Initial Responses of Oedematous Patients to Furosemide and S1520

W. P. LEARY, A. C. ASMAL, Y. K. SEEDAT, P. SAMUEL

SUMMARY

Fifteen oedematous patients were treated with furosemide 40 mg *b.d.*, or S1520 30 or 50 mg daily. Similar responses in mass loss, urinary output and electrolyte excretion occurred, but S1520 had a more profound effect on arterial blood pressure than furosemide. S1520 administration, in the dosage under consideration, may result in elevation of blood uric acid and glucose levels and also hypokalaemia, unless adequate potassium replacement is given.

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Diuretics have a defined place in the treatment of patients with oedema arising from cardiac failure, cirrhosis, or the nephrotic syndrome. A variety of effective compounds is available, but attempts to develop potent diuretics of low toxicity and relatively prolonged action, continue.

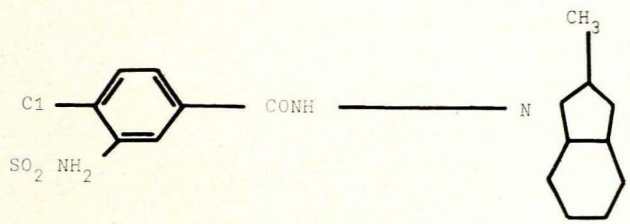

Fig. 1. The structure of N-(3-sulphonamoyl-4-chlorobenzamido)-2 methyl-indoline.

N-(3-sulphonamoyl-4-chlorobenzamido)-2-methyl-indoline (S1520), is a new sulphonamide diuretic (Fig. 1). Preliminary studies by the parent pharmaceutical company indicate that S1520 acts by inhibiting reabsorption in the proximal tubule or ascending loop of Henle, and that it is well tolerated in oral doses of up to 60 mg.[1] Animal studies suggest that the potency and toxicity of this compound are similar to those of furosemide.[2] A study of healthy volunteers showed that orally-administered S1520 is extremely potent and causes substantial water, sodium and chloride excretion by the kidneys.[3] Changes in sodium, potassium, and uric acid levels in plasma and urine were similar to those accompanying therapeutic doses of furosemide or cyclopenthiazide, and the duration of action appeared longer than that of either of these diuretics.

This study was undertaken to determine the initial effects of S1520 upon patients with oedema, and to compare them with those of furosemide.

Department of Clinical and Experimental Pharmacology, University of Natal, Durban
W. P. LEARY, D.PHIL., M.SC., M.B. B.CH., M.R.C.P., F.C.P. (S.A.)
A. C. ASMAL, M.D., F.C.P. (S.A.), M.R.C.P.
Department of Medicine, University of Natal, Durban
Y. K. SEEDAT, M.D., M.R.C.P., F.C.P. (S.A.)
Servier Laboratories, Harrow, Middlesex, UK
P. SAMUEL, B.SC.

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METHODS

Fifteen patients admitted to the medical wards of King Edward VIII Hospital, Durban, with oedema due to cirrhosis or congestive cardiac failure, were allocated to one of two treatment groups, alternately. Ten patients (Table I) were given oral S1520 50 mg/day, except for the second patient, who received 30 mg/day; 5 patients (Table II) were given oral furosemide 40 mg twice daily. All patients received S1520 or furosemide on days 0, 1, and 2 of the study, but no diuretic was given on day 3. Additional medicines were taken by most patients, and these are listed in Tables I and II.

TABLE I. PATIENTS GIVEN S1520

Patient No.	Diagnosis	Oedema	Other drugs
1	CCF	Ankles, pulmonary, ascites	Digoxin 0,25 mg *b.d.*; Slow-K 600 mg *t.d.s.*
2	CCF	Ankles	Digoxin 0,25 mg *b.d.*; Slow-K 600 mg *t.d.s.*
3	CCF	Ankles, ascites	Digoxin 0,25 mg *b.d.*; Slow-K 600 mg *t.d.s.*
4	Cirrhosis	Ankles, ascites	Slow-K 600 mg *t.d.s.*
5	Cirrhosis	Ankles, ascites	Slow-K 600 mg *t.d.s.*
6	CCF	Ankles, sacrum	Digoxin 0,25 mg *b.d.*; Slow-K 600 mg *t.d.s.*
7	Cirrhosis	Ascites, ankles	Slow-K 600 mg *t.d.s.*
8	Cirrhosis	Ascites, sacrum	Slow-K 600 mg *t.d.s.*
9	CCF, hypertension	Ankles, ascites	α-methyldopa 250 mg *q.i.d.*; Slow-K 600 mg *t.d.s.*
10	Cirrhosis	Ankles, sacrum	Slow-K 600 mg *t.d.s.*

Dose: 50 mg per day orally (except patient No. 2 who had 30 mg).
CCF = congestive cardiac failure.

TABLE II. PATIENTS GIVEN FUROSEMIDE

Patient No.	Diagnosis	Oedema	Other drugs
1	CCF	Sacrum, ankles	Digoxin 0,25 mg *b.d.*; Slow-K 600 mg *t.d.s.*
2	CCF	Sacrum, ankles	Digoxin 0,25 mg *b.d.*; Slow-K 600 mg *t.d.s.*
3	Hypertensive CCF	Ankles, ascites	α-methyldopa 500 mg *t.d.s.*; Slow-K 600 mg *t.d.s.*
4	Cirrhosis	Ankles, ascites	Slow-K 600 mg *t.d.s.*
5	CCF	Sacrum	Digoxin 0,25 mg *b.d.*; Slow-K 600 mg *t.d.s.*

Dose: 80 mg per day, as 40 mg b.d.

A blood sample was collected from each patient on admission and again 24, 48 and 72 hours after the first diuretic tablet had been given. Plasma electrolytes, bicarbonate, calcium, urea, uric acid, and glucose levels were measured in these samples, using standard laboratory techniques. Urinary output and pH were noted for 4 days after the initial dose of each preparation, and sodium, potassium, chloride, calcium and uric acid excretion were calculated for each 24-hour period during the 4 days.

Patients were weighed each morning and their arterial blood pressures recorded every 8 hours in the standing and supine positions. Statistical analyses were carried out on an Olivetti 101 computer, using a programme designed to test significant differences in paired observations,[4] when changes due to furosemide or S1520 were analysed. Comparisons between furosemide and S1520 were made using Student's *t*-test. Medical staff were asked to stop any study if it appeared in the patient's interest to do so.

RESULTS

The results are set out in Tables I - VIII.

Patients Treated with S1520

Five patients in congestive cardiac failure, and 5 with oedema from hepatic cirrhosis were admitted to the hospital. All received potassium supplements; and digoxin (4 patients), or methyldopa (1 patient), were also given (Table I).

Blood Pressures (Table III)

Statistically significant changes in arterial blood pressure occurred. The mean standing arterial blood pressure fell from 155 to 140 mmHg, systolic ($P = <0,01$), and from 91 to 78 mmHg diastolic ($P = <0,025$), in the course of the study. Supine arterial blood pressures fell from 153 to 139 mmHg systolic ($P = <0,05$), and from 90 to 77 mmHg diastolic ($P = <0,025$).

TABLE III. EFFECTS OF S1520 ON BLOOD PRESSURE AND MASS (MEAN VALUES AND SEM)*

	Standing BP		Supine BP		
Time (h)	Systolic (mmHg)	Diastolic (mmHg)	Systolic (mmHg)	Diastolic (mmHg)	Mass (kg)
0	155,5 ±6,4	91,4 ±4,5	153,5 ±4,6	89,7 ±4,0	155,4 ±5,24
24	149,8 ±5,4	87,5 ±3,4	148,8 ±3,7	83,2 ±3,4	149,8 ±5,4
48	144,0 ±7,1	86,8 ±4,7	147,0 ±5,6	85,1 ±4,7	145,7 ±6,1
72	140,0 ±4,2	78,1 ±2,1	138,8 ±4,3	77,0 ±2,3	145,9 ±5,8

* Statistical significance tested by comparing paired observations.[4]

Mass Loss (Table III)

Patients lost an average of 6 kg of mass during the study ($P=<0,001$).

Urinary Measurements (Table IV)

Urinary output rose significantly during the 72-hour period which followed initial administration of S1520 ($P=<0,05$).

The urinary sodium excretion rate was markedly increased in comparison with locally accepted normal values, but fell slightly on day 3. Urinary chloride, potassium, calcium, and uric acid excretion rates were within normal limits, although some change occurred during the study. Urine became slightly more alkaline over the 3-day period.

TABLE IV. EFFECTS OF S1520 ON URINARY EXCRETION (MEAN VALUES AND SEM)*

Time (h)	Urine volume (ml/24h)	pH	Sodium (mEq/24 h)	Potassium (mEq/24 h)	Chloride (mEq/24 h)	Calcium (mEq/24 h)	Uric acid (mEq/24 h)
24	2359,0 ±283,0	7,2 ±0,2	290,7 ±38,3	45,4 ±0,9	194,2 ±23,3	69,7 ±11,2	329,4 ±53,2
48	2828,8 ±256,8	7,48 ±0,34	322,2 ±44,6	43,9 ±2,4	188,5 ±24,5	84,0 ±11,6	506,3 ±117,9
72	3155,0 ±369,3	7,68 ±0,2	228,4 ±42,8	43,9 ±5,0	144,4 ±20,9	92,0 ±20,0	407,3 ±86,6

* Statistical significance tested by comparing paired observations.[4]

TABLE V. EFFECTS OF S1520 ON BLOOD, PLASMA AND SERUM BIOCHEMICAL VALUES (MEAN VALUES AND SEM)*

Time (h)	Urea (mg/100 ml)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Uric acid (mg/100 ml)	Glucose (mg/100 ml)
0	16,4	133,9	3,7	99,6	26,0	5,2	98,0
	±1,3	±0,8	±0,12	±1,3	±0,57	±0,38	±5,8
24	17,1	136,2	4,4	98,5	25,4	5,5	120,6
	±1,8	±0,6	±0,20	±0,9	±0,88	±0,43	±7,3
48	13,7	136,1	4,1	97,4	25,4	5,5	119,8
	±2,1	±1,9	±0,18	±1,1	±1,96	±0,36	±3,9
72	25,0	130,5	3,4	96,1	24,8	5,49	124,9
	±4,2	±0,9	±0,23	±0,4	±1,00	±0,39	±6,8

* Statistical significance tested by comparing paired observations.[4]

Blood Plasma and Serum Values (Table V)

Falls in serum sodium, potassium, chloride, calcium, and bicarbonate occurred, and there were increases in blood glucose, blood urea and serum uric acid levels. The change in blood glucose was statistically significant, 24 h ($P = <0,005$), 48 h ($P = <0,01$) and 72 h ($P = <0,005$), after initiating therapy. The change in serum sodium was significant at 72 h ($P = <0,01$), and that in serum potassium at 24 h and 72 h ($P = <0,05$). Uric acid was significantly raised after 72 h ($P = <0,05$), and chloride levels were significantly lowered at 72 h ($P = <0,05$). All these measurements were tested for statistical significance by comparing paired observations.[4]

Patients Treated with Furosemide

Four patients were admitted in congestive cardiac failure and 1 with oedema due to cirrhosis. All were given potassium supplements, and digoxin (3 patients) or methyldopa (1 patient) were also given (Table II).

Blood Pressures (Table VI)

The mean standing arterial blood pressure fell from 155 to 143 mmHg systolic, and from 100 to 92 mmHg diastolic. Supine arterial blood pressure fell from 148 to 135 mmHg systolic, and from 88 to 84 mmHg diastolic. These changes were not statistically significant ($P = <0,1$).

TABLE VI. EFFECTS OF FUROSEMIDE ON BLOOD PRESSURE AND MASS (MEAN VALUES AND SEM)*

	Standing BP		Supine BP		
Time (h)	Systolic (mmHg)	Diastolic (mmHg)	Systolic (mmHg)	Diastolic (mmHg)	Mass (kg)
0	155,5	100,0	148,0	88,0	157,6
	±16,3	±11,9	±16,3	±9,8	±12,4
24	156,0	94,0	148,0	97,2	155,5
	±11,8	±12,6	±13,3	±11,0	±12,3
48	144,0	90,8	138,0	85,2	155,5
	±14,5	±12,4	±13,6	±13,8	±12,1
72	142,5	92,0	135,0	83,5	154,0
	±14,9	±16,1	±15,6	±15,6	±12,1

* Statistical significance tested by comparing paired observations.[4]

Mass Loss (Table VI)

Patients lost an average of 3,6 kg of mass during the study ($P = <0,005$).

Urinary Measurements (Table VII)

Urinary output rose significantly during the 72-hour period which followed the initial administration of furosemide ($P = <0,05$).

Urinary sodium excretion was raised well above accepted normal values throughout the study. Potassium ex-

TABLE VII. EFFECTS OF FUROSEMIDE ON URINARY EXCRETION (MEAN VALUES AND SEM)*

Time (h)	Urine volume (ml/24 h)	pH	Sodium (mEq/24 h)	Potassium (mEq/24 h)	Chloride (mEq/24 h)	Calcium (mEq/24 h)	Uric acid (mg/24 h)
24	1850,0	7,0	313,0	57,6	171,4	153,8	606,8
	±340,2	±0,4	±17,2	±3,7	±32,5	±23,8	±156,4
48	2900,0	7,0	317,0	52,4	232,4	100,4	1207,6
	±90,0	±0,4	±24,1	±3,7	±11,8	±26,2	±333,8
72	3300,0	7,3	314,8	47,5	310,8	66,5	847,5
	±238,1	±0,5	±22,4	±4,9	±55,3	±9,8	±91,9

* Statistical significance tested by comparing paired observations.[4]

TABLE VIII. EFFECTS OF FUROSEMIDE ON BLOOD, PLASMA AND SERUM BIOCHEMICAL VALUES (MEAN VALUES AND SEM)*

Time (h)	Urea (mg/100 ml)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Uric acid (mg/100 ml)	Glucose (mg/100 ml)
0	35,6	141,3	4,6	98,0	30,1	7,6	104,0
	±4,9	±1,33	±0,4	±2,4	±1,6	±0,2	±11,0
24	36,8	146,3	4,2	100,5	31,2	8,0	107,2
	±2,1	±1,03	±0,2	±3,3	±2,2	±0,3	±7,7
48	26,8	142,5	4,4	97,0	26,5	7,5	104,2
	±3,6	±1,5	±0,2	±3,3	±2,3	±0,4	±4,5
72	28,3	142,8	4,1	98,7	28,1	7,1	90,3
	±3,4	±1,9	±0,3	±2,9	±1,6	±0,2	±5,7

* Statistical significance tested by comparing paired observations.[4]

cretion was greater than normal on days 1 and 2 of the study. Uric acid and chloride excretions were within normal limits, except on days 2 and 3 of the study, respectively. Urinary pH was constant.

Blood and Plasma Levels (Table VIII)

No significant change occurred.

Comparison Between Patients Given S1520 and Those Given Furosemide

Blood pressure. Systolic and diastolic arterial blood pressures were significantly reduced by S1520 50 mg, but not by furosemide 80 mg. There was no statistical difference between arterial blood pressures of the 2 groups of patients before treatment.

Mass loss. The mean mass loss was slightly greater in patients taking S1520 than in those given furosemide, but this difference was not statistically significant.

Urinary measurements. Urinary volumes were similar. Patients treated with furosemide excreted more sodium, potassium, chloride and uric acid than those given S1520. Potassium excretion was significantly greater after furosemide on days 1 ($P = <0,01$) and 2 ($P = <0,05$) of the study, and calcium and uric acid excretion by patients given furosemide significantly exceeded that of the group given S1520 after 24 and 72 hours respectively ($P = <0,01$). Chloride excretion particularly was increased in patients given furosemide after 72 hours' study ($P = <0,025$).

Valid comparisons could not be made between blood, plasma, and serum measurements, except in the case of glucose levels, owing to differences already present at 0 hours. Blood glucose rose significantly more after S1520 dosage than when furosemide was given ($P = <0,025$).

DISCUSSION

Several potent, relatively non-toxic, diuretics are available to clinicians. These range from familiar preparations such as the thiazides, the mercurials, and furosemide, to amiloride, a recently developed potassium-sparing diuretic. Trials of S1520 are at an early stage, and much work remains to be done before the correct place of this new agent in clinical practice can be determined. Nevertheless, preliminary remarks may be made on the basis of the results presented above.

S1520 is a potent diuretic which produces about the same effect in a single daily oral dosage of 50 mg, as furosemide 40 mg, every 12 hours. In addition to this apparent difference in duration of action, S1520 is clearly more effective than furosemide in lowering arterial blood pressure, in the dose tested. In addition, this study taken in conjunction with previous investigations,[3] suggests that S1520, in common with many other diuretics, may produce hypokalaemia, hyperuricaemia, and hyperglycaemia. In this respect S1520 appears slightly more toxic than furosemide, although clinical experience is insufficient at present for this to be stated with certainty. Further controlled trials of S1520 for hypertension and for oedema secondary to cardiac, hepatic, or renal disease, are indicated to determine what place this diuretic may have in clinical practice.

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