AN ASSESSMENT OF DISAMIDE, A NEW ORAL DIURETIC

CECIL SYMONS, M.D., M.R.C.P.

First Assistant, Cardiac Department,

AND

KATHLEEN BARBER, M.B., M.R.C.P.

*Medical Registrar,
The Royal Free Hospital*

5-chloro-2 : 4-disulphamyl toluene (Disamide) is a recently introduced oral diuretic. Experimentally in animals this substance possesses a powerful diuretic action closely resembling that of chlorothiazide.¹ In addition, there is some similarity of action to acetazolamide as the drug appears to inhibit the action of carbonic anhydrase.

Highly effective and relatively non-toxic oral diuretics are in such frequent use today that any new substance must possess powerful or specifically useful properties before it can be routinely prescribed. Any trial should include a comparison of the effectiveness of the new drug with one of the known modern diuretics. We report the results of a trial of Disamide in the treatment of patients with congestive cardiac failure in which hydrochlorothiazide was used as the diuretic for comparison.

Procedure

A single dose of Disamide was given to two normal subjects. The diet and fluid intake for the preceding day were repeated on the day the drug was taken. On both days urine and electrolyte output and urine pH were measured two hourly for the first 12 hours of the 24-hour period.

Disamide was given to 21 in-patients (11 males, 10 females) in congestive cardiac failure. Oedema was present in some degree in each case. The age range was 34-75 years with an average of 62.7 years. Eight patients had ischaemic or degenerative heart disease, five cor pulmonale, five hypertensive heart disease, two rheumatic heart disease and one had cardiomyopathy. Of these patients, six were given Disamide on alternate days (Group 1); the rest had hydrochlorothiazide alternating with Disamide. (Groups 2 and 3.)

Patients in Group 1 were on a low sodium diet (0.5 g. sodium daily) and the others on a diet containing approximately 5 g. sodium chloride

FIG. 1.—Effect of Disamide (300 mg. and 200 mg. respectively), given to two normal subjects, on volume of urine and electrolyte excretion. Two-hourly outputs are shown for a period of 12 hours on two successive days with identical diet and fluid intake (cross-hatched blocks = Disamide).

per day. Fluid intake was not restricted and the urine was collected over a 24-hour period. Where possible patients were weighed daily.

Disamide was also given to 18 other cardiac patients (including 11 out-patients) who needed oral diuretic therapy. The out-patients were seen at approximately two-weekly intervals.

Sodium and potassium were estimated by flame photometry, chlorides by Schales and Schales method² and urine pH by Cambridge pH meter. Serum electrolytes were estimated at least once weekly in in-patients, and frequently in out-

TABLE I
MEAN 24-HOUR URINE AND SODIUM OUTPUT OF PATIENTS IN GROUP 1, GIVEN DISAMIDE ON ALTERNATE DAYS

Case No.	Period observed (days)	Disamide (mg.)	Mean volume urine (ml.)		Increase (%) urine due to Disamide	Mean sodium output (mEq.)		Increase (%) sodium due to Disamide
			No drug	Disamide		No drug	Disamide	
1	12	100	830	1,010	21	15	27	82
2	14	100	1,610	1,430	-11	63	44	-30
3	10	100	1,750	1,800	3	89	92	4
4	12	200	1,270	1,480	16	52	70	34
5	12	200	1,080	1,800	67	37	74	98
6	16	300	1,940	2,210	14	76	97	27
Average					18			36

TABLE II
MEAN 24-HOUR URINE AND SODIUM OUTPUT OF PATIENTS IN GROUP 2; DISAMIDE AND HYDROCHLOROTHIAZIDE GIVEN ON ALTERNATE DAYS. DOSE OF HYDROCHLOROTHIAZIDE WAS CONSTANT AT 50 MG.

Case No.	Period observed (days)	Disamide (mg.)	Mean volume urine (ml.)		Increase (%) urine due to hydrochlorothiazide	Mean sodium output (mEq.)		Increase (%) sodium due to hydrochlorothiazide
			Disamide	Hydrochlorothiazide		Disamide	Hydrochlorothiazide	
7	14	100	1,450	1,630	12	107	152	42
8	12	100	2,030	2,280	12	183	225	23
9	10	100	2,170	1,820	-15	117	100	-15
10	16	200	1,630	1,410	-13	82	87	6
11	10	200	1,750	2,180	25	118	186	58
12	10	200	2,810	2,600	-7	126	152	21
13	10	400	1,730	1,760	2	80	97	22
14	12	400	2,280	1,690	-26	23	29	28
Average					-1			23

TABLE III
MEAN 24-HOUR URINE AND SODIUM OUTPUT OF PATIENTS IN GROUP 3 SHOWING THE RELATIVE EFFECTIVENESS OF 100 MG. HYDROCHLOROTHIAZIDE AND 300 MG. DISAMIDE

Case No.	Mean volume urine (ml.)			Increase (%) urine, hydrochlorothiazide/Disamide	Mean sodium output (mEq.)			Increase (%) sodium, hydrochlorothiazide/Disamide
	No drug	Disamide	Hydrochlorothiazide		No drug	Disamide	Hydrochlorothiazide	
15	1,090	1,180	2,300	95	72	98	163	66
16	1,250	1,530	1,930	26	93	115	181	58
17	1,420	1,860	2,190	18	98	114	165	45
18	1,220	1,410	1,560	11	61	68	132	94
19	1,230	1,240	1,820	47	38	25	174	602
20	2,030	2,000	2,890	45	60	110	221	101
21	1,270	1,490	2,050	38	55	110	167	52
Average				40				69 (excludes case 19)

Each patient observed for 18 days (for explanation see text)

patients. Blood counts and liver function tests were carried out on most patients.

Observations on Normal Subjects

One normal subject was given 200 mg. and the other 300 mg. Disamide. There was a diuresis during the first eight hours after taking the drug with an increase in sodium and chloride excretion as compared with the preceding day (Fig. 1).

Potassium loss was only slightly increased. The effect of the drug was greater after the larger dose of 300 mg.

Observations on Group 1

Six patients were given Disamide on alternate days. Each patient had the same dose throughout the period of study and this varied from 100-400 mg. The mean output of urine during the

FIG. 2.—Case 15 to show typical pattern of response to Disamide and Hydrochlorothiazide (cross-hatched blocks = Disamide; stippled blocks = Hydrochlorothiazide).

24-hour period was only slightly increased following the drug but sodium excretion was 33% higher (Table I). No consistent increase of urinary potassium was noted but both a decrease of chloride output and an alkaline urine were usual. Increasing the dose of Disamide did not appear to enhance its action.

Observations on Group 2

Eight patients were given Disamide, alternating with hydrochlorothiazide, so that Disamide was given on one day and hydrochlorothiazide on the next. Each patient had the same dose of Disamide throughout the period of study, and this varied from 100-400 mg. The dose of hydrochlorothiazide was constant at 50 mg. Both drugs appeared equally active in their effect on water loss but hydrochlorothiazide was slightly more effective in

its natriuretic effect (Table II). Potassium loss was not increased with either drug.

Observations on Group 3

Seven patients were given three-day courses of Disamide (300 mg. daily) and of hydrochlorothiazide (100 mg. daily), separated by two-day periods when no drug was given. Observations were carried out for 18 days in each patient (Table III).

Hydrochlorothiazide was considerably more effective than Disamide in respect of urine and sodium output (40% increase in water loss and 69% increase in sodium excretion). Weight loss and potassium excretion were more obvious during the periods of treatment with hydrochlorothiazide and urinary chlorides were usually decreased when Disamide was given (Fig. 2). Compared to the days without either drug, Disamide almost always increased the output of urine and sodium.

Long-Term Treatment

100 mg. Disamide morning and noon were given to 18 other patients for periods up to three months. Two patients in this group became oedematous during a respiratory infection, but none of the others gained weight whilst taking the drug.

Side Effects

Of the 24 patients who received Disamide alone, four had severe paraesthesiae of hands, feet and face which necessitated withdrawal of the drug. Three patients complained of difficulty in expressing themselves in writing, and in six patients specifically tested there was impairment of the ability to calculate whilst taking Disamide. No associated neurological findings were noted and hypotensive reactions were not encountered. Serum electrolyte levels were consistently within normal limits.

No evidence of any renal or hepatic disorder was noted, nor any abnormality of the haematopoietic system.

Discussion

It is apparent that Disamide given in a dosage of 100-400 mg. per day has a diuretic activity comparable to 50 mg. hydrochlorothiazide; it is much less effective than 100 mg. hydrochlorothiazide. The duration of action of Disamide (over a period of eight hours), the depression of urinary chloride secretion, the occurrence of paraesthesiae and the failure to note any increase in action with increase in dosage suggests that most of the activity of Disamide is due to carbonic anhydrase inhibition. It is of interest to note that urinary chloride depression did not occur in the two normal subjects. Disamide has been shown

to possess some anticonvulsant activity in the experimental animal,¹ and this suggests that the rather disturbing cerebral effects encountered in our patients may be due to inhibition of brain carbonic anhydrase. A similar action has been described with acetazolamide.²

The main advantage of Disamide over hydrochlorothiazide is that hypokalaemia does not occur with the former drug; no potassium supplement was required even after continuous treatment for three months, but the side effects of Disamide would appear to occur too frequently to merit long-term use in congestive failure.

It is possible that Disamide, like acetazolamide, may have some place in the treatment of patients with congestive failure in conjunction with other diuretics, such as the organic mercurials or when some other action depending on carbonic anhydrase inhibition is required.

Summary

Disamide (5-chloro-2 : 4-disulphamyl toluene)

was given to 39 patients. Twenty-one patients were in congestive cardiac failure. The effect of the drug was to increase the output of sodium but it was appreciably less effective than 100 mg. hydrochlorothiazide.

The action of Disamide resembled that of a carbonic anhydrase inhibitor particularly in its side effects.

Acknowledgements

We wish to thank Dr. Frances Gardner for permission to study her patients and for her criticism of this paper. We also wish to thank Dr. J. L. Hunt of the Medical Department of British Drug Houses for supplying Disamide.

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