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Duration of benzodiazepine clinical activity: Lack of direct relationship with plasma half-life

A comparison of single vs divided dosage schedules of prazepam

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Abstract. The anxiolytic activity and tolerance of two dosage schedules of prazepam, a long plasma half-life benzodiazepine, were compared under double-blind conditions in two groups of 10 inpatients each who met Research Diagnostic Criteria for Generalized Anxiety Disorder and presented chronic and severe symptomatology. Patients received prazepam 40 mg per day on one of two dosage schedules: 1) divided dosage (DD) – 10 mg in the morning and at noon and 20 mg in the evening; or 2) single dosage (SD) – 40 mg in the evening. The 3 weeks of therapy were preceded and followed by 1 week of wash-out for baseline and follow-up assessments, which were performed weekly with the Hamilton Anxiety Scale, Clinical Global Impression, rating of morning drowsiness and evening worsening of symptoms, and patient self-rating of anxiety by means of a visual analogue scale performed both in the morning and in the afternoon. The results showed a clear superiority of the DD over the SD schedule: better anxiolytic efficacy on the Hamilton Anxiety Scale ($P < 0.0005$) and on both morning and afternoon visual analogue scales ($P < 0.01$ and $P < 0.0002$); less morning drowsiness ($P < 0.0001$); and steadier anxiolytic effect during the daytime, as globally rated by the investigator ($P < 0.0001$) or measured by morning-afternoon differences on the visual analogue scale ($P < 0.005$). These results suggest that plasma pharmacokinetics alone may not be sufficient to predict the duration of benzodiazepine anxiolytic activity.

Key words: Benzodiazepines – Prazepam – Anxiety disorders – Plasma pharmacokinetics

Benzodiazepines currently represent the most widely used pharmacological treatment for anxiety disorders. Their clinical activity has been demonstrated to be superior to placebo in most studies, and generally superior to older anxiolytics such as barbiturates or meprobamate; moreover, they have very low toxicity and limited side-effects (review in Greenblatt and Shader 1978a; Greenblatt et al. 1983).

Recent developments in the study of benzodiazepine pharmacokinetics have shown wide differences among marketed compounds with respect to rate of absorption, distribution, presence of active metabolites, and rate of elimination (review in Kaplan and Jack 1983; Detti 1983). As a function of plasma half-lives, benzodiazepines have been divided into two groups: 1) short-acting (i.e., half-life shorter than 10 h), including compounds such as oxazepam, lorazepam, temazepam, or triazolam; and 2) long-acting (half-life longer than 10 h), for example, chlordiazepoxide, diazepam, clorazepate, or medazepam (Committee on the Review of Medicines 1980). Short-acting benzodiazepines are frequently recommended in the treatment of insomnia, in order to minimize morning drowsiness, whereas long-acting compounds are thought to be preferable for treatment of chronic anxiety, in order to obtain a steady "coverage" of anxiety symptoms (Greenblatt et al. 1983). On a pharmacokinetic basis, it has been argued that a single bedtime dosage of a long-acting benzodiazepine results in a stable plasma level for 24 h and may reduce daytime sedation and improve compliance (Bellantuono et al. 1980; Breimer et al. 1980; Achte 1980; Greenblatt 1980; Rickels 1980). In fact, however, no study has clearly demonstrated that the daily administration of a single dose of a long-acting benzodiazepine is as effective as divided doses in the treatment of anxiety disorders. All studies comparing single and divided dosage schedules have been performed in moderately anxious outpatients, rarely selected with well-defined criteria. These patients may present a spontaneous remission of symptomatology and are very sensitive to placebo effect and to environmental (familial, professional, social) conditions; moreover, drug compliance may be poor and difficult to control. These methodological difficulties can be largely circumvented by selecting inpatients diagnosed according to operationalized diagnostic criteria and suffering from chronic and severe anxiety, as in the current study.

Prazepam belongs to the group of long-acting benzodiazepines and actually represents a "prodrug" of desmethyldiazepam (Greenblatt and Shader 1978b), an active metabolite of many compounds (i.e., chlordiazepoxide, diazepam, medazepam, clorazepate, and ketazolam) with a plasma half-life ranging from 30 to 120 h (Kaplan et al. 1973; Post et al. 1977; Smith et al. 1979), the longest half-life of the tested benzodiazepines (Shader and Greenblatt 1980). After oral intake of prazepam, the plasma appearance of desmethyldiazepam is very slow (plasma peak 6 h later), possibly reducing the sedative effect (Greenblatt et al. 1983). The anxiolytic properties of prazepam at a daily dose of 20–60 mg have been demonstrated in many controlled studies, as both superior to placebo (Kingstone et al. 1966; Sugerman et al. 1971; Goldberg and Finnerty 1977; Rickels et al. 1977; Warnecke 1977; Weir 1978; Fabre et al. 1980) and at least equal to

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reference benzodiazepines (Dunlop and Weisberg 1968; Shaffer et al. 1968; Kingstone et al. 1969; Barbizet 1979; Fabre et al. 1980).

Recently, withdrawal symptoms or rebound anxiety more severe than the symptoms for which the drug was initially prescribed have been reported in association with the discontinuation of benzodiazepine therapy (Tyrer et al. 1981; Petursson and Lader 1981; Rickels et al. 1983; Tyrer et al. 1983). This phenomenon is more probably associated with short-acting benzodiazepines (Ayd 1984).

Accordingly, the purpose of this study was twofold: first, to compare, under rigorous methodological conditions, the anxiolytic activity and tolerance for prazepam during two administration schedules: single evening dosage of 40 mg or divided daily dosage (10, 10, and 20 mg); and second, to assess possible withdrawal symptoms after discontinuation of prazepam, comparing single and divided dosage schedules in this regard.

Subjects and methods

Subjects. Two groups of 10 inpatients each newly admitted to the Psychopharmacology Unit of the University Hospital of Liège, Belgium, and meeting Research Diagnostic Criteria (RDC) for Generalized Anxiety Disorder (Spitzer et al. 1978) were included in the study. In addition, patients were required to present: 1) chronic and steady symptomatology, with a 1-year minimum history of regular daily intake of high doses of benzodiazepines (at least 20 mg diazepam or equivalent); and 2) a high level of severity, with a minimal score of 25 on the Hamilton Anxiety Scale (Hamilton 1959) at the end of a drug wash-out period of at least 1 week. The requirement of 1 year minimum history of daily benzodiazepine intake was intended to ensure that the patients' clinical condition was sufficiently steady and that any clinical change was related mainly to pharmacologic treatment rather than to spontaneous remission. All diagnostic procedures were performed by two independent research psychiatrists. We excluded patients with pre-existing or concurrent RDC diagnoses of major or minor depressive disorder, phobic disorder, obsessive compulsive disorder, alcoholism, or drug use disorder; or with evidence of medical illness on history, physical examination, EKG, chest X-ray, EEG, and routine laboratory tests. Moreover, subjects did not meet RDC for panic disorder. All patients were hospitalized due to their long-lasting high level of anxious symptomatology, which significantly interferred with their familial, professional, and social functioning, and their poor response to previous pharmacological or psychological interventions and, prior to participation, they gave informed consent.

Design of the study. At the end of a 1 week (minimum) wash-out period on placebo following a gradual decrease of the previous anxiolytic pharmacotherapy (generally over 2 weeks), patients were randomly assigned to two different dosage schedules of prazepam 40 mg daily: either 10 mg in the morning and at noon and 20 mg in the evening (divided dosage or "DD"); or a single 40 mg dose in the evening (single dosage or "SD"). No patient exhibited true withdrawal symptoms (i.e., seizures, psychosis, delirium, or perceptual disturbances) during the wash-out period, but all patients presented an increase in their anxious symptomatology and two subjects could not be included in the study due to their inability to remain drug-free for 1 week. The study was performed double-blind, with each patient receiving three identical tablets a day (separately prepared for each patient), in order to control for any placebo effect of multiple dosage.

The dose remained unchanged throughout the 3-week study, followed by a 1-week period on placebo of the same appearance. No additional medication was allowed during the study.

Assessment. Patients were evaluated at the end of each week by means of the Hamilton Anxiety Scale and the Clinical Global Impression or CGI (Guy 1976). Two additional symptoms were also rated from 0 (absent) to 4 (severe): morning drowsiness (hang-over), and evening worsening of symptoms. The assessment was always performed by the senior author in the morning at 10 A.M. ($\pm$ 30 min). On the same days, patients completed a 100-mm visual analogue scale (Bond and Lader 1974) in the morning (at 10 A.M. $\pm$ 30 min) and in the afternoon (at 5 P.M. $\pm$ 30 min), where they had to locate themselves between two limits: "extremely relaxed" (score of 0) and "extremely anxious" (score of 100).

Data analysis. Statistical evaluation of change in clinical ratings over time during prazepam therapy employed analysis of variance (ANOVA) for repeated measures. This method allowed us to assess the global therapeutic effect for the whole sample (time-effect) and to determine possible significant differences between the two treatment groups (time-drug interaction). Clinical ratings 1 week after the end of therapy were compared to pre-treatment ratings using group and paired *t*-tests, in order to show possible withdrawal effects (i.e., higher symptom severity ratings post-treatment than pre-treatment). Correlations between morning and afternoon visual analogue scale scores were analyzed using the Pearson's product-moment correlation coefficient.

Results

Sample. No significant differences between the DD and SD groups appeared in demographical and baseline clinical measures or in previous benzodiazepine therapy (Table 1). Specifically, there was no significant difference in extent of previous treatment by short or long-acting benzodiazepines between the two groups. All patients completed the trial.

Anxiolytic effect. Changes over time on Hamilton Anxiety Scale (Fig. 1) showed a highly significant improvement for the whole sample ($P < 0.00001$) and also a clear superiority of DD over SD schedules ($P < 0.0005$). The CGI also showed a significant improvement during prazepam therapy ($P < 0.0001$), but without significant differences between administration schedules (Table 2). Improvement measured by both morning and afternoon visual analogue scales was significant for the whole sample ($P < 0.0001$ and $P < 0.0001$), with a statistical superiority of the DD over the SD schedule ($P < 0.01$ and $P < 0.0002$) (Fig. 2).

Daytime steadiness of the anxiolytic effect. Diurnal (i.e., morning vs evening) variation in anxiolytic effect was assessed in three different ways: first, through the inves-

Table 1. Characteristics of the sample

	DD Group (n = 10)	SD Group (n = 10)	P
Gender	7M, 3F	4M, 6F	NS
Age[a]	42.7 (9.1)	46.5 (9.7)	NS
Hamilton anxiety Scale[a]	32.9 (5.3)	31.4 (5.1)	NS
Illness duration (years)[a]	4.7 (1.6)	5.0 (1.8)	NS
Episode duration (years)[a]	2.1 (0.8)	2.2 (0.9)	NS
Previous treatment	Lorazepam (n = 6) Bromazepam (n = 3) Diazepam (n = 1)	Lorazepam (n = 5) Bromazepam (n = 3) Clorazepate (n = 1) Ketazolam (n = 1)	NS

[a] Mean and standard deviation

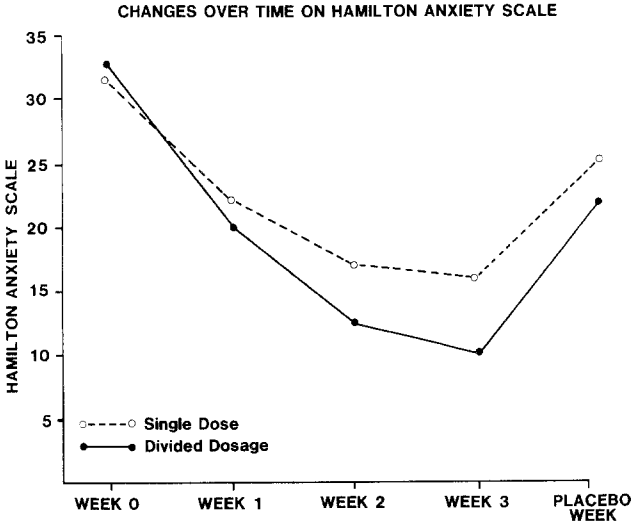

Fig. 1. Changes over time on Hamilton Anxiety Scale during treatment with prazepam 40 mg per day in single dose or in divided dosage, and 1 week after the end of therapy

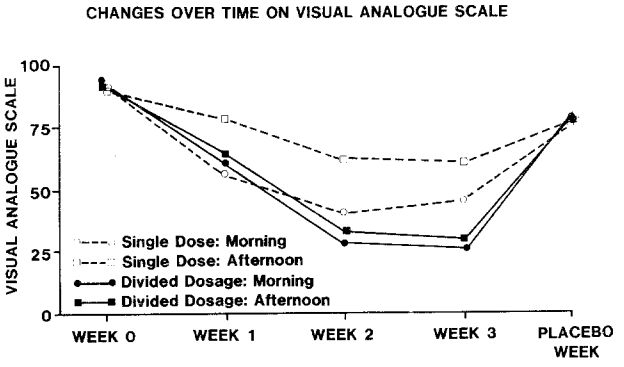

Fig. 2. Changes over time on morning and afternoon visual analogue scales during treatment with prazepam 40 mg per day in single dose or in divided dosage, and 1 week after the end of therapy

Table 2. Comparison of changes over time with prazepam 40 mg per day on a divided dose (DD) or single dose (SD) regimen

	Regimen	Week				P
		0	1	2	3	
Clinical Global Impression	DD	6.3	4.7	3.4	3.1	NS
	SD	6.3	4.9	4.0	3.9	
Morning Drowsiness	DD	0.0	0.2	0.2	0.3	< 0.0001
	SD	0.0	2.2	1.4	1.4	
Evening Worsening	DD	0.2	0.3	0.1	0.0	< 0.0001
	SD	0.0	1.8	1.9	1.8	

tigator's global rating of "evening worsening"; second, by calculation of difference in scores between morning and afternoon self-rating of anxiety on the visual analogue scale, with a more negative difference corresponding to a greater PM worsening of anxiety; and third, by the correlation coefficients between morning and afternoon scores on the visual analogue scale, with a higher correlation corresponding to a higher clinical stability.

The two groups presented an opposite pattern on the "evening worsening" item: decrease of scores in the DD group (i.e., PM diminution in anxiety) and increase in the SD group (i.e., PM worsening of anxiety) which was statistically different ($P < 0.0001$) (Table 2). The differences between morning and afternoon visual analogue scale scores increased significantly for the whole sample ($P < 0.0001$), but significantly more in the SD than in the DD group ($P < 0.005$) (Fig. 2). Moreover, the correlations between morning and afternoon visual analogue scales were very high throughout the 3-week trial for the DD group (week 1: $r = 0.98$; week 2: $r = 0.98$; week 3: $r = 0.98$; $P < 0.001$) while this correlation was always lower in the SD group, and only significant at week 2 (week 1: $r = 0.40$, NS; week 2: $r = 0.88$, $P < 0.001$; week 3: $r = 0.61$, NS).

Morning drowsiness. Morning drowsiness increased significantly during prazepam therapy in the whole sample ($P < 0.0001$), but this effect was statistically more important in the SD than in the DD groups ($P < 0.0001$) (Table 2).

Withdrawal effect. None of the assessments showed higher symptom severity 1 week after discontinuation of prazepam therapy compared to pre-drug ratings. On the contrary, the

improvement was still significant for the whole sample on Hamilton Anxiety Scale ($P < 0.001$) (Fig. 1), on Clinical Global Impression (5.1 vs 6.3, $P < 0.001$) and on both morning and afternoon visual analogue scales ($P < 0.001$ and $P < 0.002$) (Fig. 2). The DD group was still significantly less symptomatic than the SD group on the Hamilton Anxiety Scale ($P < 0.05$), but this superiority was clearly related to a lower anxiety score after the 3 weeks of active treatment. No subject experienced withdrawal effects described in some studies (Ayd 1984), i.e., seizures, delirium, psychosis, or perceptual disturbances, despite increase in anxiety rating.

Discussion

This study shows that the anxiolytic effect obtained with prazepam in divided doses is better in inpatients with generalized anxiety disorder than that obtained with a single dose. Moreover, divided dosage reduces morning drowsiness and provides a steadier anxiolytic effect throughout the day. These results extend published findings on benzodiazepine efficacy in several ways, as will now be presented.

For prazepam, three studies used a single (evening) dose design, and all three showed a superiority of prazepam over placebo (Brauzer unpublished; Rickels 1977; Goldberg and Finnerty 1977); however, none of them included a comparison with prazepam or another benzodiazepine given in divided daily doses. In addition, these studies were performed in moderately anxious outpatients, not in severely anxious inpatients.

With respect to diazepam, no study has demonstrated the anxiolytic efficacy of a single daily dose. On the contrary, a form with delayed absorption ("Valrelease") has been developed in order to decrease the sedative effects and obtain a steadier anxiolytic effect during the daytime (Amrein and Leishman 1980; Bergamo and Sudol 1982). Studies with a single daily dose of clorazepate, which like prazepam is a prodrug of desmethyldiazepam, showed anxiolytic efficacy equivalent to that of divided daily doses (Dureman et al. 1978) and to diazepam in single or divided doses (Magnus 1973; Burrows et al. 1977; Magnus et al. 1977). However, all studies were performed in *outpatients* suffering from a low-moderate level of anxiety. The first study with ketazolam in single evening dose included 15 alcoholic inpatients (Gallant et al. 1973), seven of whom required a switch to BID or TID dosage regimens due to the appearance of "unpleasant anxiety" in the early afternoon. The authors recommended two daily intakes in subsequent studies. All controlled studies showing the superiority of a single daily intake of ketazolam over placebo or efficacy equivalent to diazepam or clorazepate in divided doses were performed in moderately anxious outpatients (Fabre et al. 1976; Bowden 1978; Fabre et al. 1978; Fabre and McLendon 1979; Anhalt et al. 1980; Feighner 1980; Kim et al. 1980; Kleber 1980; Rickels et al. 1980; Owieczka et al. 1981).

The superior anxiolytic efficacy of divided doses over a single dose demonstrated in the present trial, as opposed to the lack of difference suggested in all previous studies, may result from the greater power of the methodology used. First, the use of strict, well-operationalized diagnostic criteria (i.e., RDC) increases the homogeneity of the sample (Solomon and Hart 1978); second, the selection of patients with a sufficient illness duration (at least 1 year in the current trial) ensures that the clinical condition is sufficiently steady that a spontaneous remission is unlikely (Fontaine et al. 1983); third, an inpatient setting allows for more precise control of the non-pharmacological factors (most of them remaining constant) and facilitates treatment adherence (Ansseau et al. 1984). Moreover, the drop-out rate is generally very low in inpatient studies (none in the present study) and reasons for patient attrition can always be analysed, whereas the drop-out rate among outpatients is generally reported between 25 and 50% (Blackwell 1976) – moreover, for reasons that often remain unknown. However, one may question the extent to which the sample of subjects included in the present study is representative of the general population of anxious patients who benefit from benzodiazepine therapy. In fact, most benzodiazepine anxiolytics are prescribed for mildly anxious outpatients over short periods. Only a small proportion of patients show continuous and persistent high levels of anxiety throughout the day; moreover, the rate of patients taking benzodiazepines for more than 1 year is low: about 15% of all American anxiolytic users (33% in Belgium) (Balter et al. 1984). These patients tend to be older, predominantly female, with high levels of emotional distress and chronic somatic health problems (Mellinger et al. 1984). However, in general, the most effective way to demonstrate clinical differences in therapeutic activity is to start with the subgroup having the highest severity of illness. In an analogous fashion, clinical studies of antidepressant compounds are mainly performed in severely depressed patients, selected by rigorous criteria (such as RDC for primary or endogenous depression), and often in hospital settings; those patients also represent a small fraction and specific subgroup of all depressed patients treated with antidepressant drugs (Miller et al. 1983). The current study supports the value of using a comparable methodology for the demonstration of clinical differences between anxiolytic treatment regimens.

The patients in this study did not exhibit evidence of true withdrawal symptoms during the pre-treatment wash-out period, despite their long-term use of high dose benzodiazepine anxiolytics. The increase in anxious symptomatology during this period can be attributed to the reappearance of the chronic condition (partially masked by the benzodiazepine therapy) rather than to withdrawal symptoms. However, the gradual decrease in the previous pharmacologic treatment (over 2 weeks) certainly helped to diminish the possibility of withdrawal phenomena. Moreover, subsequent prazepam therapy may possibly have treated some symptoms of benzodiazepine withdrawal, as well as those of chronic anxiety, since there is good evidence that some withdrawal symptoms may last longer than 1 week, especially with long half-life compounds (Lader 1983). In the same way, the current study did not show any evidence of withdrawal symptoms during the week following discontinuation of prazepam therapy; on the contrary, some improvement in symptomatology still persisted at this time in comparison to pre-treatment levels. This finding suggests that withdrawal of prazepam may be less likely than withdrawal of short half-life compounds to produce rebound anxiety (Ayd 1984).

The finding of clear anxiolytic superiority of a long half-life benzodiazepine in divided doses over a single dose brings into question the accuracy of inferences about

duration of clinical activity based on plasma pharmacokinetics. In fact, clinical experience with benzodiazepines shows that observable effects like sedation do not persist as long as predicted by plasma pharmacokinetic data (Kurowski et al. 1982). Moreover, no evident relationship between plasma levels and anxiolytic activity has ever been demonstrated for benzodiazepine compounds (review in Bellantuono et al. 1980). Rather, clinical effects of benzodiazepines appear to be mediated via binding to specific central nervous system receptors, and only the measurement of the amount of receptors occupied by a given benzodiazepine and the duration of that binding may be reliably correlated with the level and the duration of the clinical changes (review in Möhler and Richards 1983). Moreover, preliminary studies in animals have shown that receptor binding of benzodiazepines is widely independent of plasma levels (Haefely and Möhler 1980). For example, in the rat, diazepam receptor occupancy peaked at 30 s after IV injection and returned to baseline in 60 min; in contrast, lorazepam receptor occupancy did not occur until 10 min after IV injection and 45% occupancy was still observed after 60 min (Hoffman-La Roche 1983). The point is that plasma pharmacokinetics showed a time course opposite to that of receptor binding: diazepam half-life is about three times longer than lorazepam half-life (33 vs 13 h) and desmethyldiazepam, the direct metabolite of diazepam, possesses an even longer half-life (55–99 h) (Breimer et al. 1980).

Thus, caution is warranted in inferring clinical effects from plasma pharmacokinetic data, particularly in the absence of direct clinical evidence. For example, in inpatients with generalized anxiety disorders, the current study suggests that anxiolytic pharmacotherapy administered in divided daily doses may be more effective overall, without diurnal variation, and may be better tolerated than the administration of a single dose in the evening, notwithstanding opposite predictions from pharmacokinetic data.

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