VALUE OF MERCAPTOMERIN AND INTRAVENOUS AMINOPHYLLINE IN CARDIAC OEDEMA RESISTANT TO OTHER DIURETICS

BY

J. G. DOMENET, M.B., Ch.B.
Research Assistant

D. W. EVANS, M.B., B.Sc., M.R.C.P., D.C.H.
Registrar

AND

O. BRENNER, M.D., F.R.C.P.
Consultant Physician

From the Queen Elizabeth Hospital, Birmingham

Since the introduction of chlorothiazide and its analogues the place of mercurial diuretics in the treatment of oedema due to congestive cardiac failure has become much smaller, and their use is now practically restricted to cases which fail to respond to the benzthiazide derivatives (*Brit. med. J.*, 1959).

Nevertheless, in any extensive cardiological practice there will be found a hard core of such cases, and some of these will prove unresponsive also to mercurials by injection, in spite of concurrent salt restriction, bed rest, and digitalis therapy. Ammonium chloride may sometimes restore responsiveness to mercurials, but its administration for this purpose has proved disappointing in our experience.

It has therefore been for several years the practice of this unit to treat such resistant cases with the combination of mercaptomerin ("thiomerin") intramuscularly, and, two hours later, aminophylline intravenously. The observed response of individual patients recently treated was so impressive that a search of the records during the past four years was made in an attempt to evaluate the true efficacy of this combination in producing diuresis, natriuresis, loss of weight, and clinical improvement where other drugs (usually including chlorothiazide) had failed.

The analysis of this accumulated experience confirms the power of these diuretic agents combined in this way. No similar large-scale clinical assessment appears to have been recorded, although many years have passed since early descriptions of potentiation of mercurial diuresis by intravenous aminophylline (Goodman *et al.*, 1942; Weston and Escher, 1948; Vogl, 1953), and this may possibly account for the less widespread use of the combination than its value would seem to merit.

Material and Methods

All available records of cases of cardiac failure admitted to a single ward of the Queen Elizabeth Hospital between June, 1956, and March, 1960, were examined. Those in which there had been a satisfactory response to orally administered diuretics or to parenteral mercurials alone were discarded. The combination of a mercurial intramuscularly and aminophylline intravenously was found to have been given as a first-choice diuretic in 16 cases, 15 of which showed a good or excellent response; these also were discarded as being without comparative value. Thirty-five cases remained in which the mercaptomerin/aminophylline combination had been given because the diuretics previously used failed to produce continued diuresis and clinical

improvement, or had never produced a diuresis; the analysis of the data obtained from these 35 cases forms the basis of this study.

Nineteen of these patients were males and 16 were females. Their ages ranged from 18 to 75 (mean, 50.5 years). The aetiology of their heart disease is shown in Table I. The duration of study varied from a minimum of 12 days to a maximum of 126 days, the mean period being 52.5 days.

TABLE I.—*Aetiology of Underlying Heart Disease in the 35 Cases*

Aetiology of Heart Disease	Male	Female	Total
Rheumatic	8	13	21
Congenital	2	1	3
Arteriosclerotic	2	1	3
Hypertensive	4	—	4
Pulmonary	3	1	4

All patients were treated with bed rest and digitalis throughout their period of study, and the salt intake was restricted (in some cases to 15 mEq/day). Potassium supplements, usually in the form of potassium chloride 2 g. three times daily, were given in some cases, including all those receiving benzthiazide derivatives. The dose of chlorothiazide ("saluric") used was 1 g. twice daily on four successive days each week and that of spironolactone ("aldactone") 100–800 mg. daily. Mercaptomerin injections (2 ml. intramuscularly) were usually given thrice weekly. When the mercaptomerin/aminophylline regime was begun the aminophylline was given intravenously in a dose of 0.5 g. (made up in 20 ml. of CO₂-free water) two hours after the intramuscular injection of mercurial. At least 10 minutes were taken over the injection of the aminophylline to avoid excessive respiratory stimulation causing intense hyperpnoea and also the slight but definite risk of sudden death with more rapid administration (Dunlop *et al.*, 1953). The time of two hours between mercurial and aminophylline was chosen arbitrarily as being most likely to ensure maximal potentiation, and accords with that recommended elsewhere (Bayliss, 1959; Davies, 1959).

With the exception of spironolactone, none of these diuretic agents is now being used when the blood-urea level (estimated thrice weekly) exceeds 70 mg./100 ml., because of their tendency to precipitate progressive uraemia in such cases (Brenner, 1960).

Daily fluid intake and urinary output were measured and recorded in all but two patients who were incontinent. All but one were weighed daily on the same scales, frequently calibrated. Serum sodium, potassium, and chloride levels were estimated at least once weekly and in many cases more often. In eight patients daily urinary electrolyte estimations were carried out throughout the period of treatment, the methods used being flame photometry for sodium and potassium and that of Schales and Schales (1941) for the chloride ion.

Results

Diuresis

As a guide to expected urinary output in relation to fluid intake in normal people a regression line based on 273 observations in 25 patients without cardiac, hepatic, or renal disease has been determined (Fig. 1); no account has been taken of water in food, or insensible skin, respiratory and faecal water losses. This line has been reproduced in succeeding figures to facilitate comparison of the diuretic efficiency of the various drugs employed.

Fig. 2 shows the mean daily urinary output, compared with intake, of 19 patients during days of treatment with mercaptomerin (T) and later with mercaptomerin and intravenous aminophylline (A). It will be seen that the latter points are further to the right—that is, towards diuresis—in 16 of the 19 cases. In two the addition of aminophylline made no appreciable difference to the diuretic efficacy of the mercurial alone and in one it resulted in a lower mean daily output.

In 11 (58%) of the cases while on treatment with both drugs there was an excellent sustained response, whereas in none of the 19 was continued satisfactory diuresis achieved with mercaptomerin alone. The two cases (T_1 , T_2) with high mean daily urinary output on mercaptomerin alone had (like the others) become refractory to the mercurial with persistent oedema and suboptimal clinical response, before aminophylline was added, and owe their position so far to the right of the graph to exceptionally high outputs in the early days of treatment. Even so, they achieved a still higher mean daily output (A_1 , A_2) while receiving the combination of drugs.

Fig. 3 shows average outputs, plotted against intake, for both mercurial alone and the mercaptomerin/aminophylline combination on days when no injections were given. It is seen that, while none showed diuresis on these intervening days, the patients when given the combination of drugs certainly did no worse on these days than when previously given mercaptomerin alone.

Fig. 4 shows the results in 22 cases where a benzthiazide derivative was the original diuretic. In two cases there was no appreciable change in the urinary output, but in the other 20 there was a marked improvement while the combined injection regime was in use. Whereas none of the 22 patients showed a diuresis on the benzthiazides, 14 (63%) produced an excellent diuresis on mercaptomerin/aminophylline and only two failed to increase their output-to-intake ratio.

Fig. 5 shows that this enhanced diuresis on days of treatment with mercaptomerin/aminophylline is not offset by reduction in urinary output on non-treatment days below that obtaining while on the benzthiazides.

Fig. 6 demonstrates the response to mercaptomerin/aminophylline of seven patients previously given acetazolamide ("diamox") and 10 patients who had been given spironolactone. None of these 17 produced a diuresis while on acetazolamide or spironolactone, but when given mercaptomerin/aminophylline 15 of the 17 patients showed a greatly improved output. Altogether six patients showed a marked diuresis and another seven a moderate one. The urinary outputs on non-treatment days showed a similar pattern to those seen in Figs. 3 and 5.

Saluresis

The average daily urinary sodium excretions on treatment days in the eight patients for whom complete records are available are shown in Fig. 7. In every case the sodium excretion was highest on mercaptomerin/aminophylline, the increases over previous treatment ranging from 15% to 290%.

Table II shows the mean absolute values for sodium and potassium excretion on treatment days according to diet and potassium intake. It is seen that in all cases analysed the combination of mercaptomerin/aminophylline resulted in a higher sodium excretion and Na:K ratio than that produced by any other single diuretic, although substantial amounts of potassium were excreted.

C

FIG. 1.—Daily urinary output in relation to fluid intake values for control patients with fitted regression line ($r=0.51$, $P<0.001$).

FIG. 2.—Mean urinary output v. fluid intake on days of injections for patients originally given mercaptomerin alone. (T=mercaptopmerin alone. A=mercaptopmerin/aminophylline.)

FIG. 3.—Mean urinary output v. fluid intake on days between injections for patients originally given mercaptomerin alone. (T=mercaptopmerin alone. A=mercaptopmerin/aminophylline.)

FIG. 4.—Mean urinary output v. fluid intake for patients originally given a benzthiazide derivative. Treatment days. (C=benzthiazide derivatives. A=mercaptomerin/aminophylline.)

FIG. 5.—Mean urinary output v. fluid intake for patients originally given a benzthiazide derivative. Off-treatment days. (C=benzthiazide derivatives. A=mercaptomerin/aminophylline.)

FIG. 6.—Mean urinary output v. fluid intake for patients originally given acetazolamide or spironolactone. Treatment days. (D=acetazolamide. S=spironolactone. A=mercaptomerin/aminophylline.)

Table III shows the corresponding values for the days between treatment. It is evident that the sodium and potassium excretions on days between treatment with mercaptomerin/aminophylline were comparable with or higher than the values recorded for days between treatment with other diuretics.

Serum Electrolytes.—No significant changes in serum electrolyte concentrations were observed during mercaptomerin/aminophylline therapy.

Weight Change

Fig. 8 shows the average daily weight change in kilograms for individual cases according to the period of treatment. This demonstrates that in all but one case there was a loss of weight on mercaptomerin/aminophylline. In 31 of the 34 cases where complete daily weighings were recorded the maximum rate of loss of weight occurred while on mercaptomerin/aminophylline.

Example of Effect of Treatment

An example of the effect of mercaptomerin/aminophylline treatment is shown in Fig. 9.

The patient, a man of 42, was admitted in severe congestive cardiac failure due to cor pulmonale. There was no response to 19 days' treatment with bed rest,

FIG. 7.—Mean daily sodium excretion in individual patients according to diuretic used, chronologically represented in each case. Treatment days.

TABLE II.—Mean Daily Sodium and Potassium Excretions on Days of Treatment with Diuretics Shown

	No. of Patients	No. of Observations	Na mEq/24 hr.	K mEq/24 hr.	Na: K Ratio
A. 15 mEqNa/day diet. 90 mEq/day K Supplement					
Mercaptomerin/aminophylline ..	7	50	124.3	81.2	1.53
Mercaptomerin ..	6	46	50.4	56.0	0.90
Benzthiazides ..	7	49	16.6	61.6	0.27
B. 15 mEqNa/day diet. No K Supplement					
Mercaptomerin/aminophylline ..	1	5	67.8	26.1	2.60
Spironolactone ..	1	28	32.8	21.3	1.54
C. "No added salt" diet. No K Supplement					
Mercaptomerin/aminophylline ..	2	20	182.8	50.6	3.61
Mercaptomerin ..	1	4	49.9	74.8	0.67

TABLE III.—Mean Daily Sodium and Potassium Excretions on Days Between Treatment with Diuretics Shown

	No. of Patients	No. of Observations	Na mEq/24 hr.	K mEq/24 hr.	Na: K Ratio
A. 15 mEqNa/day diet. 90 mEq/day K Supplement					
Mercaptomerin/aminophylline ..	6	58	13.1	44.3	0.24
Mercaptomerin ..	5	56	16.7	47.2	0.35
Benzthiazides ..	6	33	9.1	52.8	0.17
B. 15 mEqNa/day diet. No K Supplement					
Mercaptomerin/aminophylline ..	1	27	13.4	73.7	0.18
C. "No added salt" diet. No K Supplement					
Mercaptomerin/aminophylline ..	3	20	55.3	50.6	1.09
Mercaptomerin ..	1	12	12.1	11.4	1.01

digitalis, oxygen (by tent), and mercaptomerin alone, but when intravenous aminophylline was added to the regime as outlined previously, there was an immediate sustained diuresis with corresponding loss of weight. Nineteen days later he was free from oedema, and able to get up and to be discharged home.

Discussion

The site of action of the organo-mercurials (of which we prefer mercaptomerin as being least likely to cause

discomfort when injected intramuscularly) is generally agreed to be in the renal tubule (Ray, 1958; Mudge and Weiner, 1958). Both proximal (Weston, 1957) and distal (Ford, 1958) tubular functions appear to be affected, and the local liberation of mercuric ions is probably a necessary intermediate stage (Mudge and Weiner, 1958). Inactivation of sulphhydryl-containing enzymes by the mercuric ions then leads to chloruresis and natriuresis (Ray, 1958). This action follows intramuscular injection of the organo-mercurial within two hours, and persists for 12 to 18 hours (Ford, 1958).

The effect of the intravenous aminophylline, given two hours after the mercurial, may thus be expected to coincide with the early mercurial diuretic phase. Its action seems also to be mainly upon the renal tubule, with inhibition of sodium and chloride reabsorption (Beyer, 1958), but direct myocardial stimulation, with increased renal blood flow and glomerular filtration rate (McMichael, 1959; Ford, 1958), may be a contributory factor.

These powerful diuretic agents may also have a general cytotoxic action, and may, in predisposed persons, cause widespread cellular breakdown with a rise in blood urea. For this reason we find it prudent to estimate the blood-urea level before each pair of mercaptomerin/aminophylline injections and to withhold such treatment whenever the level exceeds 70 mg./100 ml. With this reservation it is suggested that the mercaptomerin/aminophylline combination is always worthy of trial where mercurials alone or benzthiazide derivatives have failed to clear cardiac oedema, and that it can be expected to produce a diuresis in the great majority of these cases.

Summary

Thirty-five cases of cardiac failure, with oedema resistant to other diuretics, were treated with mercaptomerin intramuscularly and aminophylline intravenously.

Twenty-eight of these responded with sustained diuresis and clinical improvement.

Thirty-one patients showed maximum rate of loss of weight while receiving this diuretic combination.

Urinary electrolyte excretion data are presented for eight cases so treated.

We thank Miss I. Florence for some of the biochemical data and Mr. T. F. Dee for help in the preparation of the charts.

One of us (J. G. D.) was in receipt of a grant from the United Birmingham Hospitals Endowment Fund.

REFERENCES

- Bayliss, R. I. S. (1959). *Brit. med. J.*, **1**, 41.
 Beyer, K. H., jun. (1958). *Arch. intern. Med.*, **102**, 1005.
 Brenner, O. (1960). In *Modern Trends in Cardiology*, edited by A. M. Jones, p. 82. Butterworth, London.
Brit. med. J., 1959, **2**, 938.
 Davies, D. W. (1959). *Brit. J. clin. Pract.*, **13**, 677.
 Dunlop, D. M., Davidson, L. S. P., and McNee, J. (1953). *Text-book of Medical Treatment*, 6th ed., p. 639. Livingstone, Edinburgh.
 Ford, R. V. (1958). *Ann. N.Y. Acad. Sci.*, **71**, 397.
 Goodman, J. I., Corsaro, J. F., and Stacy, R. (1942). *Arch. intern. Med.*, **70**, 975.
 McMichael, J. (1959). *J. chron. Dis.*, **9**, 602.
 Mudge, G. H., and Weiner, I. M. (1958). *Ann. N.Y. Acad. Sci.*, **71**, 344.
 Ray, C. T. (1958). *Arch. intern. Med.*, **102**, 1016.
 Schales, O., and Schales, S. S. (1941). *J. biol. Chem.*, **140**, 879.
 Vogl, A. (1953). *Diuretic Therapy*, p. 181. Williams and Wilkins, Baltimore.
 Weston, R. E. (1957). *Ann. N.Y. Acad. Sci.*, **65**, 576.
 — and Escher, D. J. W. (1948). *J. clin. Invest.*, **27**, 561.

FIG. 8.—Mean daily weight change in individual patients according to diuretic used, chronologically represented in each case.

FIG. 9.—Illustrative example of use of mercaptomerin/aminophylline combination in patient with congestive cardiac failure due to cor pulmonale. (Hg=mercaptopurine alone. Hg+A=mercaptopurine/aminophylline.)