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Comparison of Sublingual and Oral Prazepam in Normal Subjects

I. Clinical Data

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Abstract. Five normal volunteers received at a 2-week interval a single dose of sublingual or oral prazepam in double-blind and cross-over conditions. All subjects completed a battery of 15 visual analogue scales before drug intake and 7.5, 15, 22.5, 30, 45, 60, 90 min, 2, 3, 5, 6, 7, 8, 9, 10 and 24 h following intake whereas a computerized assessment of vigilance (reaction time) was performed before intake, 15, 30, 60 min, 2, 3, 6, 8, 10 h following intake. Subjects rated themselves significantly more feeble, clumsy, lethargic, and incompetent following sublingual as compared to oral prazepam while a trend in the same direction was noted for the adjectives muzzy and mentally slow. In contrast, reaction time did not exhibit significantly different changes over time between the two forms. These results suggest a subjectively more rapid onset of activity following sublingual compared to oral prazepam.

Introduction

The latency of onset of the central effect of benzodiazepines after a single intake is a clinical parameter that has received too little attention. In fact, marked differences exist among benzodiazepine compounds concerning their pharmacokinetics of absorption, and particularly the latency of the plasma peak [for a review, see Kaplan and Jack, 1983; Detti, 1983]. Clinically, compounds exhibiting very short latencies seem particularly suitable for the treatment of two disorders: initial insomnia (difficulties in falling asleep) [Greenblatt et al., 1983] and panic attacks [Lader and Petursson, 1983]. Moreover, orally rapid benzodiazepines could represent an alternative to injectable forms in emergency situations.

In this context, we heard that some French practitioners had got used to administer sublingual prazepam when an immediate sedative or anxiolytic activity was needed with, in their opinion, successful results [Bonnet, pers. commun.]. However, no pharmacokinetic or clinical data exist supporting the efficacy of this method. Therefore, the purpose of our study was to compare in normal volunteers the clinical effect of sublingual and oral prazepam. The comparative plasma pharmacokinetics will be reported separately [Jacqmin et al., to be published].

Subjects and Methods

Subjects

The study was performed in 5 healthy male volunteers, aged from 28 to 36 years (mean = 30.8 ± 3.3 years), members of the medical staff of the University Hospital of Liège, Belgium. All subjects, who were not obese (weight inside 20% limits of ideal body weight), had a normal clinical examination, a biological balance sheet within normal values and had not taken any drug during the previous 2 months. Moreover, they were not allowed to use any medication throughout the study period. They were asked to keep their regular habits during this period and not to drink alcoholic or caffeine-containing beverages the day of the two sessions as well as the day before. The evening meal preceding the two session days as well as the lunches of the session day were standardized and devoid

Table I. Statistical analysis of the changes in visual analogue scale scores following sublingual or oral prazepam 20 mg in 5 normal volunteers (two-way ANOVA)

	Time effect		Drug effect		Time-drug interaction	
	F	p	F	p	F	p
Alert/drowsy	2.12	0.02	1.64	NS	1.15	NS
Calm/excited	1.08	NS	1.41	NS	0.64	NS
Strong/feeble	3.55	0.002	52.03	0.002	1.86	0.04
Muzzy/clear-headed	2.63	0.004	6.51	0.06	1.21	NS
Well-coordinated/clumsy	2.75	0.003	8.68	0.04	1.80	0.05
Lethargic/energetic	2.36	0.01	8.26	0.04	0.68	NS
Contented/discontented	1.77	0.06	0.51	NS	0.83	NS
Mentally slow/quick-witted	2.12	0.02	5.19	0.08	1.04	NS
Tense/relaxed	1.00	NS	0.02	NS	0.98	NS
Attentive/dreamy	2.71	0.003	2.50	NS	0.56	NS
Incompetent/proficient	1.15	NS	11.23	0.02	1.18	NS
Happy/sad	1.09	NS	0.63	NS	1.06	NS
Antagonistic/amicable	0.86	NS	3.40	NS	0.63	NS
Interested/bored	1.40	NS	1.04	NS	0.82	NS
Withdrawn/gregarious	1.96	0.03	1.28	NS	0.37	NS

NS = Nonsignificant.

of fat. Finally, prior to the study, all subjects were trained to the computerized assessment of vigilance in order to decrease the learning effect. The protocol was approved by the ethical committee of the University of Liège and all subjects gave their informed consent.

General Procedure

The methodology used was a double-blind cross-over comparison of a single dose of sublingual or oral prazepam 20 mg in randomized order. In two different sessions, at a 2-week interval, the subjects first took orally a tablet of prazepam with 100 cm^3 of water and second placed another tablet of prazepam under their tongue, but whereas one was the active compound, the other was a placebo of the same appearance (double-dummy technique). Drug intake took place at 08.30 h, with the subjects fasting from 20.00 h of the previous evening until 12.30 h on the session day. Assessment of psychological changes by visual analogue scales was performed just before drug intake (t_0) and 7.5, 15, 22.5, 30, 45, 60, 90 min, 2, 3, 5, 6, 7, 8, 9, 10, and 24 h after drug intake while computerized assessment of vigilance was realized before drug intake and 15, 30, 60 min, 2, 3, 6, 8, and 10 h after intake. Blood samples were also collected in order to measure benzodiazepine levels but these results will be reported in a separate article [Jacqmin et al., to be published].

Assessments

Assessments of psychological changes following prazepam intake were performed using a battery of 15 visual analogue scales [Bond and Lader, 1974; von Frenckell et al., 1986, 1987] (table I). The subjects had to indicate a mark, according to their current condition, between pairs of opposite conditions separated by 100-mm lines. Distances in millimeters from the left end were used for the analysis. Computerized assessment of vigilance measured series of 15 reaction times, with the subjects having to push on a button placed in their hand as soon as a visual signal appeared on a screen. Intersignal intervals were randomized. Mean reaction time (s), variance, and correlation between delay of presentation and reaction time were used for the analysis.

Data Analysis

First, baseline (t_0) visual analogue scale scores and reaction times of the two separate sessions were compared by paired t tests. Since no significant differences were present, comparison of changes over time from baseline levels was made by a two-way analysis of variance (ANOVA) with repeated measures. This method allows one to study the global evolution after all sessions (time-effect) and to test if the evolution after one type of intake is significantly different from that after the other (drug-effect and time-drug interaction).

Results

Psychological Changes

Statistical analysis of the changes over time in the visual analogue scale scores are presented in table I. Eight visual analogue scales exhibited significant time-

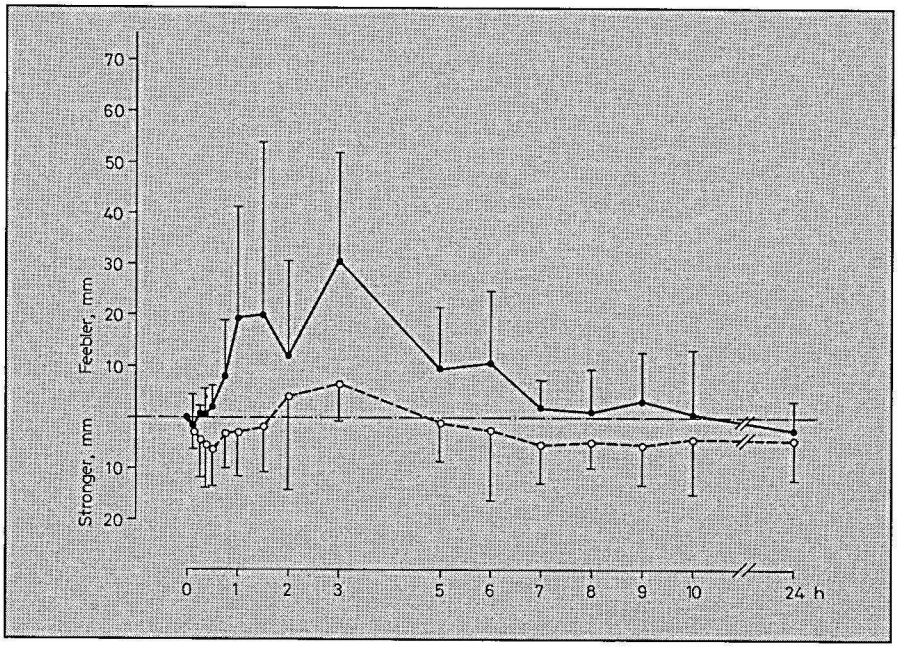

Fig. 1. Changes over time on the visual analogue scales strong/feeble following sublingual (●) or oral orazepam (○) 20 mg in 5 normal volunteers (mean and standard deviation).

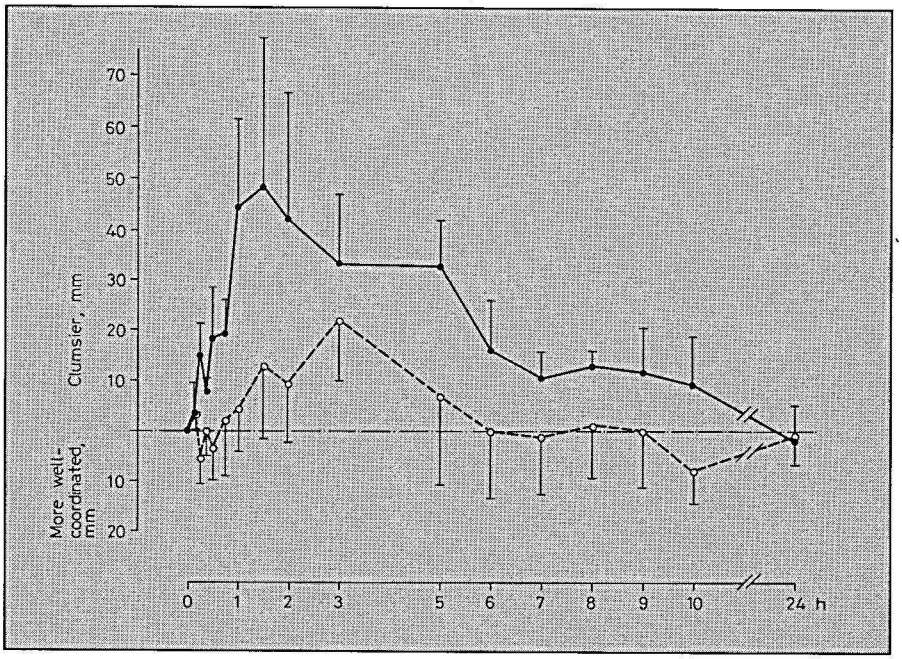

Fig. 2. Changes over time on the visual analogue scales well-coordinated/clumsy following sublingual (●) or oral prazepam (○) 20 mg in 5 normal volunteers (mean and standard deviation).

effect with patients rating themselves significantly more drowsy, feeble, muzzy, clumsy, lethargic, mentally slow, dreamy, and withdrawn following drug intake. Following sublingual prazepam, subjects also rated themselves more feeble, clumsy, lethargic, and incompetent than following oral prazepam and a trend in the same direction was also present for the adjectives drowsy and mentally slow. The changes over time in the ratings of the pairs of adjectives strong/feeble, well-coordinated/clumsy, lethargic/energetic, and incompetent/proficient following sublingual or oral prazepam are displayed in figures 1–4.

Computerized Assessments of Vigilance

The changes over time in mean reaction time following sublingual or oral prazepam are displayed in figure 5. No significant time-affect or drug-effect was present for any of the three parameters (table II).

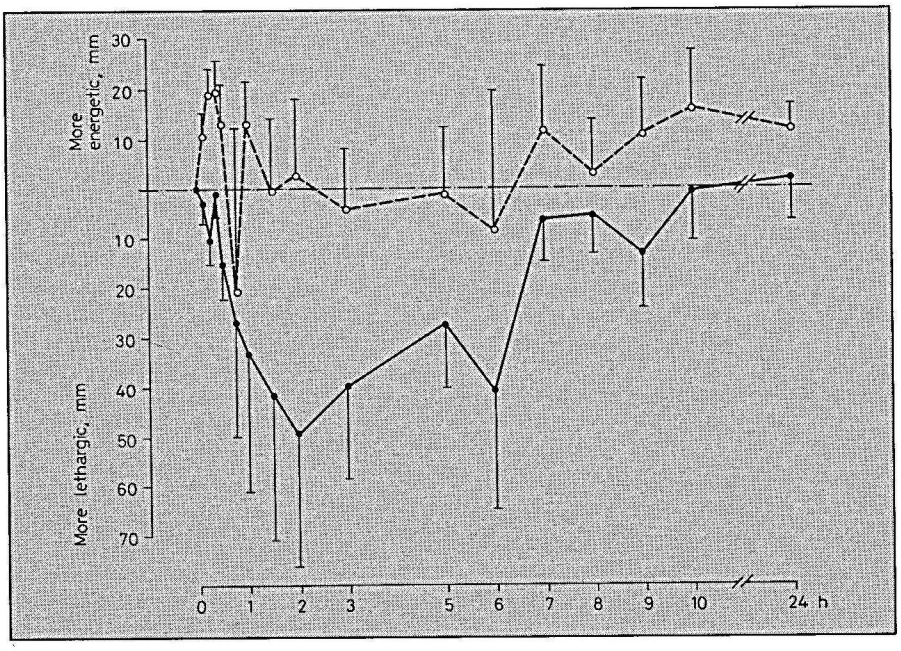

Fig. 3. Changes over time on the visual analogue scales lethargic/energetic following sublingual (•) or oral prazepam (o) 20 mg in 5 normal volunteers (mean and standard deviation).

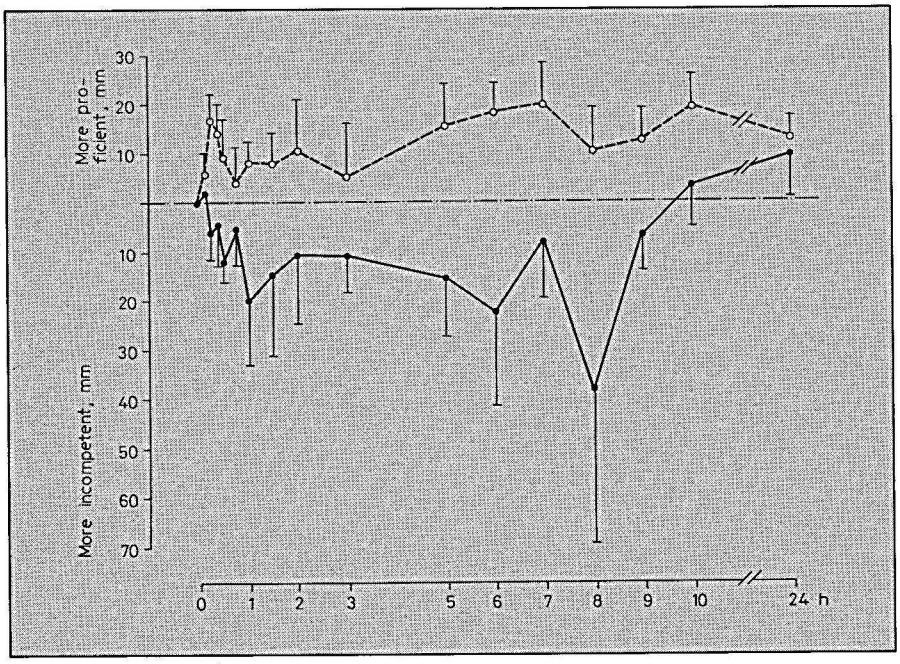

Fig. 4. Changes over time on the visual analogue scales incompetent/proficient following sublingual (•) or oral prazepam (o) 20 mg in 5 normal volunteers (mean and standard deviation).

Discussion

The results of the present study suggest that as compared to the oral form a single dose of sublingual prazepam 20 mg yields subjective sedation in normal subjects. Indeed, 4 visual analogue scales (strong/feeble, well-coordinated/clumsy, lethargic/energetic, incompetent/proficient) showed significant differences and 2 visual analogue scales (muzzy/clear-headed, mentally slow/quick-witted) showed a trend towards significant differences between sublingual and oral prazepam. All these 6 visual analogue scales belong to the same factor 'alertness', as defined by Bond and Lader [1974]. However, the 'objective' assessment of vigilance by computerized reaction time did not confirm the differences in sedative properties between the two ways of administration. Indeed, the differences in reaction time were slight and statistically nonsignificant. This discrepancy may

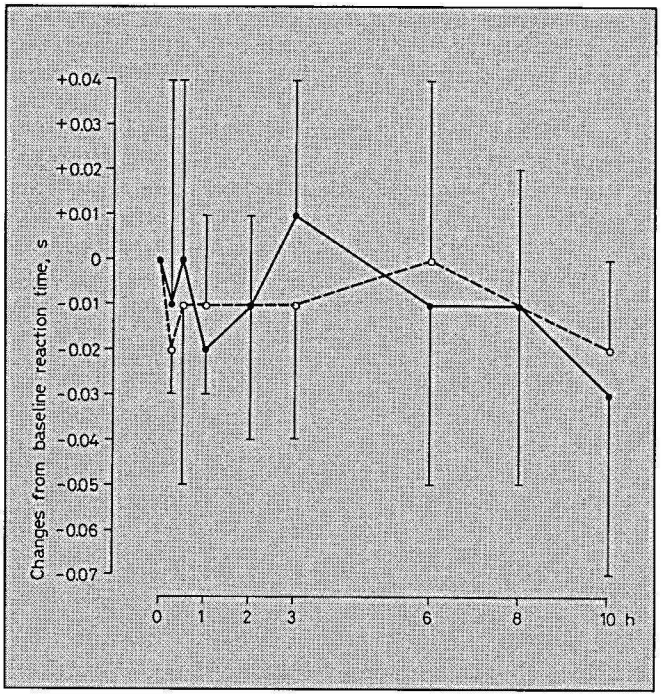

Fig. 5. Changes over time in reaction time following sublingual (•) or oral prazepam (o) 20 mg in 5 normal volunteers (mean and standard deviation).

Table II. Statistical analysis of the changes in the computerized assessment of vigilance following sublingual or oral prazepam 20 mg in 5 normal volunteers (two-way ANOVA)

	Time effect		Drug effect		Time-drug interaction	
	F	p	F	p	F	p
Reaction time	0.84	NS	0.07	NS	0.45	NS
Variance	0.69	NS	0.51	NS	1.35	NS
Correlation	1.22	NS	0.01	NS	0.31	NS

NS = Nonsignificant.

suggest more sensitivity for the 'subjective' assessment of vigilance by visual analogue scales as compared to objective methods. It is possible that healthy young volunteers need a strong pharmacological effect in order to decrease their concentration capabilities. In contrast, they are able to selectively discriminate subjective changes in their level of alertness. Visual analogue scales have already been demonstrated to be particularly sensitive to assess short-term changes in subjective feelings and have been widely used as indicators of the time-effect curve of analgesic and sedative drugs [Bond and Lader, 1974; Ansseau et al., 1984a].

The differences in sedation level between sublingual and oral prazepam may correspond to differences in absorption rate. Rapidly absorbed benzodiazepines yield more sedative activity than slowly absorbed ones [Shader et al., 1984; Ansseau et al., 1984b, c]. Prazepam is a prodrug of desmethyldiazepam which appears in blood slowly, with a plasma peak 6 h after intake [Greenblatt and Shader, 1978]. This particular pharmacokinetic profile may explain the low rate of sedation observed with prazepam [Demange, 1979; Caussanel and Ribes, 1979; Fabre et al., 1984]. This low rate of sedative effect of oral prazepam is confirmed in our study where no significant changes in alertness, measured by visual analogue scales as well as by computerized tests, were noted. In contrast, sublingual prazepam induced a significant sedative effect which peaked between 1.5 and 2 h after intake, and disappeared 7 h later. These data support the lack of a relationship between duration of clinical activity and plasma half-life of benzodiazepines [Ansseau et al., 1984b, c]. Indeed, desmethyldiazepam possesses a plasma half-life ranging from 30 to 120 h [Greenblatt and Shader, 1978]. These results support the usefulness of sublingual prazepam in anxious patients when a rapid effect is needed. Obviously, this hypothesis should be tested in a further study.

In conclusion, a single dose of sublingual prazepam appears to exhibit sedative properties as compared to the same dose of oral prazepam in normal volunteers. This difference could result from more rapid absorption of sublingual prazepam as compared to oral prazepam. This hypothesis will be discussed in a subsequent article.

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References

Ansseau, M.; Doumont, A.; Cerfontaine, J.L.; Mantanus, H.; Rousseau, J.C.; Timsit-Berthier, M.: Self-reports of anxiety level and EEG changes after a single dose of benzodiazepines. Double-blind comparison of two forms of oxazepam. Neuropsychobiology *12:* 255–259 (1984a).

Ansseau, M.; Doumont, A.; Frenckell, R. von; Collard, J.: Duration of benzodiazepine clinical activity: lack of direct relationship with plasma half-life. A comparison of single vs. divided dosage schedules of prazepam. Psychopharmacology *84:* 293–298 (1984b).

Ansseau, M.; Doumont, A.; Frenckell, R. von; Collard, J.: A long-acting benzodiazepine is more effective in divided doses. New Engl. J. Med. *310:* 526 (1984c).

Bond, A.; Lader, M.: The use of analogue scales in rating subjective feelings. Br. J. med. Psychol. *47:* 211–218 (1974).

Caussanel, P.; Ribes, M.Y.: Etude du prazepam sur simulateur de vol. Psychol. Med. *11:* 1719–1724 (1979).

Demange, J.: Etude des effets du prazepam sur la vigilance et les performances humaines. Rev. int. Servs Santé Armées *52:* 567–571 (1979).

Detti, I.: Benzodiazepines in the treatment of insomnia: pharmacokinetic considerations; in Costa, The benzodiazepines: from molecular biology to clinical practice, pp. 173–199 (Raven Press, New York 1983).

Fabre, L.F.; Johnson, P.A.; Greenblatt, D.J.: Drowsiness sedation levels in anxious neurotic outpatients. Psychopharm. Bull. *20:* 128–136 (1984).

Frenckell, R. von; Ansseau, M.; Bonnet, D.: Evaluation of the sedative properties of PK 8165 (pipequaline), a benzodiazepine partial agonist, in normal subjects. Intern. clin. Psychopharm. *1:* 24–35 (1986).

Frenckell, R. von; Scharres, M.; Ansseau, M.; Bonnet, D.: Etude des propriétés stimulantes de la pipequaline (PK-8165), un agoniste partiel des benzodiazépines, chez le volontaire sain. Psychiatrie Psychobiologie *2:* 52–57 (1987).

Greenblatt, D.J.; Shader, R.I.: Prazepam and lorazepam, two new benzodiazepines. New Engl. J. Med. *299:* 1342–1344 (1978).

Greenblatt, D.J.; Shader, R.I.; Abernethy, D.R.: Current status of benzodiazepines. New Engl. J. Med. *309:* 410–416 (1983).

Kaplan, S.A.; Jack, M.L.: Metabolism of the benzodiazepines: pharmacokinetic and pharmacodynamic considerations; in Costa, The benzodiazepines: from molecular biology to clinical practice, pp. 173–199 (Raven Press, New York 1983).

Lader, M.; Petursson, H.: Rational use of anxiolytic/sedative drugs. Drugs *25:* 514–528 (1983).

Shader, R.I.; Pary, R.J.; Harmatz, J.S.: Plasma concentrations and clinical effects after single oral doses of prazepam, clorazepate, and diazepam. J. clin. Psychiat. *45:* 411–413 (1984).

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