Drug Treatment of Disease**DIURETICS**

BY

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Strictly speaking, any substance that increases the output of urine is a diuretic, but in therapeutics the term is usually applied to compounds which are used in the treatment of oedema. Since oedema fluid is composed largely of water, sodium, and chloride, an effective diuretic must enhance the renal excretion of all these constituents. Over the years a great many diuretic agents have been introduced, but little would be gained by reviewing them all or discussing those which have only a limited use in special circumstances. Rather this is an account of those compounds which to-day are of most general value and most widely used.

Pride of place must be given to mersalyl and similar organic mercurial compounds, which, given parenterally, have been for many years the sheet anchor in the relief of oedema. Only within recent months has the position of mersalyl been seriously challenged. The newcomer is chlorothiazide ("saluric"), a non-mercurial compound with the great advantage of being effective by mouth and having an equivalent potency. In addition there are other less potent substances, unsuitable for the initial treatment of serious oedema but of value in preventing the reaccumulation of oedema fluid or for the relief of less serious oedematous conditions. Three of these compounds—ammonium chloride, aminophylline, and acetazolamide ("diamox")—are mainly used to potentiate the action of mercurial diuretics and to prevent the development of electrolyte imbalances.

Pharmacology

Diuretics can be divided into three main groups according to the mechanism by which they increase the urinary output. First are compounds, such as aminophylline, which increase the blood supply to the kidneys and thereby increase the amount of water and solutes filtered by the glomeruli. Aminophylline has only a transient diuretic action, but by increasing renal blood flow may potentiate the effects of mersalyl in refractory patients if given in a dose of 0.5 g. intravenously two hours after the injection of mersalyl.

Second are those substances which induce an osmotic diuresis by impeding the reabsorption of water in the renal tubules. Urea is an example of this type, but is seldom used because of its unpalatability.

The third, and by far the most important, group are those compounds which directly or indirectly depress the reabsorption of sodium. Normally a large proportion of the sodium ions filtered through the glomeruli are returned to the blood stream through the tubular cells. In diseases which give rise to oedema an even greater proportion of the glomerular filtrate is reabsorbed, and the excessive retention of sodium, chloride, and water is responsible for the development of oedema. If the reabsorptive activity of the tubular cells for sodium is diminished, more sodium is excreted and carries with it an increased amount of water. The exact mechanism by which this is achieved varies with the different members of the group.

Mersalyl impedes the reabsorption of chloride ions, which are excreted in increased amounts, taking with them sodium ions and water. Slightly more chloride than sodium is eliminated, and, if the treatment is too frequent or prolonged, chloride depletion and a fall in the serum chloride level develop. As a result less chloride is filtered through the glomeruli, and the effect of mersalyl is lost. Thus, despite continuing oedema, the patient becomes unresponsive. *Ammonium chloride*, given two hours before the mersalyl injection in the form of two 0.5 g. enteric-coated capsules, prevents the development of mercurial refractoriness by providing chloride ions and also has a diuretic action in its own right.

Chlorothiazide has in many respects an action similar to mersalyl, but the tendency to hypochloroemia is less marked, and seldom occurs in patients with a normal moderately restricted intake of sodium chloride. On the other hand chlorothiazide has a greater tendency to enhance potassium excretion, perhaps because of its additional mild carbonic-anhydrase inhibitory action. Potassium depletion may occur in debilitated patients with a poor appetite, and hence a low potassium intake, who avidly retain sodium and need chlorothiazide more frequently than twice a week. Hypokalaemia is usually asymptomatic but may cause malaise, apathy, weakness, and loss of deep tendon reflexes. It may precipitate neuropsychiatric disturbances in patients with portal cirrhosis, and increases the sensitivity of the heart to digitalis. Thus a fully digitalized patient when given chlorothiazide may develop anorexia, nausea, and vomiting, with undue slowing of the pulse rate and the occurrence of ventricular extrasystoles—manifestations which call for a reduction in the dose of digitalis.

Potassium depletion can be prevented by encouraging a high intake of potassium in the form of tinned pineapple juice, fresh or tinned orange juice, salt-free "marmite," blackcurrant juice, or burgundy. If chlorothiazide has to be given more often than twice weekly for several weeks on end, the dietary intake of potassium must be supplemented, preferably with a mixture of potassium chloride, because tablets or capsules may not disintegrate in the intestinal tract. A palatable mixture to be taken three or four times a day is:

R Potassium chloride	.. 1 g.
Syrup simplex	.. 2 ml.
Alcohol (95%)	.. 2 ml.
Raspberry flavouring	q.s.
Chloroform water	to 15 ml.

If chlorothiazide is given daily, potassium chloride should also be given daily. If chlorothiazide is given on three days a week, potassium chloride is taken on the other four days.

Aminoisometradine ("rolicton") also increases the renal excretion of sodium and chloride in approximately equal proportions, but, being less potent than either chlorothiazide or mersalyl, is less apt to cause electrolyte disturbances. It cannot be recommended for the initial

treatment of severe oedema, but finds a place in maintenance therapy.

Acetazolamide has a different action from the other compounds. It is an inhibitor of carbonic anhydrase and impedes the reabsorption of bicarbonate ions by the renal tubules. The bicarbonate is excreted in company with sodium, potassium, and water but little chloride. After a short time a metabolic acidosis (low serum bicarbonate and high chloride level) develops, and, because fewer bicarbonate ions are filtered through the glomeruli, acetazolamide becomes progressively less effective. It is not potent enough to be of clinical value in the initial treatment of oedema, nor can it be relied upon to prevent the reaccumulation of oedema fluid, but it is of value as an adjuvant to mersalyl because it may prevent the development of hypochloraemic alkalosis.

Chlormerodrin ("mercloran") is an oral organic mercurial compound which is sometimes of value in keeping ambulant patients, who have recovered from congestive failure, free of oedema. The smallest effective dose should be given, but even then diarrhoea may occur.

Potency

Some indication of the relative potency of the different diuretic agents is given in Tables I and II. The comparison is based on the increase in sodium excretion induced by a maximally effective single dose, and the results are expressed as a percentage of the sodium diuresis following 2 ml. mersalyl, which is taken as 100%.

Indications

Oedema due to cardiac, renal, or hepatic disease constitutes the most important indication for diuretic therapy. The fluid retention may be confined to the

legs or sacrum, or be localized to the peritoneal or pleural cavities as ascites or a hydrothorax. It may also be limited to the lungs in left-sided heart failure, and be responsible for paroxysmal nocturnal dyspnoea ("cardiac asthma"). In these circumstances the renal retention of sodium is often avid, and only one or other of the two most potent diuretics—chlorothiazide or mersalyl—is likely to be effective. To some extent diuretics are only symptomatic treatment, and in every instance appropriate measures to improve the underlying disease process must be instituted too. In some instances severe restriction of sodium intake is necessary, but most patients prefer to continue taking a diuretic and eat palatable salt-containing food rather than have a salt-free diet and no diuretic.

Diuretics are not indicated for the relief of the mild oedema in acute glomerulonephritis, but may add greatly to the comfort of the nephrotic patient with anasarca or the patient with chronic glomerulonephritis in whom oedema may be due to the renal disease or to superimposed hypertensive cardiac failure. In general, aspiration of ascites or hydrothorax is unnecessary and should be avoided because the protein content of the fluid is lost from the body.

In other conditions which call for diuretic therapy sodium retention is often less avid and the volume of oedema fluid is smaller. Oedema may develop in association with obesity; in the premenstrual syndrome, when there may be a sudden weight gain of 6 to 10 lb. (2.7–4.5 kg.) seven to ten days before menstruation begins; during administration of cortisone or hydrocortisone but less commonly with prednisone or prednisolone; and in patients who need massive doses of oestrogens to control a prostatic carcinoma. Diuretics, particularly chlorothiazide, are of value in the treatment

TABLE I.—Initial Treatment of Cardiac, Hepatic, or Renal Oedema

Drug	Route	Toxic Manifestations	Electrolyte Disturbances	Potency (see Text)	Dosage		Adjuvant Therapy
					Per Day	Frequency	
Chlorothiazide	Oral	Very uncommon. Rash. Anorexia. Malaise	Hypokalaemia causing digitalis intolerance, and in cirrhotics neuropsychiatric disturbances. Hypochloraemia	100%	1 g. twice daily	(a) Tuesdays and Fridays (b) Mondays, Wednesdays, and Fridays (c) Daily	None if appetite good and potassium intake (fruit-juice) is high Potassium chloride supplements of 2–6 g. daily on Tuesdays, Thursdays, and Saturdays Potassium chloride supplements daily
Mersalyl	Intra-muscular	Very uncommon. Pain at site of injection. Rashes. Fever. Malaise. Diarrhoea. Stomatitis. Ventricular fibrillation	Hypochloraemia causing unresponsiveness. Hypokalaemia. Hyponatraemia	100%	2 ml.	(a) Tuesdays and Friday (b) Mondays, Wednesdays, and Fridays	Ammonium chloride 1 g. in capsules 2 hours before each injection In refractory cases 0.5 g. aminophylline intravenously 2 hours after mersalyl injection

TABLE II.—Maintenance Therapy or Treatment of Mild Oedema

Drug	Route	Toxic Manifestations	Electrolyte Disturbances	Potency (See Text)	Dosage		Adjuvant Therapy
					Per Day	Frequency	
Chlorothiazide	Oral	As above	As above	100%	0.5–1.0 g. twice daily	Twice or thrice weekly	Potassium chloride supplements of 2–6 g. on non-chlorothiazide days, in patients with cardiac or liver disease
Aminoiso-metradine	Oral	Nausea, vomiting, diarrhoea. Dizziness, tinnitus, deafness. Rashes	Hypochloraemia	70%	400 to 800 mg. (1–2 tablets)	Daily	—
Chlormerodrin	Oral	Nausea, diarrhoea, stomatitis, colic. Dermatitis	None reported	50%	1 to 4 tablets	Daily or alternate days	—
Acetazolamide	Oral	Drowsiness. Headaches. Paraesthesiae	Acidosis. Hypokalaemia	25%	250 to 500 mg. (1–2 tablets)	Daily for 5 days	—

of pre-eclamptic toxæmia. The loss of oedema may be accompanied by a reduction in blood pressure, but despite the improvement in the mother the outlook for the baby is not materially better.

Diuretics are of little value in the relief of lymph-oedema, oedema due to varicose veins or venous obstruction, or the puffiness of the ankles many women experience after standing on a hot day.

Choice of Diuretic and Dosage

In the initial treatment of oedema due to cardiac, renal, or hepatic causes either chlorothiazide or mersalyl may be given. A preliminary test dose of 0.5 ml. mersalyl should always be given. If there are no untoward reactions (rigor, nausea, vomiting, pain at the injection site, or rash), the full dose of 2 ml. is given intramuscularly twice (rarely thrice) weekly, being preceded by 1 g. ammonium chloride or 250–500 mg. acetazolamide to prevent the development of hypochloraemia. The injection should always be intramuscular, because a number of sudden deaths due to ventricular fibrillation have been recorded after intravenous administration. Although mersalyl may theoretically damage the renal tubules, in practice this is very rare unless excretion is delayed. Thus proteinuria is not a contraindication to its use, but a blood urea in excess of 100 mg. per 100 ml. is.

Chlorothiazide is as potent as mersalyl in most patients, and the ease of oral administration and the flexibility of dosage allows treatment to be readily adjusted to the patient's individual needs. Indeed, there is a temptation for too frequent dosage. The optimal daily dose is 2 g. (1 g. being given at 8.30 a.m. and 1 g. at 2 p.m.). As shown in Table I, the frequency of dosage can be varied to the needs of the patient. Twice or three times a week is often sufficient, but more seriously ill patients may require treatment every day. If chlorothiazide has to be given more often than twice a week, a supplement of potassium should be given as laid down in Table I. Not only does this help to prevent any tendency to hypokalaemia but it is valuable for replacing the potassium stores, which are often depleted in consequence of the metabolic disturbances that accompany cardiac and hepatic failure.

Maintenance Therapy

In cardiac, renal, or hepatic oedema initial treatment is continued until evidence of oedema has gone, and the diuretic response, as judged by daily changes in the patient's weight, has largely ceased. This usually takes two or three weeks, and then it may be possible to stop diuretics altogether. Not infrequently, however, there is an increase in weight and recurrence of mild oedema, so that maintenance therapy becomes necessary. The patient prefers drugs administered by mouth, and four, arranged in order of relative potency, are listed in Table II. Chlorothiazide is more effective than the others, which may fail to prevent the reaccumulation of oedema fluid. The action of acetazolamide is self-limiting, and if the dose of chlormerodrin is increased diarrhoea often follows. The frequency and dose of chlorothiazide can be adjusted to the patient's needs, but, if given more often than twice weekly, potassium supplements as indicated in Table II must be given too. The duration of treatment can be judged only by the patient's response, but in cardiac and hepatic diseases

and often in renal conditions diuretics may be necessary for the rest of the patient's life.

The same methods of treatment can also be used for the initial treatment of conditions which cause a milder degree of oedema. In premenstrual oedema, the diuretic is started as soon as the symptoms develop—usually 5–10 days before the period—and continued until menstruation is well established. In pre-eclamptic toxæmia treatment is continued until delivery, and in patients with steroid-induced oedema diuretics are often required until the steroid therapy is reduced or stopped.

DECORATION OF THE ANAESTHETIC ROOM: A STUDY OF PATIENTS' REACTIONS

BY

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Originating as a small annexe to the theatre, the anaesthetic room has evolved into an integral part of the operating-block. Unfortunately it has tended to acquire the coldly utilitarian lines of the theatre, and frequently is too small. The necessary floor space has been recommended as 140 sq. ft. (13 sq. m.) (Ministry of Health, 1937) and as 196 sq. ft. (18.2 sq. m.) (Ward, 1949). The new anaesthetic room at the Chelsea Hospital for Women occupies 216 sq. ft. (20 sq. m.), and this may be reasonably regarded as the minimum space necessary for modern anaesthetic techniques.

Steps taken to relieve the austerity of the room have been discussed. Ostlere (1950) recommends that the room should be divided by a curtain, with the necessary apparatus concealed behind it so that the patient does not see it. Hewer (1955) describes a painting of a soothing and tranquil nature on the wall and ceiling of the anaesthetic room.

The value of such steps is hitherto unestablished, since it rests on two unproved assumptions. Firstly, that all or most of the patients on arrival at the anaesthetic room are sufficiently awake to see and be conscious of their surroundings. Secondly, that, if so, they are in any way appreciative of or influenced by them. The trouble and expense involved are wasted if the patients are all asleep or, alternatively, are totally indifferent to their surroundings. The object of this paper is to discuss the aims of such decorations and to assess their value by observation and questioning of a sample of patients who have been through the new and decorated anaesthetic room at the Chelsea Hospital for Women.

Aims of Schemes of Decoration

At first it might reasonably be supposed that the aim should be to exert a soporific effect on the patient and so enhance the effect of the premedication, such a painting being of the nature of that described by Hewer (1955). Alternatively, it may quite feasibly be thought that, if the drugs used for premedication have not succeeded in making the patient sleepy, it is unlikely that any form of decoration will be able to repair this deficiency. Thus, what is needed is something to amuse