001$]. Significant interactive effects of Drug × Dose [$F(1,19) = 6.140$, $P < .05$] and Time × Dose [$F(7,133) = 6.123$, $P < .0001$] were also present. At 100 mg/kg, the time course and effect size on body temperature were almost identical for the two drugs; however, at the higher dose, there was a larger peak hypothermia and slower recovery for GBL than there was for 1,4-BD.

4. Discussion

These data demonstrate that the in vivo actions of GBL and 1,4-BD are not identical. In contrast to much of the existing scientific literature which suggests that both agents exert their actions through conversion to GHB, the current findings are not totally consistent with this hypothesis. Early reports of a differential time course for the effects of these agents (for review, see Irwin, 1996), presumably due to differences in GHB formation and distribution, are not predictive of the current findings. While the current study did not assess GHB formation, distribution or disappearance following GBL or 1,4-BD administration, the observed greater stimulatory actions of 1,4-BD would not be predicted solely based on the pharmacokinetics of these agents. Multiple doses of 1,4-BD produced significant stimulation of locomotor activity, whereas GBL only produced stimulation of locomotor activity at the 50-mg/kg dose. At this dose (40-min time point), the degree of stimulation produced was similar for both drugs.

It should be noted that although the doses of GBL and 1,4-BD examined were identical on a mg/kg basis, they differed in regard to the their equivalency on a mmol/kg basis (i.e., 100 mg/kg equates to 1.16 mmol/kg for GBL and 1.11 mmol/kg for 1,4-BD). Although these differences in doses are small, they may have contributed to the findings of greater locomotor stimulation following 1,4-BD than following GBL. We believe that the testing at four doses of each compound, and the monitoring of activity across an extensive time course, decreases the probability that the observed greater stimulatory actions of 1,4-BD are solely due to pharmacokinetic differences. Nevertheless, future studies should compare these agents when administered on an equimolar basis.

Both GBL and 1,4-BD decreased body temperature with the time of peak body temperature being dose-dependent and similar for both drugs. Interestingly, GBL at 150 mg/kg produced a greater degree of hypothermia and a longer time course for hypothermic effects than did 1,4-BD. These differences are not due to differences in ambient room temperature or methodology as testing was conducted with both drugs in the same experimental sessions. It is possible that pharmacokinetic differences between GBL and 1,4-BD, including the kinetics of GHB accumulation and disappearance, could produce this difference; however, it is unclear why a similar difference between GBL and 1,4-BD was not seen at the 100-mg/kg dose. Doses of the two drugs used in body temperature testing were also not equivalent on a mmol/kg basis. Therefore, a dose effect might explain the difference at 150 mg/kg (1.74 mmol/kg of GBL vs. 1.66 mmol/kg of 1,4-BD). However, if the difference between GBL and 1,4-BD at 150 mg/kg was due to a dose effect, differences would also have been expected at the 100-mg/kg dose. While these data suggest differences between these agents in their modulation of body temperature, a more complete dose–response analysis is warranted to fully address how these agents may differ.

Kaufman et al. (1990) have reported that while high doses of GHB produce hypothermia in rats, low doses produce hyperthermia. In our study, both doses of GBL and 1,4-BD examined produced significant hypothermia which is more in agreement with the findings of Snead (1990) who saw hypothermic responses to doses of GBL under 400 mg/kg and complex effects on body temperature at higher doses. While the reason for the discrepancies between studies is not immediately apparent, there may be differences between rats and mice in the actions of these agents. Methodological differences may also explain the difference among studies, although none are readily apparent. It should be noted that the level of hypothermia detected in the present study was much greater than in either the Snead or Kaufman et al. studies. A similar greater hypothermic response has been seen in mice (de Fiebre et al., 1987) when compared to rats (de Fiebre et al., 2002) in studies of nicotine-induced hypothermia suggesting that mice are generally more susceptible to drug-induced hypothermia than rats.

Although GBL and 1,4-BD are both metabolized to GHB, the results presented here suggest that these agents do not produce identical effects in Swiss–Webster mice. Whether similar differential effects would be seen in all strains of mouse or in other species is unknown. Nevertheless, these findings support the continued study of GBL and 1,4-BD as unique pharmacological agents and not just as prodrugs of GHB. The growing abuse of both GBL and 1,4-BD also supports their continued study. The plethora of genetic models available in mice may be very useful in deciphering similarities and differences between these agents in modulating their abuse.

In summary, GBL and 1,4-BD both produce complex, time- and dose-dependent effects on the locomotor activity of Swiss–Webster mice. For both drugs, both stimulatory and inhibitory effects were seen; however, stimulatory effects were more pronounced for 1,4-BD than for GBL. Both drugs also produced hypothermia; however, the hypothermia produced by GBL was more pronounced than the hypothermia produced by 1,4-BD. These data, conducted with a limited number of nonequivalent doses of these drugs, suggest that GBL and 1,4-BD may have differential effects. These differential effects, be they pharmacodynamic

or pharmacokinetic, may contribute to the abuse potential and/or pharmacological or toxicological actions of each agent. Further study will be required to fully characterize how the actions of these agents differ and how and if these differences relate to their abuse in human populations.

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