

# Clinical Trial of a New Diuretic—Metindamide

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## SUMMARY

A controlled clinical trial of metindamide (N-(3-sulphamoyl 1-4 chlorobenzamido)-2-methyl indoline), is reported. It was compared with furosemide in 15 normal subjects and 15 patients with cardiac oedema. Metindamide was found to be at least as effective as furosemide, and produced a greater water loss, but an equivalent electrolyte loss. It had a slow onset, and a fairly prolonged effect, making it a less aggressive drug than furosemide, and one which is suitable for maintenance therapy.

In a smaller trial its effect as a hypotensive agent was demonstrated. The drug was well tolerated and side-effects were minimal.

*S. Afr. Med. J.*, 48, 546 (1974).

Preliminary reports from the Continent<sup>1</sup> indicate that S 1520 merits further attention, being an agent with a fairly smooth prolonged action, but equally as potent as furosemide. It appears to act on the proximal tubule or the ascending loop of Henle much like mefruside.

## PATIENTS AND METHODS

A recent comparative study of two diuretics was so efficient<sup>2</sup> that its format has been largely adopted here. In the event, 4 × 5 mg (20 mg) of S 1520 and furosemide 40 mg were used in an open comparative trial. The trial was divided into 2 parts—normal subjects and patients.

### Normal Subjects

Fifteen adult male Black patients convalescing from minor surgical or orthopaedic procedures, and without evidence of fluid retention or impairment of renal function, agreed to participate as a control group. They were on a standard ward diet and consumed fluids *ad lib*.

### Patients

Fifteen adult Blacks of both sexes with clinically obvious fluid retention, all due to congestive heart failure, were selected. Their ages ranged from 25 to 75 years and all agreed to participate in the trial.

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Throughout the trial period they remained at bedrest and on a standard ward diet. The cardiac condition was initially stabilised by a few days' stay in bed and all were maintained on digoxin.

In both groups, each subject provided 9 24-hour urine specimens, while alternately on S 1520 and furosemide. This was done with a control 24-hour period between each dosing day. Thus the first 24 hours represented a control period; day 2 S 1520; day 3 control; day 4 furosemide; day 5 control; day 6 S 1520; day 7 control; day 8 furosemide; and day 9 final control collection. The sequence of giving a diuretic was therefore in a given order with a control day between each dose. Although the sequence adopted and the nature of the tablets were known to the investigator, (an open comparative trial), this was regarded as being of minor significance as we were dealing with objective measurements. The bladder was emptied at 0800 and the urine discarded. The drug was administered in a single dose and urine was thereafter collected every 4 hours; i.e. at 0800, 1200, 1600, 2000, and a final 12-hour collection up to 0800. The latter was done because of difficulties at this hospital in obtaining overnight collections.

In both groups, the urine collected during each period was measured for volume, specific gravity, sodium, potassium and chloride. In addition daily serum sodium, potassium, chloride, uric acid, urea, and creatinine were estimated. On the full 24-hour urine specimen a creatinine clearance was calculated.

All subjects were weighed on the first day and every morning thereafter. The blood pressure was recorded supine and erect 4 times a day at set times.

### Patients With Hypertension

The aim of the trial was primarily that of assessing diuretic potency. This agent, like other members of the group, is reputed to have a hypotensive action. Therefore 5 patients with hypertension, under basal conditions but on no therapy, were given 25 mg of S 1520 daily for 6 successive days. The blood pressures were taken 4 times a day and the averages calculated for the 6 days.

## RESULTS

The nature and type of response to the drugs were different. Figures for controls are given in Table I and for patients in Table II. The urine volumes and electrolytes are expressed as mean values ( $\pm$  SD) for normals and patients in Table III. The mean blood pressure for normals and patients is given in Table IV.

The mean and standard deviations were calculated for the following parameters: mean blood pressure; total urinary volume; 24-hour urinary potassium, chloride and



TABLE I. CONTROLS

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Mass (kg)	68,35	68,30	67,79	68,17	67,73	68,15	67,57	68,12	67,75
<b>Blood pressure</b>									
Standing 0800 h	135/78	131/79	132/77	136/77	136/77	137/78	134/76	137/76	135/77
Standing 2000 h	136/79	130/74	136/78	130/74	137/79	129/75	137/78	130/75	137/77
Lying 0800 h	131/77	132/77	129/76	132/75	132/76	133/77	131/75	133/76	133/75
Lying 2000 h	132/78	129/73	133/77	127/72	134/77	126/73	134/77	130/74	136/76
<b>Urine</b>									
<b>Volume of urine (ml)</b>									
Period 1	353,3	660,0	303,3	741,7	435,8	401,7	406,7	683,3	405,0
Period 2	284,6	670,0	353,3	361,7	260,0	490,3	216,7	270,3	211,7
Period 3	189,0	613,4	410,7	326,8	292,0	687,7	228,0	311,7	250,0
Period 4	716,7	1 004,6	626,7	733,3	562,0	1 033,3	670,0	743,3	783,3
<b>Total</b>	<b>1 543,6</b>	<b>2 948,0</b>	<b>1 694,0</b>	<b>2 163,5</b>	<b>1 599,8</b>	<b>2 612,0</b>	<b>1 521,4</b>	<b>2 008,6</b>	<b>1 650,0</b>
<b>SG of urine</b>									
Period 1	1 009,1	1 006,2	1 012,1	1 008,1	1 009,1	1 011,9	1 012,1	1 006,5	1 013,5
Period 2	1 012,9	1 008,8	1 012,2	1 014,3	1 009,5	1 012,0	1 019,3	1 016,9	1 018,4
Period 3	1 017,2	1 009,5	1 011,1	1 014,1	1 016,9	1 006,3	1 021,9	1 015,1	1 017,1
Period 4	1 012,9	1 009,4	1 010,7	1 014,3	1 015,7	1 009,6	1 014,8	1 018,1	1 013,7
Total urinary sodium (mEq)	148,48	309,92	257,92	139,52	106,04	255,60	144,16	167,56	133,16
Total urinary potassium (mEq)	48,84	66,60	59,20	114,58	67,28	94,36	46,24	98,00	49,32
Total urinary chloride (mEq)	165,96	326,76	203,25	194,57	106,63	234,15	140,15	198,40	156,27
Urinary 24 h creatinine clearance	73,5	81,7	80,7	84,5	80,0	89,7	86,3	85,7	83,6
<b>Blood</b>									
Urea (mg/100 ml)	24,9	28,0	28,2	31,0	28,7	26,1	27,5	28,8	27,1
Sodium (mEq)	141,2	140,5	139,0	139,2	138,5	139,5	140,9	138,9	139,9
Chloride (mEq)	96,6	101,7	101,1	100,2	100,7	98,1	100,9	99,2	101,3
Potassium (mEq)	4,37	4,39	4,37	4,15	4,23	4,73	4,32	4,13	4,23
Creatinine (mg/100 ml)	1,03	0,91	1,06	1,04	1,10	0,90	0,91	1,01	1,15
Uric acid (mg/100 ml)	4,62	5,01	5,14	5,29	5,64	5,06	4,97	5,27	5,02
Alkaline phosphatase (King-Armstrong units)	6,46	6,90	7,47	8,71	7,99	8,20	8,38	8,35	8,3

sodium. Student tests with a Bessel correction for small numbers were carried out for both normal subjects and patients.

Because there is a carry-over effect with S 1520, all the results on diuretic days were compared to the day 1 control values. The first and last control day values were tested for significant differences as were day 1 and the highest control day values.

## Blood Pressure

The mean blood pressure (mmHg) was calculated in order to reduce the volume of data.

(Systolic - diastolic)

$$\text{Mean blood pressure} = \text{diastolic} + \frac{\text{Systolic} - \text{diastolic}}{3}$$

Normal subjects show a reduction in both standing and lying mean blood pressures on days when either diuretic is given. There is no significant difference between the control day values and the values on the days when diuretics are taken. In the patients both standing and lying mean blood pressures fell on the days when S 1520 was given, and rose or remained the same on the days when furosemide was given. There was no significant difference

between day 1 values and any of the diuretic days. Thus there could have been no significant difference between the diuretics with regard to the acute effect on blood pressure.

## Total Urinary Volume

S 1520 and furosemide produced a highly significant urinary volume increase in both patients and normal subjects. However, the volume excretion in normal subjects was significantly greater with S 1520 than with furosemide. Furosemide produced a greater response in patients than in normal subjects.

## 24-Hour Potassium

For both patients and normal subjects all the mean potassium excretions were significantly higher on days when diuretics were given than on the first control day.

In the normal subjects, there was a significantly higher potassium excretion on control day 5 (after furosemide) than on control day 1. In patients there was a significantly higher potassium loss on control days 3 and 7 (after



TABLE II. PATIENTS

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Mass (kg)	73,69	74,0	72,9	72,86	71,16	71,7	70,99	70,47	69,69
Blood pressure (mmHg)									
Standing 0800 h	148/83	150/81	143/79	148/86	148/83	145/81	143/80	142/80	147/79
Standing 2000 h	146/83	145/80	142/83	148/86	148/83	150/80	144/79	144/80	142/81
Lying 0800 h	145/81	145/80	141/78	144/86	144/82	141/81	139/80	138/79	141/79
Lying 2000 h	143/83	142/79	140/83	145/85	143/82	138/80	150/79	142/80	142/80
Urine									
Volume of urine (ml)									
Period 1	235,4	528,6	723,2	1 444,3	313,2	412,5	530,4	1 135,7	319,7
Period 2	190,7	451,8	398,2	530,0	210,7	401,1	275,0	612,1	278,9
Period 3	283,6	861,8	249,3	310,7	257,1	675,7	253,6	512,5	171,4
Period 4	548,6	1 021,4	558,9	523,6	584,3	1 109,3	639,3	562,5	508,9
Total	1 258,3	2 863,6	1 929,6	2 808,6	1 365,3	2 598,6	1 698,3	2 822,8	1 278,9
SG of urine									
Period 1	1 018,1	1 014,1	1 012,1	1 007,6	1 016,9	1 014,5	1 012,7	1 007,1	1 015,6
Period 2	1 017,5	1 012,2	1 015,5	1 010,5	1 017,3	1 013,5	1 015,2	1 009,4	1 017,0
Period 3	1 015,6	1 011,1	1 017,9	1 013,9	1 016,7	1 011,5	1 015,7	1 012,5	1 018,4
Period 4	1 015,4	1 010,6	1 015,9	1 014,2	1 014,6	1 008,8	1 014,8	1 014,6	1 015,5
Total urinary sodium (mEq)	130,47	214,05	138,22	228,56	118,38	194,60	160,17	236,63	121,28
Total urinary potassium (mEq)	38,33	112,85	64,55	130,37	48,20	98,52	54,82	126,26	37,22
Total urinary chloride (mEq)	96,86	220,26	196,09	231,75	123,75	215,45	147,78	252,53	127,01
Urinary 24 h creatinine clearance	55,7	56,3	60,3	58,7	57,0	60,4	60,4	56,8	57,2
Blood									
Urea (mg/100 ml)	37,6	36,9	37,8	39,6	35,7	38,8	37,6	37,6	37,6
Sodium (mEq)	137,1	140,0	140,3	140,4	141,7	140,7	140,8	140,1	140,5
Chloride (mEq)	100,4	100,0	100,3	101,5	100,9	100,9	101,3	100,9	99,8
Potassium (mEq)	4,56	4,57	4,57	4,45	4,54	4,54	4,41	4,44	4,52
Creatinine (mg/100 ml)	1,30	1,19	1,10	1,02	1,26	1,18	1,08	1,18	1,21
Uric acid (mg/100 ml)	5,03	5,10	5,16	5,44	5,29	5,1	5,26	5,27	4,84
Alkaline phosphatase (King-Armstrong units)	7,64	7,80	7,20	6,86	7,09	7,76	7,32	7,12	7,46

TABLE III. URINE VOLUMES AND ELECTROLYTES/24 HOURS IN 15 PATIENTS WITH OEDEMA AND 15 CONTROLS, MEAN  $\pm$  SD

Day	Urine vol. (ml)		Urinary sodium (mEq)		Urinary chlorides (mEq)		Urinary potassium (mEq)	
	Normals	Patients	Normals	Patients	Normals	Patients	Normals	Patients
1	1 597 ( $\pm$ 265)	1 258 ( $\pm$ 384)	148,5 ( $\pm$ 35,7)	112,9 ( $\pm$ 57,4)	166,2 ( $\pm$ 32,8)	101,5 ( $\pm$ 64,2)	49,1 ( $\pm$ 17,2)	36,3 ( $\pm$ 12,0)
2	2 882 ( $\pm$ 429)	2 942 ( $\pm$ 498)	330,1 ( $\pm$ 98,4)	214,4 ( $\pm$ 99,8)	339,9 ( $\pm$ 92,8)	220,2 ( $\pm$ 67,8)	69,7 ( $\pm$ 17,2)	122,1 ( $\pm$ 37,8)
3	1 694 ( $\pm$ 186)	1 905 ( $\pm$ 351)	170,4 ( $\pm$ 35,5)	140,3 ( $\pm$ 81,1)	202,7 ( $\pm$ 55,4)	198,4 ( $\pm$ 98,9)	60,7 ( $\pm$ 18,0)	64,5 ( $\pm$ 47,2)
4	2 132 ( $\pm$ 152)	2 801 ( $\pm$ 870)	139,5 ( $\pm$ 39,0)	219,5 ( $\pm$ 83,1)	200,4 ( $\pm$ 33,2)	214,5 ( $\pm$ 101,2)	124,3 ( $\pm$ 23,5)	135,7 ( $\pm$ 58,8)
5	1 532 ( $\pm$ 180)	1 365 ( $\pm$ 662)	106,0 ( $\pm$ 34,3)	117,6 ( $\pm$ 38,8)	106,6 ( $\pm$ 23,1)	123,0 ( $\pm$ 47,1)	65,2 ( $\pm$ 15,6)	46,0 ( $\pm$ 23,4)
6	2 619 ( $\pm$ 364)	2 680 ( $\pm$ 823)	255,6 ( $\pm$ 34,5)	194,3 ( $\pm$ 83,6)	234,1 ( $\pm$ 53,4)	217,1 (95,9)	94,3 ( $\pm$ 28,5)	98,5 ( $\pm$ 26,3)
7	1 561 ( $\pm$ 126)	1 705 ( $\pm$ 871)	145,6 ( $\pm$ 49,0)	159,8 ( $\pm$ 66,9)	141,6 ( $\pm$ 27,0)	153,1 ( $\pm$ 85,1)	46,2 ( $\pm$ 18,7)	54,9 ( $\pm$ 20,3)
8	2 015 ( $\pm$ 225)	2 659 ( $\pm$ 690)	154,4 ( $\pm$ 23,0)	230,85 ( $\pm$ 73,7)	197,9 ( $\pm$ 41,5)	245,3 ( $\pm$ 77,1)	95,0 ( $\pm$ 82,1)	125,5 ( $\pm$ 45,5)
9	1 690 ( $\pm$ 174)	1 300 ( $\pm$ 75)	133,7 ( $\pm$ 21,2)	124,5 ( $\pm$ 52,1)	158,2 ( $\pm$ 37,5)	123,5 ( $\pm$ 31,5)	50,1 ( $\pm$ 20,8)	37,7 ( $\pm$ 9,9)



TABLE IV. BLOOD PRESSURE MEAN  $\pm$  SD

Day	Normals (mmHg)		Patients (mmHg)	
	Standing	Lying	Standing	Lying
1	97,67 $\pm 12,0$	96,69 $\pm 12,13$	104,18 $\pm 10,97$	102,11 $\pm 10,7$
2	93,24 $\pm 11,15$	92,69 $\pm 12,94$	102,54 $\pm 11,95$	101,31 $\pm 10,45$
3	100,71 $\pm 24,07$	94,93 $\pm 11,06$	102,71 $\pm 9,35$	101,73 $\pm 9,09$
4	93,22 $\pm 13,74$	90,73 $\pm 13,58$	106,38 $\pm 11,14$	105,58 $\pm 11,39$
5	96,93 $\pm 13,74$	94,09 $\pm 8,69$	104,42 $\pm 10,3$	102,47 $\pm 10,47$
6	91,98 $\pm 10,49$	92,36 $\pm 10,77$	100,22 $\pm 9,58$	98,78 $\pm 10,31$
7	96,55 $\pm 10,88$	95,44 $\pm 11,45$	101,18 $\pm 9,57$	99,6 $\pm 10,58$
8	93,22 $\pm 12,67$	92,27 $\pm 12,55$	101,71 $\pm 10,2$	100,4 $\pm 10,39$
9	95,2 $\pm 11,65$	95,58 $\pm 11,01$	100,96 $\pm 7,59$	99,76 $\pm 8,79$

S 1520) than on control day 1. This would confirm a carry-over effect.

### 24-Hour Sodiums

In normal subjects S 1520 produced a significant increase in sodium excretion above day 1 control values. However, furosemide did not.

In patients, S 1520 and furosemide produced significant increases in sodium excretion above day 1 control values. In normal subjects, the sodium excretion was greater with S 1520 administration than with furosemide administration.

### 24-Hour Chlorides

Both S 1520 and furosemide produced a significant increase in chloride excretion in normal subjects. Similarly, in patients both diuretics produced a urinary chloride excretion significantly different from control day 1 values.

### Effect on Hypertensives

The results of this part of the study are shown in Table V. S 1520 produced a fall in systolic and diastolic blood pressure. After 6 days' treatment the mean blood pressure had fallen from 182/112 to 168/102 mmHg.

TABLE V. EFFECT OF S 1520 (20 mg/day) ON HYPERTENSION

Case	Diagnosis	Mean BP (mmHg)	
		Before therapy	After therapy
1	Hypertensive CVA	213/127	199/118
2	Hypertensive heart failure	168/122	147/109
3	Hypertension	170/99	154/90
4	Hypertension	184/108	171/96
5	Hypertension	174/103	170/96
Mean for 5 patients		182/112	168/102

### Side-Effects

The drug was well tolerated and produced no major side-effects. Pruritus of the skin was noted in 3 patients.

### DISCUSSION

Many diuretic trials are partly invalidated by the fact that comparisons between drugs were made in separate groups of patients. This trial compared the two drugs directly in the same group of patients.

The one difficulty encountered was that of the prolonged action of Metindamide causing a carry-over effect into the next trial period.

With this in mind, the following points emerged from the study: S 1520 in a dose of 20 mg is at least as effective as 40 mg of furosemide. It produced a significantly greater sodium and water loss than furosemide, however. The action of the drug is of rapid onset and it produced a slow increase in urine volumes, with a maximum after 12 hours and a strong suggestion of a carry-over effect into the next control day. No changes in serum uric acid or potassium levels were noted in the short period under review.

In the short-term study S 1520 had a mild and prolonged hypotensive action which should make it a useful adjunct in the antihypertensive armamentarium.

With regard to other diuretics, it compares favourably with furosemide in terms of potency and with chlorthalidone in duration of action.

We wish to thank Servier Laboratories of London for supplying the S 1520 and for the statistical calculations.

### REFERENCES

1. Data supplied by Servier Laboratories, France.
2. Auld, W. H. R. and Murdoch, W. R. (1971): *Brit. Med. J.*, 4, 786.