γ-Hydroxybutyrate (GHB) in Humans

Pharmacodynamics and Pharmacokinetics

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ABSTRACT: **Despite γ-hydroxybutyrate (GHB) therapeutic uses and the increasing concern about its toxicity, few studies have addressed GHB dose-related effects under controlled administration and their relationship with its pharmacokinetics. The study design was double-blind, randomized, crossover, and controlled. As a pilot pharmacology phase I study, increasing doses of GHB were given. Single oral sodium GHB doses (40, 50, 60, and 72 mg/kg) were administered to eight volunteers. Plasma and urine were analyzed for GHB by gas chromatography–mass spectrometry. Physiological effects, psychomotor performance, and subjective effects were examined simultaneously. GHB produced dose-related changes in subjective effects as measured by questionnaires and VAS. GHB showed a mixed stimulant-sedative pattern, with initially increased scores in subjective feeling of euphoria, high, and liking followed by mild-moderate symptoms of sedation with impairment of performance and balance. Mean peak GHB plasma concentrations were 79.1, 83.1, 113.5, and 130.1 μg/L for 40, 50, 60, and 72 mg/kg, respectively. GHB-mediated physiological and subjective effects were dose dependent and related to GHB plasma concentrations. GHB urinary excretion was mainly related to administered doses. GHB-mediated**

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subjective and physiological effects seem dose dependent and related to GHB plasma concentrations. Results suggest a high abuse liability of GHB in the range of dose usually consumed.

KEYWORDS: γ-hydroxybutyric acid; γ-hydroxybutyrate; GHB; subjective effects; abuse liability

INTRODUCTION

γ-hydroxybutyrate (GHB, "liquid ecstasy") is also known as γ-hydroxybutyric acid, 4-hydroxybutyiric acid, 4-hydroxybutanoic acid, and oxybate (sodium oxybate is the United States approved name). GHB is a short chain fatty acid that can be considered both an endogenous metabolite and a precursor of the neurotransmitter γ-aminobutyric acid (GABA). GHB acts in the central nervous system as a neuromodulator. GHB can be formed in human peripheral tissues from two precursors, γ-butyrolactone and 1,4-butanediol.[1] GHB is marketed in the United States with the name of Xyrem® (Jazz Pharmaceuticals, Palo Alto, CA) for the treatment of cataplexy in patients with narcolepsy,[2] and in some European countries as an anesthetic agent and for the treatment of alcohol withdrawal (e.g., Alcover®; CT Laboratorio Farmaceutico, SRL, San Remo, Italy). On the other hand, GHB is a recreational drug commonly consumed at nightclubs and "raves" in conjunction with alcohol, cannabis and drugs, such as 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), or ketamine, also known as "club drugs."[3] In humans, γ-butyrolactone and 1,4-butanediol have also been abused. During the last years, GHB has become a major concern in emergency rooms of some countries due to an important increase in the number of cases of intoxications.[4–6] GHB has also been used for narcotizing victims in drug-facilitated sexual assaults because its capacity to induce short-term antegrade amnesia, increased libido, and suggestibility.[7,8] Recreational users of GHB experience euphoria, relaxation, reduction of social inhibitions, decreased motor skills, and other effects similar to those reported for a moderate alcohol intoxication.[9] These effects can explain its abuse liability in humans, but this aspect has not been yet characterized under controlled administration. After GHB ingestion, a mild intoxication may be observed with nausea, dizziness, and difficulty in focusing the eyes.[10] Acute severe intoxications have been reported, where individuals may experience vomiting, extreme dizziness, disorientation, amnesia, and unconsciousness[4–6,11] that may evolve to convulsions, deep coma, and rarely death.[12] The range between high recreational doses and overdose is narrow; and acute intoxications are quite common in humans.

GHB has been detected in blood and urine of subjects after acute intoxications and in the context of clinical trials.[13–16] Results from these reports indicate that GHB is eliminated from the body very rapidly; being detection

dependent on the time elapsed between consumption and sample collection. Because GHB is an endogenous compound, there are measurable baseline concentrations in blood and urine.[17–20]

The range of GHB doses typically abused by subjects range between 2 and 6 g (25–75 mg/kg). Most reports available are focused on the pharmacokinetic of GHB in humans.[15–17,21–23] Nevertheless, little is known on the physiological and subjective effects and alterations in psychomotor performance induced by this drug in the range of doses commonly abused. In addition, despite its therapeutic uses and the increasing concern about the toxicity of GHB, few studies addressed dose-related effects under controlled administration and the correlation of drug effects and concentrations in biological fluids.

The aims of this article were as follows: (*a*) to select appropriate doses for a series of GHB clinical pharmacology studies (interval: lowest dose with noticeable effects and doses that lead to significant somnolence); (*b*) to describe time course of physiological, subjective variables, and psychomotor performance following drug administration; (*c*) to investigate the presence and the time course of GHB in plasma and urine; and (*d*) to assess the eventual correlation between GHB pharmacokinetics and drug effects in a range of doses compatible with those usually consumed by recreational users.[24]

MATERIALS AND METHODS

Human Subjects

Eight male subjects were recruited by ''word of mouth'' and included in the study. Eligibility criteria required the recreational use of GHB on at least five occasions. Exclusion criteria included daily consumption of more than 20 cigarettes and more than 30 g of ethanol (3 units per day). All subjects gave their written informed consent before inclusion and were economically compensated for inconveniences caused by their participation in the study. The study was conducted in accordance with the Declaration of Helsinki, approved by the local Ethical Committee (CEIC-IMAS), and authorized by the Spanish Ministry of Health (Agencia Española del Medicamento). Eligible subjects were interviewed by a psychiatrist (structured clinical interview for Diagnostic and Statistical Manual version N [DSM-IV-TR] in order to exclude psychiatric disorders, including schizophrenia, psychosis, and major affective disorders. Each participant underwent a general physical examination, routine laboratory tests, urinalysis, and a 12-lead electrocardiogram. The participants had a mean age of 28.1 years (range 25–32), mean weight of 71.9 kg (range 60.5–84.2), and mean height of 179.1 cm (range 167.5–194.0). Participants were non-smokers ($n = 7$) except for one, and their average consumption of alcohol was 9 units per week. All of them had previous experience with the consumption of alcohol, cannabis,

sedatives, stimulants, and "club drugs," with at least five previous consumptions of GHB. None had history of abuse or drug dependence according to DSM-IV criteria (except for nicotine dependence), nor had experienced any medical or psychiatric adverse reaction following GHB consumption.

Study Design

This study is a preliminary phase of a series of clinical trials of GHB administration in humans. As a pilot pharmacology phase I study, increasing doses of GHB were given. The study design was double-blind, randomized, crossover, and controlled. Subjects participated as outpatients in two different randomly assigned 6-h study sessions with a washout period of 7 days, in which they were given single doses of 40 (33.1), 50 (41.4), 60 (49.7), and 72 (60.1) mg/kg of sodium (GHB) or placebo by the oral route. Participants and evaluators (two physicians) were blind to treatments although they were told that GHB or placebo would be given during the sessions. Thus, in a dose escalation schedule, two different doses of sodium GHB were given to every subject (40 mg/kg dose was given in four occasions, 50 mg/kg given in four occasions, 60 mg/kg given in five occasions, 72 mg/kg given in two occasions, and placebo given in one occasion). Participants were requested to abstain from consumption of any drug of abuse during the study period and urine drug testing was performed before each study session for cannabinoids, cocaine, opiates, amphetamine/methamphetamine, barbiturates, benzodiazepines, and phencyclidine. For all groups of substances, participants tested negative before each experimental session. In each session, subjects arrived at the laboratory at 8 AM after an overnight fast and had an indwelling intravenous catheter inserted into a subcutaneous vein in the forearm of the non-dominant arm. Thereafter, they remained seated in a quiet room throughout the session. GHB (Alcover OS® sodium GHB, 17.5% syrup, CT Laboratorio Farmaceutico) or matched placebo (syrup, CT Laboratorio Farmaceutico) were orally administered around 9:00 AM in a fasting state. The different doses corresponding to appropriate volumes of syrup and placebo were diluted to 250 mL of a soda orange-based drink. Participants were told to drink the beverage as soon as possible (mean of 10.2 s; range: 5–20 s). Placebo consisted of syrup diluted to the same 250 mL of a soda orange-based drink.

Collection of Blood and Urine Samples

Blood was collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, and 6 h after GHB administration in heparinized tubes and immediately centrifuged. Urine samples were collected before, and at 0–3 and 3–6 h after drug administration. All biological specimens were frozen at -20°C until analysis. No preservatives were added to the specimens.

Determination of GHB Concentrations in Biological Fluids

Frozen, plasma, and urine samples were allowed to thaw at room temperature. Aliquots of 100 μL plasma and urine were added with 5 μg (5 μL of the 1 mg/mL methanolic solution) of GHB hexadeuterated analoge, GHB-d_6 as internal standard, and 200 μL of acetonitrile. After 30-s vortex and 5-min centrifugation at 1400 rpm, 150 μL of the organic phase were transferred to a clean extraction tube and evaporated to dryness. The dried extracts were derivatized with 50 μL of BSTFA-1% TMCS for 30 min at 70°C.

A 1-μL aliquot of derivatized samples was injected onto a Hewlett-Packard (HP) 6890 gas chromatograph coupled to a HP5973 quadrupole mass spectrometer (Agilent, Palo Alto, CA, USA). The capillary column was a cross-linked 5% phenyl-methylsilicone (12 m × 0.2 mm i.d. and 0.33-μm film thickness, Ultra-2, Agilent). The samples were injected in split-less mode and helium gas was used as carrier at a flow rate of 1.2 mL/min (measured at 180°C). The injector and detector temperatures were both maintained at 280°C, respectively. The temperature program was initially set at 60°C for 2 min and increased to 180°C at 20°C/min, then 35°C to 250°C, and then held for 4 min, being the total run time 14 min. The mass spectrometer was operated in the electron impact ionization and selected ion monitoring (SIM) acquisition mode and the following ions were monitored (underlined ions used for quantification): GHB-bis-TMS: m/z 233, 204, 117; GHB-d_6-bis-TMS: m/z 239. Under these analytical conditions, the limit of quantification (LOQ) was 0.5 μg/mL and the intra-day precision and accuracy were always better than 4.2% and 13.4%. Similarly, inter-day precision and accuracy were lower than 13.4% and 12.1% at the GHB LOQ.

PHARMACOLOGICAL EFFECTS

Physiological Measures

Non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, oral temperature, and pupil diameter were recorded at −15 min and immediately before drug administration (time 0, baseline) and at 0.25, 0.50, 0.75, 1, 1.50, 2, 3, 4, 5, and 6 h after GHB administration using a DinamapTM 8100-T vital signs monitor (Critikon, Tampa, FL). Pupil diameter was recorded with a Haab pupil gauge.[25]

Psychomotor Performance Measures

The psychomotor performance battery included the digit symbol substitution test (DSST), the Maddox-wing device, and the balance task. This battery has

been used previously in the evaluation of psychostimulants and sedatives.[26,27] The DSST is a subtest of the Wechsler Adult Intelligence Scale-Revised.[28] A computerized version was used and scores were based on the number of correct patterns keyed in 90 s (correct responses). The Maddox-wing device measures the balance of extraocular muscles and quantifies exophoria, as an indicator of extraocular musculature relaxes, and esophoria. Results were expressed in diopters along the horizontal scale of the device.[29] The Balance Task assessed the participant's ability to stand upright for a maximum of 30 s on each foot.[30] The score was the total number of seconds the participant was able to balance (maximum of 60 s). The DSST and balance task were performed at −15 min and immediately before drug administration (time 0, baseline) and at 0.50, 1, 1.50, 2, 3, 4, and 6 h after drug administration. Measurements with the Maddox-wing device were performed at −15 min and at 0.25, 0.50, 0.75, 1, 1.50, 2, 3, 4, 5, and 6 h after drug administration.

Subjective Effects Rating Scales

Subjective effects were measured using the Addiction Research Center Inventory (ARCI), the VESSPA (Evaluation of the Subjective Effects of Substances with Potential of Abuse) questionnaire, and a set of 13 different visual analog scales (VAS). ARCI is a true–false questionnaire with empirically derived scales that are sensitive to the effects of a variety of classes of drugs of abuse.[31] The Spanish validated version of a 49-item short form of ARCI was used.[32] The questionnaire included five scales: PCAG (pentobarbital-chlorpromazine-alcohol group, a measure of sedation); MBG (morphine-benzedrine group, a measure of euphoria); LSD (lysergic acid diethylamide group, a measure of dysphoria and somatic symptoms); BG (benzedrine group, a stimulant scale consisting mainly of items relating to intellectual efficiency and energy); and A (amphetamine, an empirically derived scale sensitive to the effects of D-amphetamine). ARCI was administered at −15 min (immediately before drug administration), and at 0.50, 1, 1.50, 2, 3, 4, 5, and 6 h after GHB administration. VESSPA (evaluation of the subjective effects of substances with potential of abuse) is an in-house developed and validated questionnaire specifically created to measure changes in subjective variables caused by MDMA.[33] It contains six scales: sedation (SED), psychosomatic anxiety (ANX), changes in perception (PER), pleasure and sociability (SOC), activity and energy (ACT), and psychotic symptoms (PSY). Each scale consists of six questions with a five-point Likert response (0 to 4 depending on the intensity of the effect). VESSPA scales were administered at −15 min (before drug administration), and at 1, 2, 3, 4, and 6 h after GHB administration.

A total of 13 VAS (100 mm) labeled with different adjectives marked at opposite ends with "not at all" and "extremely" were used. Subjects were asked to rate effects of "stimulated," "high", "any effect," "good effects,"

"bad effects," "liking," "content," "drunkenness," "drowsiness," "dizziness," "confusion," "depression or sadness," and "relax." Scales were administered at −15 min (immediately before drug administration), 0.25, 0.50, 0.75, 1, 1.50, 2, 3, 4, 5, and 6 h after GHB administration.

Pharmacodynamic and Pharmacokinetics Parameters

The following parameters were determined from GHB plasma concentrations over time: peak concentration (C_{max}), time to reach peak concentrations (t_{max}), area under the concentration-time curve from 0 to 6 h ($AUC_{0–6}$), elimination half-life ($t_{1/2}$), and elimination constant (Ke). Taking into account the duration of GHB physiological and subjective effects, area under the effects-time curve from 0 to 2 h ($AUC_{0–2}$), and maximal effect (E_{max}) were also determined. AUCs were calculated by the linear trapezoidal rule.

Pharmacokinetic parameters were obtained with use of specific functions of computer program (PK Functions for Microsoft Excel, Microsoft Corporation, USA).

Data Analysis: Statistical Methods

Data are represented as mean ± standard deviation (SD) or median. The nonparametric Kruskal–Wallis test was applied to compare the distributions of $AUC_{0–6}$ and C_{max} values (pharmacokinetics) and $AUC_{0–2}$ and E_{max} values (pharmacodynamics) between the different sodium GHB doses assayed without assuming any parametric form of these distributions. The Kruskal–Wallis test was applied to test the null hypothesis, which assumes equal distribution functions versus the alternative that, at least, two distributions differ with respect to the median. Since the power of the test was low because of only two observations in the GHB dose group of 72 mg/kg, posterior comparisons of GHB doses groups of 40 and 60 mg/kg were also carried out. In this latter case, the Wilcoxon Mann-Whitney test was applied. Given the small sample sizes, tests were carried out using the add-on module SPSS Exact of the statistical software package SPSS, version 12.0 (SPSS Inc., Chicago, IL).

RESULTS

A summary of results for pharmacological effects and pharmacokinetics showing statistical significant differences between treatments is presented in TABLE 1.

Pharmacological Effects

Time course of several GHB pharmacological dose-related effects in humans are presented in FIGURES 1 (physiological effects and Maddox wing),

TABLE 1. Variables showing statistically significant differences between treatments. Mean, minimum, maximum values for the four doses tested and comparisons performed

		40 mg/kg ($n = 4$)		50 mg/kg ($n = 5$)		60 mg/kg ($n = 4$)		72 mg/kg ($n = 2$)		
	Criteria	Mean	Median	Mean	Median	Mean	Median	Mean	All	40 and 60
GHB Plasma concentrations	AUC_{0-6h}	106.5	108.5	143.7	133.9	183.9	185.8	301.1	0.004	0.029
Pupil diameter	AUC_{0-2h}	1.2	1.2	.65	.69	.22	.13	1.4	0.014	
VAS any effect	AUC_{0-2h}	14.2	12.2	46.1	40.9	61.8	57.1	67.2		0.029
VAS drunkenness	AUC_{0-2h}	3.7	3.6	33.6	21.9	49.7	38.8	33.1		0.029
VAS good effects	AUC_{0-2h}	13.4	11.7	45.6	48.6	60.2	58.1	64.8		0.029
VAS high	AUC_{0-2h}	15.3	14.4	47.5	49.1	59.4	55.4	65.2		0.029
VAS content	AUC_{0-2h}	13.9	11.8	39.5	13.4	53.3	53.5	23.1		0.029
VAS stimulated	AUC_{0-2h}	7.2	6.4	34.3	16.6	53.3	57.4	68.1	0.040	0.029
	E_{max}	10.2	10.5	30.4	33.0	43.2	46.5	61.5	0.020	0.029
VAS liking	AUC_{0-2h}	14.1	12.6	44.6	47.1	54.2	54.2	58.9		0.029
VAS bad effects	AUC_{0-2h}	0.7	0.6	15.1	0.0	30.2	27.9	16.9		0.029
	E_{max}	1.7	1.5	15.4	0.0	33.2	29.0	20.0		0.029
VAS dizziness	AUC_{0-2h}	7.8	5.4	34.4	19.9	67.3	68.2	56.6		0.029
	E_{max}	10.0	9.5	32.6	32.0	63.0	67.0	62.0	0.049	0.029
VAS relax	AUC_{0-2h}	7.3	3.4	29.8	9.1	59.3	57.1	19.4		0.029
	E_{max}	7.7	5.5	25.6	15.0	49.2	48.0	9.7		0.029
ARCI A	E_{max}	1.7	2.0	3.6	4.0	4.0	3.5	2.0	0.048	0.029

[a] P values < 0.05.

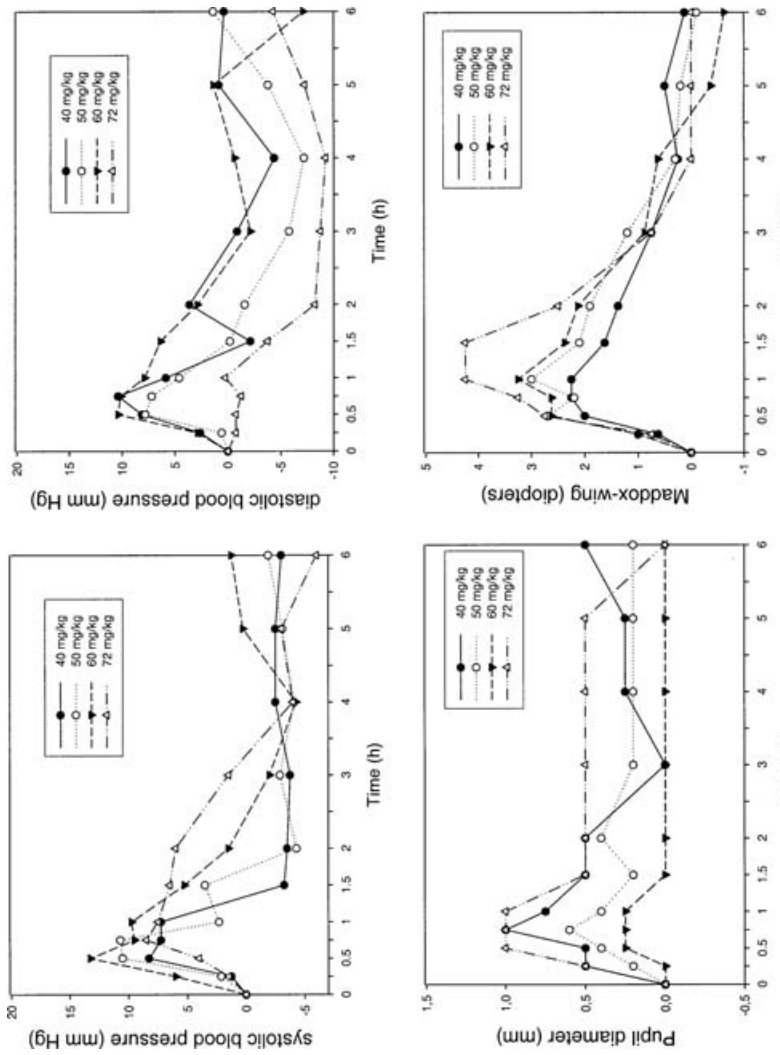

FIGURE 1. Time course of GHB dose-related physiological effects (mean values) in humans (SBP, DBP, pupil diameter, and Maddox wing).

2 (subjective effects: VAS), and 3 (subjective effects: ARCI and VESSPA and DSST performance).

Physiological Effects

GHB produced a slight increase in systolic and diastolic blood pressure for all doses tested, with a peak effect between 30 and 45 min and a return to previous values at 3 h after GHB administration, without reaching statistical significance between different doses (FIG. 1). No apparent changes in heart rate or oral temperature were observed. GHB produced a significant (AUC 0–2 h comparison) dose-related pupil diameter increase from 0.5 mm to 1 mm between 30 min and 1-h post-administration.

Subjective Effects and Psychomotor Performance

GHB administration produced dose-related changes in subjective effects as measured by questionnaires and VAS. GHB showed a mixed sedative-stimulant pattern mediating both types of effects (see FIGS. 2 and 3). GHB produced marked stimulant-like effects as measured by VAS "stimulated," ARCI A, and VESSPA activity and energy (ACT) scale. GHB produced euphoria as measured by VAS "high," "liking," and "good effects," ARCI MBG questionnaire and VESSPA pleasure and sociability (SOC) scale. Most stimulant-like effects and euphoria were dose dependent (see TABLE 1) and peaked at 45 min post-drug administration.

GHB produced objective and subjective sedation effects as reflected in VAS "drowsiness," "dizziness," and "drunkenness" scores, ARCI PCAG questionnaire and VESSPA sedation (SED) scale. Peak effects were achieved between 1 and 1.5 h after drug administration and lasted for 3 h. GHB also produced a slight deterioration of psychomotor performance apparently dose dependent with a peak effect at 30 min after administration for lower doses and at 1.5 h post-administration for the 72 mg/kg dose. GHB produced a decrease in DSST total responses (FIG. 3) ranging from -5 to -11 total responses for the E_{max} values, and in DSST correct responses, ranging from 0 to -2.75 for the E_{max} values, while there was an increase in DSST errors at the same time. Doses of 60 and 72 mg/kg were associated with an impairment of the balance task with a peak effect at 1 h post-administration ranging from -15 s to -19 s decrease for the E_{max} values from a maximum of 60 s standing on both feet. At all administered doses, GHB induced exophoria, a typical effect for sedatives, as measured by the Maddox-wing device. Thus, GHB produced an apparent dose-dependent increase in diopters with a peak effect at 1 h post-administration (E_{max} 2.25 40 mg/kg, 2.7 50 mg/kg, and 3.25 60 mg/kg), that lasted 4 h post-administration (see FIG. 1).

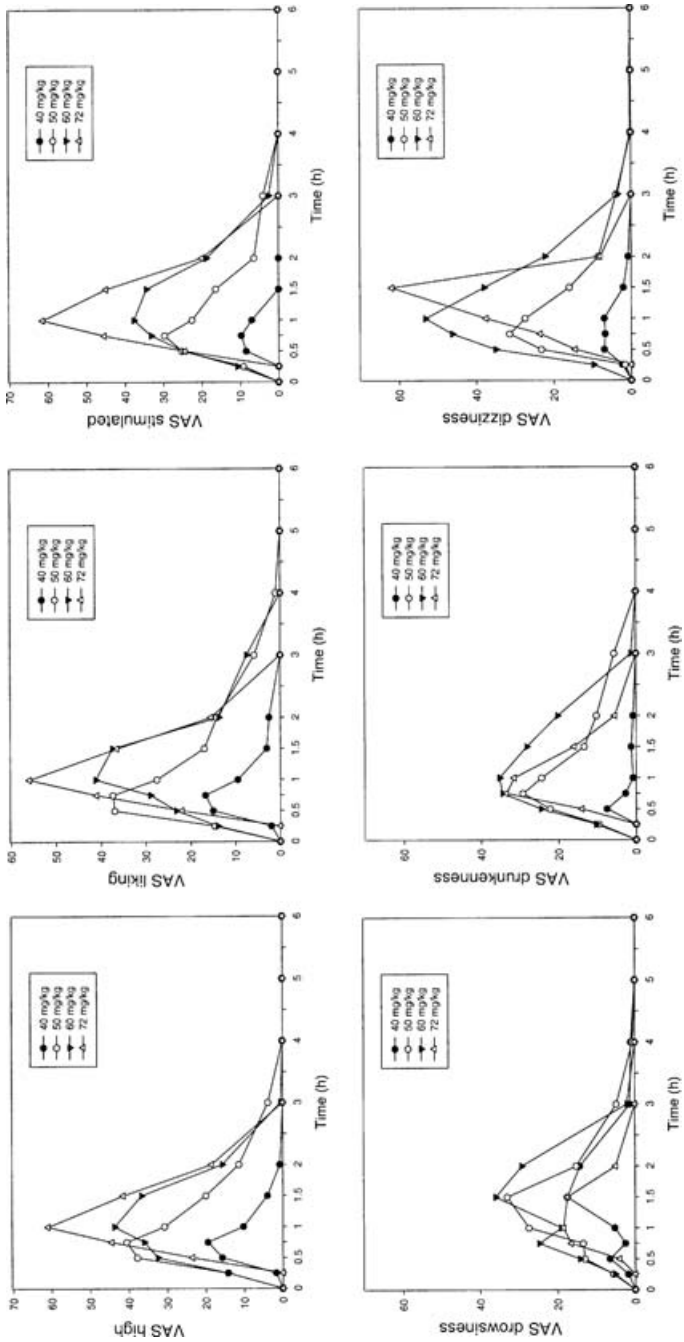

FIGURE 2. Time course of GHB dose-related subjective effects (VAS).

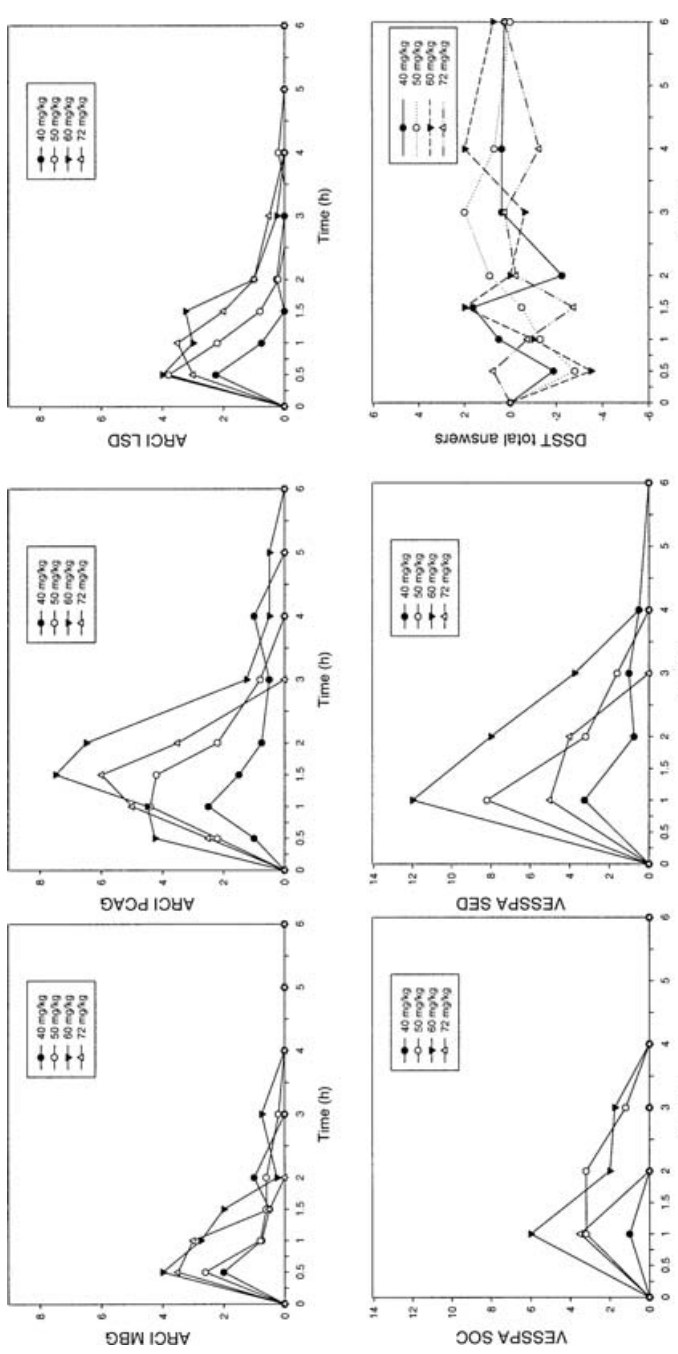

FIGURE 3. Time course of GHB dose-related subjective effects (ARCI and VESSPA questionnaires) and psychomotor performance (DSST total responses).

TABLE 2. Pharmacokinetic parameters of GHB in plasma (mean ± SD values given)

Parameter	40 mg/kg[a]	50 mg/kg[a]	60 mg/kg[a]	72 mg/kg[a]
C_{max} (μg/mL)	79.1 ± 26.4	83.1 ± 28.8	113.5 ± 20.1	130.1 ± 10.7
t_{max} (h)	0.7 ± 0.2	0.6 ± 0.1	0.6 ± 0.14	0.9 ± 0.2
AUC_{0-6} (μg/mL h)	106.5 ± 6.7	143.7 ± 36.4	183.9 ± 47.0	301.1 ± 11.4
K_e (h^{-1})	0.98 ± 0.21	1.01 ± 0.18	1.06 ± 0.18	1.23 ± 0.11
$t_{1/2}$ (h)	0.73 ± 0.17	0.71 ± 0.15	0.67 ± 0.12	0.57 ± 0.05

[a]Sodium GHB doses.

None of the participants required specific therapy or special care during the study. Serious adverse events were not observed, although one subject vomited 1 h after the administration of the 60 mg/kg dose. No hallucinations, psychotic episodes, or any other psychiatric symptoms were observed during the experimental sessions.

Concentration-Time Profiles of GHB in Plasma

Pharmacokinetic parameters of GHB in plasma after oral doses of 40, 50, 60, and 72 mg/kg of sodium GHB are presented in TABLE 2.

GHB was detected in all baseline plasma samples, with mean concentrations of 0.04 ± 0.01 μg/mL. After drug administration, concentrations peaked between 30 and 60 min after drug administration (C_{max} range: 45.8–109.3 μg/mL for 40 mg/kg; 51.0 – 123.5 μg/mL for 50 mg/kg, 90.3 – 134.7 for 60 mg/kg, and 122.5 – 137.6 for 72 mg/kg) (TABLE 2). Following the absorption phase, concentrations declined to a mean values at 6 h that ranged from 0.5 to 0.9 mg/mL for all doses tested.[13,34] GHB was readily absorbed after oral administration and rapidly eliminated (t_{max} and $t_{1/2} < 1$ h). AUC_{0-6h} derived from plasma GHB concentrations were significantly different upon comparing the four different doses ($P < 0.05$) (TABLE 1). No significant differences were observed for C_{max}, t_{max}, Ke, and $t_{1/2}$ between different drug doses. Normalized (1 mg/kg) values for AUC were similar for 40, 50, and 60 mg/kg doses (2.7, 2.9, and 3.1). For the 72 mg/kg dose, this value was higher (4.2). Normalized C_{max}, values were similar for all doses tested.

Excretion of GHB in Urine

A summary of GHB urinary excretion is shown in TABLE 3. GHB was detected in urine at baseline samples, with mean concentrations of 0.21 ± 0.14 μg/mL. The highest GHB recovery was found in the 0–3 h urine samples. Less than 2% of doses tested were recovered in urine for the 0–6 h collection period.

TABLE 3. Urinary excretion of GHB following different oral doses

		Urinary collection period		
Dose[a] mg/kg	Mean dose given (g)	0–3 h	3–6 h	0–6 h
40	2.9 ± 0.4	305.8 ± 121.4[b]	125.3 ± 214.4[b]	431.2 ± 202.4 (1.60%)[c]
50	3.7 ± 0.3	593.1 ± 297.9[b]	113.2 ± 155.0[b]	706.3 ± 433.8 (1.98%)[c]
60	3.9 ± 0.4	440.1 ± 114.1[b]	104.9 ± 118.6[b]	545.0 ± 106.8 (1.50%)[c]
72	5.2 ± 1.2	821.8 ± 149.8[b]	96.9 ± 33.3[b]	918.7 ± 116.5 (1.90%)[c]

[a]As sodium GHB.
[b]Mean ± SD, values given in micromoles.
[c]Recoveries (0–6 h) as a percentage of the administered dose.

DISCUSSION

Results of the study provide new insights on GHB pharmacodynamics and pharmacokinetics in humans. To our knowledge, there are no previous reports of the evaluation of GHB physiological and subjective effects after controlled administration of doses compatible with those consumed by recreational users. The main finding of the study is that GHB-mediated physiological and subjective effects are dose dependent and related to GHB plasma concentrations.

Our study, although somehow limited by both a dose escalation schedule design and the number of volunteers tested, provides new knowledge about its induced subjective effects and alterations of psychomotor performance. GHB produced dose-related changes in subjective effects as measured by specific questionnaires and VAS. GHB showed a mixed stimulant-sedative pattern with a biphasic time profile as described for other sedatives (alcohol or cannabis).[35,36] Psychostimulant effects were predominant in the first hour while sedative effects initiate more slowly and predominate in the second hour after drug administration. In reference to its abuse liability, GHB induced euphoria, well being, pleasurable effects, and liking effects that are on the basis of its misuse as recreational drug and similar to those reported by GHB abusers.[9,37] In the case of the sedative effects, they were similar to those elicited by low doses of benzodiazepines and alcohol[26,27] and included subjective feelings of sedation, a decrease in psychomotor performance, ataxia, and exophoria.

Regarding physiological effects, GHB administration produced a constant slight increment in SBP and DBP for all doses tested, lasting for 1–2 h post-administration that did not reached statistical significance when comparing doses assayed. Interestingly, this effect was not reported in none of the therapeutic studies previously performed. Furthermore, following GHB intoxication hypotension is frequently reported.[10] However, recent results suggest that GHB has also sympathomimetic cardiovascular effects that could induce increases

in blood pressure following its acute administratrion.[38] Further studies with a larger population of subjects are needed to confirm these findings.

GHB given by the oral route is rapidly absorbed and eliminated. Drug consumption can be differentiated from GHB endogenous concentrations both in plasma and urine in a time-window of 6 h post-ingestion. Our results are in agreement with those obtained in healthy subjects administered with 4.5 g of oxybate[13] (equivalent to 50–60 mg/kg of GHB) and lower to those observed in severe acute intoxications.[39] GHB elimination follows a nonlinear process as suggested by comparison of normalized AUCs. In the dose range of 40–60 mg/kg, elimination is linear in agreement with previous reports,[13,17] although nonlinearity can be observed at the 72 mg/kg dose. GHB elimination appears to be capacity-limited at higher doses as it has been observed in some narcoleptic patients administered at a fixed dose of 3 g twice nightly at a 4-h interval.[23] The accumulation of GHB in the body as a result of a nonlinear disposition of GHB might have some implications in the susceptibility of some subjects to develop acute intoxications.

GHB urinary excretion was mainly related to administered doses and in accordance with previous reports.[13,16,40] However, there was a slightly higher recovery of GHB for the 50 mg/kg dose than for 60 mg/kg dose. Higher mean weights of the subjects (resulting in similar total mean dose given), and an increased percentage of the administered dose recovery in the 50 mg/kg dose group, account for these results. In line with early reports, less than 2% of doses administered were recovered in the collection period.

Plasma concentrations reached in the range of doses administered are lower than that observed in acute intoxications and therefore is not surprising that, in our study, strong sedation or coma were not observed.[39] GHB plasma concentrations correlated better with psychostimulant-like effects rather than with sedative ones. At higher doses, sedative effects would predominate leading to the observed effects in acute intoxications. Our results suggest a high abuse liability of GHB in the range of doses usually abused. Further studies are needed to confirm these results.

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