Title
Effect of γ-hydroxybutyrate (GHB) on driving as measured by a driving simulator

Journal
Psychopharmacology, 235(11)

ISSN
0033-3158

Authors
Liakoni, Evangelia
Dempsey, Delia A
Meyers, Matthew
et al.

Publication Date
2018-11-01

DOI
10.1007/s00213-018-5025-2

Peer reviewed

Published in final edited form as:

Psychopharmacology (Berl). 2018 November ; 235(11): 3223–3232. doi:10.1007/s00213-018-5025-2.

Effect of γ-Hydroxybutyrate (GHB) on Driving as Measured by a Driving Simulator

Evangelia Liakoni[1,*], **Delia A Dempsey**[1,*], **Matthew Meyers**[2], **Nancy G Murphy**[3], **Dary Fiorentino**[4], **Christopher Havel**[1], **Christine Haller**[5], and **Neal L Benowitz**[1]

[1]Departments of Medicine and Bioengineering & Therapeutic Sciences: The University of California San Francisco, San Francisco CA

[2]Department of Pediatrics, Division of Adolescent Medicine: The University of California San Francisco, San Francisco, CA

[3]Department of Emergency Medicine: Dalhousie University, Halifax, Nova Scotia, Canada

[4]DF Consulting, Van Nuys, CA

[5]Ultragenyx Pharmaceutical Inc. Novato, CA

Abstract

Rationale: Gamma- hydroxybutyrate acid (GHB), a $GABA_B$ receptor agonist approved for treatment of narcolepsy, impairs driving ability, but little is known about doses and plasma concentrations associated with impairment and time course of recovery.

Objective: To assess effects of oral GHB (Xyrem®) upon driving as measured by a driving simulator, and to determine plasma concentrations associated with impairment and the time course of recovery.

Methods: Randomized, double-blind, two-arm crossover study, during which sixteen participants received GHB 50 mg/kg orally or placebo. GHB blood samples were collected prior to and at one, three and six hours post dosing. Driving simulator sessions occurred immediately after blood sampling.

Results: Plasma GHB was not detectable at baseline or six hours post dosing. Median GHB concentrations at one and three hours were 83.1 mg/L (range 54–110) and 24.4 mg/L (range 7.2–49.7), respectively. Compared to placebo, at one hour post GHB dosing, significant differences were seen for the life-threatening outcomes collisions ($p<0.001$) and off-road accidents ($p=0.018$). Although driving was not faster, there was significantly more weaving and erratic driving with GHB as measured by speed deviation ($p=0.002$) and lane position deviation ($p=0.004$). No significant impairment regarding driving outcomes was found in the GHB group at three and six hours post dose.

Correspondence to: Neal L Benowitz MD, neal.benowitz@ucsf.edu, Phone: 415-206-8324, Fax: 415-206-4956.
*These authors contributed equally to this work.

Conflict of interest: The authors have no conflicts to disclose.

Conclusion: GHB in doses used to treat narcolepsy resulted in severe driving impairment at one hour post dosing. After three to six hours there was full recovery indicating that safe driving is expected the next morning after bedtime therapeutic GHB use in the absence of other substances.

Keywords

γ-hydroxybutyrate; GHB; driving simulator; driving under the influence; DUI

Introduction

Gamma-hydroxybutyrate (GHB) is a therapeutic drug approved in 2002 by the U.S. Food and Drug Administration in the form of sodium oxybate (Xyrem®) as a Schedule III drug to treat narcolepsy and cataplexy (Product Information Xyrem®; Fuller 2004; Borgen 2002). The recommended starting dose is 4.5 grams per day divided into two doses (2.25 grams each), one taken at bedtime and the other 2.5 to 4 hours later. The dose for narcolepsy is then titrated up to therapeutic effect over days to a maximum dose of 9 grams per day, divided into two 4.5 gram doses (Product Information Xyrem®). In addition to narcolepsy and cataplexy, GHB is used in Europe for the treatment of alcohol withdrawal and dependence (Drasbek 2006). According to the website of Xyrem® (www.xyrem.com), as of 2015, almost 60000 people have been prescribed the drug. Furthermore, GHB had been marketed as a dietary weight loss supplement in health food stores and later promoted on the internet as an agent for bodybuilding (Anderson 2006; Gonzalez 2005). Due to its euphoria-producing effects, GHB is also used as a recreational substance (Miro 2017; Liakoni 2016, Busardò 2015) and has been implicated in drug facilitated sexual assault (ElSohly 1999; Gonzalez 2005). Although the exact prevalence of GHB abuse is not known and available data probably underestimate the true extent, reported estimates for lifetime use are between 0.5% and 1.4% among students, with higher estimates (3%−19%) in specific sub-populations (e.g. men who have sex with men), settings (e.g. club and dance venues) and geographical areas (EMCDDA 2008). Typical recreational doses are usually 2.5 g (~35 mg/kg for a 70-kg person) or more but vary widely (chronic users may use much higher doses several times per day) (Couper 2002).

The primary effect of GHB is depression of the central nervous system (Dempsey 2007; Thai 2006). Although it also exists as an endogenous chemical, the profound action that GHB has in high doses on the CNS is attributed primarily to a direct agonist effect on the $GABA_B$ receptor (Drasbek 2006; Snead 2005). GHB has been associated with driving impairment (Centola 2018), with the first case reported in 1994 (Stephens 1994). Since then, other cases have been described in both the USA (National Drug Intelligence Center 2002) and Europe (Bosman 2003; Al-Samarraie 2010), with clinical observations including unsafe driving behavior, extreme sleepiness and reduced consciousness. Although those reports are mostly associated with GHB abuse, some of the estimated recreational doses are in a similar range to that used in therapeutic setting and “sleep-driving” has also been reported in patients taking Xyrem® for narcolepsy (Wallace 2011).

While many reports indicate that GHB impairs driving, little is known of the dose-response and duration of impairment. The aim of the present study was to determine the effect of

therapeutic doses of GHB upon the ability to drive as measured by a driving simulator previously validated in alcohol driving impairment studies (Moskowitz 2000). We also examined the temporal aspects of the GHB effect upon driving, assessing performance for up to six hours after taking GHB, and the relationship between blood concentrations of GHB and impaired driving.

Methods

Overall design:

This was a sex balanced, randomized, double-blind, two-arm crossover study of GHB and placebo conducted on two different days. On each study day, the participants performed a baseline session on the driving simulator, and were then dosed with either placebo or GHB, in counterbalanced order. Driving simulator sessions were performed at one, three, and six hours post dosing. On both study days, blood was collected for GHB analysis at baseline and immediately prior to each driving session. GHB analyses were then performed as described below. This study was performed with informed consent and with the approval of the Committee of Human Research of the University of California, San Francisco.

Participants:

Sixteen healthy adults were enrolled. Inclusion criteria were that participants must be either naïve to, or at most an occasional user of GHB (i.e. less than three times per year), possess a valid driver's license, not be taking any prescription medications other than contraceptives and be between the ages of 21–45. Exclusion criteria included any significant medical conditions, pregnancy, obesity (Body Mass Index (BMI) ≥ 30), substance abuse or prescription drug use that could not be stopped for two weeks prior to the study and alcohol consumption of more than 5 drinks/week.

Recruitment:

Participants were recruited through newspapers and online advertisements and flyers posted in San Francisco Bay Area cafes, colleges etc. and instructed to call a phone screening line. Potential participants were initially screened over the phone and then in person. Informed consent was obtained and eligibility was determined through medical history, physical exam, blood testing and urine toxicology.

Driving Simulator:

The driving simulator used was developed by Systems Technology, Inc. of California (Hawthorne, CA) and has been used extensively in previous studies to investigate the effect of alcohol upon driving (Moskowitz 2000). This computer based system used three video monitors to present an approximately 110° viewing angle of the road ahead as well as the periphery. The image presented on all three monitors responded to input from a steering wheel, accelerator and brake, with appropriate visual and sound feedback. While the primary task was to obey the usual rules of the road, participants were also asked to simultaneously detect visual signals in their peripheral vision. The divided attention task involved monitoring the peripheral video screens for brief signals instructing them to honk the horn or signal for a left or right turn.

During the training session, participants were instructed that turn signals were required for the divided attention task, but not for the driving task of the simulator, and a study session was scheduled only after demonstrating proficiency in the test. In total, 72 signals occurred at random intervals during the drive, at a visual angle of 55 degrees from center.

To simulate normal driving conditions, the session was broken into three scenarios including urban, suburban and rural driving situations, all with 12-foot lane widths. The rural segment was a straight one-lane road with shallow curves (radii ranged from 5000 to 8333 feet). Random occasional wind gusts, based on sine waves, increased steering difficulty. Because in this segment the participants did not have to interact with other traffic on a continuous basis, speed and lane positions were measured without confounds. The suburban segment consisted of a three-lane expressway with posted speed limits of 45 to 55 mph. Frequent lane changes were necessary to pass other vehicles, or to avoid cross traffic, entering traffic, and stalled cars. The urban segment was a two-lane roadway through a city with buildings shown in the background and posted speed limits of 25 to 45 mph with 11 signal-controlled intersections. Pedestrians entered and crossed the walkways at the signals. Participants were instructed to drive as close as possible to the posted speed limit. In all scenarios, a crack appeared on the windshield and a crashing sound was heard in case of a collision, accident, or pedestrian hit. Following an accident, lane position was reset to a default position. The total drive distance for all three segments was approximately 12 miles and each driving session typically lasted 18 to 20 minutes. Table 1 gives the outcome measures used by this driving simulator.

Participants extensively practiced on the driving simulator prior to the inpatient study days to familiarize themselves with the driving interface. Practice included two 4 hour teaching sessions and an eight hour mock study day, at which the participants performed simulator sessions at 7, 8, 9 am, noon, and 3 pm. Upon reaching an acceptable level of proficiency, participants were then scheduled for the two 24 hour inpatient admissions. Thus, the entire study included the screening visit (two hours), two practice visits (four hours each), one mock study day (eight hours), and the two inpatient study days (approximately 24 hours each). Participants performed one final early morning practice session prior to the pre-dose baseline session.

Study Procedures:

This was an inpatient study conducted at the General Clinical Research Center at Zuckerberg San Francisco General Hospital and Trauma Center. Participants spent the night there before each study day. Prior to admission, participants were asked to refrain from drinking alcoholic beverages for three days and to fast and abstain from caffeine and tobacco products overnight. Participants received a light breakfast between 6:30 and 7 am and then performed the final practice driving session. Between 7 and 8 am, a peripheral venous catheter for blood sampling was placed. A baseline driving session was performed at 8 am, dosing with GHB or placebo at 9 am and post dosing driving sessions at 10 am, noon and 3 pm. Blood samples for GHB analysis were collected prior to dosing (baseline) and at one, three and six hours post dosing to correlate with each of the driving sessions. Blood samples were collected through a peripheral intravenous catheter placed in the right forearm, on a

site believed to least interfere with using the driving simulator. Prior to each driving session participants completed a brief self-assessment questionnaire regarding their perception of their ability to drive. The self-assessment questionnaire had a scale of 1 to 5, 1 being no impairment and 5 being maximally impaired. Participants completed the three driving sessions at one, three, and six hours post dosing and were discharged at 5 pm on each study day (i.e. 8 hours after dosing), unless still symptomatic, in which case they could stay overnight. The two arms of the cross-over study (i.e. GHB and placebo) were separated by at least one night.

GHB and Placebo Dosing:

Xyrem® *(Orphan Medical Co., Minnetonka, MN)* contains 500 mg/mL of sodium oxybate, corresponding to 413 mg/mL of GHB. Participants were dosed at 50 mg GHB per kg body weight. To determine the study dose, the screening weight was used, unless the study day weight was significantly different (i.e. >10% difference). The dose was calculated based on GHB and not sodium oxybate. The dose calculation was adjusted during the study due to four male participants developing nausea and vomiting (both common adverse effects of GHB (Product information Xyrem®; Miro 2017)) rendering them incapable of completing the one hour driving session after taking GHB at 50 mg/kg dose. Thus, four additional males were enrolled to replace those who became ill, and the maximum GHB dose for these participants was lowered to 3300 mg (50 mg/kg dose for a 66 kg participant), regardless of weight. Using that maximum dose, the lowest GHB dose received by a participant was 45 mg/kg. Only the 16 participants who completed all aspects of the study are included in the results. The placebo dose was the same volume of liquid as the GHB dose, and the taste and consistency of the placebo and GHB were similar. The GHB or placebo was mixed with the participants' choice of either cranberry or orange juice. Grapefruit juice and products were not allowed in order to avoid any interactions through the inhibitory effects on metabolizing enzymes.

Determination of GHB in Plasma:

The GHB plasma analysis was performed by a gas chromatography-mass spectrometry method similar to the method used in previous studies (Thai 2006; Thai 2007). The detailed description of the method can be found as Online Resource. Briefly, the plasma samples were extracted by protein precipitation with isopropanol, dried and derivatized with *Tert*-butyldimethylsiyl trifluromethane sulfonate (TBDMS triflate) and trimethylamine in heptane at 65°C with sonication to facilitate derivative formation.

Statistics:

In a within subject analysis, not normally distributed GHB results were compared with corresponding placebo results using the Wilcoxon Signed Rank Test. The effect size was calculated by dividing the Z value by the square root of the total number of observations; an r value of 0.1 is considered small, 0.3 medium, and 0.5 large effect size (Fritz 2012). For comparisons of independent groups the Kruskal-Wallis test was used. Differences in self-assessment scales were tested using a 2-tailed paired samples t test. A p value < 0.05 was considered statistically significant. Correlations between GHB plasma concentrations and

driving outcomes were investigated using the Spearman's nonparametric correlation test. Analyses were conducted using SPSS statistical software (IBM SPSS Statistics 23.0).

Results

Demographics:

16 participants (eight females) were enrolled. Eight participants performed the two sessions with one night elapsed between them while eight participants completed the study with at least one day between the sessions (range 1–6). The mean participants' age was 27 years (range 22–42). Two out of the 16 participants reported use of GHB in the past. The mean weight was 69.1 kg (range 57.9–85.3), 66.6 kg (range 59.8–85.3) for the female and 71.7 kg (range 57.9–83.5) for male participants.

Driving Questionnaire and Simulator results:

One hour after GHB ingestion, all participants assessed themselves as less able to drive an automobile compared to after the placebo ($p<0.001$). The self-assessment raw scores at one hour post GHB dosing ranged from 2 to 5 (median 4), while post placebo dosing the same raw scores ranged from 1 to 2 (median 1). At three hours post GHB dosing there was still a significant difference ($p=0.001$), with nearly a third of self-assessments scored at 3 or higher in the GHB arm. Fig. 1 displays the mean self-assessment scores for all time points in both conditions.

Table 2 presents the baseline, one, three, and six hours post dose driving data in the two groups.

Objective assessment with the driving simulator found no significant differences between the two groups at baseline, but significant differences were found at the one hour post dosing driving session. Two of the three life-threatening adverse driving outcomes, collisions ($Z= -3.526$, $p<0.001$, $r= -0.62$; all 16 participants more collisions one hour after GHB compared to placebo) and off-road accidents ($Z=-2.375$, $p<0.018$, $r= -0.42$; seven participants more off-road accidents one hour after GHB compared to placebo, no participants with more off-road accidents after placebo), were significantly more likely one hour after GHB dosing, while hitting a pedestrian did not show a significant difference (Table 2). Other significant findings included greater mean speed deviation ($Z= -3.051$, $p=0.002$, $r= -0.54$, greater deviation seen in 13 out of the 16 participants), and lane position deviation ($Z= -2.896$, $p=0.004$, $r= -0.51$, greater deviation seen in 13 out of the 16 participants) after GHB. Analysis of the results of the driving simulation testing at three hours showed no significant differences between treatment arms (Table 2), except for the self-assessed ability to drive a car (Fig 1). At six hours post dosing there was no significant impairment in the GHB group, neither in the results of the driving simulation nor in the self-assessment of the ability to drive (Fig 1), but a greater mean speed deviation was seen in the placebo arm ($Z= -2.279$, $p=0.017$, $r= -0.42$).

When comparing the one hour significant results to the other time points, significant differences were found in the GHB arm: No. of collisions at one hour compared to baseline: $Z= -3.301$, $p=0.001$, $r= -0.58$, three hours: $Z= -3.16$, $p=0.002$, $r= -0.56$, six hours: $Z=$

−3.212, p=0.001, r= −0.57; No. of off road accidents at one hour compared to baseline: Z= −2.176, p=0.03, r= −0.38, three hours: Z= −1.975, p=0.048, r= −0.35, six hours: Z= −2.132, p=0.033, r= −0.38; mean speed deviation at one hour compared to baseline: Z= −3.206, p=0.001, r= −0.57, three hours: Z= −1.965, p=0.049, r= −0.35, six hours: Z= −3.464, p=0.001, r= −0.61; mean lane position deviation at one hour compared to baseline: Z= −3.232, p=0.001, r= −0.57, three hours: Z= −2.9, p=0.004, r= −0.51, six hours: Z= −3.284, p=0.001, r= −0.58. No significant differences were found in the placebo arm for the same comparisons.

GHB dosing, blood concentrations, and correlations:

The mean GHB dose for all participants was 3333 mg (SD 400, range 2892–4265). The mean dose for the eight female participants was not significantly different from the mean dose for the eight male participants (3330 (SD 472.3) and 3336 (SD 346.8), respectively). No GHB was detected at baseline or at six hours at the 5 mg/L limit of quantitation. The plasma concentrations of GHB at one and three hours are shown in Table 3.

At the one hour time point, the GHB concentrations were not significantly different in women compared to men (p=0.208). The correlations between one hour GHB plasma concentrations and one hour individual driving outcome measures were examined. Significant correlations were found between GHB plasma concentrations and mean lane position deviations ($r = 0.532$, $p<0.05$), as well as mean speed deviations ($r = 0.588$, $p<0.05$). Correlations between other driving scores and GHB plasma concentrations were not significant.

Discussion

To our knowledge, this is the first controlled clinical study of the effect of GHB on motor vehicle driving performance. We found that doses of GHB that are used in treating narcolepsy in non-regular GHB users can severely affect driving performance. A substantial impairment was found one hour after GHB dosing, with significantly more life-threatening adverse driving outcomes (i.e. collisions and off-road accidents) and indicators of erratic driving (i.e. greater mean speed and lane position deviations). The third life-threatening outcome, hitting a pedestrian, and other outcomes of minor severity (e.g. number of speeding tickets, stops at traffic lights) did not show a significant difference, but they may have been averted by driving off-road (off-road accidents) or by collision, or in some cases not reaching significance due to large variability. We also demonstrated the time course of recovery through both subjective and objective measures. At three hours, many still rated themselves less than fully able to drive (a finding not supported by the driving simulation), but there was full recovery both objectively and subjectively by six hours post dosing.

While driving simulators do not perfectly reflect real life driving, they are an accepted method to assess the effect of acute and residual effects of therapeutic drugs, sleep deprivation, and alcohol, illicit and/or recreational drug use upon driving performance (Akinwuntan 2005; Arnedt 2005; Lenne 2003; Moskowitz 2000; Partinen 2003; Turkington 2001; Weiler 2000). Driving simulator studies can be used to develop recommendations and policies regarding drug use and safe driving. Studies involving benzodiazepine-related

hypnotics have had mixed results and their nighttime use may impair daytime driving (Partinen 2003; Staner 2005), while other studies have concluded that no restriction should be placed on the driving licenses of persons using methadone, levo-alpha-acetyl-methodol (LAAM), or buprenorphine therapeutically for the treatment of heroin addiction (Lenne 2003).

Based on our findings, it is unlikely that bedtime/nighttime GHB correct dosing will have clinically significant effects upon daytime driving. This is in accordance with the rapid clearance of GHB as demonstrated by this and other studies (Borgen 2004; Brenneisen 2004; Palatini 1993; Scharf 1998; Thai 2006). Currently, the product information of Xyrem® (Product information Xyrem®) includes a warning that patients should not engage in activities such as operating a motor vehicle for at least six hours after taking the second nightly dose. Our study demonstrated that by six hours, GHB concentrations were below 0.5 mg/L and the driving simulator scores had returned to baseline. Thus, therapeutic nighttime users of GHB should have sufficient time to recover from the GHB prior to driving in the morning.

However, driving within a few hours of GHB use appears to be hazardous. Compared to other driving simulation studies (Moskowitz 2000), the level of impairment measured in our participants by GHB at one hour was similar to that seen in drivers with breath alcohol concentrations in the range of 0.08% to 0.1%. Furthermore, the use of combinations of GHB and other substances is not uncommon (Dresen 2007) and may lead to driving impairment at lower GHB doses. In previous studies (Dempsey 2007; Thai 2006) participants who ingested both ethanol and GHB were extremely sedated and had mild respiratory depression, even when the dose of GHB was lowered to 25 mg/kg. Also when ethanol and GHB are combined, ethanol may inhibit the clearance of GHB (Dempsey 2007; Thai 2006).

The effects of GHB on psychomotor function, and presumably on driving performance, are dose-related (Liechti 2016, Centola 2018). The mean dose administrated in our study was 3333 mg (45–50 mg/kg). In human studies with lower GHB doses, 1–2 g did not significantly impair psychomotor skills related to driving (Mattila 1978). GHB at 12.5 and 25 mg/kg had no effects on attention, vigilance or psychomotor co-ordination (Ferrara 1999), at 0.32−3.2 g/70kg (4.5−45.7 mg/kg) produced dose-related changes in subjective effects but no changes in psychomotor performance (Oliveto 2010), and at 20 mg/kg had no significant effects on visual working memory, reaction time and verbal recall (Bosch 2015). In studies using higher GHB doses (Carter 2006), 8 g/70kg (114 mg/kg) produced sedation in almost all participants, and in approximately one third painful stimuli were required to elicit a response. Similar to our study, maximal effects occurred one to two hours after administration and did not last more than 3–4 hours. In studies with recreational GHB users, sedative effects reached their maximum between 1.5 and 2 hours after a dose of 40 or 60 mg/kg, and returned to baseline after about three hours (Abanades 2007). At 4.5 g/70kg (64.3 mg/kg) dose in healthy volunteers, Xyrem® significantly impaired working memory performance and encoding of episodic memory, and tended to increase response times (Carter 2009). GHB doses up to 10 g/70kg (143 mg/kg) had similar effects to alcohol dosed up to 120 g/70kg (1,714 mg/kg) regarding sedative effects and performance impairment, but less severe memory impairing effects and a shorter time course (Johnson 2013). Thus,

despite different methodological approaches (Centola 2018), a dose threshold seems to exist, with lower or moderate doses probably not leading to impairment of psychomotor and driving skills, while GHB doses similar to those used in our study (or higher) pose a potential risk.

In studies of cases of driving under the influence (DUI) of GHB, mean reported blood GHB concentrations were between 87 and 100 mg/L (range 16–350 mg/L) (Jones 2007, Pan 2001, Couper 2001, Couper 2004, Burch 2013) and reported clinical findings included slurred speech, stagger, drowsiness, stopping in the middle of the road and sleeping (Jones 2007, Pan 2001, Burch 2013). Although the one hour concentrations in our study (median 83.1 mg/L) are comparable to the reported DUI values, in the DUI cases, the blood samples were typically drawn one or more hours after the arrest. The half-life of GHB is reported to be between 20 and 50 minutes (Schep 2012; Liechti 2016; Brenneisen 2004; Schröck 2014; Thai 2006; Thai 2007), so it is assumed that the GHB concentrations were higher at the time of the arrest (Busardò 2015).

Limitations of our study include the fact that we studied only one dose of GHB, which also had to be adjusted during the study for four participants due to safety reasons. Despite this, the doses we used are between the recommended starting and maximum dose used in treating narcolepsy, so we can provide a basis for advising narcolepsy patients regarding GHB residual effects and driving restrictions. However, while sodium oxybate is used before going to sleep in narcolepsy patients, for the treatment of alcohol craving (non-FDA use) it is dosed at 50 mg/kg/day, in three divided doses during the day at intervals of at least four hours (Keating 2014; Drasbek 2006). This dosing regimen would probably result in lower individual doses and therefore probably in less driving performance impairment. Furthermore, we did not include regular GHB users, who might have shown less driving impairment due to tolerance, as seen with repeated administration in mice and rats (Bania 2003; Itzhak 2002). Another potential limitation of the study is the large amount of practice (practice effect) required to master the use of the simulator (Lenne 2003). We minimized the confounding of a practice effect by extensive training on the simulator - two 4 hours sessions, then an 8 hour session that mimicked the study day, and one final practice session 1 hour prior to the pre-dosing baseline session. Also, the order of testing GHB and placebo was balanced. Moreover, no mathematical correction for multiple comparisons was performed for the pre-designed comparisons in our study. Although this might increase the risk for Type I errors (e.g. in case of mean speed deviation six hours post dosing), avoiding Type II errors is of great importance when investigating life-threatening outcomes. Furthermore, a large effect size ($r > 0.5$) was found for most of the significant findings (including the life-threatening adverse outcome “No of collisions”) and those results remain significant even after lowering the alpha level to $p < 0.01$.

This is the first controlled clinical study of the effect of GHB on driving and could be used, similar to alcohol driving simulation studies, to optimize patient safety and regulations regarding threshold for DUI offenses. As highlighted also in a recent review about the effects of GHB on driving performance (Centola 2018), there are currently no other experimental studies based on real-driving or driving-simulators and the only knowledge in this field is derived from laboratory tests, which are not always reliable for the evaluation of

the effects on driving. Therefore, our study offers an important basis in order to be able to advise patients about possible significant risks, especially in the light of further possible GHB indications currently under investigation (e.g. fibromyalgia (Russell 2009), myoclonus, essential tremor (Frucht 2005), binge-eating disorder (McElroy 2011), and spasmodic dysphonia (Rumbach 2016)).

In conclusion, we found that at GHB doses used to treat narcolepsy, driving performance, as measured by a driving simulator, was subjectively (questionnaire) and objectively (collisions, etc) significantly impaired one hour after dosing with GHB, but the impairment resolved by three to six hours post dosing. Data presented here do not indicate that any daytime driving restriction should be placed upon driving licenses of people with narcolepsy who take GHB at nighttime and do not drive until the morning. As regards daytime dosing of GHB for other medical conditions, no recommendations can be made about the safety of its use, similar to use in non-therapeutic setting in which higher doses might be used several times per day and often in combination with other substances. The one hour GHB concentrations that we found in our study are in the range reported in the literature for GHB-DUIs. However, the DUI samples were collected one or more hours after the arrest. Although more study is needed before general driving recommendations can be made regarding GHB use, at this time, our data would indicate driving within 3–4 hours of use may be hazardous and is not recommended.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We thank the nurses and staff of the Clinical Research Center of San Francisco General Hospital for their help, and Newton Addo for statistical and technical support.

Funding: Supported by the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research, Grant Numbers MO1RR00083–44 and UL1 RR024131–01, NIDA DA14935 and DA12393.

REFERENCES

Abanades S, Farré M, Barral D, Torrens M, Closas N, Langohr K, Pastor A, de la Torre R (2007) Relative abuse liability of gamma-hydroxybutyric acid, flunitrazepam, and ethanol in club drug users. J Clin Psychopharmacol 27(6):625–38. [PubMed: 18004131]

Akinwuntan AE, De Weerdt W, Feys H, Pauwels J, Baten G, Arno P, Kiekens C (2005) Effect of simulator training on driving after stroke: a randomized controlled trial. Neurology 65(6):843–50. [PubMed: 16186521]

Al-Samarraie MS, Karinen R, Mørland J, Stokke Opdal M (2010) Blood GHB concentrations and results of medical examinations in 25 car drivers in Norway. Eur J Clin Pharmacol 66(10):987–98. [PubMed: 20717656]

Anderson IB, Kim SY, Dyer JE, Burkhardt CB, Iknoian JC, Walsh MJ, Blanc PD (2006) Trends in gamma-hydroxybutyrate (GHB) and related drug intoxication: 1999 to 2003. Ann Emerg Med 47(2):177–83. [PubMed: 16431231]

Arnedt JT, Owens J, Crouch M, Stahl J, Carskadon MA (2005) Neurobehavioral performance of residents after heavy night call vs after alcohol ingestion. JAMA 294(9):1025–33. [PubMed: 16145022]

Bania TC, Ashar T, Press G, Carey PM (2003) Gamma-hydroxybutyric acid tolerance and withdrawal in a rat model. Acad Emerg Med 10(7):697–704. [PubMed: 12837642]

Borgen LA, Cook HN, Hornfeldt CS, Fuller DE (2002) Sodium oxybate (GHB) for treatment of cataplexy. Pharmacotherapy 22(6):798–9; discussion 799. [PubMed: 12066974]

Borgen LA, Okerholm RA, Lai A, Scharf MB (2004) The pharmacokinetics of sodium oxybate oral solution following acute and chronic administration to narcoleptic patients. J Clin Pharmacol 44(3): 253–7. [PubMed: 14973300]

Bosch OG, Eisenegger C, Gertsch J, von Rotz R, Dornbierer D, Gachet MS, Heinrichs M, Wetter TC, Seifritz E, Quednow BB (2015) Gamma-hydroxybutyrate enhances mood and prosocial behavior without affecting plasma oxytocin and testosterone. Psychoneuroendocrinology 62:1–10. [PubMed: 26209926]

Bosman IJ, Lusthof KJ (2003) Forensic cases involving the use of GHB in The Netherlands. Forensic Sci Int 23;133(1–2):17–21. [PubMed: 12742684]

Brenneisen R, Elsohly MA, Murphy TP, Passarelli J, Russmann S, Salamone SJ, Watson DE (2004) Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. J Anal Toxicol 28(8):625–30. [PubMed: 15538955]

Burch HJ, Clarke EJ, Hubbard AM, Scott-Ham M (2013) Concentrations of drugs determined in blood samples collected from suspected drugged drivers in England and Wales. J Forensic Leg Med 20(4):278–89. [PubMed: 23622475]

Busardò FP, Jones AW (2015) GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. Curr Neuropharmacol 13(1):47–70. [PubMed: 26074743]

Carter LP, Griffiths RR, Mintzer MZ (2009) Cognitive, psychomotor, and subjective effects of sodium oxybate and triazolam in healthy volunteers. Psychopharmacology (Berl) 206(1):141–54. [PubMed: 19543883]

Carter LP, Richards BD, Mintzer MZ, Griffiths RR (2006) Relative abuse liability of GHB in humans: A comparison of psychomotor, subjective, and cognitive effects of supratherapeutic doses of triazolam, pentobarbital, and GHB. Neuropsychopharmacology 31(11):2537–51. [PubMed: 16880774]

Centola C, Giorgetti A, Zaami S, Giorgetti R (2018) Effects of GHB on psychomotor and driving performance. Curr Drug Metab doi: 10.2174/1389200219666180124113802. [Epub ahead of print]

Couper FJ, Logan BK (2001) GHB and driving impairment. J Forensic Sci 46(4):919–23. [PubMed: 11451079]

Couper FJ, Logan BK (2004) Addicted to driving under the influence-a GHB/GBL case report. J Anal Toxicol 28(6):512–5. [PubMed: 15516306]

Couper FJ, Marinetti LJ (2002) γ-Hydroxybutyrate (GHB) - Effects on Human Performance and Behavior. Forensic Sci Rev 14(1–2):101–21. [PubMed: 26256488]

Dempsey D, Murphy N, Benowitz NL, Wiegand T, Wu L, Haller CA (2007) Respiratory Effects of Gamma-Hydroxybutyrate (GHB) and Ethanol. Clin Pharm Thera 81(Supplement 1):S51.

Drasbek KR, Christensen J, Jensen K (2006) Gamma-hydroxybutyrate--a drug of abuse. Acta Neurol Scand 114(3):145–56. [PubMed: 16911342]

Dresen S, Kempf J, Weinmann W (2007) Prevalence of gamma-hydroxybutyrate (GHB) in serum samples of amphetamine, metamphetamine and ecstasy impaired drivers. Forensic Sci Int 20;173(2–3):112–6. Epub 2007 Mar 23. [PubMed: 17383132]

ElSohly MA, Salamone SJ (1999) Prevalence of drugs used in cases of alleged sexual assault. J Anal Toxicol 23(3):141–6. [PubMed: 10369321]

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2008) GHB and its precursor GBL: An emerging trend case study. http://www.emcdda.europa.eu/system/files/publications/505/TP_GHB_and_GBL_107300.pdf Accessed June 2018.

Ferrara SD, Giorgetti R, Zancaner S, Orlando R, Tagliabracci A, Cavarzeran F, Palatini P (1999) Effects of single dose of gamma-hydroxybutyric acid and lorazepam on psychomotor performance and subjective feelings in healthy volunteers. Eur J Clin Pharmacol 54(11):821–7. [PubMed: 10027654]

Fritz CO, Morris PE, Richler JJ (2012) Effect size estimates: current use, calculations, and interpretation. J Exp Psychol Gen 141(1):2–18. [PubMed: 21823805]

Frucht SJ, Houghton WC, Bordelon Y, Greene PE, Louis ED (2005) A single-blind, open-label trial of sodium oxybate for myoclonus and essential tremor. Neurology 27;65(12):1967–9. [PubMed: 16382538]

Fuller DE, Hornfeldt CS, Kelloway JS, Stahl PJ, Anderson TF (2004) The Xyrem risk management program. Drug Saf 27(5):293–306. [PubMed: 15061684]

Gonzalez A, Nutt DJ (2005) Gamma hydroxy butyrate abuse and dependency. J Psychopharmacol 19(2):195–204. [PubMed: 15871147]

Itzhak Y, Ali SF (2002) Repeated administration of gamma-hydroxybutyric acid (GHB) to mice: assessment of the sedative and rewarding effects of GHB. Ann N Y Acad Sci 965:451–60. [PubMed: 12105120]

Johnson MW, Griffiths RR (2013) Comparative abuse liability of GHB and ethanol in humans. Exp Clin Psychopharmacol 21(2):112–123. [PubMed: 23421353]

Jones AW, Holmgren A, Kugelberg FC (2007) Gamma-hydroxybutyrate concentrations in the blood of impaired drivers, users of illicit drugs, and medical examiner cases. J Anal Toxicol 31(9):566–72. [PubMed: 18093415]

Keating GM (2014) Sodium oxybate: a review of its use in alcohol withdrawal syndrome and in the maintenance of abstinence in alcohol dependence. Clin Drug Investig 34(1):63–80.

Lenne MG, Dietze P, Rumbold GR, Redman JR, Triggs TJ (2003) The effects of the opioid pharmacotherapies methadone, LAAM and buprenorphine, alone and in combination with alcohol, on simulated driving. Drug Alcohol Depend 72(3):271–8. [PubMed: 14643944]

Liakoni E, Walther F, Nickel CH, Liechti ME (2016) Presentations to an urban emergency department in Switzerland due to acute γ-hydroxybutyrate toxicity. Scand J Trauma Resusc Emerg Med 31;24(1):107. [PubMed: 27581664]

Liechti ME, Quednow BB, Liakoni E, Dornbierer D, von Rotz R, Gachet MS, Gertsch J, Seifritz E, Bosch OG (2016) Pharmacokinetics and pharmacodynamics of γ-hydroxybutyrate in healthy subjects. Br J Clin Pharmacol 81(5):980–8. [PubMed: 26659543]

Mattila MJ, Palva E, Seppälä T, Ostrovskaya RU (1978) Actions and interactions with alcohol of drugs on psychomotor skills: comparison of diazepam and gamma-hydroxybutyric acid. Arch Int Pharmacodyn Ther 234(2):236–46. [PubMed: 708150]

McElroy SL, Guerdjikova AI, Winstanley EL, O'Melia AM, Mori N, Keck PE Jr, Hudson JI (2011) Sodium oxybate in the treatment of binge eating disorder: an open-label, prospective study. Int J Eat Disord 44(3):262–8. [PubMed: 20209489]

Miró Ò, Galicia M, Dargan P, Dines AM, Giraudon I, Heyerdahl F, Hovda KE, Yates C, Wood DM, Euro-DEN Research Group (2017) Intoxication by gamma hydroxybutyrate and related analogues: Clinical characteristics and comparison between pure intoxication and that combined with other substances of abuse. Toxicol Lett 277:84–91. [PubMed: 28579487]

Moskowitz H, Burns M, Fiorentino D, Smiley A, Zador P (2000) Driving Characteristics and Impairment at Various BACs, DOT HS 809 075 (Tremont PJ, ed.), US Department of Transportation, National Highway Traffice Safety Administration, pp. 1–60. www.nhtsa.dot.gov/people/injury/research/pub/impaired_driving/BAC/impairment.pdf Accessed March 2018.

National Drug Intelligence Center (2002) Information Bulletin: GHB Analogs GBL, BD, GHV and GVL, National Drug Intelligence Center. https://www.justice.gov/archive/ndic/pubs1/1621/1621t.htm Accessed March 2018.

Oliveto A, Gentry WB, Pruzinsky R, Gonsai K, Kosten TR, Martell B, Poling J (2010) Behavioral effects of gamma-hydroxybutyrate in humans. Behav Pharmacol 21(4):332–42. [PubMed: 20526195]

Palatini P, Tedeschi L, Frison G, Padrini R, Zordan R, Orlando R, Gallimberti L, Gessa GL, Ferrara SD (1993) Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. Eur J Clin Pharmacol 45(4):353–6. [PubMed: 8299669]

Pan YM, Gill GN, Tilson CS, Wall WH, McCurdy HH (2001) Improved procedure for the analysis of gamma-hydroxybutyrate and ethylene glycol in whole blood. J Anal Toxicol 25(5):328–32. [PubMed: 11499886]

Partinen M, Hirvonen K, Hublin C, Halavaara M, Hiltunen H (2003) Effects of after-midnight intake of zolpidem and temazepam on driving ability in women with non-organic insomnia. Sleep Med 4(6): 553–61. [PubMed: 14607350]

Product Information: Xyrem® oral solution, sodium oxybate oral solution. Jazz Pharmaceuticals (per FDA), Palo Alto, CA, 2012

Rumbach AF, Blitzer A, Frucht SJ, Simonyan K (2017) An open-label study of sodium oxybate in Spasmodic dysphonia. Laryngoscope 127(6):1402–1407. [PubMed: 27808415]

Russell IJ, Perkins AT, Michalek JE (2009) Oxybate SXB-26 Fibromyalgia Syndrome. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial. Arthritis Rheum 60(1):299–309. [PubMed: 19116896]

Scharf MB, Lai AA, Branigan B, Stover R, Berkowitz DB (1998) Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients. Sleep 21(5):507–14. [PubMed: 9703591]

Schep LJ, Knudsen K, Slaughter RJ, Vale JA, Mégarbane B (2012) The clinical toxicology of γ-hydroxybutyrate, γ-butyrolactone and 1,4-butanediol. Clin Toxicol (Phila) 50(6):458–70. [PubMed: 22746383]

Schröck A, Hari Y, König S, Auwärter V, Schürch S, Weinmann W (2014) Pharmacokinetics of GHB and detection window in serum and urine after single uptake of a low dose of GBL - an experiment with two volunteers. Drug Test Anal 6(4):363–6. [PubMed: 23733593]

Shah VP, Midha KK, Findlay JW, Hill HM, Hulse JD, McGilveray IJ, McKay G, Miller KJ, Patnaik RN, Powell ML, Tonelli A, Viswanathan CT, Yacobi A (2000) Bioanalytical method validation--a revisit with a decade of progress. Pharm Res 17(12):1551–7. [PubMed: 11303967]

Snead OC 3rd, Gibson KM (2005) Gamma-hydroxybutyric acid. N Engl J Med 352(26):2721–32. [PubMed: 15987921]

Staner L, Ertle S, Boeijinga P, Rinaudo G, Arnal MA, Muzet A, Luthringer R (2005) Next-day residual effects of hypnotics in DSM-IV primary insomnia: a driving simulator study with simultaneous electroencephalogram monitoring, Psychopharmacology (Berl) 181(4):790–8. [PubMed: 16025317]

Stephens BG, Baselt RC (1994) Driving under the influence of GHB?. J Anal Toxicol 18(6):357–8. [PubMed: 7823545]

Thai D, Dyer JE, Benowitz NL, Haller CA (2006) Gamma-hydroxybutyrate and ethanol effects and interactions in humans. J Clin Psychopharmacol 26(5):524–9. [PubMed: 16974199]

Thai D, Dyer JE, Jacob P, Haller CA (2007) Clinical pharmacology of 1,4-butanediol and gamma-hydroxybutyrate after oral 1,4-butanediol administration to healthy volunteers. Clin Pharmacol Ther 81(2):178–84. [PubMed: 17192771]

Turkington PM, Sircar M, Allgar V, Elliott MW (2001) Relationship between obstructive sleep apnoea, driving simulator performance, and risk of road traffic accidents. Thorax 56(10):800–5. [PubMed: 11562521]

Wallace DM, Maze T, Shafazand S (2011) Sodium oxybate-induced sleep driving and sleep-related eating disorder. J Clin Sleep Med 15;7(3):310–1. [PubMed: 21677903]

Weiler JM, Bloomfield JR, Woodworth GG, Grant AR, Layton TA, Brown TL, McKenzie DR, Baker TW, Watson GS (2000) Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. Ann Intern Med 132(5):354–63. [PubMed: 10691585]

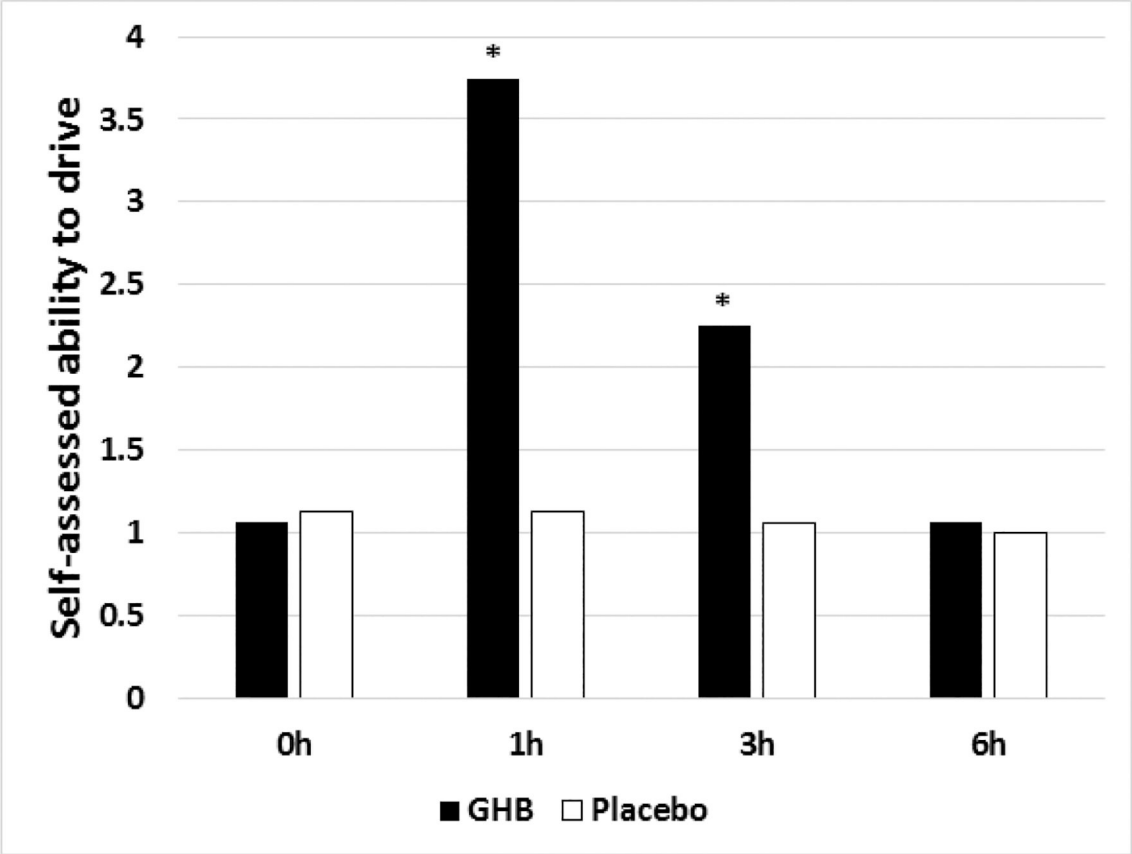

Fig. 1. Self-assessed ability to drive

(1 = Able to safely drive a car, 5 = Not able to drive a car, *significant difference ($p<0.05$) compared to placebo)

Table 1.

Driving Session Outcomes and Measures of Driving Style

Outcomes and measures	Description
Most Severe Adverse Outcomes (life threatening)	
Collisions	The number of times the participant's vehicle collided with another vehicle
Off road accidents	The number of times the participant's vehicle traveled more than 10 feet on the shoulder of the 12-feet roadway
Pedestrian hits	The number of times the vehicle collided with a pedestrian
Serious Adverse Outcomes (affect auto insurance and driving record)	
Speeding tickets	The number of speeding tickets
Traffic light tickets	The number of traffic light tickets
Measures of Driving Style that Affect Outcomes	
Stops at traffic lights	The number of times the vehicle stopped at a red light in the urban segment
Mean speed	The average vehicle speed, in mph, during the rural segment
Mean speed deviation	The standard deviation of the speed sampled during the rural segment
Speed exceedances	The number of times the vehicle exceeded the posted speed limit
Mean lane position	The lateral distance, in feet, between the center of the vehicle and the roadway's dividing line during the rural segment
Mean lane position deviation	The standard deviation of the lateral distance between the center of the vehicle and the roadway's dividing line during the rural segment
Divided Attention Tasks: beep horn, or activate appropriate turn signal	
Correct Responses	The number of correct responses in the secondary task
Incorrect responses	The number of incorrect responses in the secondary task
Missed responses	The number of secondary task signals not followed by a response
Mean response time	The average time, in seconds, between the onset of a secondary task and a response to the signal
Response time deviation	The standard deviation of the response times

Table 2.

Baseline, one, three, and six hours post dose driving simulator results (median (range, coefficient of variation)

	Baseline			One hour post dose			Three hours post dose			Six hours post dose		
Outcome	**GHB**	**Placebo**	**p**	**GHB**	**Placebo**	**p**	**GHB**	**Placebo**	**p**	**GHB**	**Placebo**	**p**
No. of collisions	0 (0–3, 1.64)	1 (0–5, 1.11)	0.23	6.5 (2–19, 0.72)	1 (0–4, 0.90)	**<0.001**	2 (0–4, 0.73)	1 (0–9, 1.46)	0.24	1 (0–5, 0.91)	0.5 (0–3, 1.17)	0.10
No. of off road accidents	0 (0–2, 2.9)	0 (0–1, 2.15)	1	0 (0–7, 1.39)	0 (0–2, 4)	**0.018**	0 (0–3, 2.04)	0 (0–1, 2.73)	0.24	0 (0–3, 4)	0 (0–2, 1.93)	0.32
No. of pedestrian hits	0 (0–2, 2.9)	0 (0, n.a.)	0.18	0 (0–1, 4)	0 (0, n.a.)	0.32	0 (0–2, 4)	0 (0, n.a.)	0.32	0 (0, n.a.)	0 (0, n.a.)	1
Mean speed (mph)	51 (45–62, 0.07)	52 (46–58, 0.06)	0.72	50 (38–54, 0.11)	52 (46–55, 0.05)	0.12	51 (47–56, 0.05)	52 (42–56, 0.06)	0.47	52 (44–54, 0.05)	51 (42–57, 0.08)	0.35
Mean speed deviation	2.6 (1.12–4.6, 0.43)	2.5 (1.38–5.31, 0.39)	0.64	4.09 (1.2–10.5, 0.55)	2.76 (1.4–6.3, 0.42)	**0.002**	2.96 (1.7–6.7, 0.45)	2.62 (1.5–6.7, 0.47)	0.16	2.26 (1.1–5.9, 0.48)	3.08 (1.3–4.9, 0.33)	**0.017**
No. of times over speed limit	3 (0–40, 1.64)	3 (1–20, 1.07)	0.79	6.5 (0–24, 0.84)	3.5 (0–28, 1.21)	0.44	4 (0–31, 1.23)	4.5 (0–27, 1.02)	0.61	4.5 (0–20, 0.93)	4.5 (0–20, 0.93)	0.70
No. of speeding tickets	0 (0–6, 1.69)	1 (0–6, 1.2)	0.44	2.5 (0–21, 1.29)	1.5 (1–10, 1.29)	0.25	1.5 (0–12, 1.28)	1.5 (0–11, 1.18)	0.97	1.5 (0–9, 1.21)	0.5 (0–8, 1.47)	0.38
No. of traffic light tickets	0 (0–2, 1.46)	0 (0–2, 1.65)	0.60	1.5 (0–3, 0.83)	0.5 (0–3, 1.15)	0.4	1 (0–2, 1.01)	0 (0–3, 1.33)	0.41	1 (0–3, 1.02)	0 (0–4, 1.44)	0.21
No. of stops at traffic lights	1.5 (0–11, 1.17)	0 (0–10, 1.44)	0.40	2.5 (0–10, 1.11)	1 (0–11, 1.15)	0.48	4 (0–11, 1.01)	2.5 (0–11, 1.05)	0.78	2.5 (0–11, 1.08)	2.5 (0–11, 1.1)	0.57
Mean lane position (feet)	4.5 (3.8–5.7, 0.12)	4.6 (3.4–5.6, 0.14)	0.06	4.6 (2.2–5.5, 0.16)	4.9 (3.9–5.8, 0.13)	0.42	4.7 (4–6, 0.12)	4.67 (3.9–5.4, 0.11)	0.15	4.7 (3.9–5.6, 0.12)	4.5 (3.9–6.2, 0.14)	0.08
Mean lane position deviation	1.15 (0.88–1.82, 0.24)	1.17 (0.59–1.54, 0.21)	0.29	1.93 (1–3.55, 0.40)	1.23 (0.82–1.75, 0.19)	**0.004**	1.28 (1.01–1.93, 0.18)	1.28 (0.74–1.74, 0.23)	0.38	1.3 (0.93–1.71, 0.18)	1.22 (0.89–1.83, 0.21)	0.61
No. of correct responses	54 (40–69, 0.11)	54 (49–55, 0.03)	0.77	69 (54–72, 0.07)	70 (62–72, 0.04)	0.25	69 (65–72, 0.03)	70.5 (65–72, 0.04)	0.43	69.5 (57–72, 0.06)	70 (61–72, 0.05)	0.65
No. of missed responses	1 (0–13, 1.41)	1 (0–6, 1.24)	0.10	2.5 (0–7, 0.83)	2 (0–10, 1)	0.44	2.5 (0–6, 0.79)	1 (0–7, 1.01)	0.18	2 (0–15, 1.25)	1.5 (0–10, 1.11)	0.53
Mean response time (seconds)	2.1 (1.7–3.6, 0.21)	2.2 (1.6–2.7, 0.15)	0.96	2.1 (1.8–3.3, 0.19)	2.1 (1.7–2.7, 0.14)	0.06	2.2 (1.6–2.6, 0.13)	2 (1.7–2.5, 0.12)	0.09	2 (1.7–2.9, 0.15)	2.1 (1.5–2.6, 0.15)	0.91
Response time deviation	0.87 (0.65–1.24, 0.22)	0.92 (0.53–1.26, 0.26)	0.16	0.94 (0.6–1.9, 0.23)	0.91 (0.57–1.24, 0.26)	0.49	0.94 (0.54–1.18, 0.2)	0.83 (0.67–1.26, 0.22)	0.62	0.91 (0.57–1.43, 0.26)	0.91 (0.51–1.32, 0.27)	0.68

Table 3.

GHB plasma concentrations (median (range))

	All participants (n=16)	Males (n=8)	Females (n=8)
1h plasma GHB (mg/L)	83.1 (54–110)	72.5 (54–102)	88.8 (58.1–110)
3h plasma GHB (mg/L)	24.4 (7.2–49.7)	24.4 (7.2–49.7)	25 (9.7–43.6)