Single dose pharmacokinetics and pharmacodynamics of oral loprazolam in the elderly

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- 1 The pharmacokinetics of the benzodiazepine hypnotic, loprazolam (1.0 mg orally), and the pharmacodynamic response to single oral doses (0.5 mg and 1.0 mg) have been compared in young and elderly healthy volunteers.
- 2 No difference between the groups in peak plasma concentration ($C_{\max}$) or in the time to peak ($t_{\max}$) was found, but the elimination half-life $t_{1/2,z}$ and area under the plasma concentration-time curve (AUC) were significantly greater in the elderly group.
- 3 The immediate effects of loprazolam on all three performance tests used (postural sway, critical flicker fusion threshold (CFFT) and choice reaction time (CRT)) and on subjective sedation tended to be more pronounced in the elderly subjects, though intersubject variability in response was high in both groups. The corresponding plasma concentrations did not differ significantly between the two groups.
- 4 The higher (1.0 mg) dosage was associated with significant residual (11 h) impairment of standing steadiness in the elderly subjects. No other hangover effects were observed.
- 5 The results are compatible with previous evidence of increased 'sensitivity' to benzodiazepines in the elderly and suggest that a lower (0.5 mg) starting dose of loprazolam would be appropriate for older recipients.
- 6 Further investigation would be necessary to establish whether clinically relevant accumulation of loprazolam occurs in the elderly following repeated dosage.

Keywords loprazolam pharmacokinetics pharmacodynamics elderly

Introduction

Benzodiazepine compounds continue to be widely prescribed for the treatment of insomnia. Advantages of this group of compounds include their associated anxiolytic effect, safety in over-dosage and low potential for interaction with other drugs. Slowly metabolised benzodiazepines with long plasma half-lives have been criticised on the grounds of their potential to cause daytime sedation and to accumulate on multiple dosage. Conversely, very rapidly eliminated preparations have been implicated in causing rebound anxiety the morning after

administration (Morgan & Oswald, 1982) and pronounced rebound insomnia on withdrawal after repeated usage (Kales *et al.*, 1979). Consequently, the development of newer benzodiazepine hypnotic drugs is commonly orientated towards preparations offering more satisfactory pharmacokinetic and pharmacodynamic characteristics.

The elderly are major recipients of hypnotic and sedative drugs (Skegg *et al.*, 1977). They are also more susceptible to the adverse effects of benzodiazepines, principally over-sedation

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(Boston Collaborative Drug Surveillance Programme, 1973; Greenblatt *et al.*, 1977; Greenblatt & Allen, 1978).

The biotransformation of most benzodiazepine compounds undergoing oxidative metabolism has been found to be slower in the elderly (particularly in males) and to correlate with antipyrine clearance (Greenblatt *et al.*, 1982). In addition, the distribution volumes are commonly greater (Klotz *et al.*, 1975; Shader *et al.*, 1977; MacLeod *et al.*, 1979; Greenblatt *et al.*, 1981) and the extent of protein binding reduced in some cases (Macklon *et al.*, 1980; Greenblatt *et al.*, 1980; Shader *et al.*, 1981; Swift, 1983). Conversely, for drugs metabolised via non-oxidative routes, such as conjugation, little change in drug handling with age is apparent (Shull *et al.*, 1976; Greenblatt *et al.*, 1979; Divoll *et al.*, 1981).

There is, additionally, evidence that responsiveness to benzodiazepines may be accentuated with age independently of alterations in plasma concentrations. This has been demonstrated after single doses of intravenous and oral diazepam (Giles *et al.*, 1978; Reidenberg *et al.*, 1978; Swift, 1983; Cook *et al.*, 1984), oral nitrazepam (Castleden *et al.*, 1977) and temazepam (Swift *et al.*, 1981).

In evaluating any benzodiazepine drug for use in the elderly and in establishing appropriate dose regimes, it is thus important to determine as far as possible the effect of age, if any, on its pharmacokinetic and pharmacodynamic characteristics.

Loprazolam (Dormonox) is a new water-soluble imidazobenzodiazepine compound with hypnotic properties in man at doses of 0.5 mg–2.0 mg (Hindmarch & Clyde, 1980). Its major route of metabolism is *N*-oxidation. We have investigated the pharmacokinetics of loprazolam after oral dosage (1.0 mg) and the response to single doses of 0.5 mg and 1.0 mg with concurrent measurement of plasma concentrations in both young and elderly healthy volunteers.

Study I: Oral pharmacokinetics

Subjects and methods

Two groups of drug free, non-smoking healthy volunteers participated, a young group ($n = 10$; mean age 28.8 years; age range 23–39 years; five male, five female) and an elderly group ($n = 9$; mean age 72 years; age range 67–83; four male, five female). Mean body weights for the two groups were 67.3 ± 11.1 kg (young) and 70.0 ± 9.1 kg (elderly) (means $\pm$ s.d.). The elderly

volunteers were fully independent, healthy individuals 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 relevant investigational indices outside the normal range for age. Informed consent was obtained following a full explanation of the nature and purpose of the study, which was approved by the local ethical committee.

Loprazolam 1.0 mg was administered by mouth in the morning following an overnight fast, and a standard light food intake permitted at 4 h. Plasma samples were taken via an indwelling cannula and subsequent venepuncture at 0, 0.25, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 12, 24, 36, 48 and 60 h after ingestion, and stored at -20°C to await analysis.

Loprazolam concentrations were measured using a sensitive specific h.p.l.c./GC method of analysis (Bevan *et al.*, in preparation) as follows. An ether extract of a basified plasma sample was evaporated to dryness, resuspended in mobile phase and injected on to an h.p.l.c. column. The column was packed with C_{18} μ Bondapak and the mobile phase was methanol: ammonium carbonate (0.1% w/v) (3:1, pH 7.2). The peak containing the loprazolam was identified at 333 nm, collected and subjected to acid hydrolysis at 70°C for 20 min. After cooling, the neutralised aqueous layer was extracted with diethyl ether. The organic layer was then removed, evaporated to dryness and the residue resuspended in butyl acetate. An aliquot of this solution was then injected on to a 3% OV17 on Chromosorb GC column at 270°C using nitrogen as the carrier gas and electron capture detection. By using an initial sample volume of 4.0 ml it was possible to achieve a detection limit of 0.25 ng ml^{-1} . Quality control samples included in the assay runs at 0.53, 2.68, 13.2 and 26.2 ng ml^{-1} had coefficients of variation of 14.7, 9.0, 6.9 and 8.4% respectively and recoveries of 102, 98, 96 and 97% respectively.

The curves were fitted using a nonlinear, interactive least-squares curve-fitting programme (Ings *et al.*, 1980).

Results

Mean plasma concentration-time profiles for young and elderly volunteers are shown in Figure 1. Standard errors are given in Table 1. In the majority of subjects, the data were indicative

Figure 1 Mean plasma concentration-time profiles after oral administration of 1.0 mg loprazolam to young (---□---) and elderly (—▲—) volunteers (limiter bars excluded for clarity—see Table 1).

of a two-compartment model, the remainder approximating more closely to a one-compartment model.

The principal pharmacokinetic parameters are outlined in Table 2. Absorption was somewhat slower than for most benzodiazepine hypnotics (range of $t_{\max}$ 0.75–4 h) but did not differ in rate

Table 1 Mean ($\pm$ s.e. mean) plasma loprazolam concentrations (ng ml^{-1}) after oral administration of 1.0 mg to young and elderly volunteers

Time (h)	Young	Elderly
0.25	—	0.52 ± 0.38
0.5	0.17 ± 0.06	—
0.75	1.55 ± 0.44	3.38 ± 0.70
1	2.66 ± 0.49	3.39 ± 0.60
1.5	3.91 ± 0.52	3.79 ± 0.34
2	3.70 ± 0.38	3.73 ± 0.33
3	3.18 ± 0.29	3.65 ± 0.33
4	2.73 ± 0.59	3.47 ± 0.27
5	2.27 ± 0.19	2.77 ± 0.22
6	2.06 ± 0.20	2.67 ± 0.37
12	1.23 ± 0.14	1.57 ± 0.10
24	0.62 ± 0.08	1.02 ± 0.13
36	0.23 ± 0.04	0.58 ± 0.08
48	—	0.28 ± 0.08

between the groups. The main finding was of a significant prolongation of elimination (terminal) half-life ($t_{1/2,z}$) in the elderly group with a corresponding increase in area under the curve (AUC). In a number of subjects there was fluctuation in plasma concentration round about the peak with poor definition of the distribution phase. For this reason distribution half-lives were not calculated.

Study II: Immediate and residual effects of oral loprazolam 0.5 mg and 1.0 mg

Subjects and methods

Two groups of 10 sex-matched healthy volunteers, a young and an elderly, fulfilling the criteria outlined under the above kinetic study participated in the study of drug response. Eight of the 10 volunteers in each group were the same as those involved in the pharmacokinetic study. The mean body-weights for the two groups were 67.1 ± 11.1 kg (young) and 68.4 ± 10.4 kg (elderly).

A protocol to allow evaluation of both immediate and residual pharmacodynamic effects was adopted as described in previous studies (Clarke & Nicholson, 1978; Swift, 1983). Administration was randomised and double-blind. Single oral doses of loprazolam (0.5 mg or 1.0 mg) or placebo were administered at night (approximately 22.30 h) and in the morning (approximately 09.00 h) on five separate occasions at least 1 week apart. Observations were made at 0.5, 2.0, 4.0 and 6.0 h 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 each dose of loprazolam. Similarly, residual effects were determined from the comparison of active drug at night/placebo in the morning with the double placebo occasion.

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

Response was measured by the following performance tests:

1 Measurement of postural sway

This was carried out using an electronic (Codoc) modification of the Wright ataxiometer (Wright, 1971), providing a digital readout in $^{\circ}\text{arc} \times 3$ of anteroposterior sway. Change in postural stability has been shown to be a sensitive index of benzodiazepine response and is perhaps of particular clinical relevance in the elderly (Swift, 1984).

Table 2 Pharmacokinetic parameters of lorazepam in young and elderly volunteers following an oral 1 mg dose

	$C_{\max}$ (ng ml ⁻¹)	$t_{\max}$ (h)	$t_{1/2,z}$ (h)	AUC (ng ml ⁻¹ h)
Young ($n = 10$)	4.3 ± 1.3	2.40 ± 1.13	11.22 ± 1.97††	46.6 ± 11.9††
(Range)	(2.6 – 6.8)	(1.5 – 4.0)	(8.70 – 14.43)	(32.8 – 74.4)
Elderly ($n = 9$)	4.2 ± 1.3	2.42 ± 1.32	19.77 ± 6.58**†	74.5 ± 18.6**†
(Range)	(2.6 – 7.1)	(0.75 – 4.0)	(9.46 – 30.68)	(43.7 – 93.6)

Values are means ± s.d.

** $P < 0.01$ vs young subjects: † $n = 8$, †† $n = 9$

2 Critical flicker fusion threshold (CFFT) and choice reaction time (CRT)

These were measured using the combined apparatus developed by Hindmarch (1975).

3 Subjective ratings

Visual analogue scales were used to assess subjective sedation and perception of standing steadiness, the scale extremes being 'wide-awake/nearly asleep' and 'completely steady/very dizzy'.

Plasma concentrations of lorazepam were measured using the same method as in Study I.

The significance of changes from placebo at each time point were assessed using the non-parametric Wilcoxon Signed Rank Test and differences between group values using the Mann-Whitney 'U' test or unpaired t -test as applicable.

Results

The effects of both doses on performance measures and subjective ratings in the two groups are shown in Figure 2, 3, 4, 5 and 6. Intersubject variability was high. All values are shown by comparison with the corresponding time point on the double-placebo occasion.

1 Postural sway (Figure 2)

This was slightly but significantly increased by 0.5 mg lorazepam at 2 h in the young group (0.80° arc) and at 4 h and 6 h in the elderly group (1.18 and 1.28° arc). After 1.0 mg, sway was significantly increased at 2 h in both young (3.05° arc) and elderly (6.05° arc) groups and was still significantly raised in the elderly group at 4, 6 and 11 h (values in brackets are medians).

2 Critical flicker fusion threshold (CFFT) (Figure 3)

In the young group a slight reduction was observed at 6 h after 0.5 mg (−0.75 Hz), but a median reduction of 2.24 Hz occurred at 4 h after the 1.0 mg dose. In the elderly group CFFT was significantly lowered at 2, 4 and 6 h by both doses, the median reduction 2 h after the 1 mg dose being 3.28 Hz. No significant effect was observed beyond the 6 h time point in either group.

3 Choice reaction time (CRT) (Figure 4)

CRT was not significantly affected by lorazepam 0.5 mg in either group. With 1.0 mg CRT was prolonged 2 h after ingestion by 55 ms and 112 ms (median values) in young and elderly groups respectively. No significant effects were observed at any other time points.

4 Subjective ratings (Figures 5 and 6)

Significant subjective sedation ('wide awake/nearly asleep' – scale) occurred after 0.5 mg at 2 h in the elderly group, but there was no effect in young subjects. After 1 mg, both groups felt sedated at 2 h (the elderly group to a greater degree) and 4 h, and this was still significant in the elderly group at 6 h. Subjective unsteadiness ('completely steady/very dizzy' – scale) occurred to a similar degree in both groups at 2 h after the 1 mg dose, and the young subjects were still aware of this effect at 4 h post dosage.

The maximal change in each measure of response vs placebo ($\Delta_{\max}$) was compared between the two groups. The results together with the mean values for all placebo recordings are given in Table 3. There was a consistent trend towards accentuation of maximal response in the elderly although this was not significant for any one measure. Intersubject variability in response was marked in both groups. Under

Figure 2 The effect of (a) 0.5 mg and (b) 1.0 mg doses of loprazolam on postural sway in young (---●---) and elderly (—●—) volunteers (* $P < 0.05$; ** $P < 0.01$ vs placebo) (Wilcoxon Signed Rank Test) (median values shown).

placebo conditions sway was significantly greater ($P < 0.001$) and choice reaction time significantly longer ($P < 0.001$) in the older group, but CFFT and subjective ratings did not differ significantly.

The plasma loprazolam concentrations of the samples taken at corresponding time points to the above observations are shown in Figure 7.

Intersubject variability was high, but the levels did not differ significantly between the groups at any given time point. No attempt was made to draw pharmacokinetic inferences from these results, nor would this be legitimate, since samples were obtained on four separate occasions, the sampling intervals are large and the sampling duration was short for pharmacokinetic purposes.

Figure 3 The effect of (a) 0.5 mg and (b) 1.0 mg doses of loprazolam on CFFT in young (---●---) and elderly (—●—) volunteers (* $P < 0.05$; ** $P < 0.01$ vs placebo) (Wilcoxon Signed Rank Test) (median values shown).

Figure 4 The effect of (a) 0.5 mg and (b) 1.0 mg doses of lorazepam on choice reaction time in young (---●---) and elderly (—●—) volunteers (* $P < 0.05$; ** $P < 0.01$ vs placebo) (Wilcoxon Signed Rank Test) (median values shown).

Discussion

The peak plasma concentrations of lorazepam obtained after 1.0 mg oral dosing are similar to those reported elsewhere (McInnes *et al.*, 1985). No difference was observed between young and

elderly groups. Drug absorption has generally been found to be unchanged with age (Stevenson *et al.*, 1980) and it is reasonable to assume this is so with lorazepam, although alterations in distribution volume and/or first pass effect have not been excluded by combined oral/intravenous

Figure 5 The effect of (a) 0.5 mg and (b) 1.0 mg doses of lorazepam on subjective sedation in young (---●---) and elderly (—●—) volunteers (* $P < 0.05$; ** $P < 0.01$ vs placebo) (Wilcoxon Signed Rank Test) (median values shown).

Figure 6 The effect of (a) 0.5 mg and (b) 1.0 mg doses of loprazolam on subjective unsteadiness in young (---○---) and elderly (—●—) volunteers (* $P < 0.05$; ** $P < 0.01$ vs. placebo) (Wilcoxon Signed Rank Test) (median values shown).

pharmacokinetic evaluation. The time to peak concentration ($t_{\max}$) was similar in young (2.40 h) and elderly (2.42 h) subjects; this is rather longer than for some other hypnotics, and has been found elsewhere to be longer still (4–5 h) after supine nocturnal administration

(McInnes *et al.*, 1985). Loprazolam has been found in clinical trials to be an effective hypnotic (Boyd & Ankier, 1983; Adam *et al.*, 1984) although significant sedation was not observed in the present study prior to 2 h post dosage, a finding to be anticipated from the slow absorption rate.

Figure 7 Plasma concentrations of loprazolam corresponding to pharmacodynamic observations after oral doses of (a) 0.5 mg and (b) 1.0 mg in young (---○---) and elderly (—●—) volunteers (values are means $\pm$ s.e. mean).

Table 3 Maximal changes vs placebo ($\Delta_{\max}$) in performance and visual analogue ratings after oral lorazepam 0.5 mg and 1.0 mg in young and elderly volunteers

		Young (n = 10)	Elderly (n = 10)	P (young vs elderly)	
Postural sway (°arc)	$\Delta_{\max}$ 0.5 mg	+ 1.8 (0.3 → 5.0)	+ 2.1 (0.9 → 7.9)	NS	†
	1.0 mg	+ 4.0 (-0.7 → 9.5)	+ 6.6 (1.0 → 30.4)	0.1 > p > 0.05	†
	{placebo}	{2.8 ± 1.4}	{5.1 ± 2.4}	{<0.001}	††
CFFT (Hz)	$\Delta_{\max}$ 0.5 mg	- 2.5 (0.1 → - 6.6)	- 3.0 (- 0.6 → - 5.5)	NS	†
	1.0 mg	- 2.4 (- 0.8 → - 5.6)	- 3.5 (- 0.3 → - 5.3)	NS	†
	{placebo}	{34.4 ± 3.4}	{34.9 ± 2.4}	{NS}	††
CRT (ms)	$\Delta_{\max}$ 0.5 mg	+ 60.5 (- 49 → 354)	+ 104.0 (- 38 → 211)	NS	†
	1.0 mg	+ 73.5 (- 48 → 694)	+ 111.5 (- 18 → 965)	NS	†
	{placebo}	{491.2 ± 55.1}	{653.8 ± 92.5}	{<0.001}	††
VA (1) (mm)	$\Delta_{\max}$ 0.5 mg	+ 13.0 (1 → 88)	+ 48.5 (1 → 74)	NS	†
	1.0 mg	+ 26.0 (- 1 → 99)	+ 59.0 (10 → 89)	NS	†
	{placebo}	{9.6 ± 11.8}	{11.5 ± 15.3}	{NS}	†
VA (2) (mm)	$\Delta_{\max}$ 0.5 mg	+ 8.0 (0 → 87)	+ 15.0 (- 5 → 51)	NS	†
	1.0 mg	+ 16.5 (1 → 97)	+ 34.0 (7 → 90)	NS	†
	{placebo}	{8.3 ± 9.4}	{7.8 ± 8.1}	{NS}	†

VA (1) = 'Wide awake - nearly asleep'

VA (2) = 'Completely steady - very dizzy'

Values given are medians with ranges in brackets {Placebo values are means ± s.d.}

† Mann-Whitney 'U' test, †† Unpaired *t*-test

The elimination half-life of lorazepam is significantly prolonged in older subjects. As indicated above, lorazepam undergoes oxidative biotransformation to the piperazine *N*-oxide. The longer half-life is compatible with some reduction in the rate of metabolic elimination of the drug in the elderly. Slight but clinically insignificant accumulation of lorazepam occurs in young subjects (McInnes *et al.*, 1985) and this may, therefore, assume greater relevance in the elderly. However, plasma half-life may also be prolonged solely due to an increase in distribution volume, in which case the potential for accumulation would be unaltered. Parallel oral/intravenous pharmacokinetic studies and/or multiple dose evaluation in older subjects are required to resolve this question.

The clinical relevance of any accumulation would depend both on the dosage and on the degree and onset of pharmacodynamic tolerance in the elderly recipients. Epidemiological data (Swift *et al.*, 1984), as well as some of the few repeated dose studies of benzodiazepine hypnotics involving elderly recipients which have been undertaken (e.g. Campbell & Somerton, 1982; Cook *et al.*, 1983), indicate that the capacity to develop tolerance is retained in old age, though the process may take longer than in younger individuals. The maximum risk period for any unwanted sedation due to accumulated 'steady-state' concentrations, should this occur

on standard dosage, would accordingly be the initial days of therapy.

The sedative response to lorazepam 1.0 mg showed a consistent trend to accentuation in elderly subjects compared with young on all three performance tests at 2 h after administration, although there was considerable inter-subject variation. In addition, the sedative effect of 0.5 mg lorazepam as measured by postural sway and CFFT was highly significant in the elderly group as distinct from the young, who showed only marginal changes in these measures (Figures 2 and 3).

When response was expressed as maximal change vs placebo the trend to accentuation in the elderly was present at both doses and in all the measures used, although variability between subjects outweighed statistical significance in the comparison for any single test.

The lack of differences between groups in the plasma concentration data obtained in Study II (as distinct from the pharmacokinetic differences shown in Study I) is readily explained by the short (0-16 h) sampling duration. During this period the concentrations in both groups were similar, the differences only becoming clearly apparent during the terminal elimination phase.

Allowing for variability our results show a tendency to an enhanced response of the elderly to a given dose of the drug in the absence of any

significant difference in the corresponding plasma loprazolam concentrations. These findings are broadly consistent with those of earlier studies suggesting that 'sensitivity' to benzodiazepine compounds is increased in old age (Castleden *et al.*, 1977; Giles *et al.*, 1978; Reidenberg *et al.*, 1978; Swift *et al.*, 1981; Swift, 1983; Cook *et al.*, 1984). The mechanisms involved have not been determined, there being no direct information to date on the status of specific benzodiazepine receptors in the ageing human brain. Possible pharmacodynamic factors suggested have included increased receptor binding affinity, changes in the CNS levels of a postulated endogenous ligand, altered regional distribution of drug within the brain or simple impairment of neurological homeostatic mechanisms. Reduced protein binding of some benzodiazepines has been shown to occur in the elderly, e.g. diazepam (Macklon *et al.*, 1980; Greenblatt *et al.*, 1980) and desmethyldiazepam (Shader *et al.*, 1981), but in the case of diazepam, free concentrations still do not exceed those in

young subjects and show no significant correlation with measurements of response (Swift, 1983). Thus, the mechanism would appear to be at least partly pharmacodynamic.

The accentuated immediate response is of clinical relevance for older people who may need to rise during night-time hours. In addition, the impairment of postural sway still detectable in the older group 11.0 h after 1.0 mg supports the view that this dosage may be too high for elderly recipients. Persistent effects of loprazolam 1.0 mg on residual performance tests have been previously reported (Nicholson & Stone, 1983), but were not seen to a significant degree in the younger recipients in the present study. Our findings suggest that 0.5 mg loprazolam would be an appropriate starting dose for use in the elderly, since the degree of sedation may well be adequate for hypnotic purposes, while the likelihood of an unsafe or unacceptable degree of psychomotor impairment, or of hangover sedation, will remain low.

References

- Adam, K., Oswald, I. & Shapiro, C. (1984). Effects of loprazolam and of triazolam on sleep and overnight urinary cortisol. *Psychopharmac.*, **82**, 389–394.
- 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.
- Boyd, D. H. A. & Ankier, S. I. (1983). A clinical trial of a new hypnotic—loprazolam. *Br. J. clin. Pract.*, **37**, 143–147.
- Campbell, A. J. & Somerton, D. T. (1982). Benzodiazepine drug effect on body sway in elderly subjects. *J. clin. exp. Ger.*, **4**, 341–347.
- 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. Pharmac.*, **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.
- Cook, P. J., Huggett, A., Graham-Pole, R., Savage, I. T. & James, I. M. (1983). Hypnotic accumulation and hangover in elderly in-patients: a controlled double-blind study of temazepam and nitrazepam. *Br. med. J.*, **286**, 100–102.
- Divoll, M., Greenblatt, D. J., Harmatz, J. S. & Shader, R. I. (1981). Effect of age and gender on disposition of temazepam. *J. pharm. Sci.*, **70**, 1104–1107.
- 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. Pharmac.*, **5**, 407–413.
- Greenblatt, D. J., Allen, M. D., Locniskar, A., Harmatz, J. S. & Shader, R. I. (1979). Lorazepam kinetics in the elderly. *Clin. Pharmac. Ther.*, **26**, 103–113.
- Greenblatt, D. J., Allen, M. D. & Shader, R. I. (1977). Toxicity of high-dose flurazepam in the elderly. *Clin. Pharmac. 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. Pharmac. exp. Ther.*, **220**, 120–126.
- Greenblatt, D. J., Divoll, M., Harmatz, J. S. & Shader, R. I. (1980). Diazepam disposition determinants. *Clin. Pharmac. 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. Pharmac.*, **12**, 631–636.
- Hindmarch, I. (1975). A 1, 4 benzodiazepine, temazepam K3917; its effect on some psychological parameters of sleep and behaviour. *Arzneimittel-Forsch.*, **25**, 1836–1839.
- Hindmarch, I. & Clyde, C. A. (1980). A preliminary investigation of a 1, 4 benzodiazepine derivative

- (HR 158) on subjective aspects of sleep and objective measures of early morning performance. *Drugs exp. clin. Res.*, **2**, 61–70.
- Ings, R. M. J., Pidgen, A. & Johnson, D. (1980). Analysis of bioavailability studies. Abstract 416, *World Conference on Clinical Pharmacology and Therapeutics*, eds, Turner, P. & Padgham, C. London: Macmillan.
- Kales, A., Scharf, M. B., Kales, J. D., Constantin, R. & Soldatos, R. (1979). Rebound insomnia. A potential hazard following withdrawal of certain benzodiazepines. *J. Am. med. Ass.*, **24**, 1692–1695.
- 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.
- 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.
- McInnes, G. T., Bunting, E. A., Ings, R. M. J., Robinson, J. & Anker, S. I. (1985). Pharmacokinetics and pharmacodynamics following single and repeated nightly administrations of lorprazolam, a new benzodiazepine hypnotic. *Br. J. clin. Pharmacol.*, **19**, 649–656.
- Morgan, K. & Oswald, I. (1982). Anxiety caused by a short half-life hypnotic. *Br. med. J.*, **284**, 942.
- Nicholson, A. N. & Stone, B. M. (1983). Imidazobenzodiazepines: sleep and performance studies in humans. *J. clin. Psychopharmacol.*, **3**, 72–75.
- 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., 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.
- Shull, H. H. Jr, Wilkinson, G. R., Johnson, R. & Schenker, S. (1976). Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann. int. Med.*, **84**, 420–425.
- Skegg, D. C. G., Doll, R. & Perry, J. (1977). Use of medicines in general practice. *Br. med. J.*, **1**, 1561–1563.
- Stevenson, I. H., Salem, S., O'Malley, K., Cusack, B. & Kelly, J. G. (1980). Age and drug absorption. In *Drug absorption*, eds, Prescott, L. F. & Nimmo, W. S., pp 253–261. Sydney, Australia: ADIS Press.
- Swift, C. G. (1983). *Studies on the response to benzodiazepine drugs in the elderly*. PhD Thesis, University of Dundee, Dundee, Scotland.
- Swift, C. G. (1984). Postural instability as a measure of sedative drug response. *Br. J. clin. Pharmacol.*, **18**, 87S–90S.
- Swift, C. G., Haythorne, J. M., Clarke, P. & Stevenson, I. H. (1981). The effect of ageing on measured responses to single doses of oral temazepam. *Br. J. clin. Pharmacol.*, **11**, 413P–414P.
- Swift, C. G., Swift, M. R., Hamley, J., Stevenson, I. H. & Crooks, J. (1984). Side effect 'tolerance' in elderly long-term recipients of benzodiazepine hypnotics. *Age and Ageing*, **13**, 335–343.
- Wright, B. M. (1971). A simple mechanical ataxiometer. *J. Physiol.*, **218**, 27–28.

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