EFFECT OF AGE AND LIVER CIRRHOSIS ON THE PHARMACOKINETICS OF NITRAZEPAM

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1 The effect of age and liver cirrhosis on the pharmacokinetics of i.v. administered nitrazepam was studied in nine healthy relatively young subjects (age 22–49 years), eight healthy elderly (age 67–76 years) and 12 patients with alcoholic liver cirrhosis (age 39–66 years).

2 The elimination half-life of nitrazepam in the elderly subjects was longer than in the young ones but the difference did not reach statistical significance. Mean values (ranges) were 38 (26–64) h and 26 (19–31) h respectively.

3 The increase in elimination half-life was primarily due to an increase in volume of distribution, mean values (ranges) being 2.93 (1.96–5.33) l/kg and 1.89 (1.44–2.23) l/kg in the elderly and young groups respectively ($P < 0.05$).

4 The protein unbound fraction of nitrazepam tended to be higher in the elderly subjects, although the difference between the two age groups was not significant: 13.9 (11.5–15.4) % and 13.0 (11.0–15.9) % in elderly and young respectively.

5 Age had no effect on the clearance of total nitrazepam nor on the clearance of unbound nitrazepam (intrinsic clearance). Mean values (ranges) were 63 (50–87) ml/min and 489 (377–635) ml/min in the young and 64 (47–91) ml/min and 456 (348–652) ml/min in the elderly subjects respectively.

6 There were no significant differences in elimination half life, clearance and volume of distribution between patients with alcoholic liver cirrhosis and the total of healthy subjects of both age groups, mean values (ranges) being 31 (21–55) h, 59 (26–85) ml/min and 2.17 (1.57–3.22) l/kg respectively in patients and 31 (19–64) h, 63 (47–91) ml/min and 2.38 (1.44–5.33) l/kg in healthy subjects.

7 The protein unbound fraction of nitrazepam was substantially higher in the patient group: 18.9 (14.8–30.3) % as compared to 13.8 (11.0–15.9) % in the healthy subjects ($P < 0.001$).

8 Clearance calculated relative to unbound nitrazepam (intrinsic clearance) was significantly lower in the patient group: 320 (163–482) ml/min as compared to healthy subjects, 472 (348–652) ml/min ($P < 0.001$).

9 The results of this study indicate that nitrazepam action following single dose administration may be more persistent in elderly than in young people; however, steady state levels of total and unbound nitrazepam during nightly intake of the drug will not be affected by age. On the other hand, steady state levels of unbound nitrazepam in patients with liver cirrhosis will generally be about 35% higher than in healthy subjects.

Introduction

Benzodiazepines are widely prescribed, particularly, for elderly people. There is evidence that elderly patients are more likely to develop adverse reactions to benzodiazepine treatment (Castleden *et al.*, 1977; Editorial, 1977; Greenblatt & Allen, 1978; Hurwitz, 1969; Miller & Greenblatt, 1976). An increased drug sensitivity may reflect changes in actual receptor

sensitivity, but alterations in drug disposition are also likely to be involved (Castleden & George, 1979; Shader & Greenblatt, 1979).

Several investigators have clearly demonstrated that age may affect the pharmacokinetics of the various benzodiazepine derivatives differently, which is dependent on the type of biotransformation

reaction. Benzodiazepines that are primarily oxidized generally exhibit longer elimination half-lives in the elderly, which is due to a lower metabolic clearance and/or a larger volume of distribution (Divoll Allen *et al.*, 1980; Greenblatt *et al.*, 1980a, 1981; Klotz *et al.*, 1975; Klotz & Müller-Seydlitz, 1979; Roberts *et al.*, 1978). On the other hand, for benzodiazepines for which glucuronide and sulphate conjugation are the primary metabolic steps, the ageing process has a minimal effect, if any, on drug disposition (Divoll *et al.*, 1981; Greenblatt *et al.*, 1979, 1980b; Krauss *et al.*, 1978; Shull *et al.*, 1976).

Similar observations have been made as to the influence of liver disease on the pharmacokinetics of the different benzodiazepine derivatives: oxidative metabolism is often quite strongly inhibited, whereas conjugation reactions are hardly affected (Klotz *et al.*, 1975; Krauss *et al.*, 1978; Roberts *et al.*, 1978; Sellers *et al.*, 1979; Shull *et al.*, 1976).

Nitrazepam is a widely used benzodiazepine hypnotic of which the primary biotransformation step is nitro-reduction. Its disposition in normal young subjects has been fairly well studied (Jochemsens *et al.*, 1982a,b; Kangas *et al.*, 1979a; Kangas & Breimer, 1981), but there is little information about elderly people and none at all about patients with liver disease. Castleden *et al.* (1977), who measured nitrazepam plasma concentrations at 12, 36 and 60 h after administration and determined elimination half-lives, suggested that nitrazepam kinetics is not influenced by age, whereas Kangas *et al.* (1979b) found that in elderly patients the elimination half-lives were significantly longer owing to a larger volume of distribution. In neither of these studies was the clearance of unbound drug (intrinsic clearance), which is the parameter reflecting the activity of the metabolizing enzymes involved, determined.

In the present study the influence of age and of

alcoholic liver cirrhosis on the disposition of i.v. nitrazepam has been investigated.

Methods

Experimental design

The subjects were:

- 9 relatively young, healthy volunteers, one female and eight males, ages 22–24, 36 and 49 years (Table 1), with normal renal and hepatic function. The 49-year-old male was a heavy smoker (> 15 cigarettes/day), the others did not smoke at all.
- 8 elderly healthy volunteers, six males and two females, age 67–76 years (Table 2), with normal renal and hepatic function. They were non- or light smokers (< 2 cigars/day) and three of them used other medications (see Table 2 for details).
- 12 patients with alcoholic liver cirrhosis, diagnosed on the basis of clinical and biochemical data (Table 3). In 10 patients the diagnosis was confirmed by liver biopsy. The patients were all heavy smokers except RO and SD, who did not smoke at all. For details of concomitant medication, see Table 3.

The experiments started at 09.00 h. Nitrazepam (5.24 mg) dissolved in propylene glycol-alcohol (2 : 3) and diluted 1 to 1 with sterile distilled water immediately before injection, was administered intravenously within about 30 s. Heparinized blood samples were subsequently obtained from the contralateral arm vein at 15, 30, 45, 60, 90 and 120 min, and at 3, 4, 6, 8, 24, 48, 72 and 96 h after drug administration, the first day of the experiment via a flexible cannula, on the other days by vene-puncture.

Nitrazepam concentrations in plasma were determined by capillary gas chromatography with a solid injection system and electron capture detection (De

Table 1 Pharmacokinetic parameters of nitrazepam in young subjects

Subject	Age/Weight (years)/(kg)	$t_{1/2,z}$ (h)	V (l/kg)	Total clearance (ml/min)	Free drug (%)	Intrinsic clearance (ml/min)
PR	23/74	26.8	2.24	72	13.0	551
TD	22/82	24.9	1.85	70	11.7	602
MG	24/67	27.8	1.77	50	13.1	379
SV	23/71	22.9	2.02	73	11.5	635
KD	23/63	27.5	1.90	50	11.0	458
FV	23/68	25.5	1.70	52	11.6	452
IV	23/80	30.8	1.91	55	14.1	387
BL*	36/71	18.8	1.44	60	15.9	377
HR	49/85	24.8	2.23	87	15.5	562
Mean	27/73	25.5	1.89	63	13.0	489
s.d.	9/7	3.3	0.25	13	1.8	100

*Female subject.

Table 2 Pharmacokinetic parameters of nitrazepam in elderly subjects

Subject	Age/Weight (years)/(kg)	$t_{1/2,z}$ (h)	V (l/kg)	Total clearance (ml/min)	Free drug (%)	Intrinsic clearance (ml/min)
BN*	73/65	24.3	1.96	61	13.9	437
JA ¹	74/80	29.1	1.97	63	15.4	406
DA	73/70	42.7	3.08	59	14.2	416
PB	75/61	29.1	2.21	54	14.2	378
BA ²	76/68	49.7	2.99	47	13.6	348
JV ^{*,3}	71/53	64.1	5.33	51	11.5	444
RU	67/92	26.2	2.07	84	14.8	571
SR	74/75	37.0	3.80	91	13.9	652
Mean	73/71	37.8	2.93	64	13.9	456
s.d.	3/12	13.8	1.17	16	1.1	103

*Female subject.

¹Other drugs: fenoterol and prednisone²Other drugs: paracetamol, nitroglycerin.³Other drugs: digoxin.

Boer *et al.*, 1978). The binding of nitrazepam to plasma protein was determined by equilibrium dialysis (Jochemsen *et al.*, 1982b).

Analysis of data

The pharmacokinetic evaluation of the plasma concentration data was performed in agreement with the procedure as published in a previous paper on the

pharmacokinetics of nitrazepam in healthy volunteers (Jochemsen *et al.*, 1982a).

Nitrazepam elimination half-lives ($t_{1/2,z}$) were calculated by least square regression analysis of the terminal log linear part of the plasma concentration vs time curve. Clearance (CL) and apparent volume of distribution (V) were calculated from the areas under the curve (AUC) determined by the trapezoidal rule and extrapolation to infinity:

Table 3 Characteristics of patients with alcoholic liver cirrhosis (normal values).

Patient	Gender	Age/Weight (years/kg)	Total bilirubin ($\mu\text{mol/l}$) (3–17)	SGOT (U/l) (2–15)	Plasma albumin (g/l) (35–50)	Prothrombin time (s) (< 14.5)	Other drugs
LS	M	61/97	51	24	36	16.3	Insulin, cimetidine Temazepam, spironolactone Chlordiazepoxide spironolactone Spironolactone, frusemide
SP	M	39/60	284	68	35	17.4	
CR	M	39/74	416	28	44	22.6	
GR	M	64/80	13	12	40	16.4	
FD	M	45/73	17	15	33	17.6	
OS	M	57/48	60	22	44	14.0	Spironolactone Digoxin Chlordiazepoxide digoxin, spironolactone, aminophylline, choline theophyl- linatate, salbutamol Oxazepam, clemastine, spironolactone Chlordiazepoxide Spironolactone, chlordiazepoxide
VL	M	53/71	23	26	30	17.0	
RO	F	60/76	228	28	27	21.2	
ST	M	66/93	30	21	40	14.8	
KS	F	58/55	23	16	39	14.8	
DV	M	55/62	45	35	30	12.8	
PL	M	38/85	16	97	37	14.0	

$$CL = \frac{D}{AUC} \quad (1)$$

and

$$V = \frac{CL \times t_{1/2,z}}{0.693} \quad (2)$$

The clearance of unbound drug (CL_u) was calculated according to:

$$CL_u = \frac{CL}{f_u} \quad (3)$$

in which f_u is the fraction of unbound drug.

For statistical analysis, the unpaired Student's *t*-test or the rank-order test of Wilcoxon was used, $P < 0.05$ being taken as the minimal level of significance.

Results

The plasma concentration vs time profile for nitrazepam was similar for the three subject groups. A representative example is given in Figure 1.

Age

The pharmacokinetic data for the two age groups are presented in Table 1 and Table 2. The mean elimination half-life was about 40% longer in the elderly subjects (38 h) than in the young ones (26 h) (Figure 2), but the difference was not statistically significant. The increase in elimination half-life could be explained by an increase in volume of distribution; mean values were 1.89 l/kg and 2.93 l/kg in the young and the elderly subjects respectively ($P < 0.05$, Figure 3).

The protein unbound fraction of nitrazepam tended to be higher in the elderly subjects, although the difference between the two age groups was not significant: 13.9% and 13.0% in elderly and young respectively. Albumin concentrations were slightly, but not significantly higher in young subjects than in the elderly (48 ± 2 and 46 ± 5 g/l respectively). There was however no correlation between total albumin concentration and protein binding ($r \leq -0.30$). When protein binding was determined in another group of 23 healthy subjects in the age range of 30 to 79 years (mean age 50), the mean unbound fraction in subjects over 50 years was higher than in subjects under 50 years: 14.3% and 13.1% respectively ($P < 0.002$, Figure 4).

Clearances of total and of unbound nitrazepam were about the same in both groups: 63 ml/min and 489 ml/min respectively in the young and 64 ml/min and 456 ml/min in the elderly subjects (Figure 5).

Alcoholic liver cirrhosis

The pharmacokinetic data of the patients with liver

Figure 1 Plasma concentration vs time profile of nitrazepam in a healthy young subject, in a healthy elderly subject and in a patient with liver cirrhosis following i.v. administration of 5.24 mg nitrazepam.

cirrhosis are presented in Table 4. There were no significant differences between elimination half-life, volume of distribution or clearance of total nitrazepam in patients with alcoholic liver cirrhosis and the combined data of the two healthy subject groups. The mean data were: 31 h, 2.17 l/kg and 50 ml/min respectively in the patients and 31 h, 2.38 l/kg and 63 ml/min in the healthy subjects (Figures 2 and 3). The protein unbound fraction of nitrazepam was higher in the patients (18.9%) than in the healthy subjects (13.8%) ($P < 0.001$, Figure 4).

Figure 2 Relationship between age and nitrazepam elimination half-life in healthy subjects (●) and in patients with alcoholic liver cirrhosis (○).

Discussion

The primary major step in the biotransformation of nitrazepam in man is the nitro-reduction, the regulation of which is virtually unknown. As nitrazepam is a low clearance drug that is highly protein bound, its removal rate from plasma depends on the activity of the metabolizing enzymes involved in its biotransformation and plasma binding. Hence the activity of the enzymes in metabolizing the drug is reflected by the plasma clearance of unbound drug (intrinsic clearance). In the present study the influence of age and liver cirrhosis on the pharmacokinetics of nitrazepam and thereby on the activity of the enzyme system responsible for the nitro-reduction has been studied. Age and liver cirrhosis seem to influence the disposition of nitrazepam differently: the elimination half-life of nitrazepam may be prolonged by a factor of 2 in some elderly

Figure 4 Relationship between age and nitrazepam protein binding in healthy subjects (●) and in patients with alcoholic liver cirrhosis (○).

people due to an increase in volume of distribution; these parameters are hardly altered by liver cirrhosis. On the other hand, the activity of the nitro-reduction enzyme system as reflected by the clearance of unbound nitrazepam is not impaired by the ageing process, but proves to be significantly decreased in patients with liver cirrhosis (about 45%). This is not reflected in clearance of total nitrazepam, since the fraction of protein unbound nitrazepam is also significantly higher (about 35%) among the patients. When the volume of distribution of nitrazepam was calculated relative to unbound drug, the increase with age was still there, possibly because of a change in body composition or in tissue binding. On the other hand, the volume of distribution of unbound nitrazepam was significantly smaller in the patient group than in the healthy subjects, which suggests that not only protein binding but also tissue binding has changed. Similar conclusions as to the effect of ageing

Figure 3 Relationship between age and volume of distribution in healthy subjects (●) and in patients with alcoholic liver cirrhosis (○).

Figure 5 Relationship between age and clearance of unbound nitrazepam in healthy subjects (●) and in patients with alcoholic liver cirrhosis (○).

Table 4 Pharmacokinetic parameters of nitrazepam in patients with alcoholic liver cirrhosis.

Subject	$t_{1/2,z}$ (h)	V (l/kg)	Total clearance (ml/min)	Free drug (%)	Intrinsic clearance (ml/min)
LR	26.3	1.98	85	22.6	376
SP	26.5	1.61	42	25.8	163
CR*	—	—	—	18.9	—
GR	28.5	1.57	51	15.6	326
FD	29.5	1.80	51	15.6	328
OS	22.4	1.60	41	14.8	276
VL	30.1	2.47	67	18.9	346
RO	37.1	3.22	76	30.3	252
ST	55.3	3.13	61	17.2	355
KS	27.2	2.36	55	15.8	349
DV	21.0	2.33	79	16.5	482
PL	31.5	1.80	38	15.0	256
Mean $\pm$ s.d.	30.5 $\pm$ 9.3	2.17 $\pm$ 0.59	59 $\pm$ 16	18.9 $\pm$ 4.3	320 $\pm$ 83

*Plasma concentrations could not be measured because of interfering peaks in the gas chromatogram.

on the disposition of nitrazepam were presented by Kangas *et al.* (1979b). In their study, however, the drug was given orally and plasma protein binding was not determined, precluding calculation of unbound nitrazepam clearance. Moreover, the elderly subjects in that study were partly to totally bedridden and therefore not very well comparable to our ambulant healthy population.

The three groups studied are not entirely comparable with regard to gender, smoking habits and concomitant drug intake. However, in a previous study it has been demonstrated that there are no gender differences in nitrazepam volume of distribution, (unbound) clearance and elimination half-life among young healthy subjects, but only a small though significant difference in protein binding (Jochensen *et al.*, 1982b). According to Greenblatt *et al.* (1982), age differences in oxidizing capacity are far greater in men than in women, while there is hardly any difference in age effect between the sexes for glucuronidation. There was little difference in smoking habits between the two age groups, but the patients with alcoholic liver cirrhosis were on the whole much heavier smokers than the healthy subjects. It has been suggested that smoking may accelerate nitrazepam clearance (Jochensen *et al.*, 1982b), which could imply that a more pronounced difference in intrinsic clearance would have been observed between patient and control group had they been better matched with regard to smoking habits. With regard to concomitant medication, the elderly subjects used only a few other drugs, none of which is known to influence enzyme activity in normal doses, including prednisone (Breimer *et al.*, 1978). It proved to be impossible to study patients with liver cirrhosis, who did not also use other drugs and even

drugs which are known to influence the metabolism of other drugs. Cimetidine, for instance, is known to inhibit oxidative metabolism (Desmond *et al.*, 1980; Klotz & Reimann, 1980, 1981; Patwardhan *et al.*, 1980), but this effect may be less pronounced in patients with liver cirrhosis (Staiger *et al.*, 1981). Most of the patients were on spironolactone, which has been demonstrated to be an enzyme inducer in healthy humans (Huffman *et al.*, 1973; Taylor *et al.*, 1972). It has been suggested that even in cirrhosis the hepatic drug-oxidizing enzymes are induced by spironolactone (Miguet *et al.*, 1980). The effect of the drug on nitrazepam is unknown, but it should be taken into consideration that, as with smoking, the differences in intrinsic clearance between patients with alcoholic liver cirrhosis and healthy subjects may partly be obscured by the use of spironolactone. The other drugs used by the patients are not likely to influence drug-metabolising enzyme activity including clemastine (Hildebrandt *et al.*, 1975).

The influence of age and liver disease has been studied for several other benzodiazepines and differential effects have been observed. Benzodiazepines that are primarily oxidized (diazepam, desmethyldiazepam, chlordiazepoxide and desalkylflurazepam) generally exhibit substantially longer elimination half-lives in the elderly and in patients with liver disease. This is due to a lower metabolic clearance and/or a larger volume of distribution (Divoll Allen *et al.*, 1980; Greenblatt *et al.*, 1980a, 1981; Klotz *et al.*, 1975; Klotz & Müller-Seydlitz, 1979; Sellers *et al.*, 1979). On the other hand, studies with benzodiazepines that are primarily conjugated have revealed a different relation of age and liver disease to drug metabolizing activity: both have a

minimal effect, if any, on elimination half-life and metabolic clearance of temazepam, oxazepam and lorazepam (Divoll *et al.*, 1981; Greenblatt *et al.*, 1979, 1980b; Krauss *et al.*, 1978; Shull *et al.*, 1976). The elimination half-life of lorazepam was however significantly increased in patients with liver cirrhosis due to an increase in volume of distribution (Krauss *et al.*, 1978).

The present study demonstrates that the effects of age and liver cirrhosis on the metabolic disposition of nitrazepam are in between the effects on the disposition of the benzodiazepines that undergo oxidative biotransformation and the benzodiazepines that undergo glucuronide conjugation: the absence of an ageing effect on the intrinsic clearance of nitrazepam is unlike the results obtained for oxidized benzodiazepines but similar to the observations made for benzodiazepines that undergo glucuronidation. On the contrary, a reduction of metabolizing capacity by alcoholic liver cirrhosis corresponds with the results obtained for diazepam and chlordiazepoxide, although the extent of the reduction is much greater for the latter two drugs, but is absent for most hydroxybenzodiazepines.

It has been reported that the elderly are more likely to develop adverse reactions to nitrazepam treatment than are the young, particularly when they take higher doses (Castleden *et al.*, 1977; Evans & Jarvis, 1972;

Greenblatt & Allen, 1978). Our study suggests that following single dose administration drug action could be more persistent in the elderly than in the young because of a longer elimination half-life. When given repeatedly also low doses of nitrazepam (5 mg) may impair psychomotor accuracy in elderly subjects (Morgan, 1982). Nitrazepam has a relatively long half-life for a hypnotic and a certain degree of accumulation will occur when the drug is taken every evening (Breimer *et al.*, 1980; Breimer & Jochemsen, 1981). The steady state levels of (unbound) nitrazepam will be unaffected by age, however (this study).

In addition to pharmacokinetic alterations, a greater sensitivity of the ageing brain to the effect of nitrazepam may also play a role in the increased frequency of side effects in the elderly (Castleden & George, 1979). When patients with liver cirrhosis take a nitrazepam tablet every night, their levels of unbound nitrazepam will be higher than in healthy subjects.

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References

- BREIMER, D.D., ZILLY, W. & RICHTER, E. (1978). The influence of corticosteroid treatment on the disposition of hexobarbital and tolbutamide. *Clin. Pharmac. Ther.*, **26**, 202–212.
- BREIMER, D.D., JOCHEMSEN, R. & VON ALBERT, H.-H. (1980) Pharmacokinetics of benzodiazepines—Short-acting versus long-acting. *Arzneim.-Forsch.*, **30**, 875–881.
- BREIMER, D.D. & JOCHEMSEN, R. (1981). Pharmacokinetics of hypnotic drugs. In *Psychopharmacology of Sleep*, ed. Wheatley, D.W., pp. 135–153. New York: Raven Press.
- CASTLEDEN, C.M. & GEORGE, C.F. (1979). Increased sensitivity to benzodiazepines in the elderly. In *Drugs and the Elderly*, eds. Crooks, J. & Stevenson, I.H., pp. 169–178. London: Macmillan Press.
- CASTLEDEN, C.M., GEORGE, C.F., MARCER, D. & HALLETT, C. (1977). Increased sensitivity to nitrazepam in old age *Br. med. J.*, **1**, 10–12.
- DE BOER, A.G., RÖST-KAISER, J., BRACHT, H. & BREIMER, D.D. (1978). Assay of underivatized nitrazepam and clonazepam in plasma by capillary gas chromatography applied to pharmacokinetic and bio-availability studies in humans. *J. Chromatogr.*, **145**, 105–114.
- DESMOND, P.V., PATWARDHAN, R.V., SCHENKER, S. & SPEEG, K.V. jr. (1980). Cimetidine impairs the elimination of chlordiazepoxide in man. *Ann. Intern. Med.*, **93**, 266–268.
- DIVOLL ALLEN, M., GREENBLATT, D.J., HARMATZ, J.S. & SHADER, R.I. (1980). Desmethyldiazepam kinetics in the elderly after oral prazepam. *Clin. Pharmac. Ther.*, **28**, 196–202.
- 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**, 1104–1108.
- EDITORIAL. (1977). Drugs and the elderly. *Lancet*, **ii**, 693–694.
- EVANS, J.G. & JARVIS, E.H. (1972). Nitrazepam and the elderly. *Br. med. J.*, **4**, 487.
- 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., DIVOLL ALLEN, M., LOCKNISAR, A., HARMATZ, J.S. & SHADER, R.I. (1979). Lorazepam kinetics in the elderly. *Clin. Pharmac. Ther.*, **26**, 103–113.
- GREENBLATT, D.J., DIVOLL ALLEN, M., HARMATZ, J.S. & SHADER, R.I. (1980a). Diazepam disposition determinants. *Clin. Pharmac. Ther.*, **27**, 301–312.
- GREENBLATT, D.J., DIVOLL M., HARMATZ, J.S. & SHADER, R.I. (1980b). Oxazepam kinetics: effects of age and sex. *J. Pharmac. exp. Ther.*, **215**, 86–91.
- GREENBLATT, D.J., DIVOLL, M., HARMATZ, J.S., MACLAUGHLIN, D.S. & SHADER, R.I. (1981). Kinetics

- and clinical effects of flurazepam in young and elderly noninsomniacs. *Clin. Pharmac. Ther.*, **30**, 475–486.
- 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.
- HILDEBRANDT, A.G., ROOTS, I., SPECK, M., SAALFRANK, K. & KEWITZ, H. (1975). Evaluation of *in vivo* parameters of drug metabolizing enzyme activity in man after administration of clemastine, phenobarbital or placebo. *Eur. J. clin. Pharmac.*, **8**, 327–336.
- HUFFMAN, D.H., SHOEMAN, D.W., PENTIKÄINEN, P. & AZARNOFF, D.L. (1973). The effect of spironolactone on antipyrine metabolism in man. *Pharmacology*, **10**, 338–344.
- HURWITZ, N. (1969). Predisposing factors in adverse reactions to drugs. *Br. med. J.*, **1**, 536–539.
- JOCHEMSEN, R., HOGENDOORN, J.J.H., DINGEMANSE, J., HERMANS, J., BOEIJINGA, J.K. & BREIMER, D.D. (1982a). Pharmacokinetics and bioavailability of intravenous, oral and rectal nitrazepam in humans. *J. Pharmacokin. Biopharm.*, **10**, 231–245.
- JOCHEMSEN, R., VAN DER GRAAFF, M., BOEIJINGA, J.K. & BREIMER, D.D. (1982b). Influence of sex, menstrual cycle and oral contraception on the disposition of nitrazepam. *Br. J. clin. Pharmac.*, **13**, 319–324.
- KANGAS, L. & BREIMER, D.D. (1981). Clinical pharmacokinetics of nitrazepam. *Clin. Pharmacokin.*, **6**, 346–366.
- KANGAS, L., ALLONEN, H., LAMMINTAUSTA, R., SALONEN, M. & PEKKARINEN, A. (1979a). Pharmacokinetics of nitrazepam in saliva and serum after a single oral dose. *Acta Pharmac. Tox.*, **45**, 20–24.
- KANGAS, L., IISALO, E., KANTO, J., LEHTINEN, V., PYNNÖNEN, S., RUIKKA, I., SALMINEN, J., SILLANPÄÄ, M. & SYVÄLAHTI, E. (1979b). Human pharmacokinetics of nitrazepam: effect of age and disease. *Eur. J. clin. Pharmac.*, **15**, 163–170.
- KLOTZ, U., AVANT, G.R., HOYUMPA, A., SCHENKER, S. & WILKINSON, G.R. (1975). The effect 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. Pharmac.*, **7**, 119–120.
- KLOTZ, U. & REIMANN, I. (1980). Influence of cimetidine on the pharmacokinetics of desmethyldiazepam and oxazepam. *Eur. J. clin. Pharmac.*, **18**, 517–520.
- KLOTZ, U. & REIMANN, I. (1981). Elevation of steady-state diazepam levels by cimetidine. *Clin. Pharmac. Ther.*, **30**, 513–517.
- KRAUSS, J.W., DESMOND, P.V., MARSHALL, J.P., JOHNSON, R.F., WILKINSON, G.R. & SCHENKER, S. (1978). The effects of ageing and liver disease on the disposition of lorazepam in man. *Clin. Pharmac. Ther.*, **24**, 411–419.
- MIGUET, J.P., VUITTON, D., THEBAULT-LUCAS, A., JOANNE, C. & DHUMEAUX, D. (1980). Spironolactone and enzyme induction in patients with alcoholic liver cirrhosis. *Gastroenterology*, **78**, 996–1000.
- MILLER, R.R. & GREENBLATT, D.J. (1976). Drug effects in hospitalized patients: experiences of the Boston collaborative drug surveillance program, 1966–1975. New York: John Wiley & Sons.
- MORGAN, K. (1982). Effect of low-dose nitrazepam on performance in elderly. *Lancet*, **i**, 516.
- PATWARDHAN, R.V., YARBOROUGH, G.W., DESMOND, P.V., JOHNSON, R.F., SCHENKER, S. & SPEEG, K.V. jr (1980). Cimetidine spares the glucuronidation of lorazepam and oxazepam. *Gastroenterology*, **79**, 912–916.
- ROBERTS, R.K., WILKINSON, G.R., BRANCH, R.A. & SCHENKER, S. (1978). Effect of age and parenchymal liver disease on the disposition of chlordiazepoxide (Librium). *Gastroenterology*, **75**, 479–485.
- SELLERS, E.M., GREENBLATT, D.J., GILES, H.G., NARANJO, C.A., KAPLAN, H. & MACLEOD, S.M. (1979). Chlordiazepoxide and oxazepam disposition in cirrhosis. *Clin. Pharmac. Ther.*, **26**, 240–246.
- SHADER, R.I. & GREENBLATT, D.J. (1979). Pharmacokinetics and clinical drug effects in the elderly. *Psychopharmac. Bull.*, **15**, 8–14.
- SHULL, H.J. Jr., WILKINSON, G.R., JOHNSON, R. & SCHENKER, S. (1976). Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann. Intern. Med.*, **84**, 420–425.
- STAIGER, CH., MANNER, CH., CZYGAN, P., WALTER, E., DE VRIES, J. & WEBER, E. (1981). The influence of cimetidine on antipyrine pharmacokinetics in patients with and without cirrhosis of the liver. *Int. J. clin. Pharmac. Ther. Tox.*, **19**, 561–564.
- TAYLOR, S.A., RAWLINS, M.D. & SMITH, S.E. (1972). Spironolactone – a weak enzyme inducer in man. *J. Pharm. Pharmac.*, **24**, 578–579.

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