Responsiveness to oral diazepam in the elderly: relationship to total and free plasma concentrations

C. G. SWIFT, J. M. EWEN, P. CLARKE & I. H. STEVENSON

University Department of Pharmacology and Therapeutics, Ninewells Hospital, Dundee, DD1 9SY

1 The immediate and residual response to single doses of oral diazepam 10 mg was measured in 11 young and 12 elderly healthy volunteers using postural sway, digit symbol substitution scores and subjective ratings.

2 The effect on postural sway was markedly accentuated in the older volunteers, but the difference between groups in the effect on the other measures used did not achieve significance.

3 The corresponding plasma total diazepam concentrations were lower in the older subjects beyond 0.5 h post dose and the concentrations of plasma desmethyldiazepam did not differ between the groups.

4 Diazepam plasma protein binding was significantly reduced in the elderly subjects, but the plasma free (unbound) diazepam concentrations did not exceed those in the young group.

5 There was poor correlation between the responses measured and the concentrations of either total diazepam, desmethyldiazepam or free diazepam.

6 The results suggest the occurrence of a non-uniform effect of age on different aspects of benzodiazepine response, and that where an accentuated effect occurs the mechanisms are substantially pharmacodynamic.

Keywords diazepam responsiveness plasma concentrations protein binding elderly

Introduction

The occurrence of sleep disorder and use of hypnotic drugs rise steadily with advancing age (McGhie & Russell, 1962; Karacan *et al.*, 1976) and it is likely that the use of anxiolytics follows a similar trend, as indicated by prescribing patterns for the main categories of psychotropic drug (Skegg *et al.*, 1977).

Anecdotal reports (Evans & Jarvis, 1972) and epidemiological data (Boston Collaborative Drug Surveillance Programme, 1973; Greenblatt *et al.*, 1977; Greenblatt & Allen, 1978) indicate that susceptibility to the adverse effects

of benzodiazepines, principally unwanted central nervous system depression, increases with advancing age. A quantitative relationship to dose occurs, however, so that at lower doses the age-related trend is largely abolished.

Numerous studies of the pharmacokinetics of benzodiazepines have now been undertaken in elderly individuals. The most important findings to emerge have been (i) a reduction in the rate of biotransformation of oxidatively metabolised compounds (especially in males) corresponding to that observed with antipyrine (Greenblatt *et*

*Present address and correspondence: Department of Geriatric Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN

al., 1982), (ii) an increase in the distribution volume of these compounds (Klotz *et al.*, 1975; Shader *et al.*, 1977; MacLeod *et al.*, 1979; Allen *et al.*, 1980; Greenblatt *et al.*, 1981) and (iii) absence of any major effect of age on the rate of elimination of those drugs metabolised *via* non-oxidative routes, such as conjugation (Shader & Greenblatt, 1981).

A further aspect studied has been protein binding. Benzodiazepines are highly protein bound, so that a small reduction in protein binding may lead to the presence of significantly increased concentrations of free (unbound) drug at the receptor site, even allowing for the characteristically large distribution volumes. Reports have conflicted, some studies showing no reduction in protein binding with age (Klotz *et al.*, 1975; Wilkinson, 1978; Greenblatt *et al.*, 1981), others demonstrating a clear and significant reduction (Macklon *et al.*, 1980; Greenblatt *et al.*, 1980; Shader *et al.*, 1981).

Studies with parenteral diazepam (Giles *et al.*, 1978; Reidenberg *et al.*, 1978; Cook *et al.*, 1984) and oral nitrazepam (Castleden *et al.*, 1977) have provided evidence that responsiveness may be enhanced in the elderly, independently of changes in plasma concentration. We have therefore undertaken a controlled study of the response to single oral doses of diazepam in young and elderly healthy volunteers, with concurrent measurement of plasma concentrations and estimation of protein binding, in order to evaluate further the role of pharmacodynamic factors in the reported increased 'sensitivity'.

Methods

Subjects and study design

Twenty-four healthy non-smoking volunteers, 12 young and 12 elderly, of mean ages 21.8 (range 19–26) and 72.3 (range 66–78) respectively, participated. Both groups contained 6 male and 6 female subjects and were of similar body weight (young 65.7 ± 8.0 kg; elderly 65.0 ± 7.1 kg) (means $\pm$ s.d.). The elderly volunteers were fully independent, healthy individuals aged over 65 living in their own homes. All volunteers underwent a routine clinical examination and haematological and biochemical screening to exclude significant disease states. Exclusion criteria included smoking, concurrent drug therapy likely to influence CNS response or drug handling and investigational indices outside the normal range for age. The study was approved by the Tayside Health Board Ethics Committee.

A protocol similar to that described by Clarke & Nicholson (1978) was adopted to allow evaluation of both immediate and residual effects. Administration was balanced and randomised. Single doses of diazepam 10 mg or placebo were administered at night (approximately 22.30 h) and in the morning (approximately 08.30 h) on three separate occasions at least 1 week apart. Observations were made at 0.5, 2.5, 4.5 and 6.5 h intervals after morning ingestion. In this way comparison of the treatment schedule placebo at night/active drug in the morning with the double placebo occasion allowed assessment of immediate effects of diazepam. Residual effects were determined from the comparison of active drug at night/placebo in the morning with the double placebo occasion.

Blood samples for assay were obtained at the same time-points as each set of observations and the plasma stored immediately at -20°C .

Measurements of response

Elderly individuals do not tolerate extensive test batteries well (Swift, 1983). In view of the need to follow the time-course of drug effects using repeated measures at frequent intervals, only two objective indices of sedation were employed together with subjective ratings, as follows:

(a) *Digit symbol substitution test (DSST)* This was selected as a psychomotor test of widely reported sensitivity to benzodiazepines (Wittenborn, 1979). Volunteers were practised to a plateau level of proficiency prior to entering the study in order to exclude learning effects.

(b) *Measurement of postural sway* This was carried out using an electronic (Codoc) modification of the Wright ataxiometer (Wright, 1971), providing a digital read-out in degrees arc $\times 3$ of anteroposterior sway.

(c) *Subjective ratings* An 'alert-drowsy' visual analogue scale was used to assess subjective sedation. Appreciation of changes in standing steadiness was assessed by means of a 'steady-dizzy' scale.

Measurement of plasma concentrations

Plasma concentrations of diazepam and its active-metabolite, desmethyldiazepam, were measured by means of gas-liquid chromatography with electron capture, the method being a modification of the procedure described by de Silva & Puglisi (1970) and measuring underivatized benzodiazepine.

Determination of percentage protein binding

The extent of diazepam protein binding was measured using the Dianorm (MSE Scientific instruments) method of equilibrium dialysis. The system consists of Teflon cells (macro D1000) made in two halves which are clamped together to hold the dialysis membrane (Spectrapor—1; Spectrum Medical Industries Inc, Los Angeles, USA) between them. The cells are loaded on to four cell carriers which are rotated at 30 rev/min in a 37° C water bath in the dark until equilibrium is achieved.

Dialysis was carried out for at least 5 h, the time found necessary to reach equilibrium, using 200 mg cold diazepam with 0.05 μCi [^3H]-diazepam in 1 ml 0.1 M phosphate buffer pH 7.4 (Geigy No. 7) against 1 ml plasma diluted 1:7 in the same diluent.

Statistical analysis

Non-parametric methods were used to analyse the results of performance tests. The significance of changes from placebo at each time-point was assessed using the Wilcoxon Signed Rank Test for repeated measures and that of differences between pairs of means using the Mann Whitney U-test. For each subject additional indices of the drug's effect on performance were derived, firstly in terms of maximal change (Δ_{max}) (i.e. the maximum drug response observed versus placebo), and secondly as the area under the immediate drug effect curve (AUEC_{imm}) (i.e. defined by the response measures to 6.5 h, using the trapezoidal rule). Apparent negative response was zero rated. Differences between group means in plasma total and free drug concentrations, in percentage protein binding and in plasma albumin levels were compared using Student's *t*-test for unpaired data.

Results

Measurements of response

The immediate and residual effects of diazepam on the various measures are shown in Figures 1, 2, 3 and 4. One young subject had to be withdrawn due to an intercurrent viral infection.

(a) *Digit symbol substitution test* (Figure 1) As expected, mean values for base-line (placebo) performance on DSST were substantially lower (range of means 54.6–55.8) in the elderly group than in the young (96.7–101.1). However, base-

Figure 1 Change in digit-symbol substitution scores vs placebo in young (----) and elderly (—) volunteers after oral diazepam 10 mg. * $P < 0.05$; ** $P < 0.01$ with respect to placebo (Wilcoxon Signed Rank Test).

line scores showed no overall increase with time in either group, indicating satisfactory exclusion of practice effect.

Diazepam significantly impaired performance on DSST in both groups at 0.5, 2.5 and 4.5 h after ingestion but not at 6.5 h. However, in the elderly group a significant residual effect was apparent at 10 h and 12 h, though not thereafter.

The magnitude of effect on scores did not differ significantly between the groups at any one time-point. The timing of peak effects on performance varied between subjects, occurring predominantly at either 0.5 h or 2.5 h post ingestion.

There were no significant differences between the group means in the derived indices of response (Table 1).

(b) *Postural sway* (Figure 2) Postural sway was significantly increased by diazepam in the elderly group alone at 0.5 h and 2.5 h, but not thereafter. The effect did not achieve significance in the young group at any one time-point, but again the timing of peak effect varied between individuals. Values for the derived indices of response were significantly higher in the older group (Table 1) indicating an accentuated effect of diazepam on sway by comparison with the young. No significant residual effect on sway was observed in either group.

(c) *Visual analogue ratings* (Figure 3 and 4) Significant subjective sedation was reported by the elderly on the 'alert-drowsy' mood-rating scale at 0.5 h and by the young group at 2.5 h post dosage. No residual sedation occurred subjectively in either group. Although there was a

Table 1 Derived indices of drug response (vs placebo) in young and elderly volunteers after oral diazepam 10 mg (mean, ranges in brackets)

	Young (n = 11)		Elderly (n = 12)	
	Δ_{max}	AUEC _{imm}	Δ_{max}	AUEC _{imm}
DSST	12.0 units (1.0–25.0)	34.6 unit h (8.0–59.3)	10.1 units (2.0–24.0)	39.5 unit h (6.5–136.8)
Postural sway	1.8° arc (0.0–5.6)	1.7° arc h (0.0–4.8)	6.5° arc** (0.0–11.5)	6.6° arc h** (0.0–15.7)
VA scale	19.0 mm (0.0–35.0)	61.8 mm h (0.0–185.8)	30.9 mm (0.0–57.0)	70.6 mm h (0.0–224.5)
Alert-drowsy				
VA scale	17.9 mm (3.0–57.0)	51.8 mm h (6.0–156.3)	21.7 mm (0.0–67.0)	48.8 mm h (0.0–162.0)
Dizzy-steady				

** $P < 0.01$ with respect to values in young subjects (Mann-Whitney U test)

trend for the elderly to report greater subjective sedation, the difference in derived indices between the two groups did not achieve statistical significance (Table 1).

Subjective appreciation of impaired steadiness ('steady-dizzy' scale) occurred only in the young group at 0.5 h. There was no residual effect in either group. No significant differences were observed between the groups in the derived indices.

Total plasma diazepam and desmethyldiazepam concentrations

(a) *Diazepam* Total plasma diazepam concentrations measured in young and elderly subjects are shown in Table 2. These were significantly lower in the older group at all time-points with the exception of 0.5 h, when the levels did not differ significantly between the groups. No attempt was made to calculate standard pharmacokinetic parameters, firstly because of the composite nature of the plasma concentration-time profile (samples from 0.5 h–6.5 h inclusive having been obtained on a separate occasion from the 10 h–16 h series) and secondly because sampling was of too short a duration to define a linear elimination phase (it is likely that for several subjects even the latest samples will have been taken during the late distributive or immediate post-distributive phase of diazepam disposition).

Maximum measured plasma concentrations (C_{max}) (0.5 h or 2.5 h) were significantly lower (161.5 ± 18.4 ng ml⁻¹) in the elderly subjects than in the young (261.72 ± 30.59 ng ml⁻¹) (mean $\pm$ s.e. mean; $P < 0.01$) though these are unlikely to be true peak concentrations. The area under the composite plasma concentration-time curve (AUC) was also significantly lower (1227 ± 116 ng ml⁻¹ h) in the elderly group

compared with the young (1982 ± 156 ng ml⁻¹ h) (mean $\pm$ s.e. mean $P < 0.001$).

(b) *Desmethyldiazepam* Plasma desmethyldiazepam concentrations are shown in Figure 5. The 0.5 h concentration was slightly, but significantly higher in the older group. Thereafter values did not differ significantly between the groups until the 10 h time-point, beyond which the elderly had lower concentrations. Again, no attempt was made to undertake pharmaco-

Figure 2 Change in postural sway vs placebo in young (----) and elderly (—) volunteers after oral diazepam 10 mg. * $P < 0.05$; ** $P < 0.01$ with respect to placebo (Wilcoxon Signed Rank Test).

Figure 3 Change in subjective sedation (visual analogue rating) vs placebo in young (----) and elderly (—) volunteers after oral diazepam 10 mg. * $P < 0.05$; ** $P < 0.01$ with respect to placebo (Wilcoxon Signed Rank Test).

kinetic analysis. The desmethyldiazepam AUC was significantly lower in the older group ($418 \pm 38 \text{ ng ml}^{-1} \text{ h}$) than in the young ($555 \pm 38 \text{ ng ml}^{-1} \text{ h}$).

Protein binding

The overall extent of protein binding was slightly lower than previously described (Klotz *et al.*, 1975; Wilkinson, 1978; Greenblatt *et al.*, 1980; Macklon *et al.*, 1980) though of similar order. percentage binding was significantly lower in the elderly group ($93.98 \pm 0.97\%$) than in the young ($95.05 \pm 0.77\%$) ($P < 0.001$). Serum albumin concentrations were $38.75 \pm 1.71 \text{ g l}^{-1}$ and $42.27 \pm 1.90 \text{ g l}^{-1}$ in elderly and young respectively ($P < 0.01$).

The concentrations of free (unbound) diazepam are shown in Figure 6. There was a trend towards lower free concentrations in elderly subjects which achieved significance at 2.5 h and 14 h after ingestion. Maximum concentrations ($C_{\max}$) of unbound diazepam were 12.78 ± 1.48

Figure 4 Change in subjective unsteadiness (visual analogue rating) vs placebo in young (----) and elderly (—) volunteers after oral diazepam 10 mg. * $P < 0.05$ with respect to placebo (Wilcoxon Signed Rank Test).

ng ml^{-1} in the young group and $9.58 \pm 1.15 \text{ ng ml}^{-1}$ in the elderly group (mean $\pm$ s.e. mean; $P < 0.05$). Values for AUC were $95.73 \pm 6.31 \text{ ng ml}^{-1} \text{ h}$ and $74.76 \pm 8.73 \text{ ng ml}^{-1} \text{ h}$ in young and elderly groups respectively ($P > 0.05$).

Relationship of clinical effects to total diazepam, total desmethyldiazepam and free diazepam concentrations

Simple visual inspection of Figures 1–6 and Table 2 identifies within each group of subjects

Table 2 Plasma concentrations (mean $\pm$ s.e. mean) of diazepam in young and elderly volunteers after 10 mg orally

		Time post-dose (h)							
		0.5	2.5	4.5	6.5	10	12	14	16
Plasma concentration (ng ml ⁻¹)	Young (n = 11)	85.08 $\pm$ 39.64	227.75 $\pm$ 30.11	156.42 $\pm$ 11.51	126.82 $\pm$ 10.42	91.18 $\pm$ 11.69	94.73 $\pm$ 13.05	94.18 $\pm$ 11.34	72.55 $\pm$ 9.67
	Elderly (n = 12)	101.67 $\pm$ 26.12	131.42 $\pm$ 16.17	105.25 $\pm$ 13.16	85.08 $\pm$ 32.23	55.83 $\pm$ 8.22	49.42 $\pm$ 7.38	45.58 $\pm$ 6.52	49.25 $\pm$ 6.04
	P* (young vs elderly)	NS	< 0.01	< 0.005	< 0.005	< 0.01	< 0.005	< 0.005	< 0.05

*Student's *t*-test for unpaired data

Figure 5 Composite desmethyldiazepam plasma concentration-time profile after oral diazepam 10 mg in young (----) and elderly (—) volunteers. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ with respect to values in young subjects (unpaired t -test).

the relatively poor correspondence between the time courses of measured drug effects and those of total diazepam, total desmethyldiazepam and free diazepam concentrations in the plasma, the 'disappearance rate' of the former being generally more rapid.

In addition the relationships between $C_{\max}$ for diazepam, desmethyldiazepam and free diazepam and $\Delta_{\max}$ for each measured response, as well as the corresponding relationships between AUC and $AUEC_{\text{imm}}$ were assessed by means of Spearman's rank correlation coefficient (r_s).

Figure 6 Composite free (unbound) diazepam plasma concentration-time profile after oral diazepam 10 mg in young (----) and elderly (—) volunteers. * $P < 0.05$ with respect to values in young subjects (unpaired t -test).

The only significant correlation observed was between $\Delta_{\max}$ for postural sway and total desmethyldiazepam $C_{\max}$ ($r_s = 0.65$; $P < 0.05$). Taken in conjunction with the remaining data this is likely to be a chance finding.

Discussion

The results with postural sway clearly show an accentuated effect of diazepam on this index of response in elderly volunteers, amounting to a more than threefold difference between groups. However, the corresponding subjective appreciation of unsteadiness failed to achieve significance in the older group, which may suggest impaired awareness of drug effect in the elderly.

Although the change in actual digit-symbol substitution scores did not differ between the groups, if the results of both performance tests are expressed as ratios to base-line, then the order of magnitude of the observed changes is greater in the elderly in both cases (maximal change in postural sway 57.69% and 100.64%, maximal change in DSST score -12.2% and -18.3% in young and elderly respectively). The difference between groups in subjective sedation marginally failed to achieve significance.

As observed in previous studies (Garattini *et al.*, 1973; Mandelli *et al.*, 1978), intersubject variability in plasma concentrations of diazepam, desmethyldiazepam and free diazepam was considerable, producing high standard errors. The finding of lower concentrations in the elderly is compatible with the occurrence of an increase in diazepam volume of distribution, as previously demonstrated (Klotz *et al.*, 1975; Greenblatt *et al.*, 1980), leading to reduced plasma concentrations and AUC after single dosage. Similarly with desmethyldiazepam, the lower AUC values in the elderly are in keeping with the reported age-related increase in the distribution volume of this metabolite (Klotz & Müller-Seydlitz, 1979; Allen *et al.*, 1980), but may also reflect reduced diazepam biotransformation. Differences in plasma concentrations due to gender were not observed in the present study, in contrast to earlier data with intravenous diazepam (Greenblatt *et al.*, 1980).

Our results confirm those of earlier studies showing a reduced degree of plasma protein

binding of diazepam in the elderly (Greenblatt *et al.*, 1980; Macklon *et al.*, 1980). In spite of the resulting increase in diazepam free fraction, the concentrations of free drug still do not exceed those obtained in younger subjects.

The accentuated response to diazepam observed in elderly subjects (as measured by postural sway) cannot therefore be fully explained on the basis of raised total drug concentrations, concentrations of metabolite or free diazepam concentrations in the elderly. The results support the view that the explanation should be sought at a pharmacodynamic level. This view is further strengthened by the poor correlation found between plasma concentrations of both free and bound drug and clinical effects. No evidence of residual sedation beyond 12 h post-dose was found in either young or elderly volunteers in spite of reported ranges of mean plasma half-life from various studies of 20 h–44 h (young) and 36 h–99 h (elderly) (Swift, 1983), suggesting the operation of a central adaptive mechanism or perhaps a closer relationship to distribution kinetics.

It is well known from the work of Braestrup & Squires (1977) and Möhler & Okada (1977) that benzodiazepines act on specific receptors localised in the synaptic membrane fraction of GABA-secreting neurones in the CNS. The status of benzodiazepine receptors in the ageing human brain is unknown, although no change in receptor binding has been observed in senescent rats (Tsang *et al.*, 1982). Alternative mechanisms of increased benzodiazepine 'sensitivity' in the elderly might include changes in the CNS levels of a postulated endogenous ligand, altered regional distribution of drug in the brain or simple impairment of homeostatic mechanisms within the nervous system. The findings with digit-symbol substitution suggest the possibility of a non-uniform change in benzodiazepine response with age, with a less marked effect on speed-dependent performance tasks than on 'physiological' measures such as postural stability.

From a clinical point of view, dose is a most important determinant of both the intensity and duration of response and should be lower in the elderly at the onset of treatment with oral diazepam. Further studies are in progress to assess the extent of similar changes in the response to other benzodiazepine compounds.

References

- Allen, M. D., Greenblatt, D. J., Harmatz, J. S. & Shader, R. I. (1980). Desmethyldiazepam kinetics in the elderly after oral prazepam. *Clin. Pharmacol. Ther.*, **28**, 196–202.
- Boston Collaborative Drug Surveillance Program (1973). Clinical depression of the CNS due to diazepam and chlordiazepoxide in relation to cigarette smoking and age. *New Engl. J. Med.*, **288**, 277–280.
- Braestrup, C. & Squires, R. F. (1977). Brain specific

- benzodiazepine receptors in rats characterized by high affinity ^3H -diazepam binding. *Proc. Nat. Acad. Sci.*, **74**, 3805–3809.
- Castleden, C. M., George, C. F., Marcer, D. & Hallett, C. (1977). Increased sensitivity to nitrazepam in old age. *Br. med. J.*, **1**, 10–12.
- Clarke, C. H. & Nicholson, A. N. (1978). Immediate and residual effects in man of the metabolites of diazepam. *Br. J. clin. Pharmacol.*, **6**, 325–331.
- Cook, P. J., Flanagan, R. & James, I. M. (1984). Diazepam tolerance: effect of age, regular sedation and alcohol. *Br. med. J.*, **289**, 351–353.
- De Silva, J. A. F. & Puglisi, C. V. (1970). Determination of medazepam (Nobrium), diazepam (Valium) and their major biotransformation products in blood and urine by electron capture gas-liquid chromatography. *Analyt. Chem.*, **42**, 1725–1736.
- Evans, J. & Jarvis, E. H. (1972). Nitrazepam in the elderly. *Br. med. J.*, **4**, 487.
- Garrattini, S., Marcussi, F., Morselli, P. L. & Mussini, E. (1973). The significance of measuring blood levels of benzodiazepines. In *Biological effects of drugs in relation to their plasma concentrations*, eds Davies, D. S. & Pritchard, B. N. C., pp 211–225. London: Macmillan.
- Giles, H. G., MacLeod, S. M., Wright, J. R. & Sellers, E. M. (1978). Influence of age and previous use on diazepam dosage required for endoscopy. *Can. med. Ass. J.*, **118**, 513–514.
- Greenblatt, D. J. & Allen, M. D. (1978). Toxicity of nitrazepam in the elderly: a report from the Boston Collaborative Drug Surveillance Program. *Br. J. clin. Pharmacol.*, **5**, 407–413.
- Greenblatt, D. J., Allen, M. D. & Shader, R. I. (1977). Toxicity of high-dose flurazepam in the elderly. *Clin. Pharmacol. Ther.*, **21**, 355–361.
- Greenblatt, D. J., Divoll, M., Abernethy, D. R., Harmatz, J. S. & Shader, R. I. (1982). Antipyrine kinetics in the elderly: prediction of age-related changes in benzodiazepine oxidizing capacity. *J. Pharmacol. exp. Ther.*, **220**, 120–126.
- Greenblatt, D. J., Divoll, M., Harmatz, J. S. & Shader, R. I. (1980). Diazepam disposition determinants. *Clin. Pharmacol. Ther.*, **27**, 301–312.
- Greenblatt, D. J., Divoll, M., Puri, S. K., Ho, I., Zinny, M. A. & Shader, R. I. (1981). Clobazam kinetics in the elderly. *Br. J. clin. Pharmacol.*, **12**, 631–636.
- Karacan, I., Thornby, J. I., Anch, M., Holzer, C. E., Warheit, G. J., Schwab, J. J. & Williams, R. L. (1976). Prevalence of sleep disturbance in a primarily urban Florida county. *Soc. Sci. Med.*, **10**, 239–244.
- Klotz, U., Avant, G. R., Hoyumpa, A., Schenker, S. & Wilkinson, G. R. (1975). The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J. clin. Invest.*, **55**, 347–359.
- Klotz, U. & Müller-Seydlitz, P. (1979). Altered elimination of desmethyldiazepam in the elderly. *Br. J. clin. Pharmacol.*, **7**, 119–120.
- Macklon, A. F., Barton, M., James, O. & Rawlins, M. D. (1980). The effect of age on the pharmacokinetics of diazepam. *Clin. Sci.*, **59**, 479–483.
- MacLeod, S. M., Giles, H. G., Bengert, B., Lui, F. F. & Sellers, E. M. (1979). Age and gender-related differences in diazepam pharmacokinetics. *J. clin. Pharmacol.*, **19**, 15–19.
- Mandelli, M., Tognoni, G. & Garattini, S. (1978). Clinical pharmacokinetics of diazepam. *Clin. Pharmacokin.*, **3**, 72–91.
- McGhie, A. & Russell, S. M. (1962). The subjective assessment of normal sleep patterns. *J. mental Sci.*, **108**, 642–654.
- Möhler, H. & Okada, T. (1977). Benzodiazepine receptor: demonstration in the central nervous system. *Science*, **198**, 849–851.
- Reidenberg, M. M., Levy, M., Warner, H., Coutinho, C. B., Schwartz, M. A., Yu, G. & Cheripko, J. (1978). Relationship between diazepam dose, plasma level, age, and central nervous system depression. *Clin. Pharmacol. Ther.*, **23**, 371–374.
- Shader, R. I. & Greenblatt, D. J. (1981). The use of benzodiazepines in clinical practice. *Br. J. clin. Pharmacol.*, **11**, 5S–9S.
- Shader, R. I., Greenblatt, D. J., Ciraulo, D. A., Divoll, M., Harmatz, J. S. & Georgotas, A. (1981). Effect of age and sex on disposition of desmethyldiazepam formed from its precursor clorazepate. *Psychopharmacology (Berlin)*, **75**, 193–197.
- Shader, R. I., Greenblatt, D. J., Harmatz, J. S., Franke, K. & Koch-Weser, J. (1977). Absorption and disposition of chlordiazepoxide in young and elderly male volunteers. *J. clin. Pharmacol.*, **17**, 709–718.
- Skegg, D. C. G., Doll, R. & Perry, J. (1977). Use of medicines in general practice. *Br. med. J.*, **1**, 1561–1563.
- Swift, C. G. (1983). *Studies on the response to benzodiazepine drugs in the elderly*. PhD Thesis, University of Dundee, Dundee, Scotland.
- Tsang, C. C., Speed, K. V. & Wilkinson, G. R. (1982). Ageing and benzodiazepine binding in the rat cerebral cortex. *Life Sci.*, **30**, 343–346.
- Wilkinson, G. R. (1978). The effects of liver disease and ageing on the disposition of diazepam, chlordiazepoxide, lorazepam and oxazepam in man. *Acta Psychiat. Scand.*, Suppl. **274**, 56–74.
- Wittenborn, J. R. (1979). Effects of benzodiazepines on psychomotor performance. *Br. J. clin. Pharmacol.*, **7**, 61S–67S.
- Wright, B. M. (1971). A simple mechanical ataxiometer. *J. Physiol. (Lond.)*, **218**, 28P.

(Received 3 October 1984,
accepted 10 April 1985)