Pergamon

Pharmacology Biochemistry and Behavior, Vol. 51, No. 4, pp. 815-819, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00039-9

Flumazenil May Attenuate Some Subjective Effects of Nitrous Oxide in Humans: A Preliminary Report

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Received 11 August 1994

ZACNY, J. P., S. YAJNIK, D. COALSON, J. L. LICHTOR, J. L. APFELBAUM, G. RUPANI, C. YOUNG, P. THAPAR AND J. KLAFTA. *Flumazenil may attenuate some subjective effects of nitrous oxide in humans: A preliminary report.* PHARMACOL BIOCHEM BEHAV **51**(4) 815-819, 1995.—Two double-blind, randomized, crossover trials were conducted to study whether the benzodiazepine antagonist, flumazenil, would interact with the subjective and psychomotor effects of nitrous oxide in healthy volunteers. In both experiments, eight subjects inhaled 30% nitrous oxide in oxygen for 35 min and were challenged, 10 min into the inhalation, with flumazenil. Experiment 1 tested a range of flumazenil doses used clinically (0, 0.25, 0.5, and 1.0 mg/70 kg) whereas Experiment 2 tested a supraclinical flumazenil dose (0 and 5.0 mg/70 kg). Nitrous oxide increased mood ratings of "high," "drunk," and "tingling," and decreased psychomotor performance as assessed by the Digit Symbol Substitution Test. Flumazenil, at the supraclinical dose, significantly lowered the mood rating of "high." Decreases, though not significant ($p < 0.10$), were also obtained on the ratings "drunk," "elated," and "drug liking". Flumazenil, in both experiments, did not interact with the psychomotor effects of nitrous oxide. It appears that flumazenil, at a dose higher than that used clinically, may antagonize some of the subjective effects produced by nitrous oxide in humans.

Nitrous oxide Flumazenil Human Volunteer Antagonist Benzodiazepine Subjective Psychomotor

NITROUS oxide is a gas that has anesthetic, analgesic, amnestic, and anxiolytic effects. Studies attempting to determine the neurochemical mechanisms underlying the effects of nitrous oxide have found nitrous oxide-induced analgesia to be mediated, at least in part, by the endogenous opiate system (1,2,19,20,24,29). However, in our laboratory, a wide dose range of the nonspecific opiate antagonist, naloxone, failed to reverse the subjective and psychomotor effects of nitrous oxide in healthy volunteers (30).

A recent series of studies performed in the animal pharmacological laboratory have found some of the behavioral effects of nitrous oxide to be mediated at the GABA/benzodiazepine/ionophore complex. Pretreatment with 10 mg/kg of flumazenil, a benzodiazepine antagonist, blocked the increased social interaction in rats induced by both nitrous oxide and the anxiolytic benzodiazepine, chlordiazepoxide (23). In another study, mice administered nitrous oxide made significantly more entries and spent more time in the open arms of an elevated plus maze than controls (indicative of reduced "anxiety"), but this behavior was antagonized by pretreatment with flumazenil (10). Moreover, pretreatment with 20 mg/kg of flumazenil effectively antagonized 30% nitrous oxide-induced decreases in defensive burying in rats (rats have a species-typical propensity to bury objects associated with aversive stimulation) (5). Also, nitrous oxide-induced shifts in number and time spent head dipping in the holeboard exploratory test were reversed in a dose-related manner by flumazenil (4).

Given the above findings in the animal laboratory suggesting that some of the behavioral effects of nitrous oxide are mediated by the benzodiazepine receptor, we speculated that

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administration of a benzodiazepine antagonist would alter the effects of nitrous oxide in humans. In the present study, two double-blind trials were conducted testing a clinical and supraclinical intravenous challenge of flumazenil on the subjective and psychomotor-impairing effects of inhaled nitrous oxide in healthy volunteers.

METHOD

Subjects

The studies were approved by our institutional review board. Candidates who met screening criteria (i.e., 21–39 years old, within 25% of ideal body weight, reporting at least one alcoholic beverage consumed per week, and no current medical problems) were scheduled for a screening interview. At the interview, they completed the SCL-90 (8) and a locally developed health questionnaire, and a semistructured interview was held to determine their psychiatric and medical status. Candidates with any history of significant psychiatric disorders or substance use disorder, except for tobacco dependence, were excluded. An anesthesiologist performed a medical history and physical examination. Also, an electrocardiogram was performed to assure normal cardiac functioning. Subjects were screened via urine toxicology testing and were excluded if they tested positive for illicit drug use. Informed written consent was obtained from subjects before the first session. In the consent form subjects were told that the drugs they would receive in the experiment may be taken from one or more of the following classes of drugs in gaseous or intravenous form: sedative, stimulant, general anesthetic (at subanesthetic doses), alcohol, opiate, opiate antagonist, benzodiazepine antagonist, or placebo. Upon study completion, subjects were paid for their participation. During an initial practice session, subjects were exposed to the different tests in the battery to gain familiarity with them.

Experiment 1 utilized eight volunteers (six males, two females; mean age: 25.5 years, range 22–34) and Experiment 2 utilized eight volunteers (six males, two females: mean age: 26.4 years, range 21–37). Subjects in Experiment 1 had a history of consuming 4.0 ± 2.4 alcoholic drinks per week; subjects in Experiment 2 had a history of consuming 4.8 ± 2.3 drinks per week.

Experimental Design and Drugs Tested

Two separate experiments were conducted allowing a wide range of flumazenil doses to be tested in conjunction with nitrous oxide. Each experiment was performed as a double-blind, randomized, crossover trial. Each subject was tested in four different test sessions during Experiment 1 and half of these subjects ($N = 4$) went on to complete the two sessions involved in Experiment 2. There was a minimum of 72 h between each session. In the first experiment, subjects received intravenous injections of 0, 0.25, 0.5, or 1.0 mg/70 kg flumazenil during inhalation of 30% nitrous oxide in oxygen. A 0.5–1.0-mg dose of flumazenil administered via intravenous injection is normally sufficient to completely reverse the effects of therapeutic doses of benzodiazepines (3). In the second experiment, we tested a dose well above the clinically used dose. Subjects received an intravenous injection of 0 or 5.0 mg/70 kg flumazenil during inhalation of 30% nitrous oxide in oxygen. Duration of nitrous oxide inhalation was 35 min. Subjects received challenge injections of flumazenil or placebo 10 min after initiation of nitrous oxide inhalation. The concentration of nitrous oxide used is approximately one-quarter of an anesthetic concentration, and about one-half of the concentration that is used clinically in combination with other anesthetics.

Session Procedures

Each experimental session was approximately 120 min in duration and took place in the morning. Female subjects had to have a negative urine pregnancy test each week that they participated in the study. On testing days, subjects were not allowed to eat for 6 h or drink for 2 h before the tests. Subjects were instructed to refrain from drinking alcohol for 24 h before sessions.

Subjects were seated in a chair during the entire testing period. Anesthetic agents and oxygen were delivered via a semi-closed circuit from an anesthetic machine (Narkomed, Drager, Inc.), and subjects inhaled through a clear anesthesia facial mask. An angiocatheter was inserted into a forearm vein prior to inhalation and was removed immediately following the end of inhalation. Noninvasive continuous measurements of heart rate, electrocardiogram, peripheral oxygen saturation, and blood pressure (Hewlett Packard Model 54; Waltham, MA) were initiated at the beginning of the session before inhalation. At the beginning of the session, and 7, 15, and 30 min after the start of the inhalation with nitrous oxide, heart rate, pulse oximetry, and blood pressure were recorded. Changes that occurred in the experiment were clinically insignificant and will not be reported in this paper. When the mask was first placed, subjects were told at this time that the air they were breathing did not contain a drug in it. Also, at this time, subjects completed several mood forms and psychomotor tests, while inhaling oxygen through the mask. Upon completion of baseline testing the nitrous oxide inhalation period began. Subjects were told that for the following 35 min they would be inhaling air that may or may not have drug in it (although they always received 30% nitrous oxide).

Intravenous injections of flumazenil or placebo were delivered 10 min into the inhalation, allowing inhaled nitrous oxide levels to reach steady state prior to injection challenge (27). Subjects were told that the injection they were receiving may or may not contain a drug. Because the peak effects of the antagonistic effects of flumazenil on the benzodiazepine response are 6–10 min postflumazenil injection, with onset of effects evident usually within the first 2 min of injection (18), we expected to detect any effects of flumazenil on nitrous oxide responses during the 25 min after the flumazenil injection while subjects were inhaling nitrous oxide. At periodic intervals during and after the inhalation period, mood and psychomotor performance were assessed by a technician who was unaware of the drug and dose being administered.

Dependent Measures

Subjective effects were measured using a visual analog scale (VAS) and a Drug Effects/Liking Questionnaire. The VAS consisted of 20 100-mm lines, each labeled with an adjective, ["stimulated," "high ('drug' high)," "anxious," "sedated," "down," "coasting (spaced out)," "elated (very happy)," "dizzy," "in control of thoughts," "in control of body," "having pleasant thoughts," "having pleasant bodily sensations," "having unpleasant thoughts," "having unpleasant bodily sensations," "tingling," "drunk," "confused," "nauseous," "carefree," and "hungry"]. Subjects were instructed to place a mark on each line indicating how they felt at the moment, ranging from "not at all" to "extremely." A locally developed Drug Effects/Liking questionnaire consisted of two questions—the

first question assessed the extent to which subjects currently felt a drug effect, on a scale of 1 to 5 (1 = "I feel no effect from it at all"; 5 = "I feel a very strong effect"), and the second question assessed the extent to which subjects like the drug effect, on a 100-mm line (0 = dislike a lot; 50 = neutral; 100 = like a lot). Subjective effects were measured during each session at baseline, at 7, 11, 15, and 30 min into the inhalation, and at 5, 30, and 60 min following the end of the inhalation.

Psychomotor performance was measured using the Digit Symbol Substitution Test (DSST) (28). In the DSST, subjects replaced a number with a corresponding symbol; the paper-and-pencil test was timed for 1 min and the dependent measure was the number of symbols correctly matched by the subject. The DSST evaluates changes in information processing performance and the ability to concentrate (17). The DSST was administered at baseline, at 15 and 30 min into the inhalation, and at 5, 30, and 60 min postinhalation during each of the sessions.

Data Analysis

Subjective and psychomotor effects data were analyzed using a repeated-measures analysis of variance (ANOVA). The factors considered were flumazenil dose and time. We considered time effects to be indicative of nitrous oxide-induced effects. Prior studies in our laboratory showed no time effects when oxygen-placebo was administered over an extended (i.e., 30 min) period. In those studies, time effects were only noted in the presence of nitrous oxide inhalation. An effect was considered significant if $p < 0.05$. Huynh-Feldt adjustments of within-factors degrees of freedom were used to protect against violations of symmetry assumptions. Tukey post hoc comparison tests were done, when appropriate.

RESULTS

Experiment 1

Subjective effects. Significant increases in time effects were obtained on the following VAS ratings, indicative of nitrous oxide-induced mood changes: "high" ($p < 0.001$), "drunk" ($p < 0.01$), "tingling" (0.001), "confused" ($p < 0.001$), "having pleasant bodily sensations" ($p < 0.001$), "coasting" ($p < 0.005$), "stimulated" ($p < 0.005$), "elated" ($p < 0.05$), "hungry" ($p < 0.005$), "having pleasant thoughts" ($p < 0.01$), and "sedated" ($p < 0.05$). Significant increases in time effects were also obtained on "feel drug effect" ($p < 0.001$) and "drug liking" ($p < 0.001$) ratings. Significant decreases in time effects were obtained with the VAS ratings of "hungry" ($p < 0.005$), "in control of body" ($p < 0.001$), and "in control of thoughts" ($p < 0.05$). Flumazenil did not significantly alter the effects of nitrous oxide (i.e., no significant flumazenil or flumazenil × time interactions). Figure 1 (left side) shows the effect of flumazenil on "high" ratings during the nitrous oxide inhalation period. The small decreases in high ratings that are evident in the left side of the figure were not related to flumazenil dose in any consistent fashion.

Psychomotor effects. A significant time effect was obtained on the DSST ($p < 0.001$). Although subjects correctly completed an average of 48 symbols while breathing oxygen, they completed an average of 43 and 41 symbols 15 and 30 min into the nitrous oxide inhalation. Flumazenil did not interact significantly with the psychomotor impairment induced by nitrous oxide.

Experiment 2

Subjective effects. Significant increases in time effects on "high" ($p < 0.001$), "drunk" ($p < 0.05$), "tingling" ($p <$

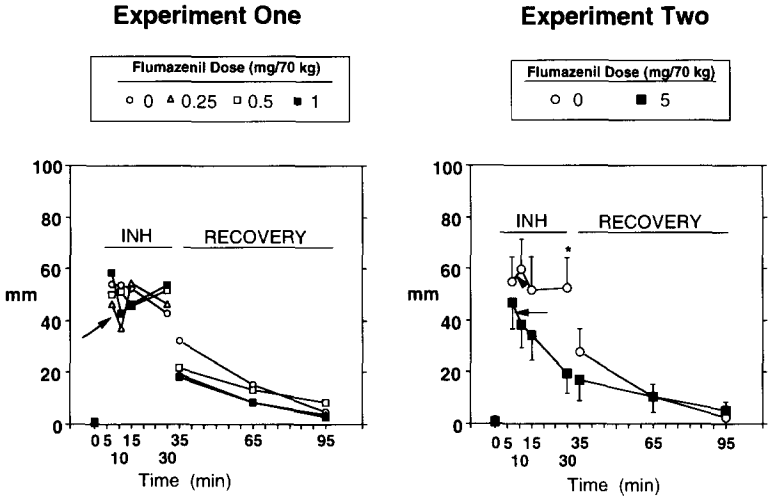

FIG. 1. Effects of placebo and flumazenil on the VAS rating of "high" (measured on a 0–100-mm scale) during and after inhalation of 30% nitrous oxide. The left side presents the results from Experiment 1 in which flumazenil doses of 0, 0.25, 0.5, and 1.0 mg/70 kg were tested. The right side presents the results from Experiment 2 in which doses of 0 and 5 mg/70 kg were tested. Flumazenil was injected 10 min into the nitrous oxide inhalation, and is represented in each graph by an arrow. Time point 0 refers to ratings prior to nitrous oxide inhalation. Ratings were also obtained 7, 11, 15, and 30 min into the inhalation period, and 5, 30 and 60 min after the inhalation period had ceased (i.e., recovery). In the right side, the asterisk indicates significantly greater "high" ratings in the saline condition than in the flumazenil condition at that time point. Brackets in the right side indicate SEM.

0.005), "confused" ($p < 0.05$), "having pleasant bodily sensations" ($p < 0.05$), "coasting" ($p < 0.005$), "anxious" ($p < 0.001$), and "feel drug effect" ($p < 0.001$) were obtained. Flumazenil administration significantly decreased subject ratings of "high" (dose × time, $p < 0.05$). The effect of flumazenil was maximal 20 min postinjection on the "high" rating, decreasing the rating by about 60% (Fig. 1, right side). Figure 2 shows subject by subject ratings of "high" both during the flumazenil and placebo injection conditions. Seven of eight subjects showed at least a 10-mm drop in "high" ratings, 20 min following flumazenil injection when compared with placebo injection. Ratings of "drug liking" (flumazenil, $p = 0.07$), "drunk" (flumazenil × time, $p = 0.10$), and "elated" (flumazenil, $p = 0.08$) were reduced by flumazenil, but the reductions were not statistically significant.

Psychomotor effects. A significant time effect was obtained on the DSST ($p < 0.05$). Although subjects averaged 49 correct symbols completed while breathing oxygen, they averaged 45 and 47 correct symbols completed 15 and 30 min into the nitrous oxide inhalation. Flumazenil did not interact significantly with the psychomotor impairment induced by nitrous oxide.

DISCUSSION

The subjective feeling of "high," a consistent finding with nitrous oxide inhalation based on this and other studies, was significantly lowered by administration of a 5.0 mg/70 kg flumazenil challenge. Additionally, "drunk," "elated," and "drug liking" ratings were reduced by flumazenil, but the reductions were not statistically significant. Results from our study provide preliminary support for the notion that the benzodiazepine receptor is involved in mediating some of the subjective effects produced by nitrous oxide. To our knowledge, this is the first study of its kind implicating the benzodiazepine receptor in mediating the subjective effects of nitrous oxide in humans. This finding is consistent with other studies showing the behavioral effects of nitrous oxide in animals to be mediated by the benzodiazepine receptor (4,5,10,23).

One possible criticism that could be directed at this study is that flumazenil was injected during, rather than before, the drug administration. Perhaps if flumazenil had been given as a pretreatment, more robust antagonism would have been obtained.

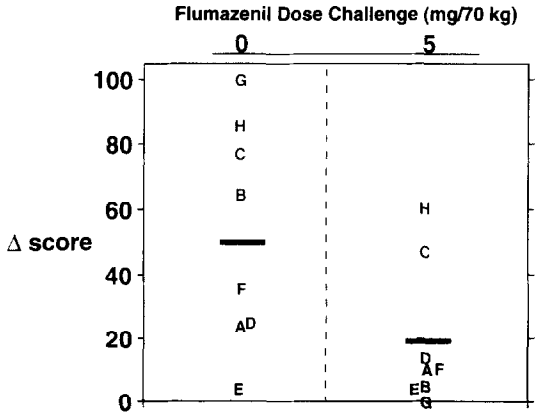

FIG. 2. Effects of 0 and 5 mg/70 kg of flumazenil on "high" ratings, expressed as a change score from baseline to 30 min into the inhalation period (and 20-min postinjection), the time point at which the saline and flumazenil conditions differed significantly from each other. Letters refer to individual subject data and the solid bars represent the average change score.

However, we were concerned that a flumazenil injection prior to inhalation would decrease the sensitivity of our procedure in detecting possible effects of the benzodiazepine antagonist. In one study that examined flumazenil and benzodiazepine interactions, for example, giving the flumazenil prior to the benzodiazepine resulted in inconsistent benzodiazepine antagonism, whereas giving the flumazenil after the benzodiazepine resulted in an orderly and uniform antagonism (9).

Clinical and supraclinical doses of flumazenil failed to interact with the psychomotor effects produced by nitrous oxide. This finding suggests that the various effects of nitrous oxide (analgesic, mood-altering, psychomotor-impairing, anesthetic) may be mediated by a number of different neurochemical phenomena. Indeed there is a substantial body of evidence indicating that the analgesic effects of nitrous oxide are mediated at the endogenous opiate system (1,2,19,20,24, 29). In addition, some nociceptive effects appear to involve the 5-HT receptors (24).

Flumazenil at the clinically recommended dose in humans is thought to act as a pure benzodiazepine antagonist. However, there is some evidence that at higher doses it behaves as a weak agonist or as an inverse agonist (i.e., anxiogenic) [cf. (14)]. In support of the notion that it has agonist effects, intravenous administration of 2–2.5 mg of flumazenil was shown to increase self-reported ratings of sleepiness in volunteers in one study (22), and, in another study (26) it produced anticonvulsant effects in epileptic patients. In another study, a dose of 3 mg of flumazenil produced a significant increase in subject ratings of dizzy or lightheaded (16). However, in Experiment 2, our subjects did not report increases in "sedated" or "dizzy" after the 5-mg injection of flumazenil. Flumazenil in both animal and human studies has also been shown to have inverse agonist effects [e.g., (11-14,25)]. It is possible that in the present study flumazenil was exerting inverse agonist effects, which, in concert with nitrous oxide, resulted in an overall altered (in this case, reduced) effect on some aspects of mood. This possibility cannot be discounted, given that flumazenil by itself was not tested in the present study. However, a recent study demonstrated that a relatively high dose of flumazenil, 7 mg, did not affect psychomotor or respiratory functioning in healthy volunteers—it was concluded in this study that the agent at this dose had no intrinsic activity (15). The decreased magnitude of subjective effects in Experiment 2 is more in line with flumazenil exerting an antagonist effect rather than an agonist or inverse agonist effect.

We feel that our results provide preliminary evidence that some of the subjective effects of nitrous oxide could be mediated at the GABA/benzodiazepine/ionophore complex, and are consistent with a number of animal studies that have demonstrated attenuation of some behavioral effects of nitrous oxide by flumazenil (4,5,10,23). We acknowledge though that the antagonism was partial, as opposed to the more complete antagonism obtained when flumazenil is given after benzodiazepine administration (6,7). It is certainly possible that we would have obtained a greater degree of antagonism had we tested higher doses. Future studies will include higher doses, and will include control conditions in which these doses are tested alone, to ensure that the doses have no intrinsic activity.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Brain Research Foundation. The authors wish to thank Ms. Maura McKay for her assistance in the conduct of the experimental sessions, as well as Robert Shaughnessy, C.R.N.A., Mary Maurer, C.R.N.A., and Nada Williamson, C.R.N.A., for their assistance in administering the agents and monitoring the physiological status of the subjects.

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