Br. J. clin. Pharmac. (1983), **16**, 391–397

THE PHARMACOKINETICS OF FRUSEMIDE ARE INFLUENCED BY AGE

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1 After a 24 h control period 80 mg frusemide was given intravenously over 2 min to a group of young and a group of elderly healthy male volunteers.

2 The serum concentration of frusemide and the excretion in urine of the drug and a glucuronidated metabolite were followed for 24 h.

3 The elimination of the drug from serum was described by an open two compartment model. The serum clearance (CL_s) was 170 ± 19 ml min^{-1} in the young and 129 ± 11 ml min^{-1} in the elderly ($P < 0.01$) and the average renal clearance (CL_r) was 67% of CL_s in the young and 58% of CL_s in the elderly (NS).

4 The average amount of unchanged frusemide in the urine during the first 30 min was 30 ± 6 mg in the young but only 20 ± 4 mg in the elderly ($P < 0.01$).

5 The albumin concentration in serum was 15% lower in the elderly but on the average the protein bound fraction of frusemide was 98.6% in both groups.

6 The V_d ss did not differ between the two age groups (0.130 l kg^{-1}) but the elimination half-life was 70 ± 20 min in the young and 102 ± 33 min in the elderly ($P < 0.05$).

7 In the young 11.4 ± 5.0 mg frusemide was excreted as a glucuronidated compound whereas this figure was only 5.4 ± 2.9 mg in the elderly ($P < 0.01$).

8 It is concluded that the age-related changes in the fate of unchanged frusemide in the organism mainly can be explained by a reduction in the tubular secretion of the drug which in turn may be caused by a reduction in renal plasma flow.

Keywords frusemide pharmacokinetics age

Introduction

Frusemide is prescribed much more frequently to elderly than to young patients (Andreasen *et al.*, 1978a; Freeman, 1979). Nevertheless most studies on the pharmacokinetics of the drug have been carried out in young healthy volunteers (cf. Cutler & Blair, 1979; Benet, 1979). It is not known whether the pharmacokinetics of frusemide are influenced by age and when attempts have been made to characterize the pharmacokinetics for groups of patients it has been necessary to construct control groups with similar age distribution. A study of the individual variation within such a group (Andreasen & Mikkelsen, 1977) did not allow any conclusions about a possible influence of a rather wide age range on the pharmacokinetics of frusemide.

For those reasons we decided to compare the pharmacokinetics and pharmacodynamics of frusemide in a group of young and a group of elderly healthy male subjects. The individual variation in kinetics and response in the group of young male subjects has been described already (Andreasen *et al.*, 1982). The present study has two purposes: (1) to establish a range of normal values for frusemide kinetics in an apparently homogenous group of healthy elderly, male volunteers and (2) to study the influence of age on the pharmacokinetics and disposition of frusemide.

Methods

The protocol for the study was described in detail in the recent publication mentioned above (Andreasen *et al.*, 1982) and therefore only a brief account of the methods is given here.

Subjects

All gave consent to the study after being carefully informed of the procedures involved. Eight normal male subjects (60–70 years) were compared with 10

Table 1 Clinical data of ten young and eight elderly healthy male volunteers.

Young subjects	*Age (years)*	*Body weight (kg)*	*Average 24 h BP (mm Hg)*	*Endogenous 24 h-creatinine clearance (ml/min)*
1	33	68	112/75	118
2	22	74	131/79	144
3	25	76	131/88	151
4	22	57	113/66	138
5	25	71	121/74	132
6	33	74	113/73	—
7	35	70	132/82	124
8	27	73	136/80	—
9	25	68	122/71	129
10	24	83	127/89	142
Mean ± s.d.	27 ± 4.8	71 ± 6.7	123/78 ± 9/7	135 ± 11.0
Elderly subjects				
1	69	78	108/70	93
2	70	83	122/77	83
3	60	85	161/95	103
4	60	81	124/86	101
5	66	71	138/85	101
6	64	64	128/84	81
7	61	73	111/66	98
8	62	70	120/77	98
Mean ± s.d.	64 ± 4.0	76 ± 7.3	126/80 ± 17/9	95 ± 8.4

normal male subjects in the age group 20–35 years. None had any history or other evidence of disease from the heart, lungs, liver or kidneys and none received permanent drug therapy. Clinical data of the two groups are given in Table 1. The listed average blood pressures (BP) are the average of 16 measurements over the 24 h control period.

Procedure

The subjects stayed in the hospital from 08.00 h until 09.00 h 2 days later. The first 24 h period (09.00 h – 09.00 h) was a control period. Between 09.00 h and 09.02 h on the second morning 80 mg frusemide was given i.v. Beginning at 09.07 h and continuing with short intervals at first and longer intervals later on blood samples were drawn. The concentrations of frusemide in serum and urine were followed during 24 h and so was the urinary excretion of the glucuronidated product.

Analytical methods

Frusemide and its glucuronidated product were measured by h.p.l.c. as previously described (Andreasen *et al.*, 1981). The binding of frusemide to serum proteins was determined by equilibrium dialysis at 37°C.

Calculations

The elimination of frusemide from serum was described by the use of an open two compartment model with elimination from the central compartment (Andreasen & Mikkelsen, 1977). Equation (1) was fitted to the time (t), serum concentration (C_s) data using a least square method (VBO1AD)

$$C_s = \frac{D}{V_1}\left[\frac{k_{21-\alpha}}{\beta-\alpha}e^{-\alpha t} + \frac{k_{21-\beta}}{\alpha-\beta}e^{-\beta t}\right] \quad (1)$$

from a HARWELL library at The Regional Computer Centre for Research and Education of the University of Copenhagen. Having obtained V_1, the volume of the central compartment, k_{21}, the rate constant for transfer from the peripheral (V_2) to the central compartment, α and β, both hybrid rate constants related to the slopes of the serum concentration curve, the remaining parameters were calculated from equations (2)–(5)

$$k_{10} = \alpha\beta/k_{21} \quad (2)$$

$$k_{12} = \alpha+\beta-k_{21}-k_{10} \quad (3)$$

$$V_2 = V_1 k_{12}/k_{21} \quad (4)$$

$$CL_s = V_1 k_{10} \quad (5)$$

Here k_{10} is the rate constant for elimination from V_1, k_{12} the rate constant for transfer from V_1 to V_2 and CL_s the serum frusemide clearance. The average renal clearance of frusemide was calculated as

$$CL_r = \frac{\text{frusemide recovered from urine (mg)}}{80\text{ (mg)}} \times CL_s$$

The non renal clearance as

$$CL_{nr} = CL_s - CL_r$$

CL_s was also calculated as the dose divided by the area under the curve. There was a very good agreement between measured and computer fitted serum concentrations and there were only slight differences between those model independent values of CL_s and the values reached by the method described above.

The statistical significance of differences was assessed by the Wilcoxon test for paired comparisons and correlations were studied by linear regression.

Results

Figure 1 shows that the average serum levels of frusemide remained at a higher level in the elderly during the entire observation period and from Figure 2 it is seen that the average amount of frusemide recovered from the urine was lower in the elderly. The difference in excretion is established during the first hour after the completion of the drug administration. In Table 2 are listed simultaneously determined serum concentrations of frusemide and of albumin. The percentage frusemide bound is also shown. In spite of the significantly lower albumin concentration in the elderly (15%, $P < 0.01$) the average percentage binding was identical in the two age groups.

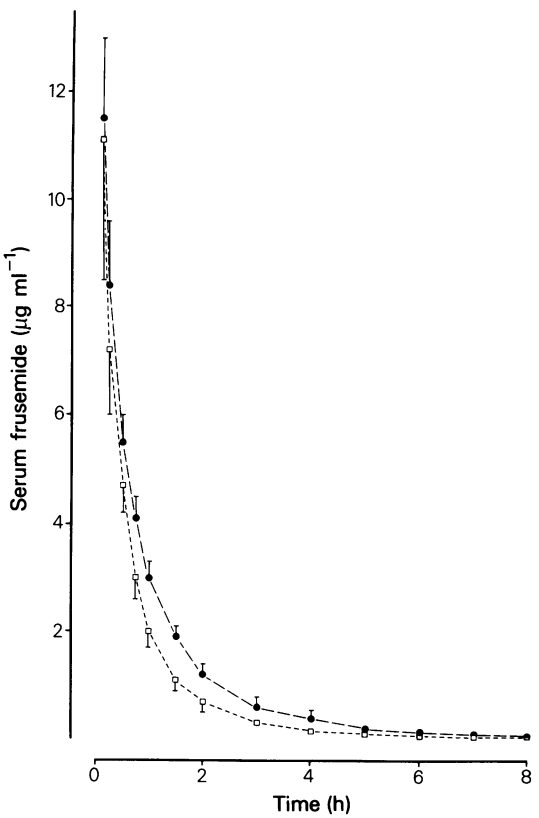

Figure 1 The mean ± s.d. concentration of frusemide in serum in ten young (---□---) and eight elderly (---●---) healthy, male volunteers after intravenous injection of 80 mg over 2 min. Values beyond 8 h are not given because most of the individual values were below the sensitivity of the method 10 h after the injection.

The more rapid initial urinary excretion of unchanged frusemide in the young subjects is quantitated in Table 3 where a 50% higher excretion rate in the young is seen during the first 30 min ($P < 0.05$).

The calculated pharmacokinetic parameters for frusemide in the two age groups are listed in Table 4, The volumes of distribution do not differ and the apparent differences indicating higher values for the rate constants k_{12} and k_{21} for the young are not significant. For both age groups k_{21} is significantly larger than k_{12} and smaller than k_{10} ($P < 0.01$). The elimination half-life is almost 50% longer in the elderly and CL_s is significantly higher in the young. The difference between the distribution half-lives is not statistically significant. In Table 5 it is seen that CL_r is significantly higher in the young subjects while CL_{nr} is the same in the two age groups.

For the young subjects a significant negative relationship exists between CL_s and the serum concentration of frusemide determined 5 min after the administration ($r^2 = 0.59$, $P < 0.05$). For the elderly no such relationship is present. In the young the CL_s is also positively correlated to V_d ss ($= V_1 + V_2$) ($r^2 = 0.61$, $P < 0.05$) and to CL_r ($r^2 = 0.74$, $P < 0.01$). None of these significant relationships were present in the elderly. On the average the CL_r was 67% of CL_s in the young but only 58% of CL_s in the elderly.

The amount of urinary recovered frusemide excreted as a glucuronidated compound, which could be cleaved by β-glucuronidase, was significantly larger in the young where a mean of 11.4 mg of the 80 mg frusemide administered was excreted as glucuronide. The glucuronidated amount excreted in the elderly was significantly lower (5.4 mg, $P < 0.01$).

By following the excretion in the urine of unchanged and glucuronidated frusemide we were able to account for 80% of the injected dose of frusemide in the young but only for 64% of the dose given to the elderly.

Discussion

The present comparison of the fate of frusemide in the young and the elderly human healthy subject represented by two groups seemed to reflect well known age related physiological changes. On the other hand the study also showed the importance of the individual variation between subjects within an

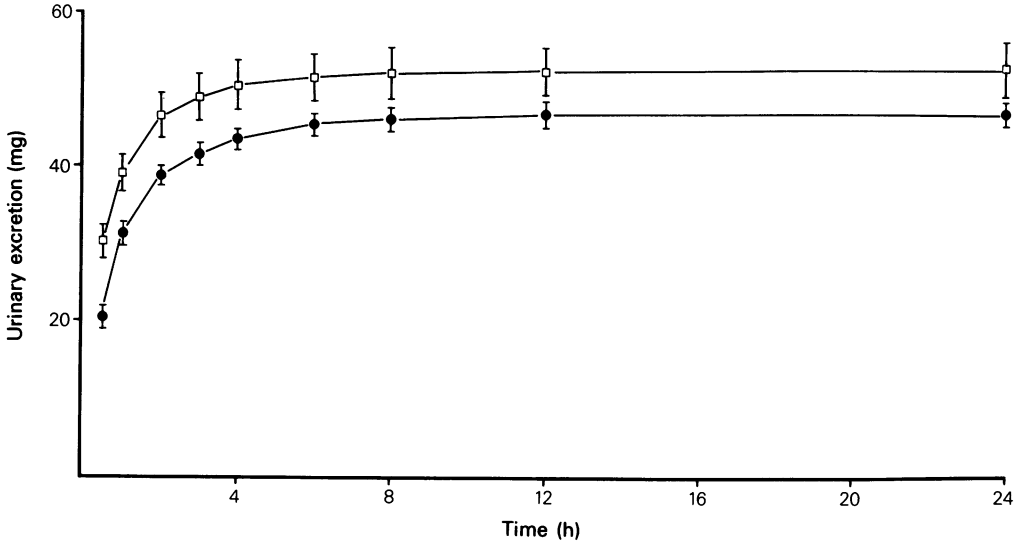

Figure 2 The mean ± s.e. mean cumulative excretion of unchanged frusemide in the urine during 24 h after intravenous injection of 80 mg to ten young (—□—) and to eight elderly (—●—) healthy male volunteers.

Table 2 The venous concentration of frusemide 5 min after the completion of an intravenous injection of 80 mg over 2 min to young and elderly healthy male volunteers. The simultaneously determined serum concentration of albumin and the percentage drug bound to serum protein at these concentrations are also shown.

	Serum concentration of frusemide (μg/ml)		*Serum concentration of albumin (μmol/l)*		*Frusemide bound to serum protein (%)*	
Subject	*Young*	*Elderly*	*Young*	*Elderly*	*Young*	*Elderly*
1	16.1	9.9	712	639	98.4	97.8
2	14.1	9.6	725	634	98.2	99.0
3	10.3	12.4	738	607	98.7	98.3
4	8.6	13.2	744	622	98.8	98.6
5	10.8	12.7	720	689	98.6	98.8
6	13.2	12.7	709	541	99.3	99.1
7	9.1	11.5	748	628	98.9	98.6
8	7.8	9.7	703	584	98.4	98.6
9	11.1	—	760		97.8	—
10	10.3	—	758		99.0	—
Mean ± s.d.	11.1 ± 2.6	11.5 ± 1.5	732 ± 21	618 ± 43	98.6 ± 0.4	98.6 ± 0.4

Table 3 Amount of unchanged frusemide excreted in the urine during the first hour after i.v. administration of 80 mg to young and elderly healthy male volunteers

	Unchanged frusemide excreted (mg)			
	0–30 min		*30–60 min*	
Subject	*Young*	*Elderly*	*Young*	*Elderly*
1	14.6	18.4	8.1	8.6
2	28.8	20.3	6.2	10.6
3	35.9	22.1	10.8	9.9
4	34.4	22.7	7.5	15.6
5	26.1	27.1	8.5	8.7
6	37.4	13.1	11.5	11.5
7	30.6	21.8	14.6	9.5
8	31.2	18.6	7.7	10.2
9	27.6		6.8	
10	33.9		9.6	
Mean ± s.d.	30.1 ± 6.5	20.5 ± 4.1	9.1 ± 2.6	10.6 ± 2.2

Table 4 Calculated pharmacokinetic parameters for frusemide after the i.v. administration of 80 mg to young and elderly healthy male volunteers

Elderly subjects	k_{12} (min^{-1})	k_{21} (min^{-1})	V_1 (l)	$V_{d\,ss}$ (l/kg)	$t_{½\,\alpha}$ (min)	$t_{½\,z}$ (min)	CL_s ($ml\,min^{-1}$)
1	0.0032	0.0060	7.23	0.1423	33	148	118
2	0.0137	0.0162	6.70	0.1492	17	95	124
3	0.0070	0.01132	6.14	0.1172	23	96	120
4	0.0162	0.01942	4.57	0.1035	13	70	123
5	0.0024	0.00994	6.54	0.1141	29	84	133
6	0.0261	0.02740	4.32	0.1319	10	62	127
7	0.0031	0.0055	6.03	0.1305	27	149	133
8	0.0014	0.0069	9.08	0.1567	36	113	153
Mean ± s.d.	0.0091 ± 0.0087	0.0128 ± 0.0076	6.33 ± 1.50	0.1306 ± 0.0183	24 ± 9	102 ± 33*	129 ± 11**
Young subjects[1] ± s.d.	0.0127 ± 0.0080	0.0182 ± 0.0084	5.72 ± 1.40	0.1315 ± 0.0223	15 ± 4	70 ± 21	170 ± 19

[1]($n = 9$) Individual values were published previously (Andreasen *et al.*, 1982).
$^{**}P < 0.01$, $^{*}P < 0.05$

Table 5 Renal (CL_r) and non-renal (CL_{nr}) clearance of unchanged frusemide from the serum of healthy young and elderly volunteers after 80 mg i.v. over 2 min

	CL_r ($ml\,min^{-1}$)		CL_{nr} ($ml\,min^{-1}$)	
Subject	*Young*	*Elderly*	*Young*	*Elderly*
1	54	65	86	53
2	92	71	71	53
3	138	76	51	44
4	—	71	—	52
5	96	93	64	40
6	138	67	30	60
7	159	73	42	60
8	127	82	62	71
9	90	—	69	—
10	129	—	32	—
Mean ± s.d.	114 ± 33	75 ± 9*	56 ± 19	54 ± 10

$^{*}P < 0.05$

Table 6 Amount of frusemide excreted during 24 h as a glucuronide after i.v. administration of 80 mg to healthy young and elderly volunteers

Young subjects	*mg*	*Elderly subjects*	*mg*
1	6.8	1	5.2
2	10.8	2	10.6
3	23.1	3	8.8
4	13.8	4	1.8
5	13.3	5	4.7
6	12.2	6	3.1
7	7.1	7	4.7
8	8.9	8	4.5
9	12.1	—	
10	6.1	—	
Mean ± s.d.	11.4 ± 5.0	—	5.4 ± 2.9

apparently homogenous group. There was a considerable overlapping of values for all pharmacokinetic parameters between the two groups.

The renal excretion pattern

Many of our efforts were directed towards clarifying the urinary excretion of frusemide. One of the reasons for this is that the clinical effect of the drug is closely related to its urinary excretion pattern (Burg *et al.*, 1973; Rose *et al.*, 1976; Homeida *et al.*, 1977; Chennavasin *et al.*, 1979; Andreasen *et al.*, 1978b, 1980). During the first 30 min after the start of the intravenous frusemide injection the young subjects excreted 30 mg unchanged drug while the elderly excreted only 20 mg ($P < 0.01$). In complete agreement with other studies (Rane *et al.*, 1978; Smith *et al.*, 1980) an average CL_r of 67% of a CL_s of 170 ml min^{-1} was found in the young. In the elderly the CL_s was reduced by 25% whereas the CL_r was reduced by 34% and constituted only 58% of the CL_s.

More than 90% of the drug is excreted by tubular secretion (Deetjen, 1966; Andreasen *et al.*, 1980). Because of a pronounced binding to serum albumin only a few per cent of the injected frusemide is excreted after glomerular filtration. The drug is a weak acid with pK_a about 3.8 and only a small amount is unionized in the preurine and likely to become reabsorbed.

Age-related changes in renal handling

The age-related changes in kidney handling of frusemide demonstrated in the present study are probably mainly due to a fall in stroke volume and cardiac output (Christensen *et al.*, 1982) which is accompanied by a decreased renal plasma flow (RPF) (cf. Kampmann & Hansen, 1979). The maximal ability of the tubular cells to secrete the drug was not reached here as an unchanged renal clearance of frusemide was seen within both age groups as the plasma concentration declined. Glomerular filtration (as estimated by endogenous creatinine clearance) was reduced in our elderly subjects. However, the unchanged and strong frusemide binding to plasma protein observed in the elderly here excluded that the decreased frusemide filtration rate was of any quantitative importance.

The better (and more rapidly occurring) ability of the young to dispose frusemide to the kidneys is confirmed or supported by observed correlations between pharmacokinetic parameters: (a) CL_s is connected with CL_r in the young but not in the elderly, (b) CL_s is connected with V_d ss in the young but not in the elderly (a pronounced accumulation in the kidney will result in a large V_d ss), and (c) the negative correlation between the initial (5 min) serum concentration and the CL_r and CL_s found in the young but not in the elderly indicates that the initial (within 5 min) distribution of frusemide has been characterized by a serum concentration lowering drug disposition in the young but not in the elderly.

Protein binding and volumes of distribution

The size of the protein bound fraction and of the V_d ss in the young are in good agreement with the results of other studies (Smith *et al.*, 1980). In a previous study we demonstrated a decreased protein binding of frusemide in elderly patients who had decreases in the concentration of serum albumin which were more pronounced than the 15% decrease found here (Andreasen & Husted, 1980). In a study where frusemide was given to anephric patients (Andreasen *et al.*, 1978b) a significant correlation was present between protein binding and V_d ss. An extrapolation of this regression line to the average binding found in the present study gives a V_d ss close to the average value of 130 ml kg^{-1} found here. The fraction of the frusemide present in the central compartment during the elimination phase can be expressed by the fraction β/k_{10}. Taking into account that a considerable amount (60%) of the serum albumin is extravascular serum albumin it is in good accordance with the influence of the protein binding on the distribution that this fraction calculated for average values is 0.33 for both age groups.

Rate constants

The rate constants k_{12} and k_{21} are determined with low accuracy. They are apparently higher in the young and the fact that the k_{10} values in both groups were higher than k_{21} indicates that the transfer from the peripheral to the central compartment could be a rate limiting step for the removal of frusemide from the serum. This assumption is in good agreement with a *rapid* exchange (k_{10}) of frusemide between transport albumin and a high affinity tubular cell surface and a comparatively *slow* transport (k_{21}) from extravascular albumin bound frusemide to the central, mainly intravascular compartment.

Metabolism

The renally excreted glucuronidated amount of frusemide in the young is very close to the 14% found by Smith *et al.* (1980). The elderly excreted a significantly smaller amount of frusemide as the glucuronide. In spite of that the non-renal clearance of unchanged frusemide did not differ between our two age groups. In patients with pulmonary oedema Perez *et al.* (1979) found that from 3–41% of administered frusemide was excreted in the urine as the glucuronidated product. More studies are needed to elucidate whether the 20 and 36%, in the elderly and in the young

respectively, which were not excreted as unchanged or a β-glucuronidase cleavable compound, are excreted with the bile or metabolized differently. It is interesting in this respect that we previously in anephric patients (Andreasen *et al.*, 1978b) found a frusemide serum clearance of 1/3 of the serum clearance in the normal group.

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(Received March 14, 1983, accepted June 9, 1983)