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Influence of Hepatic Cirrhosis and End-Stage Renal Disease on Pharmacokinetics and Pharmacodynamics of Furosemide*

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Summary. After rapid intravenous injection of furosemide 40 mg (Fu), plasma levels were determined in 7 healthy volunteers, 8 patients with liver cirrhosis with ascites and 7 patients with end-stage renal disease (ESRD). The diuretic response was evaluated by measuring the urinary excretion of sodium and potassium and the urine volume. The mean elimination half life ($t_{1/2\beta}$) of Fu averaged 51 ± 7.7 (± SD) min in healthy subjects, 52 ± 7.7 min in cirrhosis and 200 ± 57 min in ESRD. The non-renal clearance (Cl_{nr}) in healthy subjects (56 ± 28 ml/min) corresponds to the total plasma clearance in functionally anephric patients (54 ± 18 ml/min). In cirrhosis there was no significant change in the disposition parameters of Fu in comparison to the healthy volunteers, but there was a significant reduction in urine sodium and volume, whereas potassium excretion remained unchanged. Fu "excretion rate – response" curves showed diminished tubular sensitivity to Fu in cirrhosis.

Key words: furosemide, cirrhosis, end-stage renal disease; pharmacokinetic, diuretic response, urine potassium, urine sodium

Furosemide (Fu), 4-chloro-N-(2-furylmethyl)-5-sulphamoyl anthranilic acid, is used extensively, being one of the most potent and convenient diuretics available for patients with oedema of various origins. However, clinicians have noticed that the saluretic effect can be extremely variable and unpredictable, as some patients respond to small doses, but others require massive doses administered intravenously. Since its introduction in clinical medicine (Kleinfelder, 1963), the relationship between the pharmacokinetics and the pharmacodynamic response to Fu has often been studied, but even data on the disposition and elimination of Fu in healthy subjects are conflicting (Rupp et al. 1970; Cutler et al. 1974; Beermann et al. 1977; Tilstone and Fine 1978; Chennavasin et al. 1979). The results of kinetic studies on Fu elimination in renal failure appear to have depended on the sensitivity and specifity of the Fu assay (Benet 1979; Hoppe-Seyler 1980). Since Fu is highly protein bound – 95–98% (Prandotta and Pruitt 1975; Andreasen and Jacobsen 1974; Rane et al. 1978), and 30% to 40% of an intravenous dose is eliminated by non-renal routes, the effect of Fu in patients with liver disease may be influenced either by alteration in protein binding of the drug, and/or by differences in drug disposition to certain body compartments. There is inadequate information about the relationship of diuretic response to Fu kinetics in liver cirrhosis (Kind and Schmid 1969; Huang et al. 1974).

The aims of the present study were:

1. to determine the pharmacokinetic parameters of the usual therapeutic i. v. dose (40 mg) of Fu in healthy volunteers,
2. to describe possible alterations in Fu-disposition in patients with ESRD and cirrhosis of the liver with ascites, and
3. to understand the factors which may influence the relationship between plasma level, urinary excretion rate of the drug and the magnitude of the diuretic response in patients with cirrhosis.

Materials and Methods

a. Subjects and Experimental Procedure

Seven healthy subjects, 4 females and 3 males, aged 20–45 years (mean 30±9.8 years), 7 patients with

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Table 1. Clinical data for the cirrhotic patients

Patient	Sex	Age [years]	Creat. Clearance [ml min^{-1}]	Albumin $\left[\frac{g}{dl\ Serum}\right]$	Ascites	Serum Bilirubin [mg/100 ml]	Body weight [kg]	additional medication [mg/d]
M	♂	58	86	3.0	+	6.0	70	–
Le	♂	57	98	3.3	++	1.0	86	–
Fu	♂	60	75	3.6	+	5.9	90	Digoxin 0.1 Paromomycinsulfate 750
Bi	♀	75	130	2.9	++	7.3	47	Digitoxin 0.1 Allopurinol 100
St	♂	57	117	2.1	++	12.5	76	Paromomycinsulfate 750
He	♀	27	100	3.2	–	0.8	49	Thioctacid 100
Ba	♂	48	80	4.6	+	10.2	69	Allopurinol 300
Hei	♂	49	93	2.6	+	2.5	75	–

Table 2. Clinical data for the patients with ESRD

Patient	Sex	Age [years]	Creat. Clearance [ml min^{-1}]	Albumin $\left[\frac{g}{dl\ Serum}\right]$	Ascites	Body weight [kg]	additional medication [mg/d]
Sa	♂	79	2	3.8	–	50	Digitoxin 0.1
Fu	♂	72	0.7	2.3	–	56	Digitoxin 0.1 Aluminiumhydroxide 34.8 × 10^3
Ba	♂	60	0	4.0	–	72	Digitoxin 0.1 Aluminiumhydroxide 34.8 × 10^3
Ap	♂	79	0	3.3	–	48	Digitoxin 0.1 Aluminiumhydroxide 34.8 × 10^3
Sch	♂	58	0	3.9	–	51	Digitoxin 0.1 Aluminiumhydroxide 87 × 10^3
Ma	♀	69	0	2.9	–	56	Digitoxin 0.1 Aluminiumhydroxide 34.8 × 10^3 Allopurinol 100
Mar	♂	35	3.7	3.7	–	57	Prazosin 8 Metoprolol 100 Aluminiumhydroxide 34.8 × 10^3

severe renal insufficiency, 6 males and 1 female, aged 35–79 years (mean 62±15.4 years; creatinine clearance $\leq$ 3.7 ml/min), and 8 patients with hepatic cirrhosis, 2 females and 6 males, aged 27–75 years (mean 52±11.2 years) were studied. The subjects with severe renal disease required treatment by intermittent peritoneal dialysis; they were studied at least 12 h after dialysis. Patients with liver disease were excluded from this group. Subjects with liver disease with ascites (Table 1) had histologically proven cirrhosis of the liver. Clinically important parameters for members of this group are listed in Tables 1 and 2. Patients with severe anaemia (haemoglobin <10 g/100 ml) were excluded from the study. All patients and healthy volunteers were subjected to a complete medical history and physical examination, with electrocardiogram and routine laboratory tests, to exclude any additional disease. They all gave informed consent to the study procedure.

The healthy subjects and patients were maintained on a 150 meq sodium diet for 3 days prior to drug administration. After an overnight fast, Fu 40 mg was injected as an intravenous bolus. Blood samples were collected at frequent intervals (Fig. 1). Spontanously voided urine (sampling times in healthy subjects 20, 40, 60, 80, 120, 180, 240, 300 and 360 min; in cirrhotics 20, 40, 60, 75 105, ..., 315 and 345 min) was replaced volume per volume by intravenous infusion of a half-isotonic sodium chloride solution, containing 15 meq of potassium /1000 ml. Blood pressure and heart rate were measured twice hourly during the study. Body weight remained unchanged. None of the participants had received a diuretic in the 6 days prior to the study.

b. Analytical Techniques

Unchanged Fu was determined by a modified gas-liquid-chromatographic (GLC) assay according to Lindström and Molander (1974). Major modifications were the use of dichlormethane in the step one acid extraction, and the addition of bumetanide as an internal standard to plasma and urine samples prior to extraction. Fu was separated on a Varian type 3700 gaschromatograph, equipped with a 30 cm (2 mm i. d.) column packed with 5% OV 101 on Chromosorb GHP, 100–120 mesh, and detected by a ^{63}Ni electron capture detector. Peak areas were integrated by a Hewlett Packard 3380 A Integrator. The assay is highly specific for Fu; the lower limit of sensitivity in plasma and urine was Fu 20 ng/ml. Protein binding of Fu was not determined. Sodium and potassium were determined by flame photometry.

c. Calculations

Plasma level-time curves were adapted to a mamillary open two compartment model: $C_p(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$, where $C_p(t)$ = plasma level at time t, A and α, B and β are the y-intercepts and the slopes of the rapid or slow plasma level decay. B and β were calculated from least squares regression analysis. The β-elimination half life was calculated by

$$t_{1/2\beta} = \frac{\ln 2}{\beta}$$

Total body clearance was evaluated by the relation

$$Cl_B = \frac{\text{i.v. dose}}{AUC_\infty},$$

where AUC_∞ = area under the plasma-concentration-time curve estimated by the trapezoidal rule and extrapolated to infinity by dividing the last plasma level by β. The volume of distribution was calculated by

$$V_{d\beta} = \frac{Cl_B}{\beta}.$$

Renal clearance was estimated by dividing urinary recovery of Fu by the area under the plasma level-time curve

$$Cl_r = \frac{\text{Fu excr. (24 h)}}{\text{AUC (24 h)}}.$$

Student's *t*-test for unpaired data was used for statistical analysis ($p< >0.05$ range).

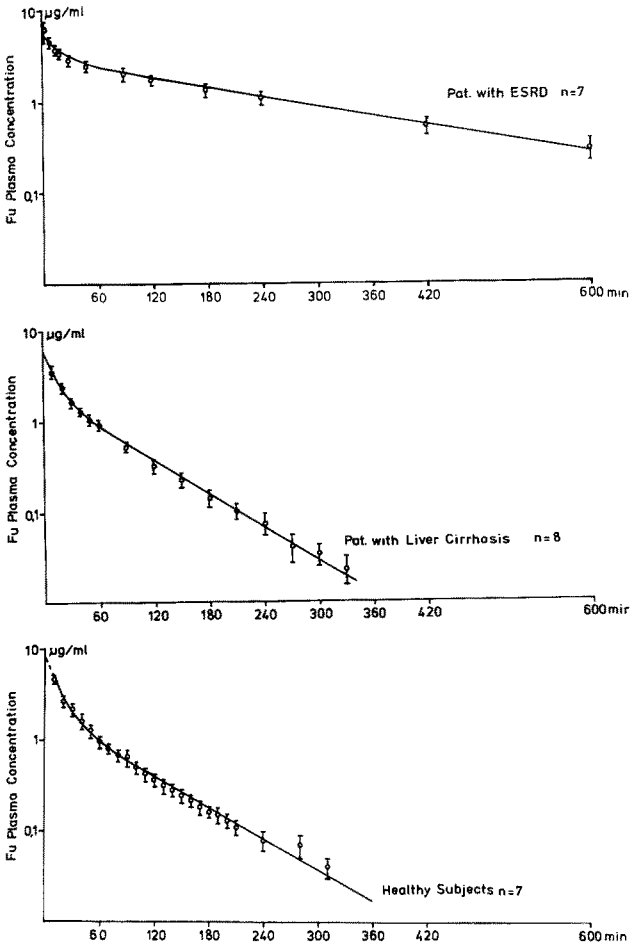

Fig. 1. Plasma level of Fu (mean ± SEM) after intravenous injection of 40 mg Fu to healthy volunteers, patients with liver cirrhosis and patients with ESRD

Results

a. Pharmacokinetics of Fu in Healthy Volunteers

After intravenous administration of 40 mg Fu, the plasma drug level declined according to a biexponential curve (Fig. 1). In the postdistributive (β) phase, the average half life ($t_{1/2\beta}$) was 51 (SD ± 7.7) min, with an apparent volume of distribution ($V_{d\beta}$) of 12.7±2.4 l. The mean total plasma clearance (Cl_B) was 174±32 ml/min. Approximately 70% of the i. v. dose was excreted unchanged by the kidney. Renal clearance (Cl_{nr}) was calculated to be 118±30 ml/min. Mean non-renal clearance (Cl_{nr}) was approximately 50% of renal clearance, or less than one third of total plasma clearance (Table 3). We were unable to detect a third, slower phase of plasma level decay (Fig. 1).

Table 3. Individual and mean pharmacokinetic parameters of Fu in healthy volunteers after a single i. v. dose of 40 mg

Healthy Subjects	$t_{½\beta}$ [min]	Cl_B [ml/min]	Cl_r [ml/min]	Cl_{nr} [ml/min]	f_{nr} [%]	$V_{d\beta}$ [L]	Body weight [kg]
Si	59	173	132	40	23	14.7	54
Do	52	129	110	19	15	9.6	73
Gö	48	216	151	65	30	15.0	76
Br	46	141	71	70	49	9.3	56
As	42	207	103	104	50	12.6	77
Ke	64	163	103	59	36	15.0	94
Bs	48	188	154	34	18	13.0	62
Mean	51	174	118	56	32	12.7	
± SD	± 7.7	± 32	± 30	± 28	± 14	± 2.4	

Abbreviations:
$t_{½\beta}$ = elimination half life of the β-phase
Cl_B = total body clearance
Cl_r = renal clearance
Cl_{nr} = non-renal clearance
f_{nr} = fraction of the dose eliminated via non-renal routes
$V_{d\beta}$ = apparent volume of distribution

Table 4. Individual and mean pharmacokinetic data of Fu in patients with cirrhosis, after 40 mg i. v. For abbreviations see Table 3

Patient	$t_{½\beta}$ [min]	Cl_B [ml/min]	Cl_r [ml/min]	Cl_{nr} [ml/min]	f_{nr} [%]	$V_{d\beta}$ [L]
M	43	221	151	69	31	13.8
Le	44	364	176	188	51	23.2
Fu	60	138	92	45	32	12.0
Bi	58	217	102	115	53	18.2
St	44	236	165	71	30	15.0
He	49	170	102	75	44	11.9
Ba	56	123	94	33	27	9.9
Hei	61	268	123	145	54	23.5
Mean	52	217	126	93	40	15.9
± SD	±7.7	±77	±33	±52	±11	±5.2

b. Pharmacokinetics of Fu in Patients with Hepatic Cirrhosis

No difference between pharmacokinetic data in healthy volunteers and those with severe impairment of liver function with fluid sequestration (ascites) could be detected, either with or without correction for body weight. There was a minor tendency to an increase in the whole body clearance (Cl_B) and the mean apparent volume of distribution ($V_{d\beta}$; Table 4), which resulted from a decrease in AUC_∞ (slightly reduced plasma levels in patients Le, St, Bi and Hei). Clinical parameters of the patients with cirrhosis (Table 1) did not suggest any correlation between individual serum albumin and bilirubin levels, the extent of ascites and the individual pharmacokinetic data.

Even in severe cases of cirrhosis (elevated bilirubin level and ascites), the pharmacokinetics were essentially unaltered. The fraction of the i. v. dose eliminated by non-renal routes did not decrease.

c. Pharmacokinetics of Fu in Patients with ESRD

The β-elimination half-life ($t_{½\beta}$) was considerably longer in patients with ESRD 200±57 min ($p < 0.001$; Fig. 1). Urinary elimination over 24 h was minimal in 3 of the patients and 4 patients were anuric (Table 2). The apparent volume of distribution ($V_{d\beta}$), as well as the non-renal clearance (Cl_{nr}), which is essentially equal to the body clearance (Cl_B) in ESRD, did not differ significantly from the values found in healthy volunteers (Table 5). As in healthy subjects and patients with cirrhosis, a third slower phase of Fu elimination could not be detected.

d. Pharmacodynamics of Fu in Healthy Subjects and Patients with Cirrhosis of the Liver

4657±694 ml of urine, 313±75 mEq of sodium and 41.7±6.5 mEq of potassium were excreted by healthy subjects in whom the volume and electrolyte lost were replaced. Patients with cirrhosis showed a considerably weaker response; they excreted only 1892±993 ml of urine and 182±85 mEq of sodium, but the same quantity of potassium 43.3±15.8 mEq (Table 6). The urinary ratio of sodium-potassium was significantly reduced in patients with cirrhosis prior to the experiment, and it never reached values comparable to those of healthy subjects after Fu 40 mg i. v. (Table 6). Both groups, patients with cirrhosis and healthy volunteers, excreted approximately the same amount of unchanged Fu in urine. This effect of liver disease on the responsiveness of the kidney to comparable rates of renal Fu excretion is depicted in Fig. 2. The diuretic response (natriuresis and volume excreted) is clearly reduced in cirrhotic patients at similar rates of Fu excretion; potassium-Fu excretion ratio remained unchanged (Fig. 2).

Discussion

There is still controversy over the disposition of Fu in healthy subjects and in patients with renal failure (Cutler and Blair 1979; Benet 1979). Kinetic data on the drug in liver disease are almost entirely lacking (Cutler and Blair 1979). The data for healthy sub-

jects presented in this study are in good agreement with results reported by Branch et al. (1977) and Beermann et al. (1977). Both authors found plasma half-lives very similar to the present results (50.47 and 51 min, respectively). The other disposition parameters reported by those authors differed only slight from our results. Disposition parameters in patients with ESRD investigated by Beermann et al. (1977) do not differ from our results, except in three cases with massive prolongation of the β-elimination half life. Beermann et al. did not discuss this problem in detail and the reason for the finding remains unknown. It is worthy of note that there was no significant alteration in non-renal clearance or apparent volume of distribution in end-stage renal failure. Thus, using the fraction of drug eliminated unchanged by the normal kidney (fr), it is possible to estimate exactly non-renal elimination or the overall elimination rate in patients with severly impaired renal function from the relation

$$fr = \frac{k_r}{k_r + k_{nr}}$$

(see Dettli 1976).

Table 5. Individual and mean pharmacokinetic parameters of Fu in patients with ESRD after a single i. v. bolus injection of Fu. For abbreviations see Table 3

Patient	$t_{½\beta}$ [min]	Cl_B [ml/min]	Cl_r [ml/min]	$V_{d\beta}$ [L]
Sa	294	43	1.4	18.3
Fu	177	75	1.2	19.3
Ba	150	70	–	15.2
Ap	219	29	–	9.3
Sch	212	50	–	15.4
Ma	117	72	–	12.3
Mar	233	39	2.3	13.0
Mean ± SD	200 ±57	54 ±18	–	14.5 ±3.6

Approximately 30% of intravenously administered Fu is excreted by non-renal routes in healthy volunteers (Table 3). Consequently, a prolongation of the plasma half-life from 51 min to 150 min (Table 5) should be expected in ESRD. The measured half-life of 200 min in our patients with renal failure is in good agreement with this calculated value. However, our results differ markedly from those of Huang et al. (1974), Tilstone and Fine (1978) and Cutler et al. (1974). In patients with ESRD, Huang et al. and Tilstone et al. found mean biological half lives of 9.7 and 14.2 h, respectively. In contrast, Cutler reported an average elimination half life of 80.7 min in 5 functionally anephric patients. Probably the controversial data on Fu kinetics are a consequence of differences in the specificity and sensitivity of the analytical assay, and some extent of the study design. These factors are discussed in detail by Benet (1979) and Hoppe-Seyler (1980). The healthy subjects were significantly younger than the patients. Andreasen and Mikkelsen did not describe any influence of age on the pharmacokinetics of Fu in normal subjects (Andreason and Mikkelson 1977), although there is little information about the question.

Two studies have demonstrated that in uraemia reduction in the plasma protein binding of Fu occurs with increasing plasma concentration of the drug (Andreasen and Jacobsen 1974; Rane et al. 1978). With the exception of a decreased renal clearance in patients with ESRD, our results showed no difference in the disposition parameters of Fu in renal failure. On administration of a relatively small dose of Fu to functionally anephric patients, decreased albumin binding seems to have little clinical relevance. In addition, ascites (7 patients) and decreased plasma albumin in cirrhosis (Table 1) did not influence Fu kinetics. This finding corresponds to the in vitro studies of Prandotta and Pruitt (1975), who found only a slight change in the plasma protein binding at albumin concentrations exceeding 2 g/100 ml.

Difficulties in comparing pharmacodynamic data from published investigations arise from differences

Table 6. Urinary Fu excretion and diuretic response (volume, sodium and potassium excretion) 5 h after Fu 40 mg i. v. in healthy volunteers and in cirrhotic patients. The sodium-potassium ratio before and after Fu is shown

	Fu Excr./5 h [mg]	Urine Volume/5 h [ml]	Na^+ Excr./5 h [mEq]	K^+ Excr./5 h [mEq]	$\frac{Na^+ \text{ Excr./5 h}}{K^+ \text{ Excr./5 h}}$	$\frac{Na^+}{K^+}$ before
Healthy Subjects (n = 7)	26.2±4.0	4657±694	313±75	41.7±6.5	7.5±2.2	3.4±1.6
Pat. with Liver Cirrhosis (n = 8)	22.8±5.2	1892±993	182±85	43.3±15.8	3.9±1.8	1.4±1.7
Significance	Ø	$p < 0.001$	$p < 0.02$	Ø	$p < 0.001$	$p < 0.025$

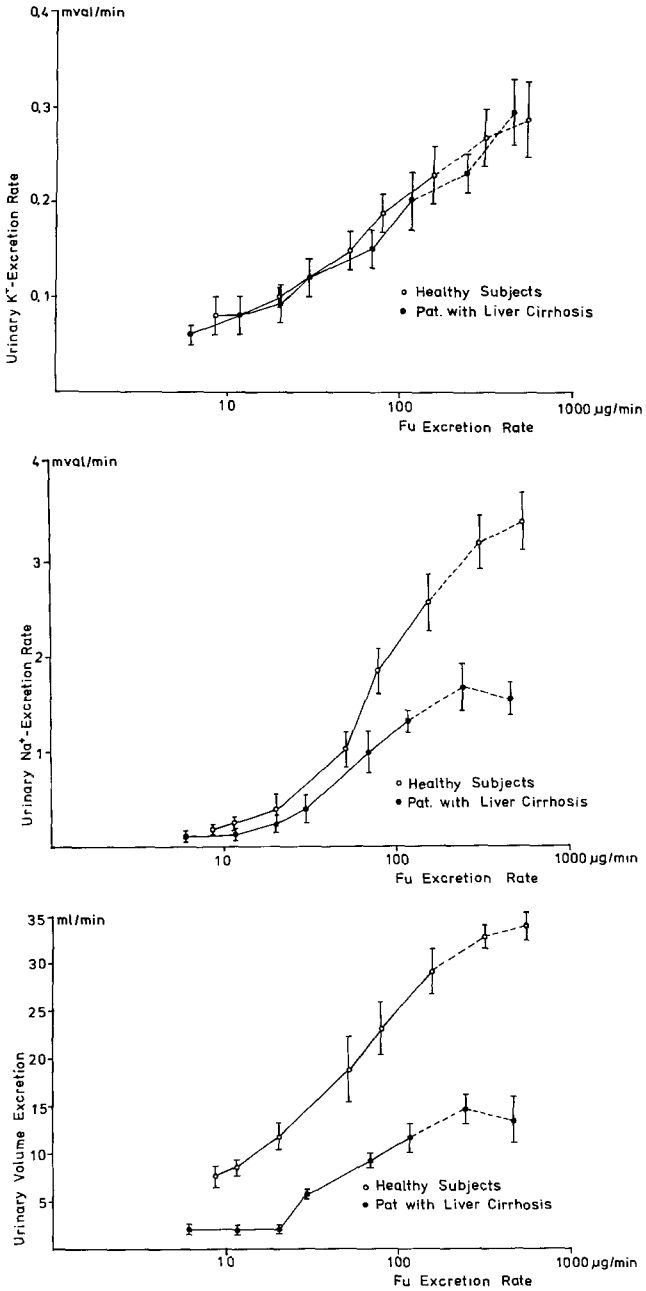

Fig. 2. Relationship between urinary excretion rate of Fu and diuretic response (volume excretion rate, sodium and potassium excretion rate). The solid lines represent the relation during the postdistributive phase of plasma level decay

in study design, but predominantly from differences in the various methods used to measure the diuretic effect. We consider that a rational approach to detecting the diuretic effect is to measure the minimal renal Fu excretion rate still causing a measurable diuresis (Fig. 2). The Fu excretion rate is closely correlated with the diuretic effect (Lawrence et al. 1978; Chennavasin et al. 1979; Cutler and Blair 1979; Brater et al. 1980). This was underlined by the recent results of Odlind and Beermann, who demonstrated that the effect of Fu depends on tubular secretion and the tubular fluid concentration of the drug (Odlind and Beermann 1980). Drug – induced diuresis in healthy volunteers and cirrhotics did not occur at a mean Fu excretion less than 10 µg/min (Fig. 2). Five hours after intravenous injection of Fu, all subjects had reached this minimal Fu excretion rate. Therefore, it seemed reasonable to compare the diuretic effect of Fu 40 mg i. v. in healthy volunteers and in patients with cirrhosis by measuring the urinary excretion of sodium and potassium, and the urine volume over a period of five hours. The marked variations in the diuretic response to Fu in various diseases are due to changes in renal responsivness to Fu (Alexander 1977), and/or to alterations in its pharmacokinetics, amongst which renal excretion of Fu is the most important (Chennavasin et al. 1979; Odlind and Beermann 1980). The renal excretion of Fu in patients with liver cirrhosis (Kind and Schmid 1969) was less than that observed in healthy subjects.

Kind described prolongation of the biological half-life correlated with the slower initial diuresis in cirrhosis. We also observed a definite diminution of the diuretic effect in these patients.

However, our results indicate that decreased diuresis was not due to change in renal excretion of the drug (Table 6). The amount of sodium reaching the site of action of Fu will be the critical factor influencing the magnitude of the diuretic effect (Branch et al. 1977). Micropuncture studies in animal models of cirrhosis and other liver diseases have suggested that the proximal tubule may be the site of increased sodium retention (Lopez-Novoa et al. 1977). In our patients with cirrhosis increased proximal reabsorption of sodium may have diminished the amount of sodium and water reaching the ascending limb of Henle's loop, the site of action of Fu.

With respect to urinary potassium excretion following intravenous administration of Fu 40 mg, the renal responsiveness in liver cirrhosis does not seem to be diminished. Therefore, in patients with cirrhosis, increasing the dose of the drug to achieve a satisfactory natriuresis and volume output may result in severe hypokalaemia, a side effect commonly observed in these patients (Naranjo et al. 1979).

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