ditioned reflex (Dekker and Groen, 1956; McFadden *et al.*, 1969).

There is some contradiction in the literature on the clinical effects of disodium cromoglycate (Pepys *et al.*, 1968; Herxheimer and Bewersdorff, 1969), but nearly all authors are agreed that it often gives useful subjective relief not always reflected by changes in the FEV₁, the most common index used. Improvements in asthma need not always be reflected in the FEV₁ (Woolcock and Read, 1965; Lane, 1969). Two authors state that the response to treatment by disodium cromoglycate cannot be predicted on allergic grounds alone (Campbell and Tandon, 1969; Ford, 1969). Its benefit in a specific case still appears to be unpredictable.

It is postulated that disodium cromoglycate can interfere with exacerbations of asthma which are emotional in nature brought about by hyperventilation consequent on the proprioceptive perception of asthma or other emotional cause, in addition to blocking the results of reagin-antigen union with its consequent asthma. Either mode of action may be at work separately or together at the same time. When an active allergic reaction is present both subjective and objective relief would be obtained. Otherwise the emotional exacerbations caused by hyperventilation together with the relief of post-exercise asthma would give considerable subjective symptomatic and functional relief not necessarily reflected in periodical measurements of ventilatory capacity in the outpatient department. Indications for the use of disodium cromoglycate are still not definite, and it is suggested that one simple test

indicating its use would be to observe whether a fall in the ventilatory capacity followed two minutes of maximum hyperventilation.

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Gross Oedema in the Nephrotic Syndrome Treated with Frusemide in High Dosage

P. D. SNASHALL

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Summary

Five grossly oedematous patients with nephrotic syndrome required frusemide in doses of 250 mg/day or more. Two cases needed albumin infusions to initiate the diuresis. As oedema was removed renal function improved in four cases. There were no side effects. It is concluded that frusemide in the high doses used is a safe and effective diuretic.

Introduction

The safety and potency of frusemide has been established by more than five years' clinical experience throughout the world (Wertheimer *et al.*, 1967; Dollery, 1968). In the absence of severe renal failure a satisfactory diuretic response is usually obtained with daily doses of 40-200 mg, but occasionally much higher doses are required (Muth, 1968; Heiland *et al.*, 1969). The safety of administration of these larger amounts of frusemide has not been adequately established in patients without severe renal failure, and therefore a series of five

grossly oedematous nephrotic patients who were treated with more than 200 mg of frusemide per day were studied.

Patients and Methods

Two women and three men aged 16 to 50 who had failed to respond to conventional doses of frusemide were studied (Table I). All had the nephrotic syndrome with gross oedema and hypoalbuminaemia (less than 1.5 g/100 ml in four cases) and more than 5 g of urinary protein loss per 24 hours. In all cases the glomerular filtration rate was below normal at the onset of treatment. All subjects were normotensive. The study was mainly retrospective, the criterion for selection being that these patients needed over 250 mg of frusemide per day. All patients treated at this hospital in the past two years who satisfied this criterion were included.

Treatment was begun with 40-80 mg of frusemide daily, but as none of the patients responded the dose was doubled, usually at daily intervals until the diuresis began. The dose was then varied according to the diuretic response, requirements tending to decrease as the oedema was removed. In two patients (Cases 1 and 4) who were uraemic the diuresis was established only after plasma volume expansion with salt-poor albumin, 25 g of which was diluted in 500 ml of water in one case and in mannitol 10% in the other, and given daily for one week. Frusemide was added to the infusion. Spironolactone or triamterene was given largely for the potassium-sparing properties. Potassium requirements

Charing Cross Hospital Medical School, Fulham Hospital, London W.6
 P. D. SNASHALL, B.Sc., M.R.C.P., Medical Registrar (Present address: Medical School, University of Southampton, 125 Tremona Road, Southampton)

TABLE I—Patients and Treatment

Case No.	Age and Sex	Glomerular Histological Lesion	Creatinine Clearance at Onset of Treatment (ml/min)	Duration of High Dose Frusemide (Days)	Average Dose per Day (mg)	Maximum Dose per Day (mg)	Potassium Supplements (mEq/Day)	Other Diuretics
1	16 M.	Proliferative	40	50	480	1,000	192	Albumin
2	17 M.	Minimal change	43	20	150	320	96	Bendrofluazide, spironolactone, triamterene
3	23 F.	Minimal change	33	35	340	480	128	Bendrofluazide, spironolactone
4	50 M.	Minimal change	59	14	300	360	None	Albumin
5	45 F.	Minimal change	14	31	570	1,000	28	Spironolactone

TABLE II—Results

Case No.	Total Weight Loss (kg)	Plasma Urea (mg/100 ml)		Creatinine Clearance (ml/min)		Plasma Albumin (g/100ml)		Plasma Volume (¹³¹ I H.S.A.)		
		Before	After	Before	After	Before	After	Before	After, % Change in ()	Predicted*
1 ..	16.8	118	62	40	78	1.1	0.9	2,000	2,725 (+31)	2,650
2 ..	19.5	96	36	43	79	1.4	1.3	2,940	3,080 (+5)	2,660
3 ..	15.5	87	70	33	39	1.4	1.4	1,740	2,150 (+24)	2,130
4 ..	10.5	150	120	59	32	2.3	3.3	3,020	2,540 (-15)	2,600
5 ..	26.7	116	54	14	67	1.4	3.4	2,530	2,205 (-15)	2,580

*Prediction based on dry weight from data of Nadler *et al.* (1962).

were assessed on the basis of the plasma potassium measured three times weekly, and always given as Slow-K, in which potassium chloride is held in a wax from which it is completely absorbed (de Wardener *et al.*, 1969).

The patients were weighed daily. Plasma electrolytes and urea were estimated at least three times a week. Twice-weekly creatinine clearances were performed and protein excretion was measured. Once a week the midstream urine was examined and liver function and uric acid were estimated. Before diuresis the plasma volume was measured by dilution of ¹³¹I-labelled human serum albumin (H.S.A.), and this was repeated once the patient was oedema-free. The standard technique involved taking two separate plasma samples after equilibration. The rate of loss of albumin from the circulation, including renal losses, could thus be calculated and allowed for. All patients had a renal biopsy.

Results

The mean weight loss was 16.4 kg in a mean of 26 days (Table II). The highest dose of frusemide given was 1 g/day for 50 days (Case 1), but in this patient and in Case 4 a diuresis was not obtained until albumin was given with frusemide. In Case 1 the dose of frusemide was rapidly increased to 480 mg/day, but his weight continued to rise and the blood urea remained stable around 120 mg/100 ml. The administration of a solution of 10% mannitol containing 25 g of albumin was associated with a rapid fall in weight by 11 kg in 10 days while the blood urea fell from 120 to 85 mg/100 ml. A similar response was found in Case 4 (see Chart). Before being given albumin he was treated with frusemide in doses up to 200 mg/day. For two weeks he received 80 mg daily, during which period his weight fell by 8 kg but blood urea rose from 80 to 140 mg/100 ml. When his weight failed to drop further, the dose of frusemide was increased to 160 mg, but despite this his weight began to increase and his urea rose to 165 mg/100 ml. His weight continued to rise on 240 mg of frusemide per day, but as soon as the course of albumin was started it fell by 10 kg in nine days while the urea fell from 168 to 110 mg/100 ml.

Potassium requirements as judged by the plasma levels varied from nil to 192 mEq/day. A rise in uric acid was predictable (Lodwin and Guntow, 1965) but was not seen on treatment. Case 4 had a serum uric acid of 11.5 mg/100 ml before any diuretic was given. No changes in the liver function tests were seen during frusemide administration.

As oedema was removed so renal function improved,

except in Case 4, whose renal function subsequently returned to normal over a period of four weeks. When the patients were very oedematous their plasma volumes were all in the normal range, but subsequently when dry weight had been achieved the plasma volumes rose by 31 and 24% in two patients (Cases 1 and 3) whose initial plasma volumes were at the lower limit of normal, while in Cases 4 and 5 plasma volume fell by 15%. There was no significant change of plasma volume in Case 2. Both patients whose plasma volumes fell during diuresis had a rise of plasma albumin, but in the other three albumin remained unchanged or fell during the course of treatment. Though Case 1 received albumin infusions to initiate diuresis, the second measurement of his plasma volume was performed more than three weeks after his last infusion of albumin, by which time he was oedema-free.

Of three renal biopsies (Cases 1, 3, and 5) performed after large doses of frusemide had been given, Cases 1 and 3 showed pronounced tubular atrophy, while in Case 5 tubular atrophy was only slight. Cases 2 and 4 had biopsies at an earlier stage in their illness before large amounts of frusemide had been given. Case 2 showed slight tubular atrophy, while

Case 4. Effect of frusemide and albumin on weight and plasma urea.

the tubules were histologically normal in Case 4. Case 1 had proliferative glomerulonephritis, while in the other cases the glomeruli were normal on light microscopy.

Discussion

The above group of patients required more than the usual doses of frusemide to initiate and maintain a diuresis. Two patients referred from other hospitals had previously been labelled "frusemide resistant," having failed to respond to conventional doses of this diuretic. The results with this group of patients, however, confirm that frusemide is a diuretic whose great potency can be safely increased by exceeding the normally recommended doses. Such doses should be given only in hospital, with close observation of fluid balance and frequent monitoring of plasma electrolytes and renal function.

In patients suffering from congestive cardiac failure and respiratory failure given conventional doses of frusemide Jewkes *et al.* (1970) found that acute natriuresis is accompanied by a fall in extracellular water and plasma volume. Renal function deteriorates with a rise of blood urea and fall of glomerular filtration rate even though the plasma volume may still be within the normal range. By contrast four of the present series of nephrotic patients showed a definite improvement of renal function during diuresis despite enormous falls in extracellular fluid volume. Thus while Case 5 lost 26.7 kg in weight her creatinine clearance rose from 14 to 67 ml/min and her blood urea fell from 116 to 54 mg/100 ml despite a high-protein diet. In a similar series of four very oedematous nephrotic patients (Silverberg and Kjellstrand, 1968) renal function did not deteriorate despite large and rapid loss of weight, and in one case there was a pronounced improvement of renal function. These authors suggest that the diuresis may improve renal function by reducing renal interstitial oedema, thus alleviating tubular obstruction.

The pronounced tubular atrophy seen on renal biopsy in two cases previously treated with large doses of frusemide raises the question of whether frusemide was the cause of this atrophy. Of course, poisoning with agents that cause tubular necrosis, such as carbon tetrachloride, ethylene glycol, or mercury bichloride, causes a deterioration in renal function leading to acute renal failure. By contrast four patients in this series showed an improvement of renal function following frusemide administration; and the fifth patient, whose renal function initially deteriorated, had histologically normal tubules. The patient with the most pronounced tubular atrophy (Case 1) had an improvement of creatinine clearance from 40 to 78 ml/min during frusemide administration. Tubular atrophy is a common histological finding in nephrotic syndrome without treatment with diuretics. The present study therefore lends no support to the view that frusemide is directly nephrotoxic.

The rise in plasma volumes seen after diuresis in Cases 1

and 3 is difficult to explain in the absence of a rise in serum albumin. Garnett and Webber (1967) described the changes in plasma volume produced by treatment in 14 nephrotic patients. Ten patients, four of whom had diuresis of more than 10 kg, showed a fall of plasma volume, while four showed a rise of plasma volume that was in each case associated with a rise of serum albumin that averaged 1.6 g/100 ml. By contrast the serum albumin in Case 1 fell from 1.1 to 0.9 g/100 ml, and in Case 3 remained steady at 1.4 g/100 ml, while the plasma volume in Case 1 rose by 725 ml and in Case 3 by 410 ml. The explanation for these changes may be connected with the raised interstitial fluid pressure that exists in extremely oedematous tissues.

Guyton (1963, 1965) studied interstitial fluid pressure in the presence of oedema in the dog. He found that as oedema increased from mild to moderate interstitial pressure remained around atmospheric pressure, but when the oedema became more severe and the skin was stretched tight then interstitial pressure rose steeply. In both Cases 1 and 3 oedema was severe and the skin was tight. It is reasonable to assume that if interstitial fluid pressure acts on the skin it will also act on the walls of blood vessels and may partially collapse the lower pressure capacitance vessels, the venules and veins. At any one time 60-80% of the blood volume is contained within these vessels (Landis and Hortenstine, 1950; Wiedeman, 1963). This reduction in volume of the capacitance system will, of course, be reversed once the interstitial fluid pressure is reduced by removal of oedema. As the interstitial pressure falls, so the veins will reopen and the plasma volume may increase.

It is concluded that in the high doses used frusemide is a safe and effective diuretic.

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