Ethacrynic Acid: Two Years' Experience with a New Diuretic

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Brit. med. J., 1965, 2, 732-735

In 1963 the first clinical reports on ethacrynic acid (2,3-dichloro-4-(2-methylene butyryl)phenoxyacetic acid) indicated that this was a new diuretic agent of unique chemical structure, and of potency equivalent to or exceeding that of organomercurial or benzothiadiazine compounds (Foltz, 1963; Melvin *et al.*, 1963; Cannon *et al.*, 1963; Daley and Evans, 1963). Subsequent work has confirmed the early conclusions and shown that ethacrynic acid is exceptionally potent, and is effective in the treatment of oedema of many different causes (Dollery *et al.*, 1964; Müller and Schaub, 1964; Bourke *et al.*, 1965; Maher and Schreiner, 1965; Cannon *et al.*, 1965).

Ethacrynic acid combines readily with sulphydryl groups (Beyer *et al.*, 1965), and its action on the renal tubule is to increase urine volume and excretion of sodium, chloride, potassium, and hydrogen ions (Cannon *et al.*, 1963; Bourke *et al.*, 1965; Ledingham and Bayliss, 1965). There is good evidence that the drug inhibits sodium transport both in the proximal tubule and in the ascending limb of Henle's loop (Goldberg *et al.*, 1964; Earley and Friedler, 1964; Beyer *et al.*, 1965; Ledingham and Bayliss, 1965). We have now been using ethacrynic acid for more than two years, the results being reported below.

Methods

Thirty-three patients with fluid retention of varying degrees of severity have been treated with ethacrynic acid alone or in combination with other diuretics on 38 separate hospital admissions. In seven patients the oedema was caused by cirrhosis of the liver, in four by the nephrotic syndrome, and in 20 by congestive heart failure; in one case the oedema was related to hypoproteinaemia from gastro-intestinal protein loss, and in another to acute nephritis. Six patients were studied under metabolic-balance conditions with a constant daily intake of sodium (22-44 mEq) and of potassium (38-62 mEq). In eight patients dietary sodium and potassium were unrestricted and in the remaining 19 sodium intake was constant (22-44 mEq) and potassium intake variable. Fluid intake was measured daily but was not controlled. Supplements of potassium chloride or bicarbonate were given as required. In 30 of the patients daily 24-hour urine collections were made for estimation of sodium, potassium, and chloride excretion. These patients, and the three in whom urine collections were not made, were weighed at the same time each day. Blood was taken for measurement of serum-electrolyte and blood-urea concentrations at frequent intervals.

The analytic methods used have been described elsewhere (Ledingham and Bayliss, 1965).

Results

The results have been assessed in terms of the loss of weight or the 24-hour urinary excretion of sodium and potassium on each day that a diuretic was given. Sodium excretion has been defined as excessive if more than 300 mEq in 24 hours; good if between 60 and 300 mEq; moderate if between 40 and 60 mEq; and poor if less than 40 mEq. In the three patients in

whom urine collections were not made, loss of weight of more than 2 kg. in 24 hours was defined as excessive, 0.5 to 2 kg. as good, 0.25 to 0.5 kg. as moderate, and less than 0.25 kg. as poor. Potassium excretion has been defined as excessive if more than 80 mEq in 24 hours, moderate if between 40 and 80 mEq, and mild if less than 40 mEq.

Ethacrynic Acid, Benzothiadiazine, or Mersalyl alone

Ethacrynic acid was given without other diuretics on 152 days to 30 patients. The dose ranged from 25 to 450 mg. a day, and the best responses were obtained when the drug was given twice or thrice daily. The results are shown in Table I. Benzothiadiazine diuretics were given to 22 of the same patients on 115 days in doses ranging from 0.5 to 2 g. daily of chlorothiazide or equivalent dosages of hydrochlorothiazide, hydroflumethiazide, or bendrofluazide. The results of benzothiadiazine therapy are shown in Table II. Seventeen of the same

TABLE I.—*Urinary Sodium and Potassium Excretion After Various Doses of Ethacrynic Acid in Terms of Days on Which a Given Response was Achieved by Each Dose in a Group of 30 Patients*

Urinary Excretion (mEq/24 Hours)	No. of Days on which Degree of Urinary Excretion was Observed Dose of Ethacrynic Acid (mg./24 Hours)									
	25	50	75	100	125	150	200	300	400	450
Sodium { > 300	—	—	—	—	—	17	6	—	—	—
60-300	2	6	4	20	1	16	16	26	1	1
40-60	—	1	1	7	—	3	7	5	1	1
< 40	3	—	—	3	—	6	5	2	2	—
Potassium { > 80	—	—	4	4	—	4	10	9	—	1
40-80	—	3	1	10	—	17	19	21	2	1
< 40	5	4	—	16	1	5	5	3	2	—
Total No. of days per dose	5	7	5	30	1	26	34	33	4	2

TABLE II.—*Urinary Sodium and Potassium Excretion After Various Doses of Benzothiadiazine in Terms of the Number of Days on Which a Given Response was Achieved by Each Dose in a Group of 22 Patients*

Urinary Excretion (mEq/24 Hours)	No. of Days on which Degree of Urinary Excretion was Observed Dose of Chlorothiazide (g./24 Hours)		
	0.5	1	2
Sodium { > 300	—	—	—
60-300	11	8	28
40-60	2	4	11
< 40	3	4	38
Potassium { > 80	2	0	6
40-80	9	8	34
< 40	5	8	37
Total No. of days per dose	16	16	77

TABLE III.—*Urinary Sodium and Potassium Excretion After 2 ml. of Mersalyl Intramuscularly in Terms of Number of Days on Which a Given Response was Achieved in 17 Patients*

Urinary Excretion (mEq/24 Hours)	No. of Days on which Degree of Urinary Excretion was Observed	
	> 300	< 40
Sodium { > 300	..	0
60-300	..	22
40-60	..	4
< 40	..	8
Potassium { > 80	..	4
40-80	..	19
< 40	..	11

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patients were given mersalyl 2 ml. on 39 days, and the results are shown in Table III.

When the effect of ethacrynic acid is compared with that of benzothiadiazines or of organomercurials (Table IV), ethacrynic acid was the most potent. A moderate or good response was observed on 80% of days after ethacrynic acid, on 66% after organomercurials, and on 56% after benzothiadiazines; poor responses were recorded on only 14% of days after ethacrynic acid compared with 34% after mercurials or 44% after benzothiadiazines. An excessive response in terms of a natriuresis exceeding 300 mEq/24 hours or a loss of weight in excess of 2 kg./24 hours occurred after ethacrynic acid on 9 (6%) days, but did not occur after either of the other two diuretics.

TABLE IV.—Percentage of Days on Which the Responses Shown Below Occurred After Treatment with Ethacrynic Acid, Benzothiadiazines, or Mersalyl

	Ethacrynic Acid	Benzothiadiazines	Mersalyl
No. of patients	30	22	17
" " days	152	115	39
Percentage of days with daily sodium excretion or weight loss:			
> 300 mEq or 2 kg. . . .	6	0	0
60–300 mEq or 0.5–2 kg. . .	62.5	41	56
40–60 mEq or 0.25–0.5 kg. .	17.5	15	10
< 40 mEq or 0.25 kg. . . .	14	44	34
Percentage of days with daily potassium excretion:			
> 80 mEq	21	7	12
40–80 mEq	50	47	56
< 40 mEq	29	46	32

Urinary potassium excretion was greatest after ethacrynic acid, excessive losses as defined above occurring on 21% of days as compared with 12% after organomercurials and 7% after benzothiadiazines.

Ethacrynic Acid or Benzothiadiazines Combined with Spironolactone (Aldactone-A)

In a group of six patients with resistant oedema, ethacrynic acid in doses of 100 to 400 mg. daily was combined with spironolactone 50 to 200 mg. daily on 37 days. In three patients the oedema was due to congestive cardiac failure, in two to the nephrotic syndrome, and in one to cirrhosis.

Sodium excretion was excessive on two occasions in one of the cardiac patients when 100 mg. of spironolactone was combined with 400 mg. of ethacrynic acid. On 21 days the natriuretic response to combined therapy was good, on 10 moderate, and on 4 poor. The poor results were observed after 200 mg. of ethacrynic acid and 200 mg. of spironolactone on three occasions, and after 150 mg. of ethacrynic acid and 50 mg. of spironolactone on another.

With this combination of diuretics excessive loss of potassium occurred on 13 days, moderate loss on 14 days, and excretion was mild (less than 40 mEq daily) on 8 days.

TABLE V.—Percentage of Days on which the Recorded Natriuretic and Kaliuretic Responses Occurred After Treatment with Spironolactone Combined with Ethacrynic Acid or Benzothiadiazine in 10 Patients with Resistant Oedema

Diuretic (mg./day)	No. of Patients	No. of Days	Percentage of Days with 24-hour Urinary Excretion of					
			Sodium (mEq)				Potassium (mEq)	
			> 300	60–300	40–60	< 40	> 80	40–80
Ethacrynic acid 100–400 and spironolactone 50–200 ..	6	37	5	57	27	11	37	40
*Benzothiadiazine 1,000–2,000 and spironolactone 100–200 ..	4	39	0	59	20.5	20.5	18	38
								44

* Expressed as chlorothiazide or equivalents of chlorothiazide.

Chlorothiazide or hydroflumethiazide was given in maximum dosage combined with spironolactone 100–200 mg. on 38 days, and in half maximum dosage on one day, to a group of four patients with resistant oedema, in two due to the nephrotic syndrome, and in the others to congestive cardiac failure or hepatic cirrhosis. Sodium excretion was never excessive; it was good on 23 days, moderate on 8, and poor on 8. Potassium excretion was excessive on 7 days, moderate on 15, and mild on 12.

The results of treatment with either ethacrynic acid or benzothiadiazines in combination with spironolactone are shown in Table V. The overall sodium loss was much the same with either ethacrynic acid or benzothiadiazine, but potassium loss was less with benzothiadiazine.

Ethacrynic Acid Combined with Benzothiadiazines

Ethacrynic acid in doses ranging from 100 to 200 mg. daily was combined with chlorothiazide or hydroflumethiazide in maximal doses on 10 days and in half maximal doses on 12 days in eight patients with resistant oedema, due to congestive cardiac failure in five, the nephrotic syndrome in two, and cirrhosis of the liver in one. On all 22 days urinary sodium excretion was good, but urinary potassium loss was excessive on seven occasions (32%), moderate on 14 (63%), and mild once (5%).

Ethacrynic Acid Combined with Benzothiadiazines and Spironolactone

Full doses of benzothiadiazine diuretic were combined with ethacrynic acid 200 mg. daily and spironolactone 200 mg. daily on 14 days, and spironolactone 100 mg. on four days, in a group of five patients. Fluid retention was caused by congestive heart failure in two, by nephrotic syndrome in two, and by hepatic cirrhosis in one. Good natriuretic responses were obtained on 12 days, moderate on five, and poor on one day in a very ill cardiac patient, who subsequently proved resistant to all combinations of diuretic. Potassium excretion was excessive on four, moderate on 12, and mild on two occasions.

Other Diuretics Combined with Ethacrynic Acid

Ethacrynic acid was combined with mersalyl on four occasions; on each the natriuretic response was good, and better than with either drug alone. Ethacrynic acid was not given in maximal dosage, however, on any occasion.

A combination of ethacrynic acid and frusemide was given, using submaximal amounts of both drugs, on seven occasions, on each of which the natriuretic response exceeded that of twice the dose of either drug given singly. Potassium loss was excessive on one occasion, moderate on five, and mild once.

Triamterene was given combined with ethacrynic acid on only three occasions. On none of them was there significant enhancement of sodium excretion, nor was potassium excretion reduced.

Blood-electrolyte Changes

There was a tendency for the serum concentrations of potassium and chloride to fall and of bicarbonate to rise after each dose of ethacrynic acid given alone or in combination, particularly if the urinary response was good or excessive in terms of sodium excretion or loss of weight. On 11 occasions in seven patients the serum-potassium concentration fell below 3.5 mEq/l. and the bicarbonate concentration rose above 30 mEq/l. In every instance urinary potassium excretion after ethacrynic acid had been high, exceeding 120 mEq/24 hours on

five occasions, with the highest rate 240 mEq/day and the lowest 60 mEq/day. On five occasions there was a particularly marked chloruresis, with 24-hour urine-chloride losses exceeding those of sodium by 128 to 325 mEq.

The most severe electrolyte disturbances were observed in the first two patients to be given the drug, and the relevant data are shown in the Chart. Potassium supplements had not been given and neither patient showed symptoms other than drowsiness during the biochemical disturbance. After experience with these two cases, supplements of potassium chloride were given with ethacrynic acid, but they were not always completely successful in preventing hypochloraemic hypokalaemic alkalosis. When supplements were given, urine potassium loss increased *pari passu*, and in one patient, despite added potassium chloride of 120 mEq daily, a single day's treatment with two 50-mg. doses of ethacrynic acid induced such kaliuresis that the serum potassium fell from 4.3 to 2.6 mEq/l. with a coincident rise in serum bicarbonate from 23 to 32 mEq/l. Supplements were well retained when subsequently given on alternate days with ethacrynic acid.

Urinary electrolyte excretion and serum-electrolyte levels in two patients with hepatic cirrhosis before and after treatment with 50 mg. of ethacrynic acid six-hourly for 48 hours. Both patients responded well, but chloride excretion exceeded sodium loss and hypochloraemic hypokalaemic alkalosis developed.

Side-effects

As may occur with any potent diuretic, several patients experienced fatigue after the diuresis induced by ethacrynic acid. The drug was well tolerated and there was little gastric disturbance provided the tablets were given with or after food. Two patients developed agranulocytosis during treatment and died; both were taking other drugs known to cause depression of the white cells, and both were in the terminal stages of their illness, in one case systemic lupus erythematosus and in the other ischaemic heart disease. No other patients developed depression of the white corpuscles, and none showed abnormalities of liver-function tests.

Discussion

Ethacrynic acid is best given in divided doses two or three times daily after food. Our experience shows that it is much

more potent than either organomercurial diuretics or benzothiadiazines, but individual patients were encountered in whom the response was better with the older-established agents. In most cases the increased potency of ethacrynic acid was reflected in a response from previously resistant patients or by a better response without troublesome side-effects. However, on 11 occasions out of a total of 244 on which the drug was given the diuretic and natriuretic responses were excessive, with a considerable liability to the development of severe degrees of hypokalaemic and hypochloraemic alkalosis. Such results were observed after submaximal doses of ethacrynic acid and could not be predicted from the previous response to other diuretics. As has been observed by Cannon *et al.* (1965), the effectiveness of ethacrynic acid tends to remain constant in any given patient, and can be predicted from the six-hour response to a single dose of 50 mg. We therefore recommend that, in order to determine the correct dose and to avoid excessive loss of fluid and electrolytes, a preliminary assessment of the six-hour response be made to one dose of 50 mg.

Loss of potassium after ethacrynic acid is in many cases similar to that after benzothiadiazines, but sometimes excessively large amounts are excreted. Chloride excretion is also greater, and potassium supplements, obligatory whenever ethacrynic acid is prescribed, are therefore better given as the chloride rather than as the bicarbonate salt. Such supplements may not always prevent hypochloraemic hypokalaemic alkalosis, but this can be corrected, if it arises, by giving ethacrynic acid intermittently and potassium chloride daily. High rates of urinary potassium excretion were still observed on those occasions when ethacrynic acid was combined with spironolactone or triamterene. These combinations were, however, given only to patients with resistant oedema, in whom a high degree of secondary hyperaldosteronism would be expected, and Cannon *et al.* (1965) have shown that urinary potassium loss after ethacrynic acid is considerably influenced by the rate of endogenous aldosterone production. It is probable, therefore, that spironolactone or triamterene may be more effective in reducing potassium excretion with ethacrynic acid if the combination is given to less-resistant cases of oedema; however, such patients when treated with ethacrynic acid alone would be expected to respond well without biochemical abnormalities developing when given potassium-chloride supplements, or to be managed successfully with the older-established diuretic agents.

The high incidence of hypokalaemia and hypochloraemia with a raised serum-bicarbonate level after ethacrynic acid therapy is related not only to the potassium depletion but also to excessive urinary losses of chloride and hydrogen ions (Cannon *et al.*, 1965; Ledingham and Bayliss, 1965). The disturbance is apparently symptomless and correctable with potassium chloride, nor does it decrease the patient's responsiveness to ethacrynic acid in the same way that hypochloraemic alkalosis renders the patient refractory to organomercurials (Stock *et al.*, 1951).

On the basis of our experience ethacrynic acid is not recommended as the diuretic of first choice, for the very reason of its great potency and because of the need for frequent checking of the serum-electrolyte concentrations and of the white-cell count, although this last may prove unnecessary with continued experience.

On the other hand, ethacrynic acid is particularly recommended for the treatment of patients resistant to conventional diuretics, in whom the new diuretic given alone is usually successful. All our patients who were resistant to ethacrynic acid by itself responded well to the combination of ethacrynic acid and benzothiadiazine, which in our experience is the most potent regimen available and which does not lead to urinary potassium losses any greater than those induced by ethacrynic acid alone. The new diuretic in submaximal doses also induced an additive effect on the few occasions when it was given with organomercurials or frusemide.

Summary

Ethacrynic acid is an effective diuretic in doses ranging from 25 to 450 mg. daily. It is more potent than either organomercurial or benzothiadiazine diuretics. An excessive diuresis may occur after ethacrynic acid, and a test dose is recommended for patients new to the drug. Benzothiadiazines given with ethacrynic acid formed the most potent combination of diuretics tried.

Urinary potassium losses are greater after ethacrynic acid than after benzothiadiazines. In resistant cases spironolactone (Aldactone-A) given with ethacrynic acid did not prevent high rates of potassium excretion. Potassium chloride supplements are desirable whenever ethacrynic acid is prescribed, alone or in combination with potassium-sparing agents. The incidence of hypochloreaemic hypokalaemic alkalosis is discussed.

Agranulocytosis was observed in two patients, but the causal relationship was not established with any certainty.

Ethacrynic acid is best used in the treatment of patients with resistant oedema: in such cases we have found it invaluable.

Part of this work was done when J. G. G. Ledingham was in receipt of a Leverhulme Research Fellowship at the Institute of

Clinical Research, and especial thanks are expressed to Dr. J. D. N. Nabarro for encouragement and advice at that time. We are grateful to Dr. J. J. F. Merry, of Messrs. Merck Sharp and Dohme, for supplies of ethacrynic acid.

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Maternal and Neonatal Listeriosis: Report of Case and Brief Review of Literature of Listeriosis in Man

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[WITH SPECIAL PLATE]

Brit. med. J., 1965, **2**, 735-738

Listeria monocytogenes, 40 years after its first isolation and description by Murray, Webb, and Swann (1926), remains, at least for the epidemiologist, a baffling microbe (see Gray, 1963). Animals, birds, and humans are all susceptible to infection, but in view of its widespread distribution in nature such infections are relatively rare and the mode and source of infection are in nearly all cases obscure.

In humans, infection usually takes the form of meningitis, "infectious mononucleosis," or a septicaemic condition of the foetus or newborn infant usually referred to as granulomatosis infantiseptica. In some parts of the world, notably Germany (Potel, 1958) and the United States (Seeliger and Cherry, 1957), the latter appears to be the most frequent form of infection and several recent reports suggest that genital infection with *Listeria monocytogenes* may be a cause of repeated abortion (Rappaport *et al.*, 1960; Gray, 1960; Dungal, 1961; Toaff *et al.*, 1962).

In Britain, until recently, the disease not only appeared to be more rare than in many other places but of the 11 cases reported in medical journals all but one (Webb, 1943) were meningeal infections (see Beck, 1961). Since 1961 three further cases, all meningitis, have been reported in medical journals (McKinnon and Swithinbank, 1961; Harding and Brunton, 1962), bringing the total to 14. In addition the weekly report of the Public Health Laboratory Service has recorded an increasing number of cases of listeriosis since 1961, and in the first six months

of 1965 the number is already eight, but again all the infections have been meningeal. Although five of the 13 fully reported meningeal infections were neonatal (Edmunds *et al.*, 1957; Barrow and Pugh, 1958; Moore and Whitmore, 1960; Harding and Brunton, 1962), in only one was there any suggestive evidence that infection was from the mother (Barrow and Pugh, (1958), and this was unproved. The case reported here represents, therefore, the first bacteriologically confirmed infection in both mother and infant recorded in Britain, although even in this case the patient was not British. Moreover, although *Listeria monocytogenes* has been isolated from the vagina in patients with a history of abortion (Rappaport *et al.*, 1960) the authors do not know of another case where the organism has been isolated from a septicaemic infection in a pregnant woman and subsequently in the newborn infant.

Case Report

History and Clinical Findings

The patient, a Ghanaian woman aged 21, who had arrived in England three weeks previously, was admitted to this hospital on 21 April 1965. She was 28 weeks pregnant and gave a history of cough associated with scanty blood-stained sputum and upper abdominal pain for eight days, and fever for two days. She had had malaria four years previously and had been taking suppressive therapy until three weeks before admission. She had had a normal pregnancy and delivery in 1960 and the child was alive and well.

On admission the temperature was 102° F. (38.9° C.) and blood-pressure 120/80 mm. Hg. No signs of abnormality were detected in the chest, cardiovascular system, abdomen, or central nervous

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