



Modulation of rate of onset and intensity of drug effects reduces abuse potential in healthy males[☆]

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Abstract

Low, medium, and high doses of flunitrazepam were tested in three independent randomized, double-blind, balanced cross-over, placebo-controlled trials to study the influence of rate of onset of effects and dose administered on its acute effects. Three groups of 12 healthy male volunteers received six oral doses of placebo or flunitrazepam in slow and fast onset conditions as follows: six capsules of 0.16 mg (slow) and a single capsule of 0.8 mg (fast) in the low dose trial; six 0.25 mg (slow) and a single 1.25 mg (fast) capsules for medium dose; and six 0.4 mg (slow) and a single 2 mg (fast) capsule for high dose. At each dose level, slow or fast increasing flunitrazepam plasma concentrations lead to similar peak levels, but induced differential subjective and behavioral effects. In addition to objective and subjective sedation, flunitrazepam induced some pleasurable feelings, which were more intense in the fast than in the slow conditions. At the highest dose, unpleasant sedative effects surmounted positive effects, while at the lowest dose pleasurable effects were of low intensity. At the medium dose, the balance between pleasurable and unpleasant feelings resulted in euphorogenic effects, which were evident in the fast condition but were blunted in the slow condition. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Rate of onset and intensity of effects are believed to modulate the abuse potential of a given drug (Farré and Camí, 1991). Nicotine, cocaine, and heroin are usually smoked, injected or insufflated, which are the routes of administration that provide higher bioavailability and faster onset of drug effects. In the

case of benzodiazepines, although there are reports of intravenous or intranasal administration, the oral route is the most common mode of illicit administration. In these conditions, the rate of onset and the intensity of effects are mainly determined by the rate of absorption and distribution to brain, the dose administered and the drug potency.

Epidemiologic and experimental studies among drug abusers consistently show higher preference and reinforcing effects for large doses of benzodiazepines with fast rate of onset of effects and high potency, like diazepam, flunitrazepam or alprazolam (Griffiths and Weerts, 1997). However, few experimental studies have compared the abuse potential-related effects of a given benzodiazepine at different rates of onset of effects. A preliminary report by Busto et al. (1990) administering midazolam intravenously at different delivery rates reported similar peak concentrations but differential intensity in subjective effects (liking, euphoria), cognitive

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impairment, and motor skills. More consistent findings were reported by de Wit et al. (1993) with a double-blind design in which diazepam single (fast onset) or divided (slow onset) oral doses were given to healthy social or moderate drinkers. The slow onset rate condition induced less euphoria and signs of intoxication than the fast onset rate condition. Mumford et al. (1995) compared the effects of immediate-release and extended-release alprazolam formulations in subjects with history of drug abuse, and found decreased positive subjective effects and drug reinforcement-related measures with the extended-release formulation. In order to control for expected differences in peak alprazolam plasma concentrations between formulations, higher doses of extended-release alprazolam were tested. However, to our knowledge no study has systematically explored the differences between fast and slow onset rate conditions at different dose levels. Taking into account that as dose increases the rate of onset is made steeper, and interaction between dose and rate of onset could exist.

Flunitrazepam (Rohypnol[®], Roche), a hypnotic benzodiazepine marketed in most countries of the European Union, South America, Asia and Australia, is a remarkable drug within its class as it combines fast rate of onset of effects and high affinity and efficacy at central benzodiazepine receptors (Mattila and Larni, 1980). Besides its effectiveness in treating insomnia and inducing anaesthesia, its higher abuse liability has received much attention (Woods and Winger, 1997; Griffiths and Weerts, 1997). Flunitrazepam appears to be frequently abused by opioid dependent patients and poly-drug abusers, who rated the drug as the most liked benzodiazepine because it was the 'strongest' and gave a good 'high' (Navaratnam and Foong, 1990; Barnas et al., 1992; San et al., 1993a,b; Darke et al., 1995; Gelkopf et al., 1999). In experimental studies, increases in drug 'liking' scales and drug-induced euphoria have been observed either in normal subjects (Bond et al., 1994; Farré et al., 1996), opioid dependent patients (Farré et al., 1998) and sedative abusers (Mintzer and Griffiths, 1998). Flunitrazepam was chosen as a suitable pharmacological probe to challenge the rate of onset model.

This study was designed to test the hypothesis that slowing the onset of drug effects may decrease its abuse liability, and to evaluate the interaction between dose and rate of onset of effects. The importance of dose was tested by using three different doses: low, medium and high. Three randomized, double-blind, balanced cross-over, and placebo-controlled clinical trials were carried out. Measures included flunitrazepam plasma concentrations, psychomotor performance tasks, different subjective effects questionnaires related to reinforcing and abuse liability properties, and physiologic measures.

2. Methods

2.1. Subjects

Thirty-six healthy male volunteers divided into three groups of 12 participated in the study. All were recreational or social alcohol drinkers and had experience with acute alcohol intoxication. They underwent a full medical history and examination, psychiatric screening, 12-lead electrocardiogram, complete blood cell count, and biochemical profile including serological tests for viral hepatitis, HIV testing, and urinalysis. All participants were found in good health and were medication-free. Participants had no history of alcohol- or drug-related problems or psychiatric disorders according to DSM-IV criteria, and were urine tested for detection of drugs of abuse before inclusion to the study. All of them gave the written informed consent and were paid for their participation in the study. The protocol was approved by the Institutional Review Board and authorized by the Spanish Health Authorities. The study was designed and conducted in accordance with the Declaration of Helsinki.

As shown in Table 1, characteristics of participants included in each of the three groups were similar.

2.2. Study design and procedure

The effects of low, medium, and high doses of flunitrazepam were assessed in three independent clinical trials in which the randomized, double-blind, balanced cross-over and placebo-controlled design described by (de Wit et al., 1992, 1993) was used. Each group of 12 volunteers participated in three experimental sessions, conducted once a week, in which they received placebo,

Table 1
Baseline characteristics of the 36 healthy male participants

	Doses of flunitrazepam		
	Low	Medium	High
Subjects, no.	12	12	12
Age, years			
Mean	26	25	27
Range	18–38	21–31	23–33
Body weight, kg			
Mean	74	74	69
Range	65–85	58–87	63–78
Alcohol use, drinks/week ^a			
Mean	7	4	4
Range	1–12	1–9	1–14
Current smokers	6	3	8
Cannabis experience	10	6	10
Stimulant experience	6	4	4

^a One drink equals one alcohol unit, approximately 9 g of ethanol.

Table 2
Flunitrazepam administration schedule and doses: on each experimental session subjects received in double-blind conditions a total of six capsules, containing drug or placebo, administered at 30 min intervals over 2.5 h

Study	Condition	Administration dose (time)						Total (mg) ^a
		1 (0 h)	2 (0.5 h)	3 (1 h)	4 (1.5 h)	5 (2 h)	6 (2.5 h)	
Low dose	Placebo	0	0	0	0	0	0	0
	Fast ^b	0	0	0	0	0	0.8	0.8
	Slow ^c	0.16	0.16	0.16	0.16	0.16	0.16	0.96
Medium dose	Placebo	0	0	0	0	0	0	0
	Fast ^b	0	0	0	0	0	1.25	1.25
	Slow ^c	0.25	0.25	0.25	0.25	0.25	0.25	1.5
High dose	Placebo	0	0	0	0	0	0	0
	Fast ^b	0	0	0	0	0	2	2
	Slow ^c	0.4	0.4	0.4	0.4	0.4	0.4	2.4

^a Doses for the fast and slow conditions were selected to produce equal peak plasma concentrations; accumulated doses in the slow condition resulted 20% higher than those in the fast condition.

^b Fast condition corresponds to the usual single dose administration.

^c Slow condition corresponds to a divided doses administration, which represents a manipulation of administration directed at slowing drug input rate.

single and divided doses of flunitrazepam as described below.

On each experimental session, subjects arrived at the laboratory at approximately 08:00 h after an overnight fast, and were provided a light breakfast. An indwelling catheter was inserted into a forearm vein of the non-dominant arm for blood sampling and normal saline was infused at lowest rate to secure catheter patency. Drug administration began 60 min later. Study parameters were intensively measured before drug administration (baseline) and over a period of 8.5 h thereafter, plus a 24 h assessment. Subjects were allowed to smoke 4.5 h after dosing. A standard lunch was provided 5 h after start of drug administration. During the session, subjects were free to engage in leisure activities (e.g. talking, reading, watching TV) but working or studying was not permitted. In order to simulate a social, recreational setting, subjects were tested in groups of 2–4 and investigators interceded to ease the relationships.

2.3. Measurements

Study parameters were as follows: flunitrazepam plasma concentrations, a battery of psychomotor performance tasks, four questionnaires to assess subjective effects, a questionnaire to identify the class of drug received, and physiologic measures. The schedule of measurements used in the high dose trial was slightly modified in the low and medium dose trials. Blood samples were drawn at baseline and at 1, 2, 2.5, 2.75, 3, 3.25, 3.5 (low and medium), 3.75 (high), 4, 4.25 (high), 4.5 (low and medium), 4.75 (high), 5, 6.5, 8.5, and 24 h after drug administration. Urine was collected before drug administration, from baseline to 4.5 h, from 4.5 to 8.5 h, and from 8.5 to 24 h after drug administration

(data not shown). Psychomotor tasks, subjective effects, questionnaires and physiologic measures were completed at baseline and at 1, 2, 2.75, 3, 3.25 (high), 3.5 (low and medium), 3.75 (high), 4, 4.25 (high) 4.5, (low and medium), 4.75 (high), 5, 6.5, 8.5, and 24 h after drug administration except for the Profile of Mood States, which was administered at 2, 3.5 (low and medium), 3.75 (high), 4.5 (low and medium), 4.75 (high), 6.5, 8.5, and 24 h after drug administration. The drug class identification questionnaire was administered only at the end of the trial (8.5 h).

2.4. Study drugs

On each experimental session, subjects received in double-blind conditions, a total of six capsules containing drug or placebo, administered at 30 min intervals over 2.5 h (first capsule at 0 h, immediately after baseline measures, and last capsule 2.5 h after first one). Participants were informed that they might receive stimulants, sedatives, or placebo, that the purpose of the study was to assess the effects of these drugs at different onset rate of effects on mood and behaviour, and that they could be administered active treatment in any of the six capsules or placebo in all of them. Drugs were supplied by the Pharmacy Department of Hospital del Mar and consisted of identically appearing opaque green soft-gelatin capsules, which were administered with 100 ml of tap water. Doses were selected in accordance with previous studies carried out with flunitrazepam in similar populations (Farré et al., 1996; Arasteh et al., 1999), and tested in a pilot study in two subjects (data not shown).

Details of flunitrazepam administration are shown in Table 2. Flunitrazepam was administered in single dose

(fast onset condition), which corresponds to the usual administration condition, and in divided doses (slow onset condition), which represents a manipulation of administration conditions directed at slowing drug input rate. Conditions were placebo (six placebo capsules), flunitrazepam single dose (five placebo capsules and a last active capsule, fast administration), and flunitrazepam divided doses (six active capsules, slow administration). Doses for the fast and slow conditions were selected, according to the pharmacokinetic model described by Cano et al. (1977), to produce equal peak plasma levels at similar time but at different rates of increase in drug plasma concentrations. Accumulated doses in the slow condition were set at 120% of that of single doses in the fast condition.

2.5. Plasma flunitrazepam concentrations.

Blood samples (7 ml) were collected through an indwelling catheter or venopuncture (24 h sample) into heparinized tubes. Samples were centrifuged at 0°C and 3000 rpm and plasma separated and stored frozen at –20°C until assayed. Plasma concentrations of flunitrazepam were determined by capillary gas chromatography with electron capture detector and flurazepam as the internal standard. Flunitrazepam metabolites were not determined, as they do not contribute to the pharmacologic action of the parent drug. Samples were extracted in solid-phase cationic exchange and hydrophobic interaction columns (Bond Elut Certify, Harbor City, MI) at pH 6. Extracts were injected in a gas chromatographic system (HP5890A Series II, Hewlett-Packard, Palo Alto, CA) fitted with an automatic injector (HP7673A) and coupled to an electron capture detector using as emission source Ni⁶³. Separation was performed in a fused silica capillary column, 5% phenyl-methylsilicone (HP, Ultra-2), 12.5 m long, 0.2 mm i.d. and 0.3 µm film thickness. Recoveries for flunitrazepam and flurazepam were around 85%. Good linearity was obtained over the range 1–20 ng ml⁻¹. Intra-assay and inter-assay coefficients of variation estimated at 1, 10 and 20 ng ml⁻¹ ranged between 7 and 10%. Quantification limit was set at 1 ng ml⁻¹.

2.6. Psychomotor performance tests

The psychomotor performance battery included the Digit Symbol Substitution Test (DSST), simple reaction time, and the Maddox-wing. All subjects attended a training session of 4–5 h before starting study sessions, to familiarize them with testing procedures and questionnaires, and to achieve a steady performance in the DSST and simple reaction time, as described by Farré et al. (1996, 1998).

The DSST is a computerized test in which subjects used a numeric keypad to enter a geometric pattern associated with one of nine digits displayed on the computer screen (McLeod et al., 1982). Scores were the number of correct patterns keyed in 90 s, and reflect cognitive and manual performance. Simple reaction time was measured using the Vienna Reaction Unit (PC/Vienna System, Schuhfried, Austria), in which subjects had to press a button in response to a light as rapidly as possible. Results were expressed in milliseconds as the mean of the response time to 20 stimuli. The Maddox-wing device measures heterophoria in diopters along its horizontal scale (Hannington-Kiff, 1970), which is an index of the tone and coordination of extraocular muscles: a change towards exophoria reveals relaxation and is associated with psychomotor impairment.

2.7. Subjective effects questionnaires

Subjective effects were measured using four instruments: visual analog scales (VAS), the 49-item short form of the Addiction Research Center Inventory (ARCI), the Profile of Mood States (POMS) questionnaire, and a drug class identification questionnaire. Visual analog scales consisted of 15 horizontal 100-mm lines labelled from ‘not at all’ on the left to ‘extremely’ on the right in association with the following items: ‘stimulated’, ‘high (feeling good)’, ‘any effect’, ‘good effects’, ‘bad effects’, ‘liking’, ‘drunken’, ‘drowsiness’, ‘active’, ‘passive’, ‘nervous’, ‘calm’, ‘concentration’, ‘performance’, and ‘have more drug’. Subjects indicated how they felt crossing the line with a mark (Farré et al., 1996, 1998).

A Spanish validated version of the ARCI was administered, consisting of five scales, which measure sedation (pentobarbital–chlorpromazine–alcohol group, PCAG); euphoria (morphine–benzedrine group, MBG); dysphoria and psychotomimetic effects (lysergic acid diethylamide scale, LSD); typical stimulant effects mainly related to intellectual efficiency and energy (benzedrine group, BG); and typical amphetamine effects (amphetamine scale, A) derived from items of MBG and BG scales (Lamas et al., 1994; Arasteh et al., 1999). A 72-adjective version of the POMS from which ten scales are derived was used. These included anxiety, depression, anger, vigour, fatigue, confusion, friendliness, elation, arousal, and positive mood (McNair et al., 1971; Johanson and Uhlenhuth, 1980). At 8.5 h after drug administration and before leaving the laboratory, each subject filled out the drug class questionnaire in which he was requested to indicate the class of drug (placebo, stimulants, sedatives or other) believed to have been administered.

2.8. Physiologic measures

Physiologic measures included systolic and diastolic blood pressure, heart rate, and oral temperature, which were measured using an automatic device (Dinamap 8100-T, Critikon, Tampa, FL).

2.9. Data analysis

Values from all variables other than flunitrazepam concentrations were transformed to changes from baseline measures. The peak effect (maximum absolute change from baseline values) and time to peak effect were determined for each variable. For each separate study, peak effects were analyzed by a one-way repeated measures analysis of variance (ANOVA), with treatment condition as the factor. When ANOVA showed a significant treatment effect, Tukey's post-hoc multiple comparisons were performed. Time course of effects was compared using a two-way repeated measures ANOVA with treatment condition and time as factors. When treatment condition or the treatment condition \times time interaction were statistically significant, multiple Tukey's post-hoc comparisons were performed at each time-point using the mean square error term of the treatment condition \times time interaction. The main comparisons of results between the slow onset and the fast onset flunitrazepam administration conditions were based on peak-effects data, and were corroborated by effects along the time-course function at those time points in which peak plasma concentrations appeared, between 3 and 3.5 h. The study design and sample size allowed only a comparison of treatment conditions within each study, but not between studies. Flunitrazepam pharmacokinetic parameters were peak plasma concentration (C_{max}), time to peak (t_{max}), and the 24 h area under the time-plasma concentration curve (AUC) calculated by the trapezoidal rule. These parameters were compared by ANOVA and 90% confidence intervals of the paired within-subjects log transformed ratio between the slow and fast conditions, following the standard statistic analysis used in pharmaceutical bioequivalence studies. Differences associated with P values lower than 0.05 were considered to be significant.

3. Results

3.1. Plasma flunitrazepam concentrations

Plasma concentrations and pharmacokinetic parameters of flunitrazepam are shown in Fig. 1 and Table 3, respectively. Mean peak concentrations obtained with the slow onset administration were similar to those in the fast onset administration in the low and the high

dose studies — on the average peak concentrations of the slow condition were about 10% lower. In the medium dose study, the peak concentration reached with the slow condition was on average 22% lower than with the fast one. Median time to peak concentrations (between 3 and 3.25 h) was similar in both fast and slow conditions at all dose levels, while the rate of increase was much more rapid in the fast condition: peak concentrations appeared around 40 min after the single dose was given (2.5 h). Flunitrazepam plasma concentrations almost overlapped from 3 h after administration and so forth. The AUCs for the slow condition in all three studies were greater than for the fast condition, with a difference approximately similar to the 20% derived from dose adjustments.

3.2. Psychomotor performance tests

Flunitrazepam decreased DSST scores, increased reaction time, and induced exophoria in Maddox-wing at all three dose studies compared to placebo. Peak effects appeared at a similar time, on average around 3–3.5 h after starting of drug administration, and were of similar magnitude in both fast and slow conditions with the

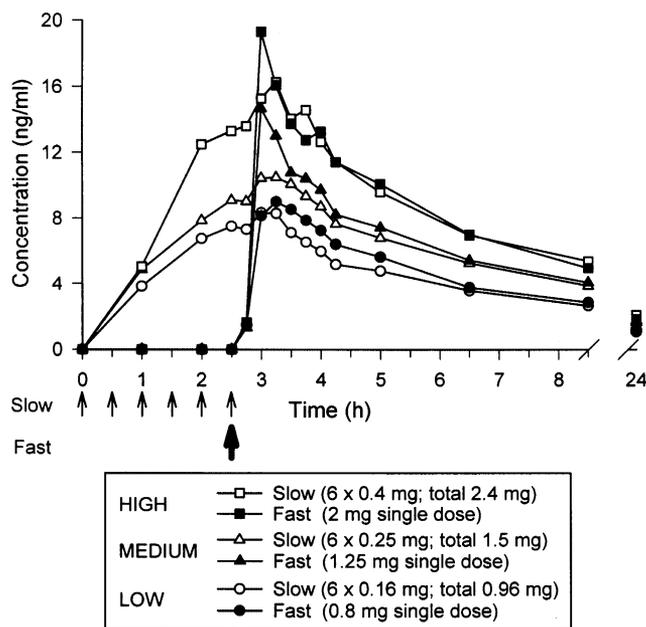


Fig. 1. Mean flunitrazepam plasma concentrations (ng ml^{-1}) of the low, medium and high dose studies. Data points are means of 12 subjects. Arrows below the abscissa indicate flunitrazepam administration. In the low dose study, subjects received six 0.16 mg capsules in the slow administration (total 0.96 mg) and a single 0.8 mg capsule in the fast administration; in the medium dose study, subjects received six 0.25 mg capsules in the slow administration (total 1.5 mg) and a single 1.25 mg in the fast administration; and in the high dose study, subjects received six 0.4 mg capsules in the slow administration (total 2.4 mg) and a single 2 mg capsule in the fast administration. Accumulated slow administration schedule doses were adjusted to reach a similar peak concentration (see text for details).

Table 3
Pharmacokinetic parameters of the low, medium and high flunitrazepam dose studies. Data are means (medians for t_{\max}) of 12 subjects, and percentual ratio between the slow and fast onset conditions with 90% confidence interval

Parameter	Doses of flunitrazepam ^a					
	Low		Medium		High	
	Slow ^b (0.96 mg)	Fast ^c (0.8 mg)	Slow ^b (1.5 mg)	Fast ^c (1.25 mg)	Slow ^b (2.4 mg)	Fast ^c (2 mg)
AUC (ng ml ⁻¹ h ⁻¹)	68.4	60.9	95.8	86.0	132.7	106.0
C_{\max} (ng ml ⁻¹)	109% (97 ÷ 123)		110% (97 ÷ 125)		126% (119 ÷ 134)	
	9.3	10.2	11.8	15.4	18.3	21.2
t_{\max} (h)	92% (82 ÷ 102)		78% (67 ÷ 91)		91% (76 ÷ 109)	
	3.00	3.25	3.25	3.00	3.25	3.13
	89% (83 ÷ 96)		101% (91 ÷ 104)		100% (71 ÷ 112)	

^a Doses for the fast and slow conditions were selected to produce equal peak plasma concentrations; accumulated doses in the slow condition were set at 120% of that of single doses in the fast condition.

^b Slow condition corresponds to a divided doses administration, which represents a manipulation of administration directed at slowing drug input rate.

^c Fast condition corresponds to the usual single dose administration.

exception of DSST in the medium dose study, in which peak effects were more intense in the fast condition (Fig. 2). The time-course of effects showed a clear difference in the rate of onset between both active conditions (Fig. 3); differences appeared before 3 h, i.e. before the single active dose of the fast condition was effective, and at various time points between 3 and 5 h. The differences at 3 and 3.5 h in DSST scores in the medium dose study were in accordance with peak-effect differences. Nevertheless, peak intensity and duration of effects were proportional to doses of flunitrazepam.

3.3. Subjective effects

Flunitrazepam induced subjective feelings of intoxication, sedation and some pleasurable effects compared to placebo. In the drug class identification questionnaire, all subjects in the high dose study ($n = 12$) correctly identified both the fast and slow active conditions as a sedative; in the medium dose study, all subjects ($n = 12$) correctly identified the fast condition as a sedative, and all but one ($n = 11$) correctly identified the slow condition; in the low dose study, 11 subjects correctly identified the fast condition and 10 identified the slow condition as a sedative.

Peak effects in VAS 'any effect' were greater for the fast administration in the medium dose study (Fig. 4), and accordingly, differences appeared at 3.5, 4 and 4.5 h along the time course (Fig. 5). Peak effects in VAS 'drunken' were not statistically different between fast and slow conditions, although some differences appeared between 3 and 4 h along the time-course. The different time-course profile of effects between both active conditions was similar to that of plasma concentrations. However, peak effects in the slow condition

appeared before 3 h after starting the administration of flunitrazepam, whereas in the fast condition peak scores were attained after 3.5 h.

Subjective sedation showed a dose-effect relationship, and at the highest dose, subjects easily fell asleep. Effects observed in the high and medium dose studies were consistently different from placebo, while at the low dose trial only ARCI-PCAG and ARCI-BG showed differences in peak effects as compared with placebo (Figs. 4 and 5). No differences were observed in peak effects of any of these variables between the fast and slow conditions. Time to peak effects in the slow condition appeared before 3 h after start of drug administration, while in the fast condition were reached later (after 3.5 h).

Both active conditions induced pleasurable-related effects compared to placebo at all three dose levels (Figs. 6 and 7). Peak effects showed a feeble dose relationship, but rather seemed dependent on onset rate. In the medium dose study, peak effects for the fast administration were greater than those of the slow one in VAS 'high (feeling good)' ratings, and were different than placebo for the key measure ARCI-MBG. Differences between fast and slow conditions appeared between 3 and 4 h in VAS 'high (feeling good)', 'good effects', and 'liking' in medium and low dose studies, and also in ARCI-MBG scores in the medium dose trial. As with subjective sedative effects, peak scores in pleasurable drug effects were attained before 3 h in the slow condition and after 3.5 h in the fast one. Nevertheless, in the high dose study peak scores of VAS 'good effects' and 'liking' with the slow onset condition appeared early in the time-course of effects (1 h after start of administration).

Flunitrazepam also induced uncomfortable or unpleasant feelings, that were most evident at the highest dose (Figs. 6 and 7). At the high dose level, both active conditions increased scores in VAS 'bad effects' and LSD scale of ARCI. At the medium dose, both active conditions increased scores in the LSD scale and only the fast condition in VAS 'bad effects'. At the low dose, the fast condition increased scores in VAS 'bad effects'.

3.4. Physiologic measures

Systolic blood pressure decreased in the slow condition as compared with placebo at all three fluni-

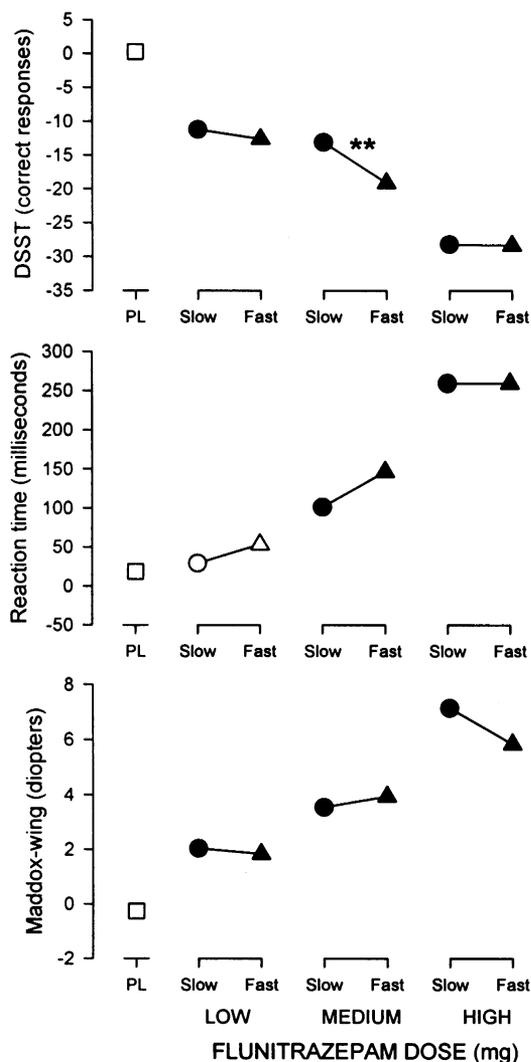


Fig. 2. Peak drug effects on DSST, reaction time and Maddox-wing (differences from baseline) of low, medium and high dose studies. For comparison purposes, placebo values have been averaged across the three studies ($n = 36$) and active condition values ($n = 12$) have been plotted relative to the corresponding placebo within each dose level study. Filled symbols indicate significant differences from the corresponding placebo; differences between slow and fast conditions are represented by: * = $P < 0.05$; ** = $P < 0.01$. For dosing details see legend of Fig. 1.

trazepam dose studies. In the medium dose study, peak decrease in the slow condition was statistically significant in comparison with the fast condition. Oral temperature decreased in both active conditions at the medium and high dose studies.

4. Discussion

The profile of effects induced by flunitrazepam was consistent with the results of previous studies (Bond et al., 1994; Farré et al., 1996, 1998; Mintzer and Griffiths, 1998) and confirmed that besides its objective and subjective sedative effects, flunitrazepam induces some pleasurable feelings related to drug abuse potential. The effects observed in the fast condition were similar to those of a previous study in healthy volunteers (Farré et al., 1996). However, in the former study those effects were observed with a 2 mg dose of flunitrazepam, while in this study positive effects were maximized at the medium dose (1.25 mg), and included increases in the key measure ARCI-MBG. Effects on most measures for the slow onset condition were statistically different from placebo and the fast onset condition at 1, 2 and 2.75 h, which reflects that flunitrazepam effects were readily and consistently detected even at the lowest dose.

Flunitrazepam plasma concentrations were in agreement with previous studies at similar doses (Grahén et al., 1991; Ingum et al., 1992). Plasma concentrations for the fast and slow conditions increased at a very different rate, but resulted in similar peak concentrations that were attained at the same time. However, in the medium dose study peak concentration in the slow condition was lower than in the fast one. This exceptional difference could partly account for the differences found in drug effects between fast and slow administration conditions.

The present findings are in agreement with those of de Wit et al. (1992, 1993) and provide further support to the assumption that the rate of onset of drug effects modulates its reinforcing ability. A novel aspect of this study is the analysis of the influence of intensity of effects by testing three different doses of flunitrazepam. Peak effects for psychomotor performance impairment, sedation, and bad effects due to excessive drowsiness showed a strong dose-relationship, while measures related to drug-induced euphoria and well-being seemed rather dependent on onset rate. Overall, flunitrazepam-induced euphoria, liking, and well-being feelings were less intense in the slow than in the fast condition. At the highest dose, unpleasant sedative effects may have surmounted positive effects, while at the lowest dose pleasurable effects were of low intensity. At the medium dose, the balance between pleasurable and unpleasant feelings resulted in euphorogenic gross effects, which

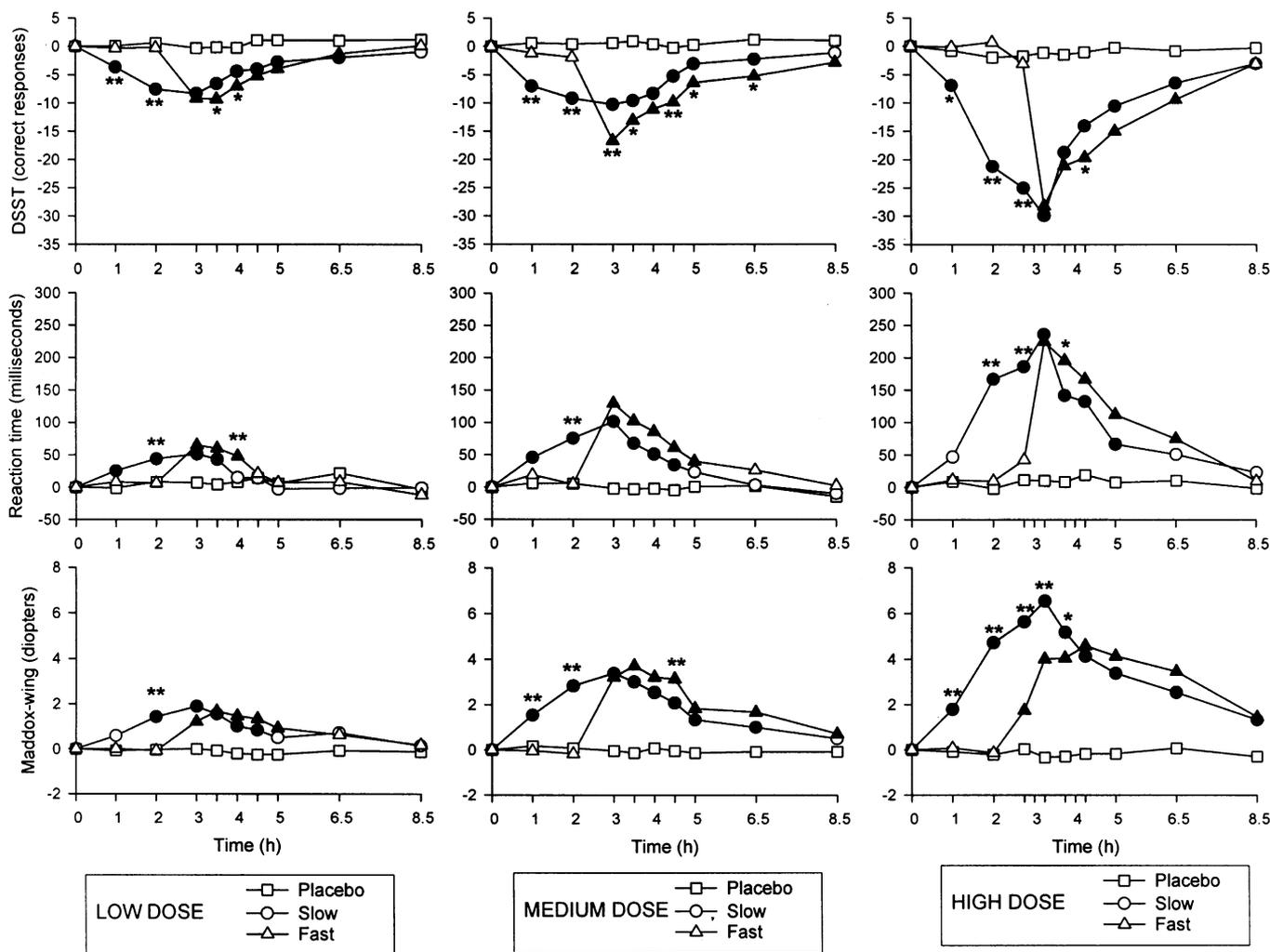


Fig. 3. Time course of drug effects on DSST, reaction time and Maddox-wing (differences from baseline) of low (left column), medium (middle column) and high (right column) dose studies. Data points are means from 12 subjects. Filled symbols indicate significant differences from the corresponding placebo; differences between slow and fast conditions are represented by: * = $P < 0.05$; ** = $P < 0.01$. For dosing details see legend of Fig. 1.

were evident in the fast condition but appeared to be blunted in the slow condition. Nevertheless, the difference in flunitrazepam peak plasma concentrations might be contributing to this finding.

The main comparisons of results between the slow onset and the fast onset flunitrazepam administration conditions were based on peak-effects data, and were corroborated by effects along the time-course function at those time points in which peak plasma concentrations appeared, between 3 and 3.5 h. Other than DSST peak effects at the medium dose, no differences were observed between the fast and slow conditions in any sedative-related measure or psychomotor task. Nevertheless, differences between the two administration conditions were evident for those effects assumed to be related to the reinforcing ability of flunitrazepam. The fast condition induced more intense pleasurable feelings and increased scores in euphorogenic scales.

The differences found in subjective and behavioral effects between the fast and slow onset rate conditions were similar to those described by (de Wit et al., 1992, 1993) using pentobarbital and diazepam. The most plausible explanation for these findings might be the development of acute tolerance to flunitrazepam effects, as reported in other studies (Ingum et al., 1994). Analysis of the time-course data reveals disappearance of effects in the slow condition before plasma concentrations began to fall, which was most evident in subjective measures from 2 h forth. In addition, peak effects in subjective measures were attained earlier in the slow than in the fast condition, whereas peak effects coincided in time in psychomotor performance tasks. Finally, significant differences appeared between fast and slow conditions from 3.5 to 5 h on most measures, while plasma concentrations almost overlapped. Among subjective effects, pleasurable feelings and eu-

phoria appeared to be more affected by tolerance than sedation, as the differences between time to peak effects were greater with the former, and more differences were detected in the comparison between fast and slow conditions from 3.5 to 5 h.

Several experimental studies not aimed at assessing

substance abuse liability demonstrate differences in subjective and behavioral effects of benzodiazepines determined by modulation of the rate of onset of effects (see below). It is difficult to draw clear conclusions as most of them were not designed to allow for direct comparison of peak effects at the time of maximum plasma

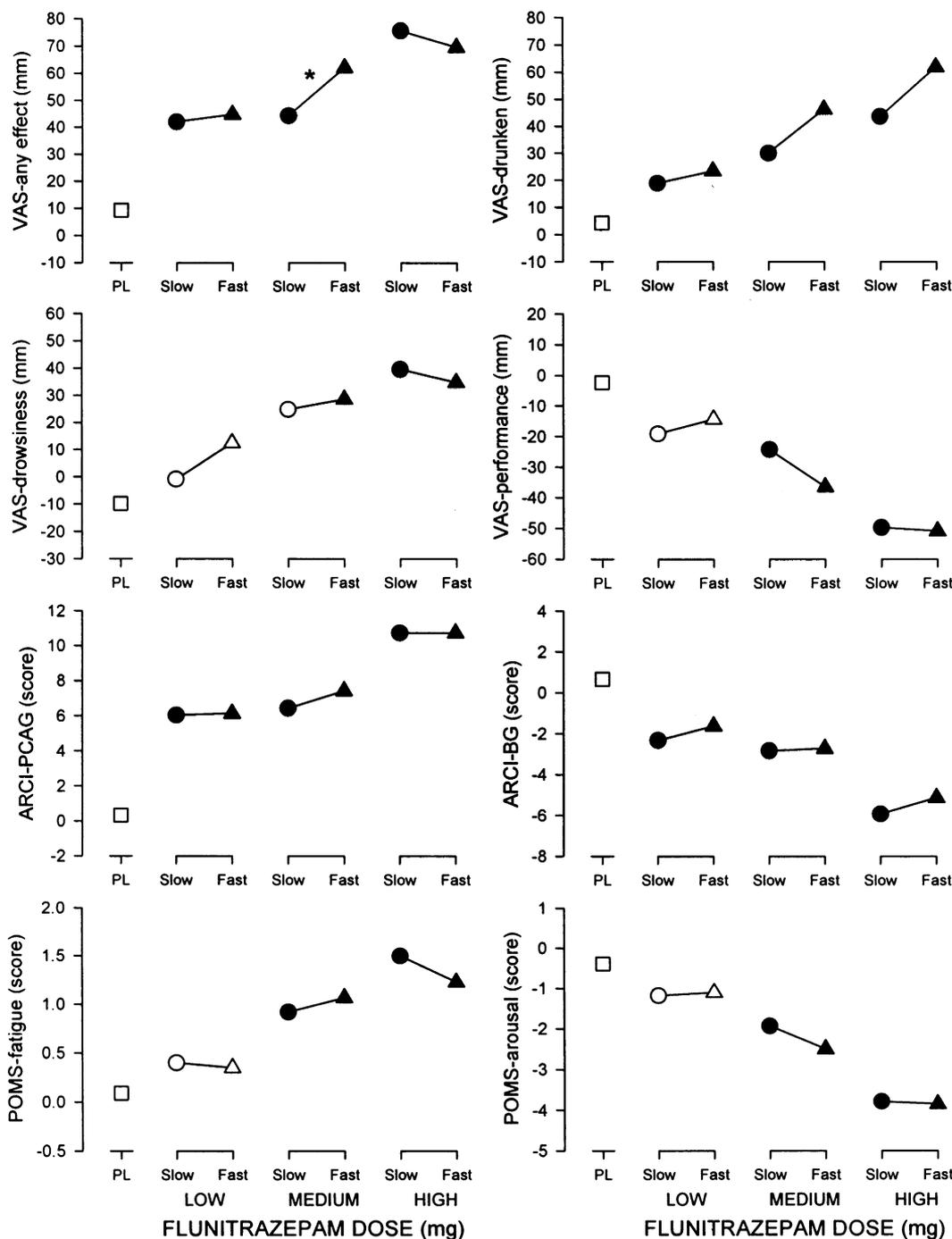


Fig. 4. Peak drug effects on VAS 'any effect', 'drunken', 'drowsiness', 'performance', ARCI-PCAG, ARCI-BG, POMS 'fatigue' and POMS 'arousal' (differences from baseline) of low, medium and high dose studies. For comparison purposes, placebo values have been averaged across the three studies ($n = 36$) and active condition values ($n = 12$) have been plotted relative to the corresponding placebo within each dose level study. Filled symbols indicate significant differences from the corresponding placebo; differences between slow and fast conditions are represented by: * = $P < 0.05$; ** = $P < 0.01$. For dosing details see legend of Fig. 1.

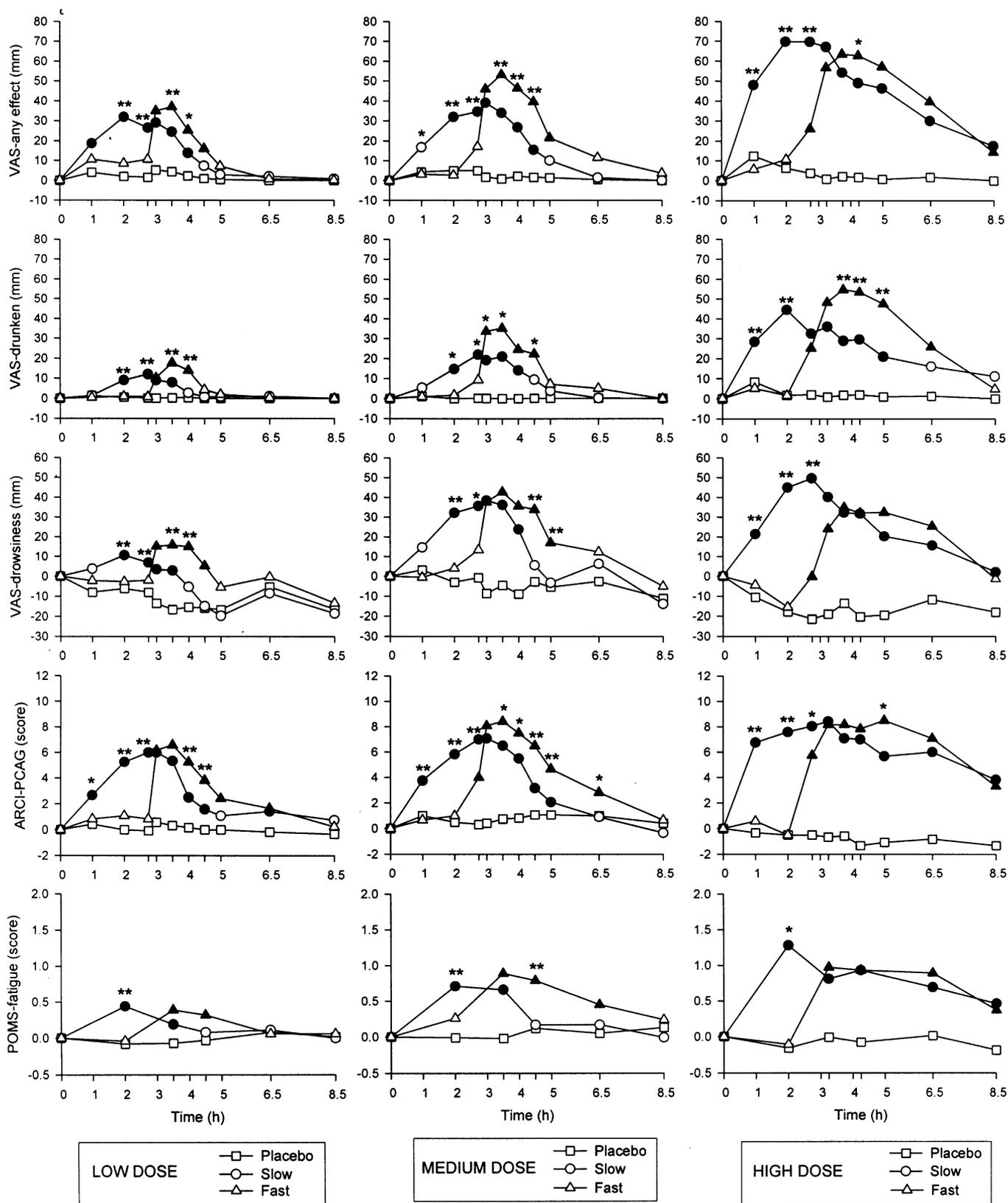


Fig. 5. Time course of drug effects on VAS 'any effect', 'drunken', 'drowsiness', ARCI-PCAG and POMS 'fatigue' (differences from baseline) of low (left column), medium (middle column) and high (right column) dose studies. Data points are means from 12 subjects. Filled symbols indicate significant differences from the corresponding placebo; differences between slow and fast conditions are represented by: * = $P < 0.05$; ** = $P < 0.01$. For dosing details see legend of Fig. 1.

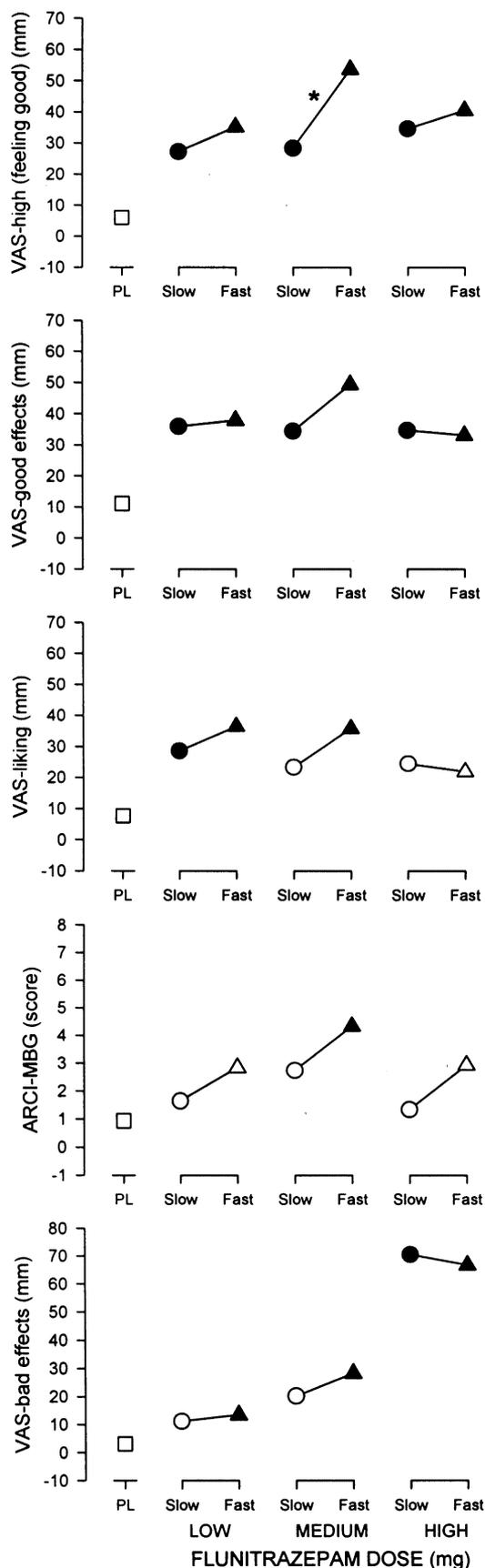


Fig. 6.

concentrations, and results are often confounded by differences in actual peak plasma concentrations. However, a reduced intensity of peak effects in slow onset conditions, more evident in subjective than in objective measures, appears to be a consistent finding.

In the study of Greenblatt et al. (1976, 1977), slowed absorption of chlordiazepoxide resulting from the combined administration with an antacid reduced the intensity of effects on VAS 'spacey', but induced similar sedation (VAS 'thinking slowed down'). Pierce et al. (1984) comparing a tablet and a fast-release soft gelatin capsule of lormetazepam expected to lead to similar peak concentrations, found less intense but slightly more long lasting impairment on psychomotor performance with the tablet formulation. The results of Mattila et al. (1985); Tuomainen (1989) and Salonen et al. (1986) comparing soft gelatin capsules and tablets of temazepam showed that the tablet formulation led to slower absorption and lower peak concentrations, which induced less impairment in psychomotor performance. In a study comparing diazepam controlled-release capsules and plain tablets, Mattila (1988) found less objective and subjective sedative effects with the controlled-release capsule, but lower plasma concentrations were also obtained. Fleishaker and Wright (1992) and Fleishaker et al. (1993) showed that subjective sedation and psychomotor and memory impairment of adiazolam were attenuated when administered in a sustained-release formulation. Smith et al. (1993) found less psychomotor impairment and memory deficit, but similar sedation, with a slow releasing formulation of triazolam, compared to the conventional immediate release tablet. And van Steveninck et al. (1994) reported differences in electroencephalogram beta amplitudes after fast or slow intravenous temazepam infusions adjusted to reach similar pseudo steady-state concentrations.

The only studies specifically aimed at assessing abuse liability of sedatives as a function of the rate of onset of effects have been reported by de Wit et al. (1992, 1993) and Mumford et al. (1995). In fact, the studies of de Wit et al. with pentobarbital (1992) and diazepam (1993) provided the first systematic experimental demonstration that a slower rate of increase in drug plasma concentrations produces lower reinforcing effects. In their studies with moderate social drinkers, peak plasma concentrations and maximal subjective

Fig. 6. Peak drug effects on VAS 'high (feeling good)', 'good effects', 'liking', ARCI-MBG, VAS 'bad effects' and ARCI-LSD (differences from baseline) of low, medium and high dose studies. For comparison purposes, placebo values have been averaged across the three studies ($n = 36$) and active condition values ($n = 12$) have been plotted relative to the corresponding placebo within each dose-level study. Filled symbols indicate significant differences from the corresponding placebo; differences between slow and fast conditions are represented by: * = $P < 0.05$; ** = $P < 0.01$. For dosing details see legend of Fig. 1.

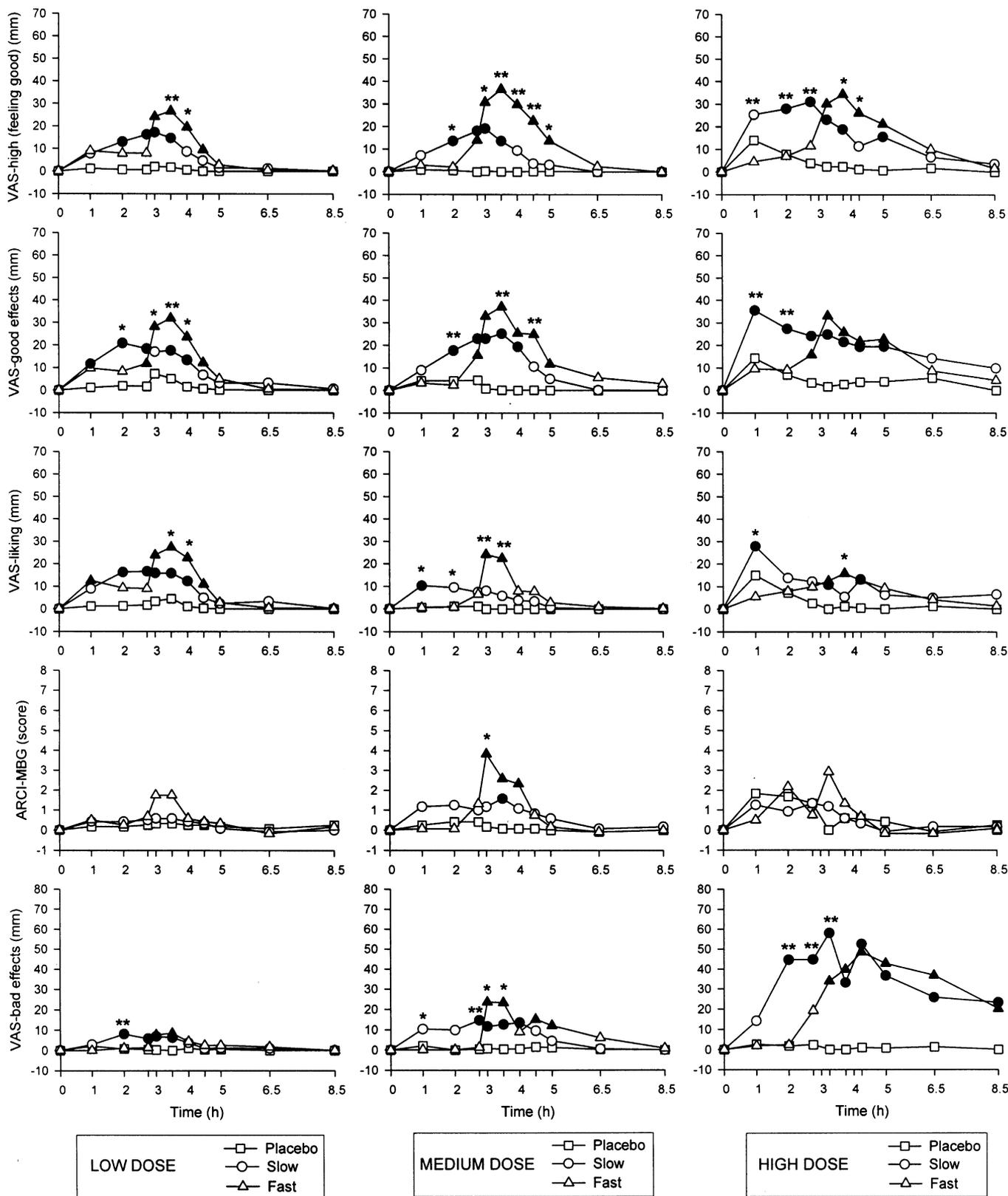


Fig. 7. Time course of drug effects on VAS 'high (feeling good)', 'good effects', 'liking', ARCI-MBG and VAS 'bad effects' (differences from baseline) of low (left column), medium (middle column) and high (right column) dose studies. Data points are means from 12 subjects. Filled symbols indicate significant differences from the corresponding placebo; differences between slow and fast conditions are represented by: * = $P < 0.05$; ** = $P < 0.01$. For dosing details see legend of Fig. 1.

sedation resulted of similar magnitude in the fast-single dose and slow-divided dose administration conditions, whereas drug-induced euphoria and liking were greater with the fast onset rate. Mumford et al. (1995) evaluated the behavioral, subjective and reinforcing effects in sedative abusers of immediate-release and extended-release alprazolam. Extended-release alprazolam showed lower potential for abuse than immediate-release alprazolam, and behavioral and subjective effects following extended-release alprazolam were less intense despite plasma concentrations were higher than after immediate-release alprazolam. However, as different release-rate formulations were compared, differences on their subjective effects might have been confounded by the time of peak effects: a difference of several hours lasted between the maximal effects of both formulations. Using stimulants, Kollins et al. (1998) described similar results when comparing the acute behavioral effects of sustained-release and immediate-release methylphenidate. Our results add evidence supporting that slowed absorption rate can blunt subjective effects intensity, and further corroborates that this dampening affects especially the drug-induced euphoria and liking feelings related to abuse liability.

The influence of dose on the reinforcing effects of flunitrazepam seemed to be related to the balance between pleasant and unpleasant effects and the intensity of effects. At the highest dose, flunitrazepam induced intense sedation and feelings of drowsiness and intoxication that were experienced as unpleasant and even aversive. At the medium dose, the relevant magnitude of pleasurable effects along with the positive balance between pleasant and unpleasant effects could have induced clear euphoric effects. At the low dose, although the balance between pleasant and unpleasant effects was positive, the moderate intensity of effects gave no significant drug-induced euphoria. Moreover, the peak scores in positive subjective effects with the slow onset condition at the highest dose appeared 1 h after administration started, and were similar to the fast condition. Taking into account that those effects correspond to a 0.8 mg flunitrazepam dose administered in two capsules, which is very similar to the fast condition of the low dose trial, the evidence for an interaction between dose and onset of effects is strongly suggested. These findings are consistent with the results of Bond et al. (1994), that found a higher 'liking' with 1.5 mg than with 2 mg snorted flunitrazepam in healthy subjects, probably due to the excessive sedation experienced with the highest dose. This relation between intensity or dose and reinforcing effects has been only partly shown in drug abusers. Although the studies by Mumford et al. (1995) with alprazolam and Farré et al. (1998) with flunitrazepam showed that lower drug doses did not induce clear euphoria or liking, no doses high enough

to induce unpleasant or aversive sedation-related effects were tested. The results reported by Mintzer and Griffiths (1998) did evidence greater scores in 'bad effects' and ARCI-LSD (dysphoria scale) with the highest dose of triazolam (1 mg), but with 8 mg of flunitrazepam the balance between bad and good effects favoured the latter.

It is uncertain whether those findings can be extrapolated from male healthy social or moderate drinkers to drug abusers. Although experimental studies demonstrate little preference or liking for benzodiazepines among normal subjects, diazepam has been shown to function as a reinforcer in social or moderate drinkers. It has been suggested that moderate non-problematic alcohol and recreational drug use history may be associated to benzodiazepine reinforcement among normal subjects (Griffiths and Weerts, 1997). Our volunteers were moderate alcohol drinkers and had experience with cannabis and stimulants, and hence might have been prone to feel positive effects on sedatives similarly than abusers of alcohol, sedatives, or opioids.

In conclusion, the present results indicate that the rate of onset of drug effects is related to the drug reinforcing ability and provide further data for the influence of dose or intensity of effects on the reinforcing balance between pleasant and unpleasant effects. Lowering the dose administered and slowing the rate of onset of flunitrazepam effects decreased its reinforcing potential.

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