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Experiences with Furosemide in Renal Disease. (29835)

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This paper presents data on the renal hemodynamic and diuretic effects of a new compound, furosemide.* This compound is an anthranilic acid derivative whose structure differs from that of the thiazides and ethacrynic acid (Fig. 1). A symposium held in Germany in 1963 (unpublished) furnished sufficient data to suggest that furosemide was a potent diuretic with relatively few side effects. Our particular interest has been an examination of its acute effects in patients with renal disease associated with various degrees of reduction in renal function.

Material and methods. a. Intravenous studies. Fifteen patients were selected from the wards of the Louisville General Hospital and the renal clinic. All but 3 were edematous. The patients ranged in age from 21 to 75 years and included 8 with the nephrotic stage of chronic glomerulonephritis, 2 with Kimmelstiel-Wilson's disease, and 5 with chronic pyelonephritis. Cirrhosis and congestive failure, respectively, had produced edema in 2 of these five. Two subjects were studied a second time after an interval of a few months and a change in renal function.

On the day of the study, the subjects drank a water load of 10-20 ml/kg and were suitably prepared with bladder catheters and infusions for para-aminohippurate (PAH), and other clearances. After a period of stabilization, two 30-minute periods were used to measure the clearances of endogenous creatinine, PAH, and in most cases, sodium, potassium, chloride, free water(1), and total osmols. At the end of the second control period, 40 mg of furosemide were injected intravenously and the measurements were repeated as above for three 30-minute periods.

Standard methods were employed for measurement of creatinine(2) and PAH(3). Sodium and potassium concentrations in blood and urine were measured by flame photometry; osmolality was determined by cryoscopy and chloride by the Cotlove chloridometer.

b. Oral studies. Six subjects (Table III) were studied using divided, daily doses of 160-640 mg. They were restricted in salt intake and were receiving no other diuretic drugs. Observations made included body weight, serum electrolytes, BUN, uric acid and peripheral blood counts. Twenty-four hour urines were collected and analyzed for sodium, potassium and chloride, but the collection problems on the general medical wards precluded calculations based on urine volumes. Four of the 6 subjects had also taken part in the intravenous studies.

Results of intravenous studies. a. Creat-

* Kindly furnished by Lloyd Brothers, Inc., Cincinnati, Ohio.

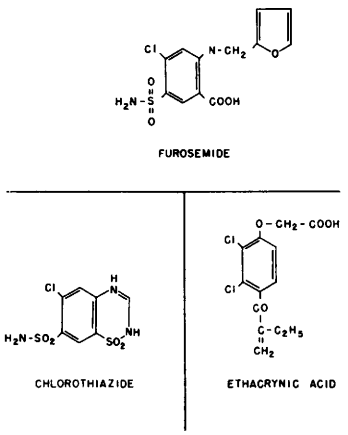

FIG. 1. Structural formula of furosemide 4-chloro-N-(2furylmethyl)-5-sulfamoylanthranilic acid, compared with those of chlorothiazide and ethacrynic acid.

inine and PAH clearances. The pre-injection clearances of endogenous creatinine ranged from 4 to 128 ml/min/1.73M^2, with a mean of 39 ml/min. The values following injection showed remarkably little change. The mean for the first post-injection period was 40 ml/min. Similarly, the PAH clearances had a pre-injection mean of 179 ml/min/1.73M^2 and a post-injection mean of 181.

b. Diuretic effects (Fig. 2, Table I). All patients exhibited an increase in urine volume following furosemide which had its onset within 5 minutes after injection, reached a peak in the first 30 minutes, and continued to be evident, although declining, during the 90 minutes of observation.

The magnitude of the diuresis was related to the clearance levels as would be expected. It is of particular interest that the group of patients with creatinine clearances of 40-60 ml/min increased their urine flow to 4.5 times the control level. The individual post-injection urine flows during the first 30 minutes in this group amounted to 10-55% of the simultaneously measured creatinine clearances.

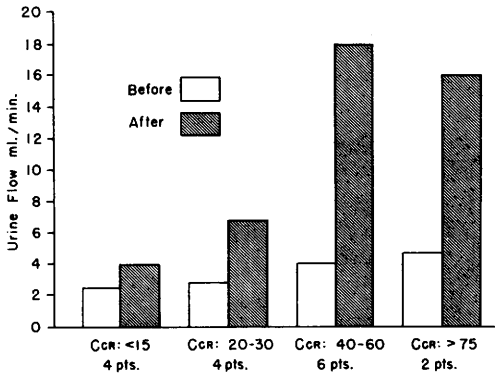

FIG. 2. Urine flow, before and after intravenous injection of 40 mg of furosemide. Patients are grouped according to creatinine clearance (Ccr) and means for each group are shown.

c. Patterns of solute excretion. The control urines were characterized by osmolar clearances ranging from 0.4-3.0 ml/min, and in addition some free water resulting from the water loading before the experiment. The diureses produced by furosemide were accompanied in every instance by a sharp increase in osmolar clearance which accounted for 89-109% of the increment in urine volume (Table II). Thus, the major effect was a marked increase in solute excretion. Furosemide also produced in some patients a small increase in free water clearance beyond the control values.

Urinary concentrations of sodium and

TABLE I. Urine Flow Before and After Intravenous Injection of 40 mg of Furosemide. Patients are grouped according to creatinine clearance, and mean and range of values for each group are shown.

No. of patients	Creat clearance (ml/min/1.73M^2)	Urine flow mean and range (ml/min) Pre-injection	Post-injection	Post/pre
4	<15	2.4 (1.4–3.3)	3.8 (3.6– 4.1)	1.6
4	20–30	2.8 (2.0–3.5)	6.7 (5.1– 8.7)	2.4
6	40–60	4.0 (1.9–9.1)	18.0 (8.9–26.0)	4.5
2	>75	4.6 (3.6–5.6)	15.9 (14.7–17.0)	3.5

TABLE II. Increment in Osmolar Clearance (ΔCosm) Expressed as Percentage of Increment in Urine Flow (ΔV) Before and After Intravenous Injection of 40 mg of Furosemide. Also shown are percentages of filtered sodium appearing in urine before and after injection. Patients grouped according to creatinine clearances.

No. of Patients	Creat clearance (ml/min/1.73M²)	ΔCosm/ΔV × 100	% filtered sodium in urine	
			Pre-injection	Post-injection
3	20–30	109 (103–119)	3.5	14.6
5	40–60	90 (83– 97)	3.0	25.4
2	>75	89 (88– 90)	1.5	6.4

TABLE III. Clinical Data and Results of Oral Furosemide in 6 Patients.

Patient	Age	Diagnosis	Furosemide (mg/day)	Weight loss		BUN Before–After
				(kg)	(days)	
CA	27	Chr glomerulonephritis Nephrotic syndrome	640	24	9	25–25
AL	74	Cirrhosis with ascites	160	5	9	11–20
GP	59	Chronic pyelonephritis Cirrhosis with ascites	160	9	6	31–15
MR	50	Chronic pyelonephritis Congestive failure	320	13	6	87–71
DR	67	Kimmelstiel-Wilson's	160	4	6	120–85
TD	5	Acute glomerulonephritis	160	0	6	40–36

chloride increased markedly following furosemide while that of potassium remained relatively constant. Excretion of potassium, therefore, increased only in proportion to the increase in volume of urine, while the increase in sodium and chloride excretion was far out of proportion to the increase in volume. Table II presents the percentage of filtered sodium which appeared in the urine. It is apparent that even with substantially reduced creatinine clearances the "tubular rejection fraction" of filtered sodium is strongly influenced by furosemide. It may be noted that the post-injection excretion of chloride approximated the combined excretion of sodium and potassium in each case. The mean ratio, excreted Na + K/excreted chloride, was 0.95. This figure indicates an absence of any significant amounts of bicarbonate in the urine, and, therefore, an absence of any carbonic anhydrase inhibiting effect of furosemide.

d. Other effects. No changes in plasma concentrations of sodium, potassium and chloride were noted during the 90-minute post-injection period. A plasma chloride concentration between 70-80 mEq/l in four patients did not interfere with the diuretic response.

No symptoms were produced by the 40 mg injection, nor did arterial blood pressure and pulse change. In other experiments, patients have received 60 and 80 mg intravenously without adverse reaction. One patient who was given 120 mg intravenously experienced a transient tingling and flushing of the face.

e. Results of oral administration. The clinical data and the effects of oral furosamide in various doses are presented in Table III. Five of the 6 patients lost weight, the mean loss being 11 kg with a range of 4 to 24. It is clear that a BUN as high as 87 mg/100 ml does not preclude a satisfactory response to furosemide. No symptomatic effects were noted, nor were there any changes in serum uric acid concentrations or peripheral blood counts. The patient (AL) with a slight rise in BUN probably represented dehydration following diuresis. In one patient (CA) with a 24 kg diuresis, serum potassium concentration was lowered 3.4 to 2.7 mEq/l. This patient received a larger dose than the others, but the data are too few to comment on dose-response relationships. The pattern of solute excretion was similar to that found in the intravenous studies, with sodium and

chloride being the predominant urinary electrolytes.

Discussion. The data demonstrate that furosamide, given intravenously, is capable of markedly increasing the excretion of sodium, chloride, and water. A much smaller, but definite increase in potassium accompanies these effects. The diuresis is produced without a change in glomerular filtration rate as estimated by endogenous creatinine clearance, or the effective renal plasma flow (PAH clearance). Although very low creatinine clearances may not accurately measure filtration rate, the lack of change in clearance following furosemide argues for a corresponding lack of change in glomerular filtration rate.

One site of action of furosemide is clearly the proximal convoluted tubule as shown by some of the urine flow/creatinine clearance ratios presented. Additional sites are not excluded by the data although it is possible to examine the question clinically by observations of free water clearance and tubular reabsorption of free water during various states of hydration(4). Suki has presented data from dog studies from which he concludes that furosemide inhibits sodium reabsorption in the proximal convoluted tubule and the ascending limb of Henle's loop(5).

The eventual place of furosemide in clinical medicine will depend on accumulated experience with its oral usage in various edema producing diseases particularly in comparison with other diuretics. The present data demonstrate that it is a non-toxic, potent, diuretic under the conditions described above. It is evident that the very large diureses that may be produced by furosemide can lead to dehydration and on occasion to hypokalemia. Care is required with its use, just as with any powerful drug.

The evidence thus far is sufficient to warrant intensive clinical trials with furosemide, including observation in patients with substantially reduced kidney function.

Summary. A new diuretic compound, furosemide, has been studied in patients with renal disease. Doses of 40 mg intravenously were capable of producing large diureses of sodium, chloride, and water without adverse effects. Preliminary results with oral administration suggest that the drug may prove to be a useful therapeutic agent.

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Hexose Content of Guinea Pig γ_1 and γ_2 Immunoglobulins.* (29836)

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A considerable number of investigations in recent years have been concerned with the problem of the heterogeneity of the immunoglobulins. Three main types of γ-globulins have been recognized, and have been designated γ_2, γ_{1A} (or β_{2A}) and γ_{1M} (or β_{2M}). They have been characterized in various ways, namely by their antigenic determinants, electrophoretic mobility, sedimentation constant, carbohydrate content and molecular structure(1,2).

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