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ORIGINAL INVESTIGATION

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A comparison of the acute behavioral effects of flunitrazepam and triazolam in healthy volunteers

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Abstract Flunitrazepam is an hypnotic benzodiazepine marketed in different European countries. Epidemiological studies have shown that it is frequently abused by opioid addicts. In a survey, "liking" scores for flunitrazepam in methadone maintenance patients were higher than ratings for other benzodiazepines. A double-blind, placebo controlled, crossover clinical trial was conducted to assess the acute behavioral effects of flunitrazepam (0.50 and 2 mg) and triazolam (0.25 and 0.50 mg) in healthy male volunteers. Drug effects on physiological measures, psychomotor performance, and subjective rating scales, including specific questionnaires to evaluate abuse liability (e.g., ARCI or "liking" scores), were assessed before and 6 h after drug administration. Flunitrazepam 2 mg produced the most intense disruptive effects on all the performance tasks, triazolam 0.50 impaired performance except balance. All study drugs at all doses produced sedation symptoms in all or part of the subjective effects questionnaires. Only flunitrazepam 2 mg induced significative increases in some of the scales ("liking", "good effects", "high") that could be related to a possible abuse potential. The results seem to indicate that flunitrazepam, when administered to healthy subjects, produces some pleasurable subjective feelings, that could indicate a higher abuse liability of this drug as compared with other benzodiazepines.

Key words Flunitrazepam · Triazolam · Performance · Subject ratings · Abuse liability

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Introduction

Benzodiazepines are the most widely prescribed psychotropic drugs. It has been reported that between 10% and 20% of the adult population of the Western countries have taken a sedative-hypnotic benzodiazepine during the past year, and between 1% and 3% of these remain on these drugs for more than a year (Balter et al. 1984).

Experimental studies in humans have shown the abuse liability/potential of some benzodiazepines (Griffiths and Sannerud 1987). The prevalence of benzodiazepine dependence has been estimated around 1–3% of all treated patients (Balter et al. 1984). Benzodiazepines seem to be misused or abused, usually by two groups: a) patients who take benzodiazepines initially for medical indications (anxiety, insomnia) and use them for a longer period than generally recommended, especially when prescribed as hypnotics; and b) polydrug users, that consume benzodiazepines outside medical indications and supervision (Cappell et al. 1987; San et al. 1993; King 1994). Data from different narcotic treatment centers have shown that as many as 70% of patients are likely to be using and/or abusing benzodiazepines as indicated by positive urine testing. There is also a relatively high rate of abuse of benzodiazepines in patients included in methadone maintenance programs (DuPont 1988; Iguchi et al. 1993). The psychoactive effects of benzodiazepines seem to be the main reason for their consumption by drug addicts, to enhance or boost the effects of heroin (to obtain a better "high") and to prevent or suppress withdrawal symptoms (Stitzer et al. 1981; Navaratnam and Foong 1990).

Flunitrazepam, an hypnotic benzodiazepine, is marketed in different European countries. Recent studies carried out in Spain, Austria, and Malaysia indicate that flunitrazepam is misused by opioid-dependent subjects and seems to be the most preferred benzodiazepine in this population (Navaratnam and Foong 1990;

Table 1 Statistical results of physiological, psychomotor performance, and subjective evaluations (area under the curve effects; AUC). Abbreviations used are: *F2* flunitrazepam 2 mg; *F0.5* flunitrazepam 0.5 mg; *T0.5* triazolam 0.5 mg; *T0.25* triazolam 0.25 mg; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *RT* reaction time; *F* ANOVA's *F* value (df 4,9); *P* level of statistical significance; Tukey's Test statistical significance: □ $P < 0.05$; ■ $P < 0.01$; N.S. not significant; *blank* not done (ANOVA not significant)

	ANOVA		Tukey multiple comparison test									
			P				F2			F0.5		T0.5
Variable	*F*	*P*	F2	F0.5	T0.5	T0.25	F0.5	T0.5	T0.25	T0.5	T0.25	T0.25
Psychological measures												
SBP	1.39	0.2553										
DBP	51.35	<0.0001	■	N.S.	N.S.	■	■	■	N.S.	N.S.	■	■
Heart rate	91.71	<0.0001	N.S.	■	■	N.S.	■	■	N.S.	□	■	■
Temperature	6.87	0.0003	■	N.S.	N.S.	N.S.	□	N.S.	□	N.S.	N.S.	N.S.
Performance tasks												
Simple RT	17.21	<0.0001	■	N.S.	■	N.S.	■	N.S.	■	■	N.S.	□
Motor time	6.23	0.0006	■	N.S.	□	N.S.	□	N.S.	□	N.S.	N.S.	N.S.
Decision time	13.02	<0.0001	■	N.S.	■	N.S.	■	N.S.	■	■	N.S.	N.S.
DSST	31.56	<0.0001	■	N.S.	■	N.S.	■	■	■	■	N.S.	■
Balance	11.97	<0.0001	■	N.S.	N.S.	N.S.	■	■	■	N.S.	N.S.	N.S.
Maddox - wing	25.44	<0.0001	■	N.S.	■	N.S.	■	□	■	■	N.S.	□
ARCI												
PCAG	40.56	<0.0001	■	N.S.	■	■	■	■	■	■	N.S.	N.S.
MBG	2.49	0.0603										
LSD	4.11	0.0076	□	N.S.	N.S.	N.S.	N.S.	N.S.	■	N.S.	N.S.	N.S.
BG	27.61	<0.0001	■	■	■	■	■	■	■	N.S.	N.S.	N.S
A	1.42	0.2461										
POMS												
Anxiety	0.42	0.7961										
Depression	2.44	0.0644										
Anger	1.76	0.1582										
Vigor	1.66	0.1805										
Fatigue	3.04	0.0295	□	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Confusion	5.20	0.0021	■	N.S.	N.S.	N.S.	■	N.S.	□	N.S.	N.S.	N.S.
Friendliness	0.97	0.4356										
Elation	1.69	0.1737										
Arousal	3.75	0.0119	□	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Positive mood	2.37	0.0710										
Visual analog scales												
Stimulated	1.95	0.1227										
High	9.98	<0.0001	■	N.S.	N.S.	N.S.	■	■	■	N.S.	N.S.	N.S.
Any effect	13.02	<0.0001	■	N.S.	N.S.	N.S.	■	■	■	N.S.	N.S.	N.S.
Good effects	5.71	0.0011	■	N.S.	N.S.	N.S.	■	N.S.	■	N.S.	N.S.	N.S.
Bad effects	9.71	<0.0001	■	N.S.	N.S.	N.S.	■	■	■	N.S.	N.S.	N.S.
Liking	6.58	0.0004	■	N.S.	N.S.	N.S.	■	■	■	N.S.	N.S.	N.S.
Drowsiness	11.62	<0.0001	■	N.S.	■	N.S.	■	N.S.	□	■	N.S.	N.S.
Drunken	4.12	0.0075	■	N.S.	N.S.	N.S.	□	N.S.	□	N.S.	N.S.	N.S.
Active	4.44	0.0051	■	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Passive	3.34	0.0200	□	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Nervous	0.52	0.7218										
Calm	0.45	0.7707										
Concentration	3.94	0.0094	■	N.S.	N.S.	N.S.	N.S.	N.S.	□	N.S.	N.S.	N.S.
Performance	6.14	0.0007	■	N.S.	N.S.	N.S.	N.S.	N.S.	■	N.S.	N.S.	N.S.

Barnas et al. 1992; San et al. 1993). When methadone-maintenance patients ranked their liking for different oral benzodiazepines, flunitrazepam scored higher than diazepam, triazolam, lorazepam or oxazepam (Barnas et al. 1992). Flunitrazepam seems to be mainly abused via the oral route, although there are reports of snorting administration (Bond et al. 1994). The pharmacological or pharmacokinetic bases that may explain the preference for this compound are unknown. In addition to intrinsic pharmacological properties, others factors such as local fashion or availability should also be considered.

In order to assess acute subjective and psychomotor effects of flunitrazepam in healthy volunteers, we conducted a randomized clinical trial using triazolam and placebo as control medications. For testing the

clinical abuse liability, questionnaires such as the Addiction Research Center Inventory (ARCI), "liking" or "high" scales, were used.

Materials and methods

Subjects

Ten healthy male volunteers with a mean age of 26 years (range 20–29 years) and a mean weight of 70 kg (range 62–86 kg) were included in the study and were paid for their participation. They underwent a full medical examination, including 12-lead EKG, and routine laboratory test. They were medication-free and had no history of psychiatric or medical illness, alcoholism or drug abuse. None of the subjects had a history of benzodiazepine or other sedative-hypnotic use. Eight subjects were cigarette smokers.

The study protocol was approved by the local Ethical Committee and the Spanish Ministry of Health (DGFPS 93/125). All volunteers gave their written informed consent prior to inclusion in the study. In order to avoid subjective effects of expectancy, subjects were informed that they would receive single doses of stimulants, tranquillizers or placebo.

Procedure

Subjects participated as outpatients in five experimental sessions that were carried out with at least a 2-day wash-out period. The study was conducted as a double-blind, controlled, cross-over comparison according to a balanced 5×5 latin-square design. The five drug conditions were as follows: flunitrazepam 0.5 and 2 mg; triazolam 0.25 and 0.5 mg; and placebo.

Subjects reported to the laboratory at 8:00 a.m. after an overnight fast. A light breakfast was provided at 8:15 a.m. and the study drug was administered 45 min later. Each 6-h session consisted of a baseline recording of physiological measures, psychomotor performance tasks, and administration of subjective effects questionnaires. Simple reaction time, Digit Symbol Substitution Test (DSST), balance task, Maddox-wing device, visual analog scales (VAS), and physiological measures were performed at baseline (predrug) and 0.5, 1, 1.5, 2, 3, 4 and 6 h after drug administration. The 49-item short form of ARCI and the 72-item version of POMS were administered at baseline and 1, 2, 3, 4 and 6 h after drug administration (at 4 h only ARCI was administered). At 5 h, subjects had a light lunch. During the sessions volunteers were seated in a chair, they were free to engage in leisure activities of their choice (e.g., watching TV, reading, talking), but they were not allowed to work, study or sleep. If drug effects were still evident at the end of the session, subjects remained in the laboratory until effects had disappeared.

Physiological measures

Physiological parameters included systolic and diastolic blood pressure and heart rate. They were measured using an automatic device (Dinamap, Critikon, Tampa, Fla.). Body temperature was measured in the axilla with a standard thermometer.

Performance tasks

The psychomotor performance battery included four different tests: simple reaction time, DSST, balance task, and Maddox-wing device. These tests were selected on the basis of their sensitivity to benzodiazepine effects (Hindmarch 1980). Each participant was pretrained on the psychomotor tasks. The simple reaction time task was to be conducted at least 20 times and the balance procedure to be repeated five times. The criterion for a stable response in DSST training was a coefficient of variation of less than 5% in the correct number of responses in five consecutive trials after at least 20 had been performed.

The simple reaction time is a measure of the sensory-motor performance (Hindmarch 1980) and was assessed using the Vienna Reaction Unit (PC/Vienna System, Schufried, Austria). Details of

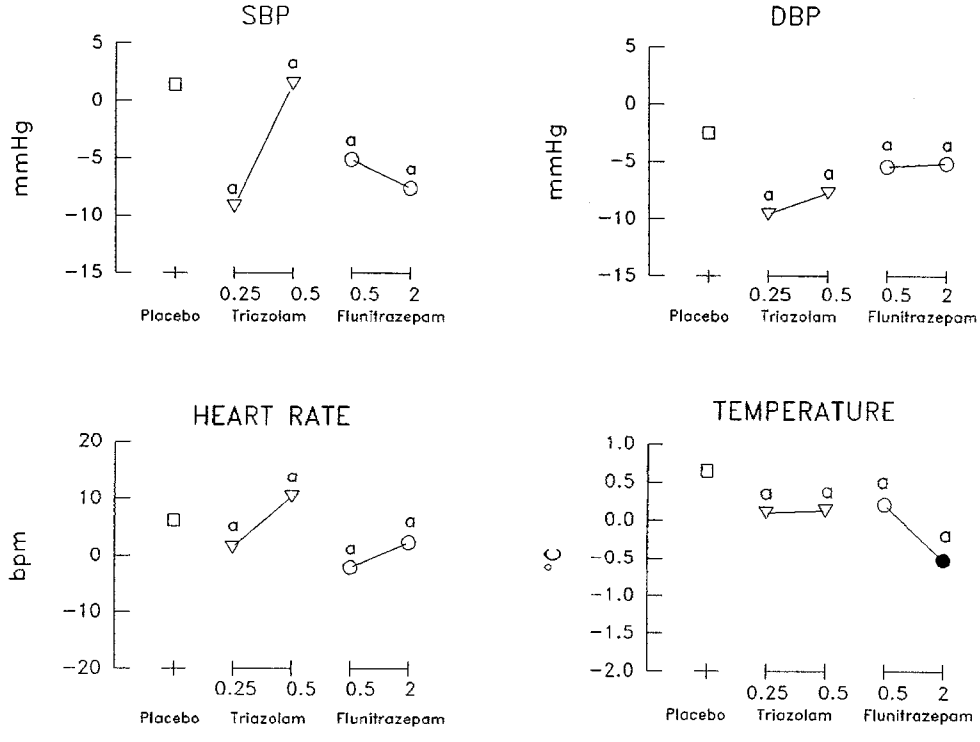

Fig. 1 Dose-response during peak drug effects (differences from baseline) on the physiological measures. Data points represent means from ten subjects. *Filled symbols* indicate a significant difference from placebo ($P < 0.05$). *Letters a, b* and *c* indicate comparisons among the four drug doses; within the same panel any two means designated with the same letter are not significantly different from each other at $P < 0.05$ (Tukey's post hoc tests). *Symbols*: ○ flunitrazepam, ▽ triazolam, □ placebo. *Abbreviations*: *SBP* systolic blood pressure, *DBP* diastolic blood pressure

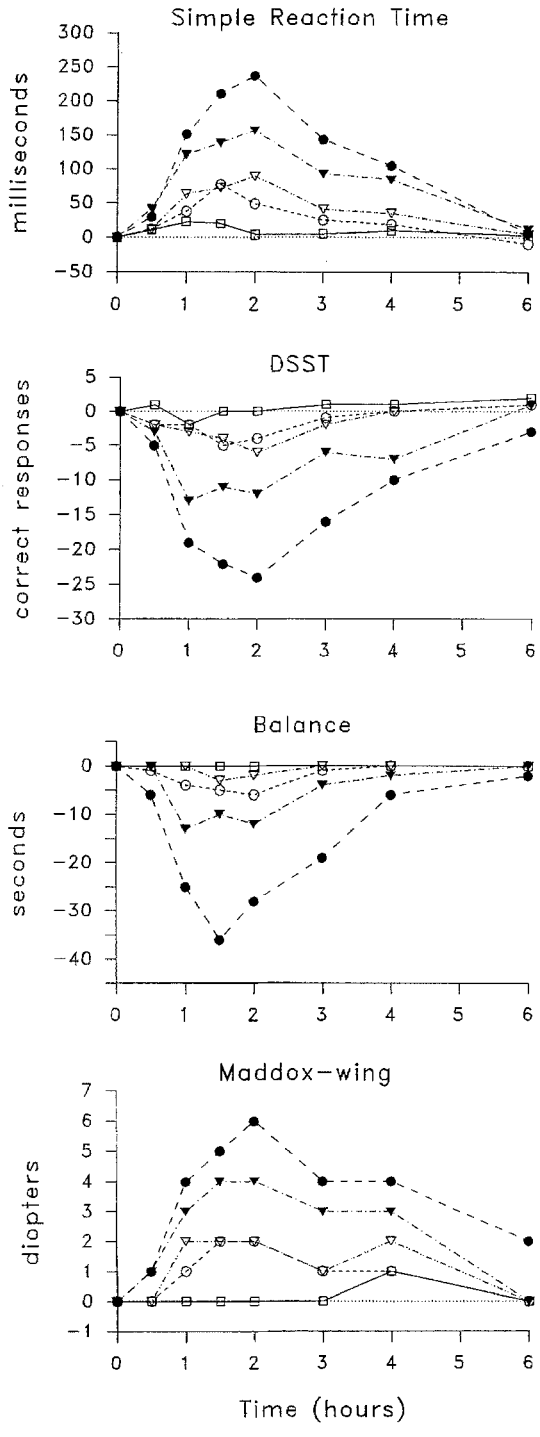

Fig. 2 Time course of drug effects on psychomotor performance tasks (differences from baseline). Data points represent means from ten subjects. *Symbols*: ● flunitrazepam 2 mg, ▼ flunitrazepam 0.5 mg, ▼ triazolam 0.5 mg, ▽ triazolam 0.25 mg, and □ placebo

the procedure have been previously described (Farré et al. 1993) Results were expressed in milliseconds as the mean of the response time to the 50 stimuli for the simple reaction time (total), decision time, and motor time.

The DSST, designed to evaluate recognition and recording of visual information (Hindmarch 1980), is a subtest of the Wechsler Adult Intelligence Scale-Revised (Wechsler 1981). A computerized version was used (McLeod et al. 1982). Scores were the number of correct patterns keyed in and number of patterns attempted in 90 s.

The balance task measured the subject's ability to stand upright on one foot with his eyes closed and arms extended to the side at shoulder height. The score for this task was the sum of the time the subject was able to remain erect without touching the raised foot to the floor when tested for 30 s on each foot; maximum possible score was 60 s (Evans et al. 1990).

Maddox-wing device measures the balance of extraocular muscles and quantifies exophoria and esophoria, expressed in diopters, along the horizontal scale of the device. Exophoria is considered an indicator of psychomotor impairment (Hannington-Kiff 1970).

Subjective effects questionnaires

Three subjective effects questionnaires were used: ARCI (Haertzen 1974), POMS (McNair et al. 1971), and a series of visual analog scales.

A short form of the ARCI consisting of five scales with a total of 49 items (Martin et al. 1971) was used. The five scales were PCAG (pentobarbital-chlorpromazine-alcohol group, a measure of sedation); MBG (morphine-benzedrine group, a measure of euphoria); LSD (lysergic acid dyethylamide scale, a measure of dysphoria and somatic symptoms); BG (benzedrine group, a stimulant scale consisting mainly of items relating to intellectual efficiency and energy); and A scale (amphetamine, an empirically derived scale sensitive to the effects of *d*-amphetamine). A Spanish validated version was administered (Lamas et al. 1994).

Visual analog scales included a series of 14 horizontal 100-mm lines, each labelled with an adjective ("stimulated", "high", "any effect", "good effects", "bad effects", "liking", "drowsiness", "drunken", "active", "passive", "nervous", "calm", "concentration", "performance"). The left ends of the lines were labelled "not at all" and the right ends "extremely". Subjects were instructed to place a mark on each line indicating how they felt at the moment.

At the end of each study session, subjects filled out a drug class identification questionnaire in which the class of drug they believed had been given (stimulant, tranquillizer or placebo) was indicated.

Study drugs

Drugs used were flunitrazepam 0.50 and 2 mg (Rohipnol, Laboratorios Roche, S.A., Madrid, Spain), triazolam 0.25 and 0.50 mg (Halcion, Upjohn Farmoquímica, Madrid, Spain), and placebo (lactose). Drugs were supplied by the Pharmacy Department of Hospital del Mar as identically appearing opaque, white, soft gelatin capsules, and administered with 120 ml tap water. The doses of flunitrazepam were selected according to a previous pilot study (Terán et al. 1993). The doses of triazolam were selected after a pilot dose run-up trial in which doses of 0.125, 0.25, and 0.50 mg were evaluated.

Statistical analysis

Values from all variables were transformed to changes from baseline measures. The peak effect (maximum absolute change from baseline values) and the 6-h area under the time-effect curve (AUC) calculated by the trapezoidal rule, were determined for each variable. These transformations were analyzed by a one-factor repeated measures analysis of variance (ANOVA) with drug doses as factor. When ANOVA showed significant differences between treatments, post-hoc multiple comparisons were performed using the Tukey's test. Differences associated with P values lower than 0.05 were considered to be significant.

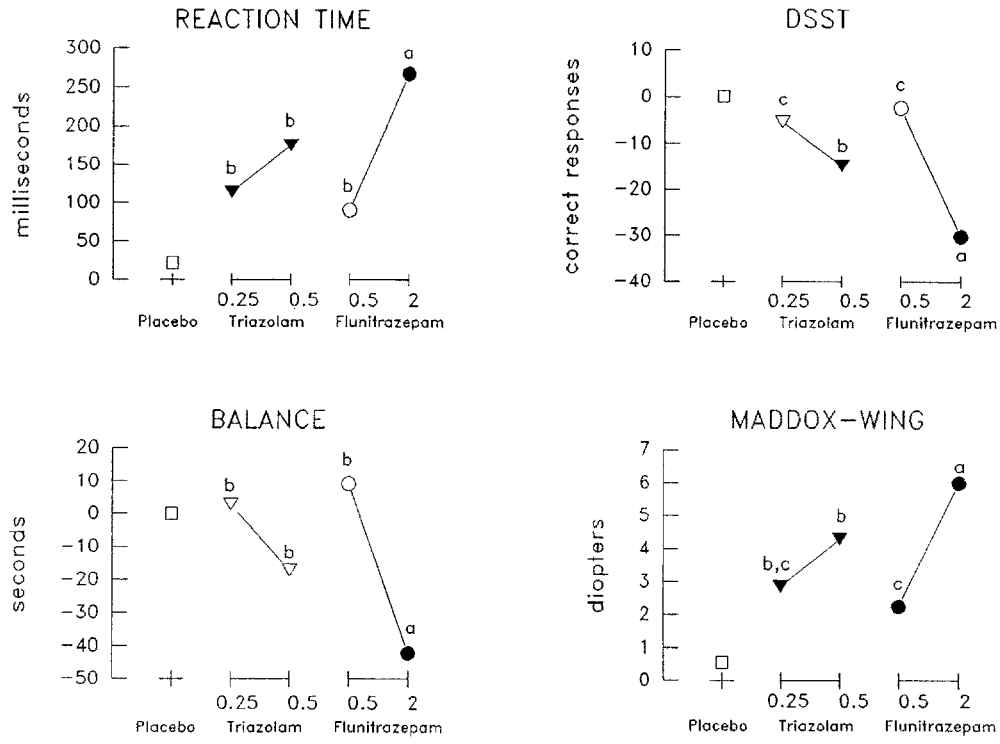

Fig. 3 Dose-response during peak drug effects (differences from baseline) on the psychomotor performance tasks. Other details of the figure are similar to those for Fig. 1

Results

Statistical comparisons of AUC values for each variable are shown in Table 1. Statistical comparisons of peak effects are shown in Figs. 1, 3, 5, 6, and 9.

Physiological measures

In comparison to placebo, flunitrazepam 2 mg and triazolam 0.25 mg decreased the diastolic blood pressure. Triazolam 0.50 mg and flunitrazepam 0.50 mg produced a slight decrease in heart rate. Only flunitrazepam 2 mg induced a fall in body temperature with a mean difference of 1°C. Peak effects changes are presented in Fig. 1.

Psychomotor performance

Triazolam 0.50 mg and flunitrazepam 2 mg significantly impaired the performance of the simple reaction time and DSST. Triazolam 0.25 augmented the simple reaction time (peak effects). All drugs at all doses produced a marked exophoria measured by the Maddox-wing device (peak effects). The effects of triazolam on the simple reaction time and exophoria showed a dose-response relationship (AUC). Only flunitrazepam 2 mg impaired the balance time. Flunitrazepam 2 mg produced greater impairments on the performance tasks than triazolam 0.50 mg. Flunitrazepam 2 mg was the most disruptive drug, followed by the high and low doses of triazolam and by flunitrazepam 0.50 mg, which only increased the scores of exophoria (peak effects). Figure 2 shows the time-course effects of the drug treatments on simple reaction time, DSST, balance, and Maddox-wing tests. Peak effects results are presented in Fig. 3. The maximal change on DSST after triazolam 0.50 mg was observed 1 h after administration; the maximal impairment on reaction time and exophoria occurred after 2 h. In the case of flunitrazepam, the maximal impairments on performance tasks were observed 2 h after drug administration, except for balance, which peaked at 1.5 h.

Subjective effects

All active drugs at all doses produced a significant increase in the scores of the PCAG scale of ARCI in comparison to placebo (peak effect). The increase was dose-related for flunitrazepam (peak effects). The scores of the BG scale were reduced by all the active drugs and doses; this reduction was dose-related in the case of flunitrazepam (peak effects, AUC). Only the high dose of flunitrazepam increased scores of the LSD scale in comparison to placebo. Neither drug increased ratings of the MBG (euphoria) scale in relation to placebo. These results are shown in Fig. 4 (time-course) and Fig. 5 (peak effects).

In the POMS questionnaire, the highest dose of flunitrazepam produced a significant increase in the scores of depression, anger, fatigue and confusion scales, and a significant decrease in the scores of arousal

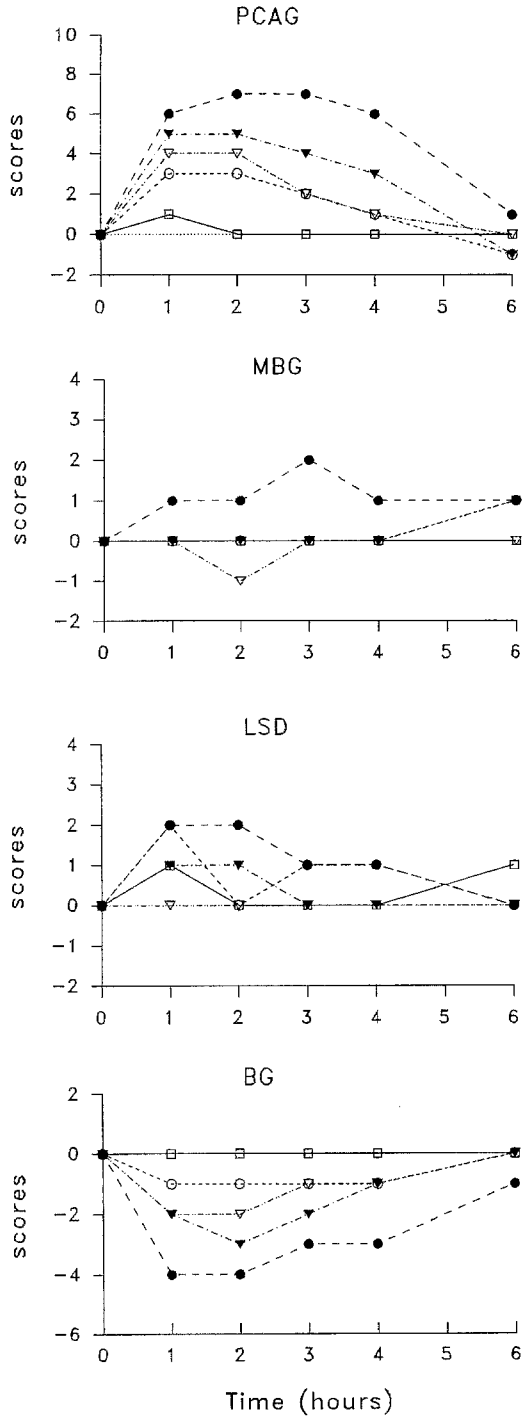

Fig. 4 Time course of drug effects on the ARCI scale scores (differences from baseline). Other details of the figure are similar to those for Fig. 2

and positive mood (Fig. 6). Triazolam 0.50 mg decreased scores of arousal and positive mood (Fig. 6). Triazolam 0.25 produced a decrease in ratings of arousal (Fig. 6). Low dose of flunitrazepam and placebo were not different in any scale.

With regard to the visual analog scales, flunitrazepam 2 mg caused a significant increase in the ratings of "high", "any effect", "good effects", "bad effects", "liking", "drowsiness", "drunken", "passive" or "concentration", and significant decreases in "active" and "performance" as compared with placebo (Figs 7, 8, and 9). Triazolam 0.50 mg produced an increase in ratings of "any effects" and "drowsiness". The effects of flunitrazepam 0.50 mg and triazolam 0.25 mg were not different from placebo scores.

The maximal effects on subjective variables after the administration of flunitrazepam 2 mg, peaked between 1.5 and 2 h. After triazolam 0.50 mg, the effects on PCAG and the "drowsiness" scale were observed at 1 h.

In the pharmacological class identification questionnaire, nine and seven subjects identified the highest doses of flunitrazepam and triazolam as a tranquillizer, respectively. Subjects classified the effects of the lowest doses of either flunitrazepam or triazolam most often as placebo. Placebo administration was identified as a tranquillizer, stimulant and placebo by three, one, and six subjects, respectively.

Discussion

Our findings confirm the characteristic effects of flunitrazepam and triazolam on performance and subjective variables as potent sedative drugs. These results are in agreement with other studies (Grahnén et al. 1991; Ingum et al. 1992; Rush et al. 1993a, b). Flunitrazepam 2 mg produced the greatest sedation, followed by triazolam 0.50 mg, triazolam 0.25 mg, and flunitrazepam 0.50 mg. The doses administered were in the range of those recommended for hypnotic purposes (flunitrazepam: 0.5–1 mg, maximum dose 2 mg; triazolam: 0.125–0.25 mg, maximum dose 0.5 mg) (Association of the British Pharmaceutical Industry 1994; Physician's Desk Reference 1995). Some instruments used in this study (e.g., ARCI or Maddox-wing) were able to detect sedative effects for all study drugs at all doses, while more commonly used scales (e.g. visual analog) failed to demonstrate these effects when the lowest doses of both drugs were administered.

Flunitrazepam and triazolam produced a slight decrease in diastolic blood pressure. In studies in which benzodiazepines were given intravenously, their effects on diastolic blood pressure have been attributed to a decrease in cardiac output and/or a decrease in peripheral vascular resistance (Rao et al. 1972; Mattila et al. 1980). In this study, flunitrazepam decreased skin temperature. In addition to the sedative effects of the drug, several experiments in animals have implicated GABA in the control of body temperature through simultaneous activation of $GABA_A$ and $GABA_B$ receptors (Sancibrian et al. 1991).

All study drugs induced some degree of sedation, they increased the PCAG-ARCI scores, decreased the BG-ARCI scores, and produced exophoria. Flunitrazepam 2 mg appeared more disruptive than

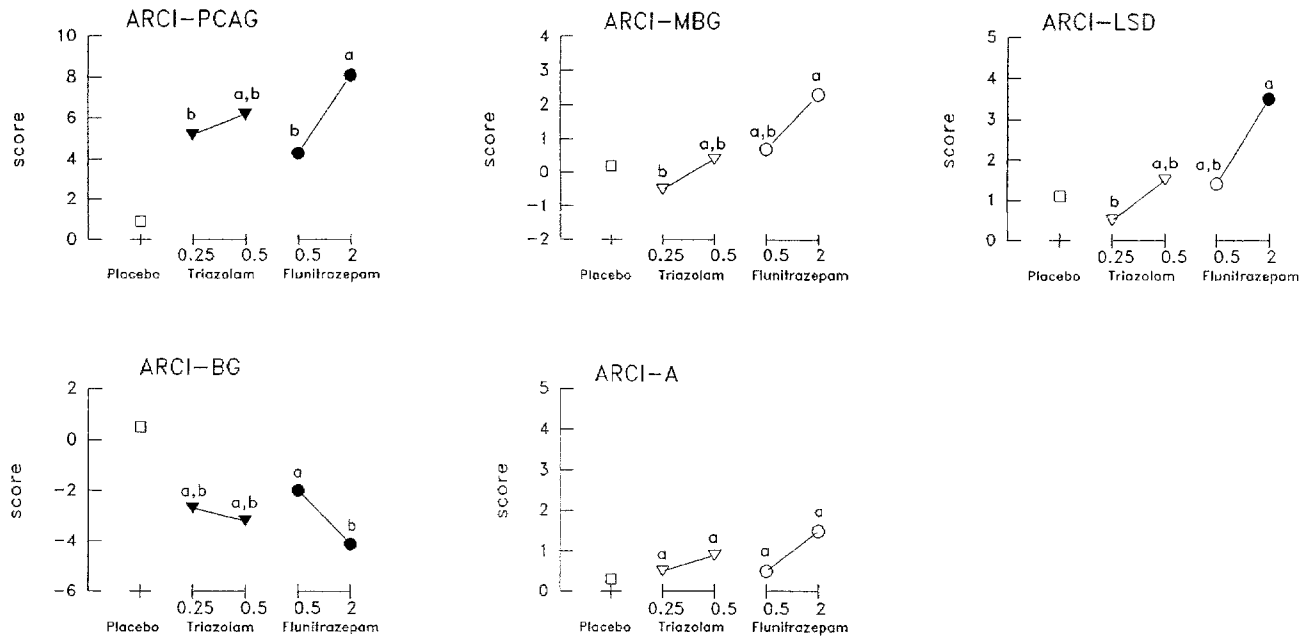

Fig. 5 Dose-response during peak drug effects (differences from baseline) on the ARCI scales scores. Other details of the figure are similar to those for Fig. 1

triazolam 0.50 mg, producing greater decreases in the psychomotor performance (simple reaction time, DSST, Maddox-wing) and higher scores of sedative manifestations. Subjects reported a constellation of symptoms related to sedation, such as drowsiness, passivity, poor concentration, and poor performance. This dose of flunitrazepam also produced feelings suggestive of some degree of intoxication as the reported sensation of "drunkenness" or "bad effects". Flunitrazepam 2 mg also produced increases in the LSD scale of ARCI which has been used as an indicator of dysphoria. These data add evidence to previous studies showing that some benzodiazepines could produce increases in the LSD scale when administered to healthy volunteers (de Wit et al. 1984; Rush et al. 1993a, b). In the case of flunitrazepam 0.50 mg, only the PCAG and BG scales of ARCI, and Maddox-wing tests allowed to differentiate between its effects and placebo. Triazolam 0.50 mg caused a marked impairment in all performance tasks. In contrast to flunitrazepam 2 mg, triazolam 0.50 mg only increased the "drowsiness" scores in the visual analog scales. Triazolam 0.25 mg also produced changes in the simple reaction time. The effects observed after the administration of the low dose of triazolam are of a lesser strength as compared with those found by others (Mattila et al. 1992; Berlin et al. 1993).

Only flunitrazepam 2 mg impaired the balance task. However, in the study of Patat et al. (1986) both triazolam and flunitrazepam impaired the body sway. Our balance task failed to detect any difference between placebo and triazolam 0.25 and 0.50 mg. This finding may be related to the simplicity of the balance measure as opposed to more sophisticated methods (biomechanics force platforms or posturography) (Patat et al. 1986; Robin et al. 1991).

On the other hand, flunitrazepam 2 mg was the only dose that produced an increase in a variety of subjective measures that could be related with a positive mood, such as "high", "good effects" or "liking". In fact, increased "liking" scores seem to be one of the most sensitive measures of subjective effects associated with drug abuse liability (de Wit and Griffiths 1991). However, flunitrazepam 2 mg did not increase the MBG scale of ARCI (developed to measure euphoria produced by opioids and amphetamine-like drugs). The discrepancy between the MBG scale and direct questions of drug "liking" and "good effects" has been previously reported by Rush et al. (1993a, b) when administered triazolam and lorazepam in healthy volunteers, and by Preston et al. (1989, 1992) in sedative abusers who received lorazepam and methocarbamol. The intravenous administration of some opioids (dezocine, morphine) to healthy volunteers produced clear-cut increases in the MBG scores, but other opioids (fentanyl, buthorphanol) failed to produce this effect (Zacny et al. 1992a b; Zacny et al. 1994a, b). In the case of benzodiazepines, increases in the MBG scores and drug "liking" "good effects", and "high" have been described when some compounds (lorazepam, triazolam, diazepam) were administered to sedative abusers or, to subjects with previous or current history of opiate abuse/dependence (Roache and Griffiths 1985; de Wit and Griffiths 1991). When flunitrazepam was administered by snorting to healthy volunteers, doses of 1.5 and 2 mg were associated with increased scores of "liking" or drug strength scales (Bond et al. 1994).

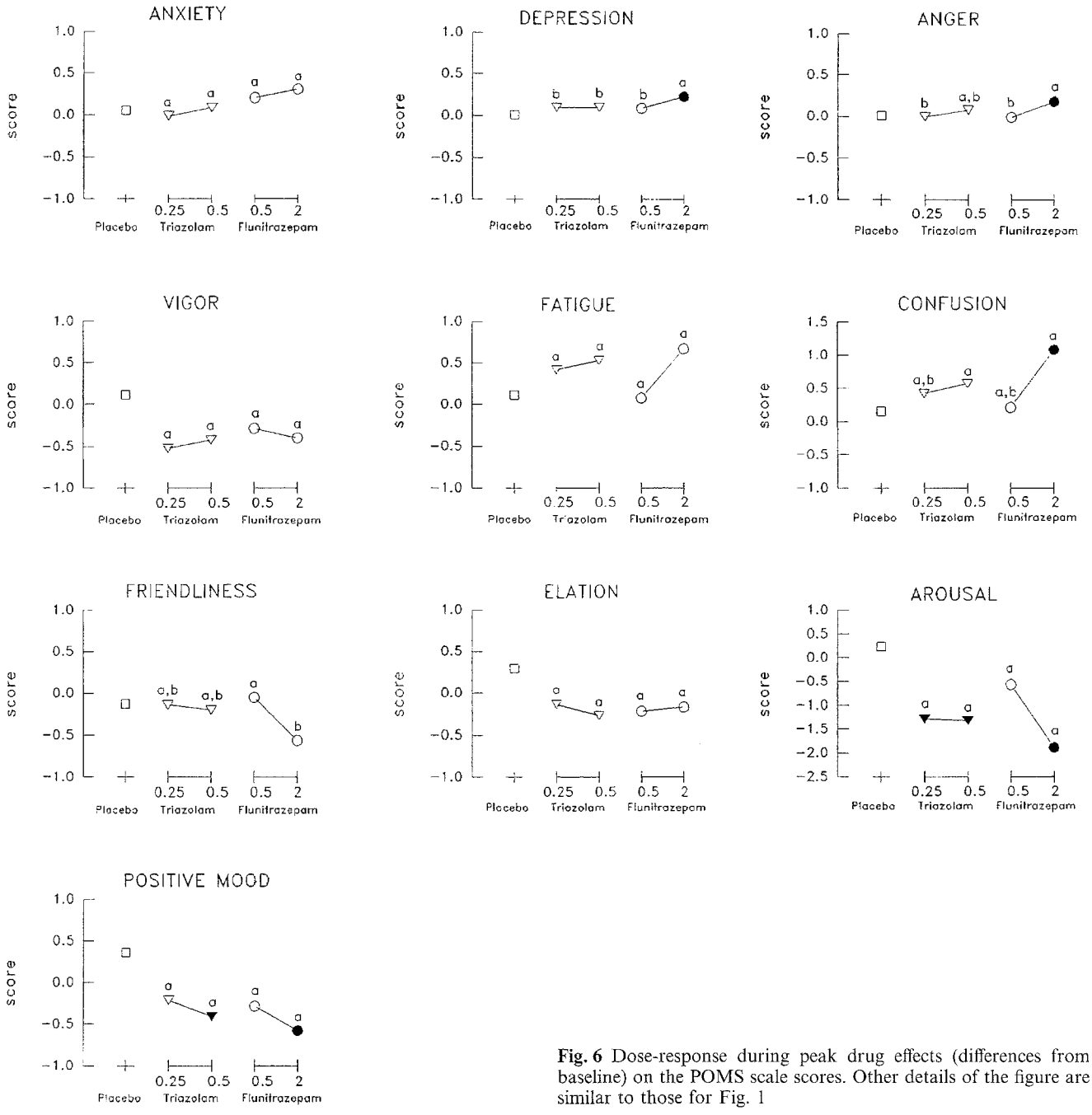

Fig. 6 Dose-response during peak drug effects (differences from baseline) on the POMS scale scores. Other details of the figure are similar to those for Fig. 1

Although flunitrazepam shared many effects with triazolam, it exhibited a different pharmacological profile. The mechanisms underlying these differences are unclear, but they may be related to the high affinity of flunitrazepam for the benzodiazepine receptor, its higher intrinsic efficacy, or its greater lipid solubility. Flunitrazepam has a very fast absorption and seems to penetrate into the brain tissue rapidly from plasma (Arendt et al. 1983; Ingum et al. 1994). It has been suggested that substances with rapid brain penetration and rapid onset of effects could have a higher likelihood of drug abuse liability (Farré and Camí 1991).

In summary, the presence of positive mood symptoms in healthy volunteers after oral administration of flunitrazepam together with results obtained with snorted flunitrazepam (Bond et al. 1993) and epidemiological evidence of flunitrazepam abuse in opioid-dependent patients (San et al. 1993), seem to indicate that the abuse potential of this drug is higher as compared with other benzodiazepines.

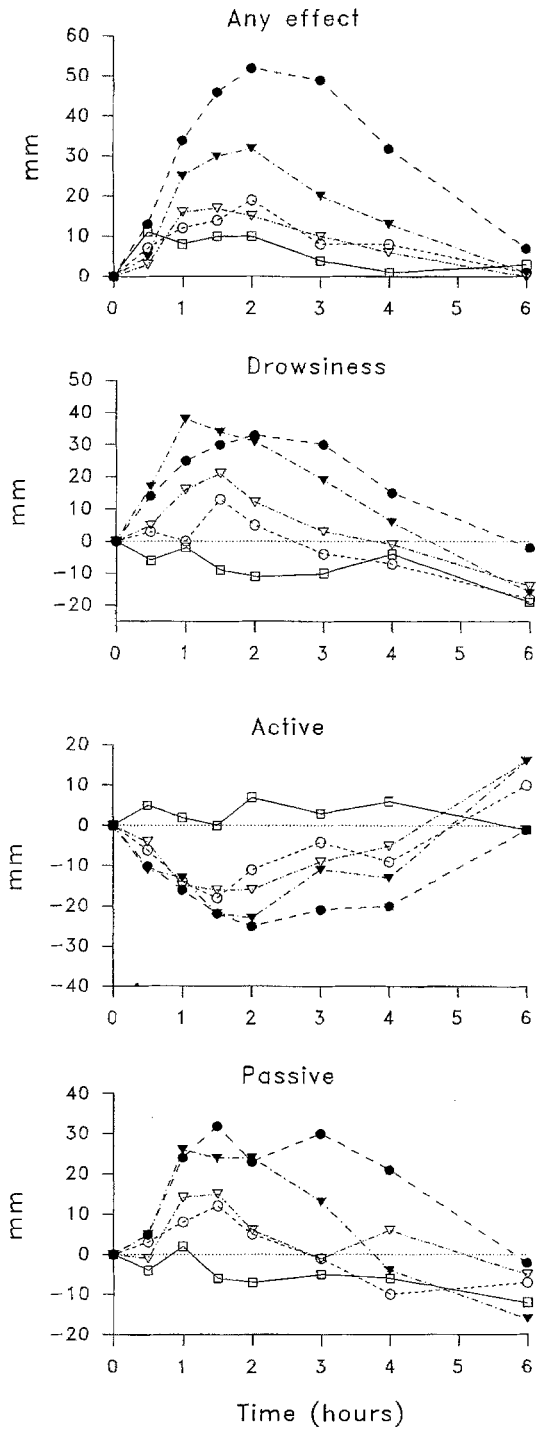

Fig. 7 Time course of drug effects on the "any effect", "drowsiness", "active" and "passive" VAS scores (differences from baseline). Other details of the figure are similar to those for Fig. 2

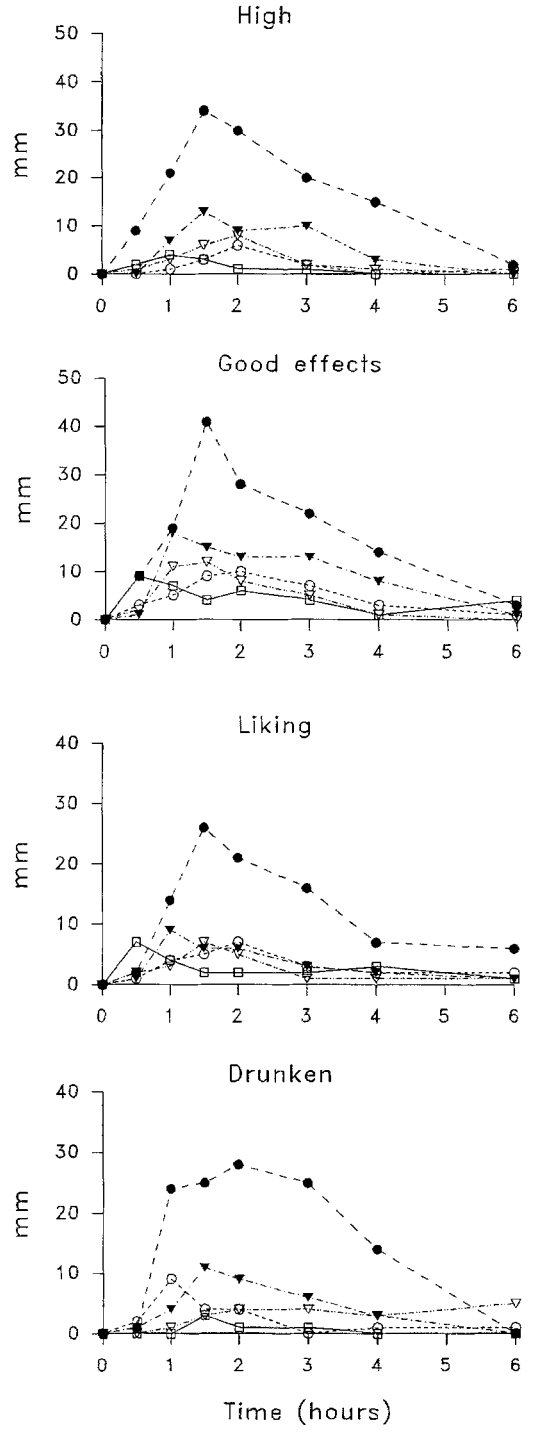

Fig. 8 Time course of drug effects on the "high", "good effects", "liking" and "drunken" VAS scores (differences from baseline). Other details of the figure are similar to those for Fig. 2

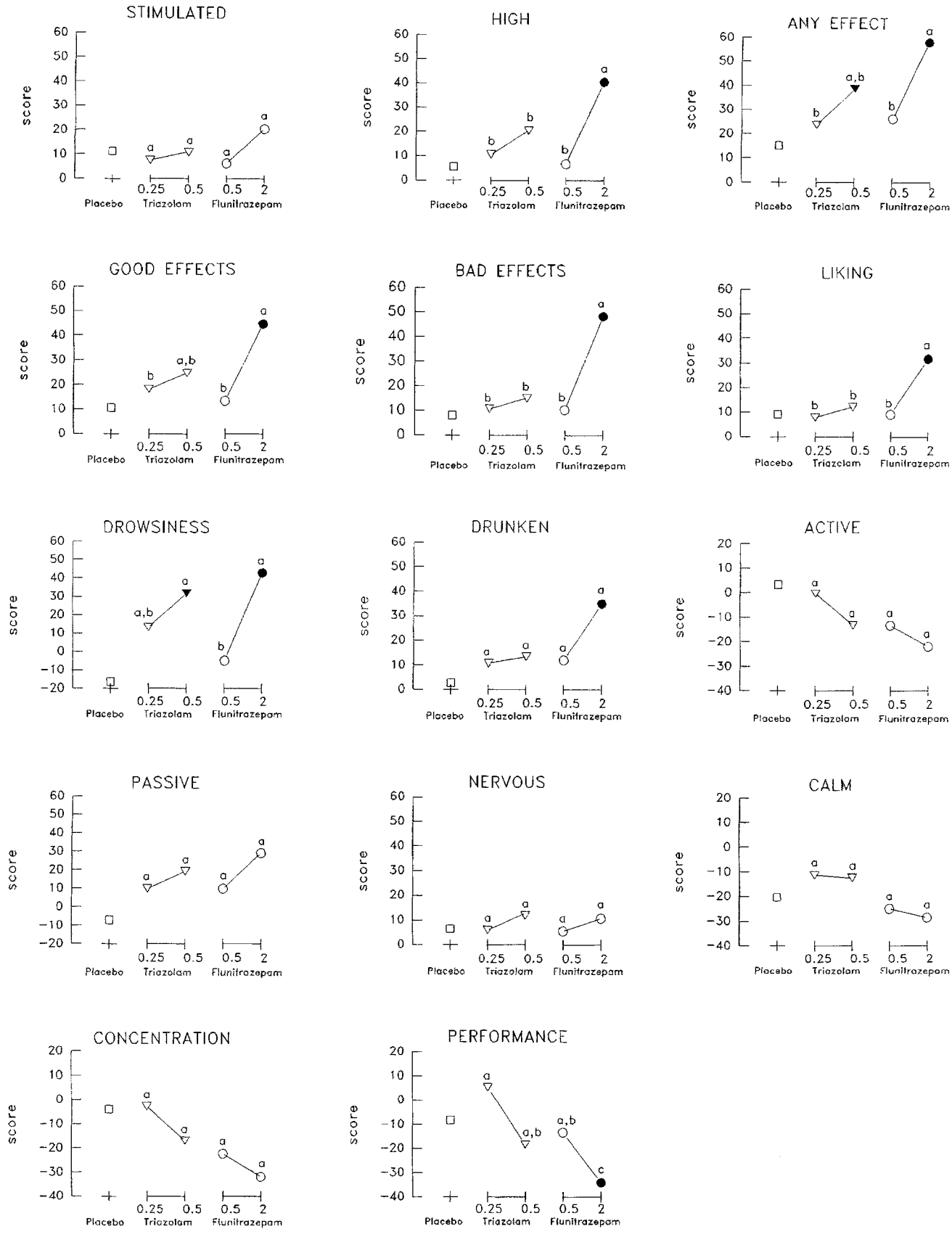

Fig. 9 Dose-response during peak drug effects (differences from baseline) on the VAS scores. Other details of the figure are similar to those for Fig. 1

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