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Choice of Sevoflurane and Its Subjective and Psychomotor Effects In Light and Moderate Drinkers

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Abstract

Background—Sevoflurane, an inhalant of the volatile anesthetic class, has neurobiological and behavioral effects in common with abused inhalants and ethanol. We sought to determine if choice for subanesthetic doses of sevoflurane, and its subjective and psychomotor effects, would differ as a function of alcohol-drinking status in healthy volunteers.

Methods—The effects of four concentrations of sevoflurane (0, 0.2, 0.4, 0.8% sevoflurane in oxygen) were studied in 16 light drinkers and 16 moderate drinkers. During each of four sessions, subjects sampled a concentration of sevoflurane and 100% O₂ (placebo) for 10 min each. Subjective and psychomotor testing commenced 5 min into each sampling trial. Later, within the session, subjects chose nine times, once every 5 min, among sevoflurane (e.g., “Agent A”), placebo (e.g., “Agent B,” 100% O₂), or neither (and were administered 100% O₂, identified as “drug-free air”).

Results—Choice for sevoflurane at the 0.4% concentration was significantly higher in the moderate drinkers than in the light drinkers. A number of subjective effects reported during inhalation of sevoflurane were markedly lower in the moderate-drinking group than in the light-drinking group. However, psychomotor impairment induced by sevoflurane was similar in magnitude in both groups.

Conclusions—Alcohol-drinking status affected sevoflurane choice. The results are consistent with several studies comparing light and heavier drinkers, using other drugs. Although both drinking groups were similarly impaired by sevoflurane, the moderate drinkers reported less of a subjective response than light drinkers, suggestive of cross-tolerance.

Keywords

Sevoflurane; Choice; Preference; Reinforcing effects; Subjective effects; Psychomotor; Cross-Tolerance; Inhalants; Human

1. Introduction

Inhalants are a diverse group of substances that are abused. They can be grouped into three classes based on their pharmacological and behavioral effects: nitrous oxide; volatile alkyl nitrites (e.g., “poppers”); and volatile solvents (paints, degreasing agents, toluene), fuels (e.g.,

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gasoline, butane) and anesthetics (e.g., ether, isoflurane) (Balster, 1998). The abuse of inhalants is widespread throughout the world. In the 2006 National Survey on Drug Use and Health, a US epidemiological survey tracking incidence and prevalence of non-medical and illicit use of drugs, 9.3% or an estimated 23 million people aged 12 years and older reported lifetime use of inhalants (Substance Abuse and Mental Health Services Administration, 2007). To put this in perspective, this lifetime prevalence rate is lower than that of cocaine (14.3%) and prescription pain relievers (13.6%), but higher than that of ecstasy (4.7%) and prescription sedatives (3.6%). Inhalant abuse is a serious public health problem associated with both morbidity and mortality (e.g., Chalmers, 1991; Winek et al., 1995; Marelich, 1997; Yamanouchi et al., 1998). Thus, it is important to characterize the effects of inhalants, ranging from their cellular and molecular effects to their behavioral effects. A number of researchers over the years have examined the psychopharmacological effects of such inhalants as nitrous oxide, volatile anesthetics, alkyl nitrites and toluene (for reviews, see Wood, 1979; Glowa, 1985; Evans and Balster, 1991; Bowen et al., 2006).

Our laboratory has embarked on several lines of research with both nitrous oxide and volatile anesthetics in healthy volunteers. One line of research examined whether subjective and reinforcing effects of nitrous oxide, a gaseous anesthetic, could be modulated by such factors as information, pain, and drug history. For example, we examined choice of nitrous oxide (0–40%) in light drinkers (LDs) and moderate drinkers (MDs). It is known from other studies using these subpopulations of healthy volunteers that abuse liability-related subjective effects and/or reinforcing effects of diverse drugs such as amphetamine (Stoops et al., 2003) and the benzodiazepines, alprazolam and diazepam (de Wit et al., 1989; de Wit and Doty, 1994; Evans et al., 1996; Evans and Levin, 2004), can be modulated by alcohol-drinking status. The drugs are chosen more often, and/or have a more positive profile of subjective effects in MDs than in LDs. In our study the median number of times nitrous oxide was chosen differed significantly between the LDs and the MDs, with the MDs choosing more often (Cho et al., 1997). There are other anesthetics that differ in structure and composition from nitrous oxide. The purpose of the present study was to examine whether alcohol-drinking status modulated reinforcing, subjective, and psychomotor effects of a volatile anesthetic, sevoflurane.

We hypothesized that MDs would choose to inhale sevoflurane to a greater extent than LDs and to report more positive subjective effects from sevoflurane, based on two lines of reasoning. First, the human literature to date suggests that MDs exhibit this patterning of responding to a number of abused drugs from different pharmacological classes (e.g., amphetamine, nitrous oxide, diazepam). Second, there are neurobiological and behavioral characteristics that both ethanol and volatile anesthetics have in common. For example, volatile anesthetics and ethanol enhance γ -aminobutyric acid (GABA)_A and glycine receptor function (Mihic et al., 1997; Beckstead et al., 2001, 2002). Interestingly, other volatile solvents such as toluene also have these effects, indicating that sevoflurane is a valid proxy for studying other more commonly abused inhalants that could not be studied in healthy volunteers (Beckstead et al., 2000). Behaviorally, volatile anesthetics share discriminative stimulus effects with ethanol in mice (Rees et al., 1987; Bowen and Balster, 1997). Thus, the similarity between ethanol and volatile anesthetics (both on neurobiological and behavioral levels) formed, in part, the basis of our hypothesis.

2. Methods

Subject inclusion and exclusion criteria (apart from alcohol consumption requirements), the screening procedures, procedural aspects of the study, and dependent measures have been previously described (Walker and Zacny, 2001) and therefore will be briefly described below.

2.1. Subjects

We recruited participants from the university and surrounding community, primarily from newspaper advertisements and flyers. Individuals who were 1) between the ages of 21–39, 2) had obtained a high school diploma or equivalent, 3) were verbally fluent in English, and 4) drank alcohol at a certain level, were eligible for the study. Subjects had to be healthy, report some level of recreational drug usage, and have no history of drug dependence (American Psychiatric Association 2000). Subjects who met inclusion criteria signed a written informed consent form that described the study in detail. In the consent form, subjects were told that the drugs to be used in the study were drugs commonly used in medical settings and could come from one of six drug classes delivered via a gaseous or aerosol form: sedative/tranquilizer (for example, Valium®), stimulant (for example, amphetamine or speed), general anesthetic (at subanesthetic doses), opiate (for example, morphine), alcohol, or placebo. A debriefing session took place at least 24 hours after the last experimental session and participants were paid for their participation. The study received approval from the local Institutional Review Board.

As stated above, subjects had to drink alcohol at a certain level. LDs had to meet 2 criteria: 1) drink at least 1 drink/month but no more than 4 drinks/week, and 2) drink 2 or fewer drinks/occasion. MDs had to meet 2 or more of the following criteria: 1) drink 7 or more drinks/week, 2) drink 3 or more drinks/occasion at least once/week, and/or 3) drink at least 4 days/week. A “drink” was defined to participants as one shot of liquor, one bottle/can of beer, one mixed drink, or one glass of wine. The criteria for moderate drinking were identical to that used in several other studies that have examined drinking status as a modulating variable of other drugs’ effects (Evans et al., 1996; Cho et al., 1997; Stoops et al., 2003).

2.2. Setting, experimental design and drugs

The experimental room included a reclining chair, television, anesthesia machine, and resuscitative equipment. A randomized, double-blind, placebo-controlled, crossover design was used. The anesthetist was not blind to the dose of sevoflurane being delivered but had minimal verbal contact with the subject. Four sevoflurane concentrations were examined across four different sessions: 0, 0.2, 0.4, and 0.8% sevoflurane in O₂. (The 0% sevoflurane dose was 100% O₂). These concentrations were subanesthetic: a concentration that is used to maintain a state of anesthesia is approximately 2% (Smith, 1996). One of the four doses and placebo (100% O₂) were sampled for 10 min during each session. Following the sampling period, the choice period took place in which participants chose what they wanted to inhale: one of the two sampled agents or “neither” (in which case they received 100% O₂). A Latin square was used to randomize the order of dose conditions, and the order of sevoflurane vs. placebo samples was counterbalanced across sessions. During the 0% sevoflurane condition, the two agents and the “neither” option were all 100% O₂.

2.3. Experimental sessions

The study consisted of four 3.5-hour sessions, each separated by at least three days. All sessions began at 1300 h. Before each session female participants provided a urine sample for pregnancy screening and all participants were given a breath alcohol test. A urine sample was obtained and toxicology screening performed for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and phencyclidine before the second session (subjects were told in the consent form they could be tested before one or more experimental sessions). Participants sat in the recliner and were fitted with a blood pressure cuff, pulse oximeter, and the anesthesia mask. Drops of peppermint oil were placed in the breathing circuit bag before experimental sessions in an attempt to mask any scents associated with drug versus no-drug conditions. The anesthetist delivered 100% O₂ through the mask, and participants were told by the research technician, “You are now breathing drug-free air.” Dependent measures were assessed during this baseline period.

Immediately following the baseline period, a sampling period began. The sampling period consisted of two 10-min sampling trials, separated by 30 min. Participants were told at the beginning of each trial by the research technician, "For the next 10 min you will be inhaling Agent ___ [e.g., Agent A, Agent B], which may or may not contain a drug," and the anesthetist began administering the agent (sevoflurane or placebo). Five min into each sampling trial, dependent measures were assessed. At the start of the choice period, participants were told, "The inhalation period will be 45 min long. Every 5 min I'll ask you what you would like to inhale for the next 5 min. I'll ask you this every 5 min until the 45 min is up. You can choose Agent ___ [e.g., A], Agent ___ [e.g., B], or neither. If you choose neither, you will receive drug-free air. Whatever you choose is entirely up to you." Nine trials occurred during the 45-min choice period, and a 60-min recovery period followed. Subjects were transported home by a transportation service after the anesthetist approved their discharge.

2.4. Dependent measures

Inspired and expired concentrations of sevoflurane were displayed on a gas analyzer (Datex-Ohmeda Capnomac Ultima; Louisville, CO) and recorded by the anesthetist 2, 5, and 9 min into each sampling trial. Observer ratings of sedation were recorded at 5 min into the trial, but will not be discussed further because the ratings were not affected by sevoflurane concentration (including 0% sevoflurane). Blood pressure, heart rate, and arterial O₂ saturation were recorded at baseline, during and after the sampling trials, and also after the choice period. The latter three measures were not altered by sevoflurane in either drinking group, and will not be discussed further.

The number of sevoflurane, placebo, and "neither" choices were recorded for each concentration of the drug. Following are the subjective and psychomotor effects in the order in which they were assessed. Although the measures were periodically assessed throughout the experimental session, only those measures assessed 5 min into each sampling trial were subjected to data analysis (except where otherwise noted). The Visual Analog Scale questionnaire, locally developed, consisted of 26 100-mm lines, each labeled with a potential drug effect, and participants were instructed to place a mark on each line indicating how they felt at that moment, ranging from 0 ("not at all") to 100 mm ("extremely"). The Drug Effect/Drug Liking/Inhale Again (DEL/IA) questionnaire assessed the extent to which participants currently felt a drug effect on a scale of 1 ("I feel no effect from it at all") to 5 ("I feel a very strong effect"). Participants were then asked to place a mark on a 100-mm line indicating how much they currently liked the drug effect, ranging from 0 ("dislike a lot") through 50 ("neutral") to 100 mm ("like a lot"), and how much they would want to inhale each of the agents again on another session if given the opportunity, ranging from 0 mm ("definitely would not") through 50 mm ("don't care") to 100 mm ("definitely would"). Two variants of the DEL/IA questionnaire were also used: one was completed at the end of the session, and subjects were asked to complete the other one 24 h after the conclusion of the session. On both forms subjects were asked to rate overall drug liking and overall "want to inhale drug again." The Digit Symbol Substitution Test (DSST) was a 1-min paper-and-pencil test that required participants to replace digits with corresponding symbols according to a digit-symbol code on the top of the paper (Wechsler, 1958). The Odor Detection/Liking questionnaire assessed the extent to which participants currently detected an odor on a scale of 1 ("I do not smell an odor at all") to 5 ("I smell a very strong odor"). Participants were then asked to place a mark on a 100-mm line indicating how much they liked the odor, ranging from 0 ("dislike a lot") through 50 ("neutral") to 100 mm ("like a lot").

The Inhalant Effects checklist is sensitive to psychedelic and somatic drug effects (Atkinson et al., 1977; Block et al., 1990). It consists of 53 brief descriptions of possible drug effects, and participants were asked to place a checkmark next to those items they had experienced since

the onset of the most recent sampling trial. The descriptions fall into seven categories. The number of checkmarks in each category was summed to yield seven different scores: changes in body awareness/image; alterations of time perception; experiences of a dreamy, detached reverie state; diminished cognitive-motor proficiency; happy, euphoric mood changes; changes in sensation/perception; and adverse, dysphoric effects. This questionnaire was given 5 min into the recovery period following the sampling of each agent.

2.5. Data analysis

Differences in characteristics of LDs and MDs were tested using unpaired t-tests for continuous variables and Fisher's exact test for categorical variables. All dependent measures obtained during the experimental sessions were analyzed by repeated-measured analysis of variance (ANOVA). Inspired and expired sevoflurane concentrations during sampling trials in which sevoflurane was being delivered were analyzed using the factors, group (light vs. moderate drinker), concentration (0, 0.2, 0.4, 0.8% sevoflurane), and time (2, 5, 9 min).

Sevoflurane choice totals and preference ratios were analyzed using group and concentration as factors. We calculated preference ratios for each concentration, which were defined as "total sevoflurane choices/(total sevoflurane choices + total placebo choices)." If sevoflurane and placebo were never chosen, the preference ratio (undefined because of division by 0) was said to be 0.

Subjective and psychomotor effects at the 5-min testing point within the sampling trials were analyzed using group (light vs. moderate drinker), concentration (0, 0.2, 0.4, 0.8%), and sample drug (sevoflurane and placebo). When results of ANOVAs were statistically significant ($p \leq 0.05$), Tukey post hoc testing was conducted to identify which differences were statistically significant. The exception to this was with the choice and preference ratio measures: because we hypothesized that MDs would choose sevoflurane to a greater extent than would LDs, *a priori* testing was done using the Tukey test (regardless of the overall p value), comparing choice and preference ratios between LDs to MDs at each concentration.

3. Results

3.1. Characteristics of study participants

Table 1 presents characteristics of the 32 subjects in the study, as a function of their drinking status. Alcohol use in the last 30 days, by definition, differed significantly between the groups. MDs had higher Michigan Alcoholism Screening Test (MAST, Selzer, 1971) scores than did LDs, but it is important to point out that no subjects achieved a score of 5 or higher, indicative of alcoholism. MDs consumed more caffeinated beverages than did LDs, and there were significantly more marijuana smokers in the moderate drinking group. Regarding lifetime (ever used) recreational drug use, more MDs consumed drugs from several classes than did LDs – in some cases there was a trend, and in others the differences were statistically significant. In regards to recreational inhalant use, six MDs had used N₂O, one had used "household products," and another had used amyl nitrite. Repeated measures analyses of covariance were done to determine if the differences in drug use impacted on the results obtained in the repeated measures ANOVA; the covariates had minimal impact and these analyses will not be discussed further.

3.2. Sevoflurane concentrations and observed sedation

Inspired and expired sevoflurane levels during the sampling trials did not differ as a function of Group, but there was a significant Concentration $\times$ Time interaction ($p < 0.001$). Inspired and expired levels increased as a function of concentration, and levels also increased slightly across the 10-min sampling trial for the active sevoflurane concentrations. At the time that testing

began (5 min intra-inhalation), mean inspired (expired) sevoflurane levels were 0.00 (0.00), 0.23 (0.15), 0.42 (0.27) and 0.80 (0.54)% for the 0, 0.2, 0.4, and 0.8% sevoflurane concentrations, respectively.

3.3. Sevoflurane choice and preference ratios

Fig. 1 shows that MDs averaged approximately two more choices for 0.2 and 0.4% sevoflurane, relative to LDs. There was neither a main effect of Group nor a significant Group $\times$ Concentration interaction. Testing at specific concentrations per the *a priori* hypothesis revealed, however, that MDs chose 0.4% sevoflurane significantly more times than did the LDs ($p < 0.05$). There was also a trend at the 0.2% concentration (the critical difference was 2.096 and the difference between the two groups in sevoflurane choices was 2.0).

Preference ratios on average were higher in the MD group than in the LD group at each of the concentration levels. The biggest difference between groups was observed at the 0.2% concentration. As with choice levels there was neither a Group effect nor a Group $\times$ Concentration interaction. Preference ratios did not differ between LDs and MDs when compared at specific concentrations.

A secondary analysis examined number of choices of the three options (sevoflurane, placebo, neither) using Group, Concentration, and Agent as factors. There was a significant Agent effect: the neither option was chosen significantly more than the placebo option (mean values of 4.6 vs. 1.6 choices, respectively).

3.4. Subjective effects

Table 2 shows those subjective effects in which a significant Group $\times$ Concentration $\times$ Drug interaction was found. In all cases, sevoflurane effects were greater in the LD group than in the MD group. Differences were most marked in the 0.8% sevoflurane condition. In most cases, ratings between the placebo and the sevoflurane condition in the active sevoflurane conditions did not differ significantly in the MD group. Two exceptions were with the VAS ratings of “high” and “sedated,” in that both MDs and LDs had significantly higher ratings in the 0.8% sevoflurane condition when comparing placebo to active drug. However, at this concentration as with the 0.4% concentration, LDs had significantly higher ratings than did the MDs. Although magnitude of effect did not differ significantly between the groups on ratings of “feel drug effect,” there was a trend for higher ratings in the LD group, and was most evident in the 0.4 and 0.8% sevoflurane conditions.

Significant Concentration $\times$ Drug interactions were found with the following VAS adjectives: “difficulty concentrating,” “elated,” “having pleasant bodily sensations,” “having pleasant thoughts,” and “stimulated.” All ratings were increased by sevoflurane relative to placebo, but in general the increases were significant only at the 0.8% sevoflurane condition. A significant Drug effect was found with the rating of “sleepy.” When examining the mean values for the above ratings in the non-significant Group $\times$ Concentration $\times$ Drug interactions, in all cases, there was a trend for LDs to have higher scores than MDs. Significant Concentration $\times$ Drug interactions were found with the following categories of the Inhalant Effects checklist: changes in body awareness/image, alterations of time perception, experiences of a dreamy detached reverie state, diminished cognitive-motor proficiency, happy, euphoric mood changes, and changes in sensation/perception. With the exception of time perception and changes in sensation/perception, scores tended to be higher in the LD group than in the MD group.

No significant effects were obtained on ratings of drug liking and inhale again, measured within the sampling trials, at the end of the session, and 24 h following the session. However, there was variation between subjects on the drug liking and inhale again ratings assessed during the

sampling period, with some subjects showing increases to varying degrees in one or more of the active sevoflurane conditions (comparing drug ratings to placebo ratings).

There were significant Concentration $\times$ Drug interactions on the ratings of odor detection and odor liking. No differences were detected in the 0% sevoflurane condition (both placebo and “drug” were 100% oxygen), but increases in odor detection were obtained in the three active sevoflurane conditions when comparing placebo to drug. The increases were not dose-related. A similar pattern was obtained with odor liking except drug ratings were lower than placebo ratings (indicative of dislike of the odor).

3.5. Psychomotor performance

There was a significant Group $\times$ Concentration $\times$ Drug interaction on total number of symbols drawn on the DSST (Table 2). The Group $\times$ Concentration $\times$ Drug interaction on number of symbols drawn correctly approached significance ($p=0.06$). However, on both measures there was a main effect of Group, with MDs drawing more symbols than LDs, and this pattern was present at each of the concentrations, even in the placebo condition. We therefore conducted a change score analysis (in each group subtracting number of symbols drawn and drawn correctly in the drug condition from the placebo condition for each of the 4 concentrations). There was a significant Group $\times$ Concentration interaction ($p<0.05$) on total number of symbols drawn: there was a significant difference between the 0% and the 0.4% conditions in the LDs only, but within conditions, no differences existed between LDs and MDs. Performance was impaired to a marked and similar degree in the 0.8% condition relative to the 0% condition in both LDs and MDs. There was no Group $\times$ Concentration interaction when analyzing number of symbols drawn correctly, and similar degrees of performance impairment were noted in the 0.8% condition relative to the 0% condition in LDs and MDs.

4. Discussion

The major results of the study can be summarized as follows: sevoflurane at the 0.4% concentration was chosen significantly more times by MDs than by LDs; there were substantial differences in the magnitude of a number of subjective effects of sevoflurane with MDs showing much less of an effect than LDs; and there were no significant differences in degree of psychomotor impairment between the groups.

The choice concentration effect curve was of an inverted U-shaped function (Fig. 1) in MDs with the two lower concentrations generating more choices than did the highest concentration tested. Such a function is typical in nonhuman studies, and we detected such patterns in a previous sevoflurane study (Walker et al., 2004) as well as in a study with nitrous oxide (Walker and Zacny, 2003). At the 0.4% concentration, MDs chose sevoflurane significantly more times than did LDs. Preference ratios, although not significantly different between groups, followed the same pattern as that of choice, i.e., an inverted U-shaped function in MDs with the two lower concentrations generating higher ratios than did the highest concentration tested. Greater choice in MDs in the present study is consistent with several other studies comparing choice of drugs (benzodiazepines and nitrous oxide) as a function of alcohol-drinking status (de Wit et al., 1989; de Wit and Doty, 1994; Evans et al., 1996; Cho et al., 1997; Evans and Levin, 2004).

A number of subjective effects differed markedly in magnitude as a function of drinking status, with MDs reporting lesser effects than LDs (Table 2). This stands in contrast to findings in other studies in which some subjective effects of such drugs as diazepam and *d*-amphetamine were of a stronger magnitude in MDs relative to LDs (de Wit et al., 1989; Stoops et al., 2003). One possibility for the MDs reporting lesser subjective responses to sevoflurane in the present study is cross-tolerance, in that both volatile anesthetics and ethanol enhance γ -aminobutyric

acid (GABA)_A and glycine receptor function (Mihic et al., 1997; Beckstead et al., 2001, 2002). Behavioral evidence suggestive of shared neurobiological mechanisms of action (and potential cross-tolerance) comes from preclinical drug discrimination studies in which volatile anesthetics share discriminative stimulus effects with ethanol in mice (Rees et al., 1987; Bowen and Balster, 1997). There is also preclinical literature showing that mice exposed chronically to ethanol, relative to controls, and “short-sleep” mice (bred for being resistant to hypnotic effects of ethanol), relative to “long-sleep” mice (bred for being sensitive to hypnotic effects of ethanol) require higher concentrations of volatile anesthetics to achieve a given anesthetic endpoint (loss of righting reflex, insensitivity to noxious stimuli) (Johnstone et al., 1975; Koblin and Deady, 1981). In the clinical literature, alcoholism is a factor that is associated with increased volatile anesthetic requirements to induced unconsciousness (Stanski, 1994). Thus the possibility exists that the differences in magnitude of subjective effects might be related to differential degrees of cross-tolerance between alcohol and sevoflurane in LDs and MDs.

The above notion that cross-tolerance occurred to the subjective effects of sevoflurane in MDs is somewhat complicated by the finding that psychomotor impairment as measured by the DSST was not differentially impacted by drinking status. It would seem that the two separate measures should be affected in the same manner if there is cross-tolerance between ethanol and volatile anesthetics. It should be pointed out, though, that several studies have shown that heavier drinkers report less sedative-like subjective effects to ethanol than do LDs, but show similar degrees of impairment relative to the LDs (de Wit et al., 1989; Holdstock et al., 2000; King et al., 2002; King and Byars, 2004). It has been suggested that chronic tolerance might develop to some ethanol effects and not to others (Holdstock et al., 2000). This suggestion has some credence to it in that with other drugs, differential degrees of tolerance develop depending on the particular domain in question (Nies and Spielberg, 1996). It must be acknowledged however that other studies examining responses from light and heavier drinkers to alcohol or CNS depressants have not found a dissociative effect that was evident in the present study (i.e., differences in magnitude of subjective effects but no differences in magnitude of psychomotor impairment) (Cole-Harding and de Wit 1992; de Wit and Doty, 1994; Doty et al., 1997; Evans and Levin, 2002; Stoops et al., 2003; Evans and Levin, 2004). Still other studies using multiple measures of psychomotor tests have shown that in some tests similar degrees of ethanol-induced impairment are found between light and heavier drinkers, but in other tests, heavier drinkers show less impairment than do LDs (Evans and Levin, 2004; King and Byars, 2004). In sum, our findings put in the context of the other studies cited above are not necessarily disparate with the extant literature, but the question still remains why there is such variation in that literature.

While we have presented some evidence that the differences in subjective effects between the LDs and MDs might be influenced in part by differential degrees of cross-tolerance between alcohol and sevoflurane in the two groups, this can only be put forth as a possibility. It is certainly plausible that MDs may have differed from LDs on a number of variables that could have accounted for the differences in magnitude of subjective effects. For example, it could be that light and moderate drinkers were using different metrics, or frames of reference, when rating many of their subjective effects. It may be the case that LDs had a limited history of experiencing strong subjective effects from alcohol as well as from other psychotropic drugs, and may have been more disposed to give higher ratings to effects that were “novel” to them. Conversely, MDs may have had a more extensive history of experiencing strong subjective effects from alcohol and from other psychotropic drugs, and may have been disposed to give lower ratings to effects that they had experienced before and were “used to.”

It was somewhat surprising that liking ratings and “inhale again” ratings in the 0.4% sevoflurane condition, when active agent was compared to placebo, did not differ between the LD and MD groups, given the differences between groups in number of times sevoflurane was

chosen. Also, in the 0.4% condition, positive subjective effects either did not differ between LDs and MDs (e.g., increases in happy, euphoric mood changes in the Inhalant Effects checklist was significantly increased but there was no Group effect), or were absent in the MD group (“having pleasant bodily sensations,” “having pleasant thoughts”). These findings are concordant with other studies showing self-administration of a dose of a drug in the absence of positive subjective effects, indicating that self-administration of a drug is not necessarily accompanied by traditional subjective effects measures of abuse liability (Fischman, 1989; Lamb et al., 1991; Comer and Collins, 2002).

In conclusion, alcohol-drinking status affected sevoflurane choice in a concentration-dependent manner. The results are consistent with several studies comparing light and heavier drinkers, using other drugs. Although both drinking groups were similarly impaired by sevoflurane, the moderate drinkers reported less of a subjective response than light drinkers, suggestive of cross-tolerance. However, it cannot be ruled out that the mechanism of reduced effects reflected an inherent population difference, rather than cross-tolerance, per se.

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Mean Number of Sevoflurane Choices

Figure 1.

Mean ($\pm$ SEM) number of sevoflurane choices in light drinkers (LDs, open bars) and moderate drinkers (MDs, solid bars) as a function of sevoflurane concentration. The 0% Sevoflurane concentration is 100% oxygen. Mean number of choices can range from 0 to 9. The asterisk indicates that the mean number of 0.4% sevoflurane choices by MDs is significantly higher than that of the LDs (Tukey post hoc test: $p < 0.05$).

Table 1

Demographic characteristics of subjects

	Light Drinkers	Moderate Drinkers	Significance
N	16	16	
Sex (males/females)	8/8	8/8	
Age (years)	26.2 (5.6)	23.9 (4.6)	n.s.
Body Mass Index	22.4 (1.3)	23.4 (2.3)	n.s.
Family history of alcoholism (number)	3	3	n.s.
Race (number)			
Black	2	1	n.s.
White	11	15	n.s.
Asian	3	0	n.s.
Hispanic ethnicity (number)	2	2	n.s.
MAST score	0.3 (0.7)	1.8 (1.2)	p<0.001
Current drug use (last 30 days)			
Alcohol: drinks per week	0.7 (0.3)	13.9 (5.1)	p<0.001
Caffeine: drinks per week	2.3 (2.0)	9.0 (9.0)	p<0.01
Tobacco (number of smokers)	2	6	n.s.
Marijuana (number of smokers)	1	10	p<0.005
Stimulants (number of users)	0	1	n.s.
Lifetime recreational drug use (number, ever used)			
Marijuana or hashish	10	14	n.s.
Hallucinogens/psychedelic drugs	2	10	p<0.01
Club drugs	1	7	p<0.05
Stimulants	1	6	n.s.
Tranquilizers	1	1	n.s.
Opioids	0	4	n.s.
Inhalants	0	6	p<0.05

Results shown are means ($\pm$ SD) or number of volunteers. Comparisons between LDs and MDs involving continuous data were analyzed by unpaired t-tests. Comparisons involving number of volunteers with a given characteristic (e.g., used a drug) were analyzed by Fisher's Exact Test. n.s.=not significant.

Table 2

Mean subjective effects and psychomotor values in which a significant Group (light [LD] vs. moderate drinking [MD] history) X Concentration (0, 0.2, 0.4, 0.8%) X Drug (placebo [PLC], sevoflurane [SEVO]) interaction was found.

Concentration History Drug	0.2%			0.4%			0.8%		
	LD	SEVO	PLC	LD	SEVO	PLC	LD	SEVO	PLC
VAS (mm) ¹									
Coasting ('spaced out')	4.8	11.3	1.1	3.9	3.8	6.6	14.7	5.8	1.4
Confused	1.4	2.3	0.4	0.6	1.8	0.9	0.7	3.4	0.8
Dreamy	2.8	11.9	0.4	3.0	5.1	4.5	10.0	5.5	0.8
Drunk	1.5	9.4	0.3	1.4	1.8	0.4	1.5	3.9	0.5
Floating	3.1	10.1	0.4	4.1	2.3	2.6	13.1	4.3	0.7
Heavy feeling	2.0	14.8	0.8	5.4	6.6	4.3	11.2	6.3	7.4
High	2.3	12.9	1.1	4.3	2.9	1.9	12.0	3.4	1.0
In control of thoughts	89.6	84.7	96.8	90.6	86.1	96.3	96.3	86.6	97.9
In control of body	89.6	79.5	97.6	90.1	86.6	96.9	96.1	86.5	88.1
Lightheaded	8.9	16.4	1.4	5.9	9.6	3.6	14.3	4.8	2.6
Sedated (calm)	14.1	21.7	2.7	9.5	7.9	7.6	13.3	5.7	2.9
Tingling	1.3	2.4	0.4	2.1	2.3	0.6	2.4	1.6	1.7
DELTIA ¹									
Effect (scale: 1–5)	1.2	2.6	1.3	2.4	1.3	1.3	2.9	1.3	1.4
Psychomotor ¹									
DSST (# completed)	52.9	51.0	58.5 [*]	52.8[*]	51.9	56.5 [*]	50.2[*]	53.1	57.4
Inhalant Effects checklist ²									
Dysphoria (scale: 0–13)	0	0.1	0.1	0	0.2	0.2	0.1	0.2	0

For the sake of clarity the 0% sevoflurane condition is omitted.

Numbers in bold font indicate that values differ significantly from placebo as determined by Tukey post hoc testing.

¹Data presented are dependent measures assessed at 5 min into the sampling trials.

²Data presented are dependent measures assessed 5 min after sampling trials.

* Tukey post hoc testing determined significant differences existed between LD (light drinkers) and MD (moderate drinkers).