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Abuse liability of intra-nasal midazolam in inhaled-cocaine abusers

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Abstract

Intra-nasally instilled benzodiazepines have been proposed for acute anxiety episodes. However, routes with faster absorption may increase abuse liability. This study compared abuse liability of intra-nasal midazolam between subjects with a history of intra-nasal drug abuse and non-psychiatric subjects on a single-blind randomized controlled trial. Thirty-one inhaled-cocaine abusers and 34 normal volunteers received either 1 mg intra-nasal midazolam or active placebo. Visual analogue scales assessing desire to repeat the experience (ER) and Experience Liking (EL) assessed abuse liability. Profile analysis for repeated measures showed a significant effect of time over ER ($F_{[5,57]}=3.311$, $p=0.011$) and EL ($F_{[5,57]}=3.947$, $p=0.004$), diagnostic group (cocaine abusers scoring higher on both — $F_{[5,57]}=5.229$, $p=0.026$; $F_{[5,57]}=4.946$, $p=0.030$), regardless of the administered substance. It is concluded that the intra-nasal route does not seem to pose risks for non-psychiatric individuals, but it may represent a risk in itself for subjects with a history of drug abuse through this path.

1. Introduction

Midazolam is an imidazobenzodiazepine (Walser et al., 1976) mostly used orally as a hypnotic, but also intramuscularly as a sedative for agitated patients (TREC Collaborative Group, 2003), or intravenously for an even faster onset of action, as in the treatment of status epilepticus (Marik and Varon, 2004). It is also recommended for use before painful diagnostic and anesthetic procedures (Brown et al., 2005).

Another possible administration route is intra-nasal (IN). The IN route attains maximal blood concentration much faster than the oral route and almost as fast as the IV route (Björkman et al., 1997). Although initially indicated for preanesthetic sedation of preschool children (Wilton et al., 1988), it is now used in sedation, preanesthetic procedures and seizure control (Primosch and Bender, 2001; Kogan et al., 2002; Smith and Carley, 2005).

In psychiatry, Schweizer et al. (1992) suggested that an average dose of 0.5 mg IN midazolam aborted panic attacks in panic patients. Its use was also investigated in agitated

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patients (Cheng, 1993), and in claustrophobic, panicking patients (Hollenhorst et al., 2001; Tschirch et al., 2007). The rationale behind Schweitzer's proposal was that, as cumulative exposure to BZD is associated with cognitive impairment (Stewart, 2005; Griffiths and Weerts, 1997; Gorenstein et al., 1994; Bernik et al., 1989), the occasional use of BZDs, symptomatically during panic attacks, could be a clinically sound decision. This points to a potential market for fast acting routes for administering BZDs. These have already been investigated, such as sublingual alprazolam and triazolam (Garzone and Kroboth, 1989), and proposed, such as sublingual midazolam (Odou et al., 1998), and even produced, such as sublingual clonazepam, first marketed in Argentina, 1998, and currently available in several countries (F. Hoffmann-La Roche, Ltd., personal communication, 2006).On the other hand, even though the abuse potential of oral BZDs is lower than that of barbiturates, preparations leading to a higher and faster plasma peak and onset of action may appeal to recreational drug users (Quinn et al., 1997; Griffiths and Johnson, 2005; Grudzinskas et al., 2006). Accordingly, there is evidence of the reinforcing effect of midazolam IV self-administration in monkeys (Munzar et al., 2001) and abuse in humans (Klintz et al., 2005).

Following reports of small epidemics of snorted flunitrazepam abuse amongst substance abusers in Chile, Bond et al. (1994) tested the effects and abuse liability of snorted flunitrazepam. However, in their study, only normal volunteers were tested and flunitrazepam powder is not the fastest acting combination of drug and administration route. In our opinion, if sold outside hospitals, inhaled midazolam would be the BZD of choice for recreational purposes. The abuse liability of BZD has been studied a fair amount among sedative abusers (Mintzer and Griffiths, 2005; Mintzer and Griffiths, 1998; Roache et al., 1995), but there are no studies testing the abuse potential of IN midazolam in subjects with a diagnosis of substance abuse.

The goal of this study was to address intra-nasal midazolam abuse liability among two groups: psychiatric subjects with a particular vulnerability, i.e. acquaintance with intra-nasal drug abuse contrasted to a group of non-psychiatric subjects. The subjective effects of IN midazolam and placebo in inhaled-cocaine abusers and healthy control subjects matched for age and school education were compared. We restricted the sample to male subjects to avoid the mood influencing consequences of the female hormonal cycle. The cocaine abusers were chosen given their experience with the IN administration route. In addition, an investigation of this nature would yield insights into whether such liability could be extended to other types of drug abusers, including cocaine abusers, since BZD may be misused to alleviate cocaine-induced anxiety (Paine et al., 2002; Bond et al., 1994).

2. Experimental procedure

2.1. Subjects

Fifty male subjects with a history of inhaled-cocaine use, drug free for at least 15 days, were previously selected. They were recruited through local advertisements and referrals from three university treatment centers, located in the same region. After a structured psychiatric interview, sixteen subjects were ruled out because of comorbidity with psychotic disorders, gross cognitive impairment or acute mood disorder. Of the remaining 34, three failed to meet criteria for cocaine abuse or dependence. Thirty-one male subjects with a history of inhaled-cocaine abuse (77. 23%) or dependence (24. 77%) were selected for the trial. The controls were thirty-four healthy male volunteers recruited through local advertisements and referrals by the Institute of Psychiatry staff. As with the cocaine users, the controls were interviewed using the Structured Clinical Interview for DSM-IV (SCIDCV; First et al., 1997) to exclude possible current psychiatric diagnoses that could impair self-assessment, such as mental retardation, dementia, psychotic disorders, major mood disorders or any other condition implying in cognitive impairment that could have impaired self-assessment.

All participants gave written informed consent to take part in the study, and the Hospital Ethics Committee approved the study protocol. The study fully complied with the guiding policies and principles for experimental clinical procedures of the World Medical Association Declaration of Helsinki (2002).

2.2. Design and procedure

The study was a single-blind randomized placebo-controlled design; the subjects were blind to whether they received IN midazolam or an active placebo. The cocaine subjects (CS) were divided in two groups. One milligram IN midazolam hydrochloride (0.1 ml in each nostril of a 5.0 mg/ml aqueous solution) was administered with a micropipette (to ascertain precision) to one subgroup of the CS. The same volume of active placebo was used for the other half of the CS. Since midazolam causes a slight burning sensation, active placebo was produced diluting 50 μl of 70% ethanol in a 30 ml vial of a 30% aqueous NaCl solution. The same procedure was repeated for the control volunteers (CV).

The subjects were tested for their psychomotor performance and mood state at baseline. They received instructions that after the IN administration of a substance, that might or might not have a subjective effect on them, they would perform additional tests. Although these instructions could skew responses towards an effect expectation, these contingencies tried to simulate those that naturally occur when individuals are offered abuse drugs, i.e. they are told that the substance should cause a psychoactive effect. Besides, it came as an ethical requirement that subjects should be warned about potential subjective alterations caused by the substance administration.

2.3. Measurements

Abuse liability was assessed by the desire to repeat the experience and appreciation of it. Experience Repetition (ER) and Experience Liking (EL) were set as the primary outcome variables, similar to the methodology previously applied by Bond et al. (1994) for the investigation of snorted flunitrazepam abuse liability. ER was defined as the desire to repeat the experience of the nasal administration of the drug or placebo, measured by a 100 mm visual analogue scale ranging from "would not like to use the substance ever again" to "would like very much to use the substance again". EL was measured using a 100 mm visual analogue scale ranging from "none" to "very much". Mood, arousal and psychomotor effects were assessed as secondary outcome variables.

Mood effects were assessed by a modified version of the Visual Analogue Mood Scale (VAMS — Bond and Lader, 1974), comprising items 2 (Calm/Excited), 13 (Happy/Sad) and 16 (Withdrawn/Gregarious) from the original scale. The VAMS is a 16-item visual analogue scale meant to assess mood states. VAMS items 2, 13 and 16 were selected because they best represent the mood altering effects likely related to the reinforcing effects of drugs.

Arousal effects were assessed by a modified version of the Bodily Symptoms Scale (BSS — Guimarães et al., 1989), comprising items 4 (tremors), 9 (palpitation) and 10 (excitement) from the original