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Cognitive, psychomotor, and subjective effects of sodium oxybate and triazolam in healthy volunteers

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Abstract

Rationale—Illicit gamma-hydroxybutyrate (GHB) has received attention as a “date rape drug” that produces robust amnesia; however, there is little experimental evidence in support of GHB’s amnestic effects.

Objectives—This study compared the cognitive effects of GHB (sodium oxybate) with those of triazolam in healthy volunteers.

Materials and methods—Doses of sodium oxybate (1.125, 2.25, and 4.5 g/70 kg), triazolam (0.125, 0.25, and 0.5 mg/70 kg), and placebo were administered to 15 volunteers under repeated measures, counterbalanced, double-blind, double-dummy conditions. The time course and peak physiological, psychomotor, subjective, and cognitive effects were examined.

Results—Sodium oxybate and triazolam produced similar increases in participant ratings of drug effects. Performance on psychomotor, working memory, and episodic memory tasks was impaired to a greater extent after triazolam than sodium oxybate.

Conclusions—Together, these data suggest that sodium oxybate produces less psychomotor and cognitive impairment than triazolam at doses that produce equivalent participant-rated subjective effects in healthy volunteers.

Keywords

GHB; Xyrem; Human; Memory; Amnesia; Sexual assault

Introduction

Illicit gamma-hydroxybutyrate (GHB) is often referred to as “the date rape drug” for its purported involvement in drug-facilitated sexual assaults (Smith 1999; O’Connell et al. 2000; Schwartz et al. 2000). It has been suggested that the common illicit formulation of GHB as a colorless odorless liquid facilitates the unsuspected addition of GHB to the drinks of individuals in bars and clubs (Smith 1999; Schwartz et al. 2000; Varela et al. 2004). Several pharmacological effects of GHB such as sedation, euphoria, decreased inhibitions, enhanced sex drive, and anterograde amnesia have been cited as effects that would lend illicit GHB for use in drug-facilitated sexual assault (Smith 1999; O’Connell et al. 2000; Varela et al. 2004). However, there is evidence that despite its reputation, illicit GHB is involved in a relatively small percentage (1–5%) of cases involving drug-facilitated sexual assault (ElSohly and Salamone 1999; Varela et al. 2004; Association of Chief Police Officers 2006).

There are a few reviews and case reports in the scientific literature that suggest that acute doses of illicit GHB produce anterograde amnesia (i.e., a deficit in the ability to remember new information) in humans (Smith 1999; Schwartz et al. 2000; Varela et al. 2004); however, there have been few experimental studies that have examined the effects of GHB on learning and memory. Three studies have reported that repeated administration of GHB to rats impaired spatial learning and memory (Sircar and Basak 2004; García et al. 2006; Kueh et al. 2008). Other studies have shown that acute doses of GHB did not impair working memory or cognitive (Go/No-go) task performance in rats and rhesus monkeys, respectively (Nakamura et al. 1987; Laraway et al. 2007).

GHB has been developed as a therapeutic for the sleep disorder narcolepsy under the non-proprietary drug name sodium oxybate (trade name Xyrem®). Thus, GHB/sodium oxybate has been studied extensively in clinical trials for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy (Xyrem Prescribing Information 2009). Experimental studies in humans that have examined the effects of sodium oxybate on cognitive processes have typically not studied a broad range of doses of sodium oxybate (e.g., Grove-White and Kelman 1971a, b; Mattila et al. 1978; Ferrara et al. 1999; Abanades et al. 2007), not studied large doses of sodium oxybate (e.g., Grove-White and Kelman 1971a, b; Mattila et al. 1978; Ferrara et al. 1999), or have not studied the effects of sodium oxybate on episodic memory (i.e., memory for a personally experienced event, associated with a specific spatial and temporal context, e.g., Grove-White and Kelman 1971a; Mattila et al. 1978; Ferrara et al. 1999; Abanades et al. 2006, 2007). However, there are some data that sodium oxybate can impair working memory (i.e., short-term memory that enables the temporary maintenance and on-line manipulation of information in the service of behavioral goals, e.g., Grove-White and Kelman 1971b) and episodic memory encoding processes (i.e., processes that are engaged during an event and lead to the creation of a representation or trace of the event) in humans (e.g., Carter et al. 2006).

In a previous study in this laboratory (Carter et al. 2006), the effects of sodium oxybate (Xyrem) on working memory and episodic memory were studied in 14 volunteers with histories of sedative drug abuse. In that study, sodium oxybate significantly decreased the number of words recalled in a free recall test that assessed episodic memory; however, the effects of sodium oxybate on all working memory and episodic memory measures were significantly less than those of comparable doses of the benzodiazepine triazolam and the barbiturate pentobarbital (Carter et al. 2006). There were also several limitations to the Carter et al. (2006) study, including the evaluation of cognitive effects in a drug-abusing population, which might not accurately reflect the effects of sodium oxybate in a population that does not abuse drugs, the relatively low performance of the participants on the cognitive tasks under placebo conditions, and the inability to assess the cognitive effects of the largest dose of sodium oxybate that was

studied due to the marked behavioral impairment that occurred at that dose (8 g/70 kg sodium oxybate).

Thus, the primary purpose of this study was to examine the effects of a range of doses of sodium oxybate that produced subjective drug effects, but not marked sedation or behavioral impairment that would interfere with cognitive task performance, on several different measures of working memory and episodic memory in healthy individuals without a history of drug abuse. Another aim was to compare the effects of sodium oxybate to those of triazolam, a drug that is known to produce robust anterograde amnesia (Mintzer and Griffiths 2002; Carter et al. 2006), across doses of the two drugs that resulted in similar behavioral and/or subjective effects. Doses were chosen on the basis of a previous study in drug abusers (Carter et al. 2006) to be comparable with respect to participant-rated drug effect. Lower doses of both drugs were tested because the participants in this study were less experienced with strong drug effects than the participants in the previous study who had histories of drug abuse. However, we hypothesized that, as observed in the previous study, the amnestic effects of sodium oxybate would be less than those of triazolam in this study of participants without histories of drug abuse. In addition to specific memory tasks, several psychomotor and subjective measures were also included to provide information about the effects of sodium oxybate on memory versus non-memory measures and to more fully characterize the overall profile and time course of the effects of sodium oxybate in healthy individuals without a history of drug abuse.

Materials and methods

Participants

Fifteen adult volunteers (ten males) completed this study. Participants ranged in age from 19 to 46 years (median 23 years) and in weight from 52 to 82 kg (median 68 kg). Nine participants were Caucasian, four were Asian, and two were African-American. Participants reported having completed 12 to 20 years of education (median 16 years). Thirteen participants reported consuming one to nine alcoholic beverages per week (median three alcoholic beverages/week for all participants); one participant reported infrequent use of marijuana. Fourteen participants reported consuming 4 to 500 mg caffeine per day (median 150 mg caffeine per day for all participants). Two participants reported smoking cigarettes regularly, but reported smoking less than a pack (20 cigarettes) per day and being comfortable with not being allowed to smoke for the duration of the experimental sessions.

Volunteers were excluded from participating in the study if they reported having a history of: drug or alcohol dependence; a significant psychiatric condition (e.g., schizophrenia or bipolar); a chronic medical problem (e.g., diabetes or heart disease); seizures; sleep apnea; or a hypersensitivity, allergy, or other contraindication to sedatives or anesthetics. Female volunteers who reported to be nursing or had a positive urine pregnancy test were also excluded. The Johns Hopkins University School of Medicine Institutional Review Board approved this study. Participants gave their written informed consent before beginning the study and were paid for their participation.

Drugs

Triazolam (Pharmacia Corp./Pfizer Inc., Kalamazoo, MI, USA) and lactose monohydrate (placebo; Amend Drug and Chemical Company, Irvington, NJ, USA) were orally administered in opaque capsules. Sodium oxybate (500 mg/ml sodium oxybate solution) and sodium oxybate placebo [an equimolar sodium citrate (389 mg/ml) solution matched for pH] were orally administered as solutions (Jazz Pharmaceuticals, Palo Alto, CA, USA). The dose of sodium oxybate was adjusted by varying the volume of sodium oxybate in the administered solutions; however, the combined volume of sodium oxybate and sodium citrate was always 15 ml to

keep the sodium concentration constant. The total volume of the sodium oxybate and sodium oxybate placebo solutions that was administered was 500 ml and was prepared by diluting 15 ml of sodium oxybate and placebo, or placebo alone, with distilled/deionized water and fruit juice.

General procedures

Seven conditions (placebo; 1.125, 2.25, and 4.5 g/70 kg sodium oxybate oral solution; 0.125, 0.25, and 0.5 mg/70 kg triazolam in capsules) were studied during seven separate approximately 6-h outpatient experimental sessions at the Behavioral Pharmacology Research Unit using a double-blind, double-dummy, crossover design. The order of drug conditions across the seven sessions for the first 14 participants was determined by two Latin squares using the Williams method to achieve balance in presentation order and in the order of drug conditions relative to one another (Williams 1949); the 15th participant was randomly assigned to one of the previous 14 dose order conditions. Consecutive sessions were separated by at least 48 h. Participants were informed they could receive placebo, various sedatives, anxiolytics, stimulants, and weight loss medications during the study. Participants were told that the purpose of the study was to see how the performance on tasks testing skills like attention, memory, thinking, decision making, balance, and hand—eye coordination is affected by drugs.

Prior to the first session, participants practiced the experimental tasks to become familiar with them and to achieve a stable level of performance. Participants were told that on the morning of their experimental sessions, they should consume their usual amount of tobacco or caffeine and a low-fat breakfast before arriving at the laboratory. They were told to refrain from using any drugs other than non-prescription pain relievers, tobacco, and caffeinated products while enrolled in the study. On each session before drug administration, participants' urine was tested for the presence of cocaine, benzodiazepines, and opioids using an EMIT system (Syva Co., Palo Alto, CA, USA), and participants' expired air was tested for the presence of alcohol using a breathalyzer test. During each session, an oral solution (containing sodium oxybate or placebo) and a capsule (containing triazolam or placebo) was administered; data were collected before and after drug administration using several different procedures described below. Psychomotor performance, subjective effects, and working memory measures were assessed at 35, 110, and 230 min after administration of drug or placebo. Episodic memory measures were assessed as described below. All procedures performed on a computer utilized an Apple Macintosh microcomputer (Apple Computer, Cupertino, CA, USA).

Psychomotor performance measures

Balance—This task began with the participant raising one foot off of the floor with his or her eyes closed. The time that a participant remained on one foot without opening his or her eyes or touching the floor or another part of his or her body with the raised foot was measured for up to 30 s with each foot and summed across both feet (60 s total).

Circular lights—This is a hand—eye coordination task that has been previously described in detail (Mumford et al. 1995). The dependent measure was the number of correct presses (i.e., lights extinguished) in 60 s.

Digit symbol substitution task—This was a computer version of the digit symbol substitution task that has been previously described in detail (McLeod et al. 1982). The dependent measure was the number of correct patterns that were reproduced within 90 s.

Subjective effects measures

This questionnaire was based upon a previously described questionnaire in which participants were instructed to rate how they felt at present in response to 34 questions (e.g., “Do you feel sleepy?”) on a five-point scale (see Rush et al. 1999 for a list of all questions). The questionnaire was modified to also include the questions, “Do you feel alert?” and “Do you dislike the drug effect?” Instead of a five-point scale, participants were instructed to rate how they felt at the current time by using a computer mouse to make a perpendicular mark on each of 36 100-mm lines, which were presented sequentially and labeled, “no, not at all” and “yes, alot” at the left and right ends of the scale, respectively.

Working memory measures

The two working memory tasks are variants of the classic Sternberg task (Sternberg 1969) and were administered using procedures similar to those described by Mintzer and Griffiths (2007). During each experimental session, standardized instructions were read to the participants before each task (each block of the modified Sternberg manipulation task; see below), and practice trials were presented before the experimental trials to ensure that the participants understood and performed the tasks correctly.

Modified Sternberg maintenance task—A memory set consisting of seven randomly selected and randomly ordered consonant letters (e.g., ZHFKDXW) was presented on the screen followed by a probe consisting of a letter—digit pair (e.g., f—4), and participants were asked to decide whether the probed letter had appeared in the memory set in the ordinal position represented by the digit (e.g., 4=4th position in the memory set). Participants completed 36 trials consisting of 12 trials in each of the three conditions: non-memory control (i.e., the memory set remained on the screen during probe presentation), 0-s delay (between memory set and probe presentation), and 12-s delay. The order of presentation of trials from the three conditions was random and the probed digit represented the correct position of the probed letter on half of the trials. Dependent measures included the accuracy of the response (i.e., yes or no) and reaction time from the onset of the probe to a participant’s response (see Mintzer and Griffiths 2007 for further detail).

Modified Sternberg manipulation task—Effects on manipulation processes were tested by parametrically varying the number of separate sequencing steps performed (0, 1, 2). Participants were either asked to make a decision about the ordinal position of the probed letter in the memory set (as described above), to mentally alphabetize the letters prior to responding, or to mentally alphabetize the letters and mentally move the final letter in the alphabetized string to the beginning of the alphabetized string prior to responding. Maintenance requirements were held constant using a consistent delay (0 s) and memory set size (five stimuli) across trials. The order of three separate 15-trial blocks in each of the three conditions (position, alphabetize, alphabetize and rotate; a total of 45 trials) was counterbalanced across all participants (see Mintzer and Griffiths 2007 for further detail).

Episodic memory measures

Stimuli for these tasks were subsets of 36 concrete nouns equated on word length and frequency of use from the Thorndike and Lorge (1944) word corpus that the participants were asked to remember. During each session, participants studied two subsets of 36 words (i.e., word lists), which were presented serially with a stimulus duration of 2 s for each word, and participants were required to categorize each word as artificial (i.e., man-made) or natural. Participants were later presented with those words in addition to two other subsets of 36 words during the word recognition tasks (see below). One additional subset of 36 words was used for the source memory task (see below). Thus, participants were presented with sets of 180 words each session

and a total of 1,260 words across the seven sessions. The five subsets of 36 words within each set were counterbalanced across participants.

Free recall—One 36-word list was studied approximately 15 min before drug administration (list 1); participants' memory for these words (i.e., free recall) was tested during the period of anticipated peak drug effect (to measure the effect of triazolam and sodium oxybate on retrieval). A second 36-word list was studied approximately 100 min after drug administration (list 2) during the time of anticipated peak drug effect (to measure the effect of triazolam and sodium oxybate on encoding); participants' memory for the second list of words was tested approximately 210 min after drug administration after the effects of the drugs were anticipated to have dissipated. Free recall was assessed twice each session, once for each list approximately 100 min after that list was studied, by giving participants 5 min to write down all the words they could remember on a sheet of lined paper. The dependent measure was the number of correct words recalled (written down) within 5 min.

Recognition memory—Recognition memory was tested twice each session immediately following the test of free recall. Words from the study lists (36 "old" words) were randomly presented with words from a subset that had not been previously studied (36 "new" words). Words appeared one at a time on the computer screen, and participants indicated the degree to which they recognized (old) or did not recognize (new) the word using a six-point confidence scale (definitely old, probably old, maybe old, maybe new, probably new, definitely new). The dependent measures for each study list were the proportion of old words correctly identified as old (collapsed across definitely old, probably old, and maybe old; this is the hit rate), the proportion of new words incorrectly identified as old (collapsed across definitely old, probably old, and maybe old; this is the false alarm rate), and signal detection measures of sensitivity in distinguishing between old and new words (d') and response bias (C ; Snodgrass and Corwin 1988).

Metamemory was assessed by calculating the Goodman—Kruskal gamma correlation (a correlation between confidence and correctness in recognition; Goodman and Kruskal 1954) for the word recognition memory task. It is presumed that greater metamemory or awareness of the state of one's memory results in greater confidence in correct responses and lower confidence in incorrect responses. Gamma values can range from -1 (complete discordance between confidence ratings and recognition memory accuracy) to 1 (complete concordance between confidence ratings and recognition memory accuracy). The dependent measure is the gamma correlation from the word recognition task for list 1 and list 2.

Source memory—Once per experimental session [approximately 4.5 and 2.75 h after studying the first and second lists of words (list 1 and list 2), respectively], source memory was assessed. In the source memory task, words from list 1 and list 2 were randomly presented along with words from a third list of 36 words (36 "new" words) that had not been previously studied or used in the word recognition tasks (a total of 108 words were presented). Words appeared one at a time on the computer screen, and participants categorized the words as being from list 1, list 2, or "new." The dependent measures were the number of words correctly identified from each list (list 1, list 2, or new) and the proportion of words identified as old (i.e., from either list 1 or list 2) that were also correctly identified as being from list 1 or list 2 (i.e., list 1 items identified as list 1; list 2 items identified as list 2; conditional source memory).

Statistical analyses

Data were analyzed in an analysis of variance (ANOVA) model using PROC MIXED in SAS (SAS Institute Inc., Cary, NC, USA). Modified Bonferroni corrections were used if the number of simple effects tests exceeded the degrees of freedom. The mean $\pm$ standard error of the mean

(SEM) is presented throughout. Two sets of analyses were conducted, time course and dose effect analyses. Time course analyses examined the effects of measures assessed repeatedly after drug administration (i.e., psychomotor performance, subjective effects, and working memory). These analyses used two-factor repeated measures ANOVA with condition (placebo; 0.125, 0.25, and 0.5 mg/70 kg triazolam; 1.125, 2.25, and 4.5 g/70 kg sodium oxybate) and time (0, 35, 110, and 230 min after administration) as factors ($N=15$). When the interaction between condition and time was significant ($p \leq 0.05$), comparisons between placebo and the six active drug conditions at each post-drug time point were conducted using simple effects tests with Bonferroni corrections as appropriate (Keppel 1991). Dose effect analyses used one-factor repeated measures ANOVA with condition (placebo; 0.125, 0.25, and 0.5 mg/70 kg triazolam; 1.125, 2.25, and 4.5 g/70 kg sodium oxybate) as the factor. When the F statistic of the ANOVA was significant ($p \leq 0.05$), comparisons between placebo and the six active drug conditions, and between the two largest and the two moderate doses of triazolam and sodium oxybate, were conducted using simple effects tests with Bonferroni corrections as appropriate (Keppel 1991).

The analyzed data for the dose effect analyses included peak psychomotor measures, peak subjective effects ratings, peak working memory measures, and raw data from the episodic memory, metamemory, and source memory tasks that were administered at single time points during the experimental session. For the subjective effect ratings and working memory response time, peak effects for each participant were defined as the maximum value observed after drug administration. For the balance, circular lights, and working memory number correct, peak effects for each participant were defined as the minimum value observed after drug administration. For the working memory tasks, response time data were analyzed for correct responses only and median response times were used to minimize the influence of outliers. Analyses of data from the working memory tasks included an additional factor of delay or manipulation condition as appropriate. Analyses of data from the episodic memory and metamemory tasks included an additional factor of list.

Results

Time course of drug effects

Both drugs produced dose- and time-related behavioral and subjective effects. Figure 1 shows the time course of triazolam (left column) and sodium oxybate (right column) on participant ratings of drug effect, balance, and circular lights performance. In general, the maximal effects of both drugs occurred between the first two time points studied (35–110 min after administration). The onset of subjective effects was rapid (i.e., evident at 35 min; see Fig. 1, top panels) and was similar for both drugs, although the duration of action of sodium oxybate was shorter than that of triazolam. Both drugs produced equivalent participant ratings of drug effect at the largest dose that was administered (Fig. 1, top panels); however, triazolam produced greater deficits in balance and psychomotor performance over the range of doses that was studied (c.f., Fig. 1).

Subjective effects

Similar to the participant ratings of drug effect shown in Fig. 1, peak participant ratings of “sedating or depressant,” “limbs heavy or rigid,” “lightheaded or dizzy,” and “fatigued or weak” were similar after triazolam and sodium oxybate and not significantly different from each other at the largest dose of each drug that was studied (Table 1). Participant ratings related to cognitive functioning were also generally similar. Ratings of “confused or disoriented,” “difficulty concentrating,” and “forgetful” after the largest doses of triazolam and sodium oxybate were not significantly different from each other (Fig. 2 and Table 1), although ratings of “mentally slowed down” were greater after 0.5 mg/70 kg triazolam compared to 4.5 g/70

kg sodium oxybate (Table 1). Consistent with greater participant ratings of “mentally slowed down” after triazolam, participants also reported feeling more “sleepy,” more “tired or lazy,” less “energetic,” and less “alert” after 0.5 mg/70 kg triazolam compared to 4.5 g/70 kg sodium oxybate (Fig. 2 and Table 1). Participants also reported that 4.5 g/70 kg sodium oxybate made them feel significantly more “unsteady” and “queasy” and had significantly greater “bad effects” (Fig. 2 and Table 1). Participant ratings of “liking” or “good effects” were not significantly increased at any dose of triazolam or sodium oxybate studied (data not shown).

Working memory

Modified Sternberg maintenance task—ANOVA showed that there were significant main effects of condition and delay on the number of trials correct [$F_{(6,84)}=10.46, p<0.001$; $F_{(2,28)}=65.59, p<0.001$] and on the median response time [$F_{(6,84)}=24.71, p<0.001$; $F_{(2,28)}=42.75, p<0.001$] on the modified Sternberg maintenance task. There was a significant interaction between condition and delay for the number of trials correct [$F_{(12,168)}=3.99, p<0.001$], but not for response time [$F_{(12,168)}=1.16, p=0.32$]. As shown in the top left panel of Fig. 3, when the prompt remained on the screen, participants responded correctly on 11.3 ± 0.2 (mean $\pm$ SEM) out of 12 trials under placebo conditions. The number of correct responses was not significantly decreased by any of the doses of triazolam or sodium oxybate when the prompt remained on the screen and memory was not required (Fig. 3); however, the mean response time was significantly increased after the two largest doses of triazolam and the largest dose of sodium oxybate (Table 2). The increase in response time after the largest dose of 0.5 mg/70 kg triazolam was significantly greater than the increase observed after the largest dose of 4.5 g/70 kg sodium oxybate (Table 2).

When the probe appeared immediately after the prompt disappeared (0-s delay condition), the largest dose of triazolam significantly decreased the number of correct trials compared to placebo, whereas none of the doses of sodium oxybate resulted in a significant decrease in the number of correct trials completed (Fig. 3). The effect of the largest dose of triazolam on the number of correct responses was significantly greater than the largest dose of sodium oxybate in the 0-s delay condition (Fig. 3). Similarly, response times were significantly increased after all doses of triazolam, and not after any of the doses of sodium oxybate in the 0-s delay condition (Table 2). The effect of the largest dose of triazolam on response time was significantly greater than the largest dose of sodium oxybate in the 0-s delay condition (Table 2).

In the 12-s delay condition, triazolam and sodium oxybate impaired performance to a greater extent than in the 0-s delay condition, as evidenced by fewer correct trials and increased reaction times at the largest doses of 0.5 mg/70 kg triazolam and 4.5 g/70 kg sodium oxybate (Fig. 3 and Table 2). The two largest doses of triazolam and the largest dose of sodium oxybate significantly decreased the number of correct trials compared to placebo in the 12-s delay condition (Fig. 3). All doses of triazolam significantly increased response times, whereas only the largest dose of sodium oxybate resulted in a significant increase in response time (Table 2). The effect of the largest dose of triazolam on response time was significantly greater than the largest dose of sodium oxybate in the 12-s delay condition (Table 2).

Modified Sternberg manipulation task—ANOVA showed that there were significant main effects of condition and manipulation on the number of trials correct [$F_{(6,84)}=23.59, p<0.001$; $F_{(2,28)}=14.79, p<0.001$] and on the median response time [$F_{(6,84)}=24.91, p<0.001$; $F_{(2,28)}=48.97, p<0.001$] on the modified Sternberg manipulation task. As shown in the bottom left panel of Fig. 3, when a manipulation was not required (position only), the two largest doses of triazolam and sodium oxybate resulted in significant decreases in the number of correct trials relative to placebo (Fig. 3), and all doses of triazolam significantly increased response times, whereas none of the doses of sodium oxybate did (Table 2). The effects of the largest dose of

triazolam on correct trials and the two largest doses of triazolam on response time were significantly greater than the effects of the corresponding doses of sodium oxybate (Fig. 3 and Table 2).

In the alphabetize and the alphabetize and rotate manipulation conditions, participants responded correctly on fewer trials compared to the position only condition of the task after doses of triazolam (Fig. 3). In each condition, the two largest doses of triazolam and the largest dose of sodium oxybate significantly decreased the number of trials correct. The effect of the largest dose of triazolam was significantly greater than the largest dose of sodium oxybate in each condition (Fig. 3). Similarly, all doses of triazolam significantly increased response time in all manipulation conditions, whereas response times were only increased after the two largest doses of sodium oxybate in the alphabetize condition and after the largest dose in the alphabetize and rotate condition (Table 2). The increases in response time after the two largest doses of triazolam were significantly greater than those after the two largest doses of sodium oxybate across all conditions of the Sternberg manipulation task (Table 2).

Episodic memory

ANOVA showed that there were significant main effects of condition on the number of words correctly recalled in the free recall task [$F_{(6,84)}=3.57, p<0.02$] and on the discriminative index (d') from the word recognition task [$F_{(6,84)}=14.52, p<0.001$] for words that were studied before (list 1) and during (list 2) the period of drug effect.

Retrieval (list 1)—As shown in the top left panel of Fig. 4, when words were studied prior to the administration of placebo, participants correctly recalled an average of 11.3 ± 1.8 words that were previously studied. The number of words recalled was not significantly decreased by any of the doses of triazolam or sodium oxybate when the words were studied before administration of the drug (Fig. 4, top left panel). However, participants' ability to discriminate between words that had and had not been previously studied (i.e., “new” and “old” words) in the word recognition task was significantly decreased after the largest dose of 0.5 mg/70 kg triazolam (Fig. 4, bottom left panel). This effect appears to be a primary result of participants identifying “new” words as “old” after 0.5 mg/70 kg triazolam, as evidenced by a lack of an effect on hit rate (correct identification of “old” words as “old”) and a significantly greater false alarm rate and significantly lower response bias (C) after triazolam was compared to placebo (Table 2). The effects of sodium oxybate were not significantly different from placebo at any dose studied on any measures for list 1. The effects of the two largest doses of triazolam on false alarm rate and response bias were significantly greater than those of the two largest doses of sodium oxybate (Table 2).

Encoding (list 2)—When words were studied during the period of peak drug effect and recalled after the period of drug effect, each dose of triazolam significantly decreased the number of correct words recalled from 10.7 ± 2.1 after placebo to 5.4 ± 1.8 , 3.5 ± 1.3 and 0.2 ± 0.1 after 0.125, 0.25, and 0.5 mg/70 kg triazolam, respectively (Fig. 3, top right panel). The largest dose of sodium oxybate also significantly decreased the number of correct words recalled when words were studied during the period of peak drug effect; however, the mean number of words recalled after 4.5 g/70 kg sodium oxybate (5.1 ± 1.5) was significantly greater than the number of words recalled after the largest dose of triazolam (c.f., Fig. 3, top panels). Similarly, the two largest doses of triazolam and the largest dose of sodium oxybate significantly decreased participants' ability to discriminate between new words and words studied during the period of peak drug effect (Fig. 4, bottom right panel). The effects of the two largest doses of sodium oxybate on the discriminative index (d'), or participants' recognition of words from list 2, were significantly less than those of the two largest doses of triazolam (Fig. 4). The differences between triazolam and sodium oxybate on the discriminative index is a result of significantly

lower false alarm rates and significantly higher hit rates for sodium oxybate compared to triazolam (Table 2).

Source memory and metamemory—ANOVA showed that there were significant main effects of condition on the participants' identification of words as belonging to list 1, list 2, or a list that they had not studied (new) in the source memory task [$F_{(6,84)}=20.4$, $p<0.001$]. The largest dose of 0.5 mg/70 kg triazolam significantly decreased the number of words that were correctly identified in each list, whereas the largest dose of 4.5 g/70 kg sodium oxybate only decreased the number of words correctly identified from list 2, and did so to a lesser extent than triazolam (Table 2). A conditional source memory measure was calculated by analyzing the proportion of words whose list membership was correctly identified in list 1 and list 2 from all of the words that were identified as belonging to either list 1 or list 2 (i.e., proportion of words correctly identified as list 1 or list 2 from all words identified as old). The dose of 0.5 mg/70 kg triazolam was the only dose that significantly decreased the conditional source memory measure compared to placebo and was also significantly different from the largest dose of sodium oxybate (Table 2).

Metamemory was assessed by calculating Goodman—Kruskal gamma correlations between the relative confidence in responses and the correctness of the responses from the word recognition memory tasks. For list 1, all gamma correlations were positive and were not significantly different from each other (Table 2). For list 2, all gamma correlations were positive, but there was a significant main effect of condition on the correlation [$F_{(6,83)}=4.5$, $p=0.001$; Table 2]. Gamma correlations for list 2 were significantly decreased after the two largest doses of triazolam were compared to placebo and were significantly lower than those after the two largest doses of sodium oxybate (Table 2). Sodium oxybate did not affect the correlation between confidence ratings and recognition memory accuracy at any dose studied (Table 2).

Discussion

The present study was designed to examine the effects of sodium oxybate on several different measures of working memory and episodic memory in healthy individuals without a history of drug abuse. There are several important findings from this study. First, sodium oxybate significantly impaired working memory and the encoding of episodic memory during the period of drug effect. Second, at doses that produced equivalent subjective ratings of “drug effect,” “confused or disoriented,” and “difficulty concentrating,” sodium oxybate had significantly less of an effect on memory compared to triazolam. Third, neither drug increased ratings of “liking” or “good effects,” and the only subjective effects measures that were significantly greater after 4.5 g/70 kg sodium oxybate compared to 0.5 mg/70 kg triazolam were “unsteady,” “queasy,” and “bad effects,” suggesting that sodium oxybate might have a lower likelihood of abuse than triazolam in this group of healthy individuals without a history of drug abuse.

The finding that doses of sodium oxybate impaired working memory and the encoding of episodic memory in the present study is consistent with reports of illicit GHB being able to produce anterograde amnesic effects (Smith 1999; Schwartz et al. 2000; Varela et al. 2004). The doses of sodium oxybate that were examined in the present study (1.125–4.5 g/70 kg) are larger than those that have been administered in other studies that have examined cognitive effects of sodium oxybate in individuals without a history of drug abuse (e.g., Grove-White and Kelman 1971a, b; Mattila et al. 1978; Ferrara et al. 1999). The doses of sodium oxybate examined in this study resulted in relatively high participant ratings of subjective “drug effect,” which were comparable to those observed after the doses of triazolam that were examined (Fig. 1).

Although sodium oxybate significantly decreased the number of correct trials across the different conditions of the Sternberg working memory tasks in a similar manner as triazolam, the effects of sodium oxybate on the number of trials correct were often significantly less than those of triazolam (Fig. 3). Likewise, sodium oxybate tended to increase response times on these tasks at the largest dose that was studied (4.5 g/70 kg sodium oxybate), whereas triazolam tended to do so at all doses and to a significantly greater extent than sodium oxybate at the two largest doses that were studied (Table 2). Although the largest dose of 4.5 g/70 kg sodium oxybate significantly decreased participants' recall and recognition of words studied during the period of drug effect, the effects of sodium oxybate were significantly less than those of triazolam (Fig. 4, list 2). For example, participants recalled an average of 0.2 ± 0.1 words after 0.5 mg/70 kg triazolam, whereas 5.1 ± 1.5 words were recalled after 4.5 g/70 kg sodium oxybate. These findings suggest that even though sodium oxybate decreased recall and recognition memory compared to placebo, administration of sodium oxybate did not result in the near-complete amnesia for the studied words that was observed after triazolam.

The relatively modest amnesic effects of sodium oxybate observed in this study suggest that other factors such as loss of consciousness or co-administration of drugs such as ethanol with illicit GHB (Barker et al. 2007) might contribute to the case reports of marked amnesia following ingestion of illicit GHB. It is possible that a dose of sodium oxybate larger than those examined in this study could result in greater amnesic effects without loss of consciousness. However, the participants in this study reported strong drug effects and began to exhibit signs of behavioral impairment after the largest dose of sodium oxybate that was studied, suggesting that larger doses would have resulted in marked behavioral impairment or loss of consciousness that was observed in a previous study that examined larger doses in drug-experienced individuals (Carter et al., 2006). Doses of ethanol alone can result in anterograde amnesia (Mintzer and Griffiths 2002; Söderlund et al. 2005). The combination of GHB and ethanol might have greater effects on the encoding of episodic memory than the same doses of either drug alone; however, most evidence suggests that interactions between GHB and ethanol in rodents and humans are additive and not synergistic (Lamb et al. 2003; Cook et al. 2006; Thai et al. 2006).

In this study, sodium oxybate and triazolam both dose-dependently increased several subjective effects measures and decreased psychomotor performance (Fig. 1 and Table 1). Consistent with a previous study in sedative drug abusers, there were doses of sodium oxybate that produced statistically significant increases in ratings of drug effect or drug strength with relatively small or absent concomitant decreases in psychomotor performance (c.f., Carter et al. 2006, Fig. 1; current study, Fig. 1). Also consistent with the effects of sodium oxybate and triazolam in sedative drug abusers, individuals without a history of drug abuse in this study reported feeling significantly more unsteady and queasy after sodium oxybate than after comparable doses of triazolam (c.f., Carter et al. 2006, Table 3; current study, Table 1). These data suggest that the overall profile of effects of sodium oxybate is not markedly different between individuals with and without a history of drug abuse and that the significantly greater magnitude of bad effects experienced after sodium oxybate (compared to triazolam) might limit the likelihood of recreational use or abuse of sodium oxybate and illicit GHB relative to other sedative/hypnotic drugs.

In summary, at the doses studied, sodium oxybate impaired psychomotor performance, working memory performance, response time, and the encoding of episodic memory. However, at doses that produced comparable participant ratings of "drug effect," the impairments in psychomotor performance, working memory performance, response time, and the encoding of episodic memory after sodium oxybate were significantly less than those after triazolam. Moreover, triazolam had significant effects on metamemory and conditional source memory, whereas sodium oxybate did not (Table 2). Together, these results provide important new

information about the cognitive effects of sodium oxybate in individuals without a history of drug abuse. Furthermore, these data, in conjunction with a previous study of the effects of sodium oxybate in sedative drug abusers (Carter et al. 2006), suggest that the amnestic effects of sodium oxybate are modest compared to those of triazolam. Although the estimated prevalence of non-medical use of GHB/sodium oxybate is low (Carter et al. 2009), illicit GHB is thought to be frequently co-administered with ethanol. Studies designed to compare the effects of sodium oxybate and ethanol administered alone or together on memory might address some of the issues raised by this study.

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Fig. 1.

Time course of effects of triazolam (*left panels*) and sodium oxybate (*right panels*) on participant-rated drug effect, balance, and circular lights. Y-axes: rating on a visual analog scale in millimeters, time balanced on one foot (summed across both feet; 60 s total) in seconds, and number of correct responses, respectively. X-axes: time after drug administration in minutes (0 indicates pre-drug; measures were assessed approximately 35, 110, and 230 min after administration). Data points show means ($N=15$), brackets show ± 1 SEM, and the absence of brackets indicates that 1 SEM fell within the area of the data symbol. Filled symbols indicate values that are significantly different from the corresponding placebo value at the same time point ($p < 0.05$).

Fig. 2.

Peak participant-rated subjective effects of triazolam and sodium oxybate. Y-axes: rating expressed as peak effect, which is the mean of the maximum value for individual participants across the 4-h session (measures were assessed approximately 35, 110, and 230 min after administration). X-axes: dose in milligrams (triazolam) or grams (sodium oxybate) per 70 kg (log scale). PL designates placebo. Data points show means ($N=15$), brackets show ± 1 SEM, and the absence of brackets indicates that 1 SEM fell within the area of the data symbol. Filled symbols indicate values that are significantly different from placebo; the letter "t" above 4.5 g/70 kg sodium oxybate indicates that that data point is significantly different from 0.5 mg/70 kg triazolam ($p<0.05$).

Delay Conditions **Manipulation Conditions** **Fig. 3.**

Peak effects of triazolam and sodium oxybate on working memory. *Y*-axes: number of trials correct expressed as peak effect, which is the mean of the minimum value for individual participants across the 4-h session (measures were assessed approximately 35, 110, and 230 min after administration). *X*-axes: dose in milligrams (triazolam) or grams (sodium oxybate) per 70 kg (log scale); *PL* designates placebo. Data points show means ($N=15$), *brackets* show ± 1 SEM, and the *absence of brackets* indicates that 1 SEM fell within the area of the data symbol. *Filled symbols* indicate values that are significantly different from placebo; the letter “*t*” above 4.5 g/70 kg sodium oxybate indicates that that data point is significantly different from 0.5 mg/70 kg triazolam ($p<0.05$)

Fig. 4.

Effects of triazolam and sodium oxybate on episodic memory. *Y*-axes: number of words recalled (*top panels*) or discriminative index (d' , *bottom panels*) for words studied before drug or placebo administration (list 1, *left panels*) or during the period of drug effect (100 min after administration; list 2, *right panels*). *X*-axes: dose in milligrams (triazolam) or grams (sodium oxybate) per 70 kg (log scale). PL designates placebo. Data points show means ($N=15$), brackets show ± 1 SEM, and the absence of brackets indicates that 1 SEM fell within the area of the data symbol. Filled symbols indicate values that are significantly different from placebo; the letter "t" above 2.25 or 4.5 g/70 kg sodium oxybate indicates that that data point is significantly different from 0.25 or 0.5 mg/70 kg triazolam, respectively ($p < 0.05$)

Table 1

Summary of significant peak subjective effects measures relative to placebo and high-dose comparisons between 0.5 mg/70 kg triazolam and 4.5 g/70 kg sodium oxybate

Subjective effect	Drug vs. placebo comparison ^a		High-dose comparison ^b
	TRZ vs. PL	SXB vs. PL	
Drug effect	+	+	NS
Sedating or depressant	+	+	NS
Limbs heavy or rigid	+	+	NS
Lightheaded or dizzy	+	+	NS
Fatigued or weak	+	+	NS
Confused or disoriented	+	+	NS
Difficulty concentrating	+	+	NS
Forgetful	+	+	NS
Dry mouth	+	+	NS
Speech slurred	+	NS	NS
Numbness or tingling	+	+	NS
Dislike drug effect	+	+	NS
Energetic	–	NS	TRZ>SXB
Alert	–	–	TRZ>SXB
Sleepy	+	+	TRZ>SXB
Tired or lazy	+	+	TRZ>SXB
Easy going or mellow	+	NS	TRZ>SXB
Mentally slowed down	+	+	TRZ>SXB
Limp or loose	+	NS	TRZ>SXB
Blurred vision	+	+	TRZ>SXB
Unsteady	+	+	SXB>TRZ
Queasy	NS	+	SXB>TRZ
Bad effects	+	+	SXB>TRZ

^aThese columns show the results of simple contrasts between placebo and doses of triazolam (TRZ) and sodium oxybate (SXB) on peak effects data. Symbol (+ or –) indicates that at least one dose of drug was significantly different from placebo ($p<0.05$) and the direction of the drug effect. NS indicates that no dose of that drug was different from placebo

^bThis column shows the results of simple contrasts between the largest dose of triazolam (0.5 mg/70 kg) and sodium oxybate (4.5 g/70 kg). The drug to the left of the > symbol produced a significantly greater effect ($p<0.05$). NS indicates that the effects produced by the two doses were not significantly different

Table 2

Summary of the effects of triazolam and sodium oxybate on response time on the working memory tasks (Sternberg delay and manipulation tasks) and on different measures from the episodic memory tasks (Word recognition and Source memory tasks)

Cognitive measure	Placebo	Triazolam (mg/70 kg)			Sodium Oxybate (g/70 kg)		
		0.125	0.25	0.5	1.125	2.25	4.5
Sternberg delay response time (ms) ^{a,b}							
Prompt on screen	1,744	1,923	2,393	2,786	1,867	1,916 ^t	2,011 ^t
0-s delay	2,126	2,446	2,745	3,092	2,217	2,245 ^t	2,231 ^t
12-s delay	2,202	2,647	3,022	3,492	2,515	2,378 ^t	2,511 ^t
Sternberg manipulation response time (ms)							
Position only	1,722	1,898	2,429	2,952	1,982	1,887 ^t	1,937 ^t
Alphabetize	1,895	2,312	2,870	3,451	2,120	2,183 ^t	2,298 ^t
Alphabetize and rotate	2,285	2,872	3,438	3,877	2,573	2,464 ^t	2,770 ^t
Word recognition (List 1—retrieval)							
Hit rate	0.84	0.90	0.88	0.87	0.88	0.85	0.80
False alarm rate	0.11	0.17	0.19	0.28	0.13	0.12 ^t	0.10 ^t
Discriminative index (<i>d'</i>)	2.52	1.93	2.43	1.93	2.61	2.53	2.40
Response bias (<i>C</i>)	0.16	-0.18	-0.14	-0.31	-0.01	0.11 ^t	0.20 ^t
Gamma correlation ^c	0.62	0.59	0.39	0.50	0.58	0.51	0.75
Word recognition (List 2—encoding)							
Hit rate	0.87	0.78	0.67	0.60	0.84	0.86 ^t	0.82 ^t
False alarm rate	0.14	0.18	0.26	0.39	0.16	0.14 ^t	0.20 ^t
Discriminative index (<i>d'</i>)	2.49	1.99	1.27	0.64	2.44	2.59 ^t	1.99 ^t
Response bias (<i>C</i>)	-0.03	0.11	0.13	0.03	-0.02	-0.02	0.00
Gamma correlation ^c	0.74	0.53	0.34	0.21	0.64	0.70 ^t	0.64 ^t
Source memory							
List 1 (words correct)	21.1	21.7	19.5	16.3	22.3	21.7	21.7 ^t
List 2 (words correct)	26.1	22.1	19.5	15.3	25.5	24.4 ^t	21.6 ^t
New list (words correct)	32.6	30.9	28.5	23.7	32.6	32.6 ^t	32.1 ^t
Conditional memory ^d	0.73	0.69	0.64	0.56	0.73	0.72	0.68 ^t

^a Bold values indicate data at doses of triazolam and sodium oxybate that are significantly different from placebo ($p < 0.05$)

^b The superscript "t" next to values for 2.25 or 4.5 g/70 kg sodium oxybate indicates that those data points are significantly different from 0.25 or 0.5 mg/70 kg triazolam, respectively ($p < 0.05$)

^c Goodman—Kruskal gamma correlations (a correlation between confidence and correctness in recognition; Goodman and Kruskal 1954). Gamma values can range from -1 (complete discordance between confidence ratings and recognition memory accuracy) to 1 (complete concordance between confidence ratings and recognition memory accuracy)

^d The conditional memory measure is the proportion of words identified as old (i.e., from either list 1 or list 2) that were also correctly identified as being from list 1 or list 2