SHORT REPORTS

Diuretic resistance: reduced bioavailability and effect of oral frusemide

Some patients respond poorly to diuretics. This could be due to changes in the pharmacokinetics or the pharmacodynamics of the diuretic. We report a case in which frusemide given by mouth to an oedematous patient had little effect owing to a much reduced bioavailability.

Case report

A 42-year-old woman was admitted to hospital on 25 occasions from 1971 to 1979 severely overhydrated. Idiopathic oedema[1] was diagnosed after exclusion of other possible causes. She was treated with salt restriction, frusemide intermittently (20-40 mg/day, higher doses when necessary), and potassium chloride. Periodically spironolactone or amiloride was added. Indomethacin 50 mg thrice daily had no effect. After a three-week remission without treatment in 1978 she was readmitted free of oedema and put on a diet containing 20 mmol (mEq) sodium a day. The results of routine serum and urine tests, chest radiographs, cortisol excretion, and creatinine clearance were all normal. There was no orthostatic change in glomerular filtration rate or renin and aldosterone concentrations (the last two were uniformly high). Free water clearance was normal in the supine position after a 1·5 litre water load (51, 309, 305, and 109 ml/min respectively at hourly intervals) but severely diminished when the patient was standing (2, 2, 7, and 15 ml/min). Surprisingly, when she was oedematous frusemide 250-500 mg by mouth had a minimal effect, whereas 40 mg intravenously resulted in a brisk diuresis. We therefore determined the bioavailability and effect of the diuretic (80 mg by mouth and intravenously on two consecutive days) while she was recumbent on two separate occasions—when she was oedematous and when she was free of oedema. No other medication was allowed and food was withheld overnight. Plasma frusemide concentrations were measured[2] repeatedly over an eight-hour period and recorded according to a two-compartment open model. Pharmacokinetic values were calculated by conventional methods.

The pharmacokinetics and pharmacodynamics of frusemide in the oedematous and the oedema-free states are summarised in the table. The most striking finding was the low bioavailability (17·3%) of the diuretic in the oedematous compared with 74·7% in the oedema-free state. Intravenous frusemide induced over three times as much diuresis in the oedematous as in the oedema-free state. Frusemide by mouth was less effective in the oedematous than in the oedema-free state, though the difference was less pronounced than would be expected from the differences in bioavailability. This discrepancy might be explained by the fact that the apparent volume of distribution of frusemide in the oedematous state was only half what it was in the oedema-free state, which led to higher plasma concentrations than expected from the bioavailability. This mechanism is shown when the bioavailability is estimated from the effect. Bioavailability in the oedematous and in the oedema-free state would then be 30% and 90% respectively. Thus the relation is roughly the same as when the bioavailability is calculated from the plasma concentrations of frusemide.

Pharmacokinetics and pharmacodynamics of frusemide in the oedematous (O) and oedema-free (O-F) state

	By mouth		Intravenous	
	O	O-F	O	O-F
$T_{\frac{1}{2}}$ (h)	1·15	1·52	1·15	1·69
$AUC_{0-\infty}$ (ng/ml/h)	1930	6179	11 168	8 272
$V_D\beta$ (l)	12·0	21·3	12·0	23·6
Cl (ml/min)	120	162	119	161
Bioavailability (%)	17·3	74·7	—	—
Diuresis (ml/24 h)	2000	2600	7000	3000
Fluid intake (ml/24 h)	1300	920	1300	2040
Change in body weight (kg/24 h)	−1·5	−0·8	−7·5	−1·0

$T_{\frac{1}{2}}$ = plasma half life. $AUC_{0-\infty}$ = area under plasma concentration time curve $V_D\beta$ = apparent volume of distribution. Cl = plasma clearance.

Comment

The response to diuretics may be poor in renal failure or ascites due to cirrhosis,[3] but our patient suffered from neither of these. Although the bioavailability of frusemide is slightly reduced in patients with renal failure and nephrotic syndrome this has not been shown to be the cause of "diuretic resistance."[4] Our case, however, shows that an apparent resistance to treatment with oral frusemide can be explained by reduced bioavailability of the drug in the oedematous state, presumably owing to reduced absorption of the drug from the gastrointestinal tract, which may also have been affected by oedema. When oral diuretic treatment of oedema fails it may therefore be worth trying the intravenous route. Ultrafiltration treatment has been suggested for diuretic-resistant oedema,[5] although this has been criticised.[3] Resistance to diuretic treatment is reported to have been reversed after ultrafiltration in some patients[5]; but we cannot easily evaluate this claim (or the justification for giving ultrafiltration treatment) without knowing how the diuretic had been administered. To avoid confusion we suggest that the diagnosis of diuretic resistance should be restricted to cases of poor response to diuretics in which changes in the pharmacokinetics (such as reduced bioavailability) of the drug have been ruled out.

1 Thorn GW. Cyclical edema. *Am J Med* 1957;**23**:507-9.
2 Beermann B, Dalén E, Lindström B. Elimination of frusemide in healthy subjects and in those with renal failure. *Clin Pharmacol Ther* 1977;**22**:70-8.
3 Anonymous. Diuretic resistance? *Lancet* 1979;i:253-4.
4 Benet LZ. Pharmacokinetics/pharmacodynamics of frusemide in man: a review. *J Pharmacokinetic Biopharm* 1979;**7**:1-27.
5 Asaba H, Bergström J, Fürst P, *et al.* Treatment of diuretic-resistant fluid retention with ultrafiltration. *Acta Med Scand* 1978;**204**:145-9.

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Malignant scleroderma associated with autoimmune neutropenia

Several haematological complications, which have an immunological basis, may occur in patients with scleroderma, including autoimmune haemolytic anaemia, autoimmune thrombocytopenia,[1 2] and pancytopenia.[3] We describe here a patient with malignant scleroderma and acute renal failure, who developed an isolated autoimmune neutropenia, a previously undescribed complication of scleroderma.

Case report

This 64-year-old woman developed painful oedematous feet and hands and Raynaud's phenomenon in January 1978. In May 1978 she was admitted to a peripheral hospital after a haematemesis. Gastric erosions were seen on endoscopy. During a blood transfusion acute pulmonary oedema and hypotension occurred. She became anuric after this 30-minute hypotensive period. After three weeks of peritoneal dialysis she was transferred to North Shore Hospital. She had not been hypertensive and her white cell count was normal during her initial stay in hospital.

On examination we found thickening and induration of the skin of the hands, feet, and face, blood pressure of 135/75 mm Hg, and no splenomegaly or other abnormality. Investigations showed a haemoglobin of 10·8 g/dl, a total white cell count of $1·2 \times 10^9$/l with 43% segmented neutrophils, a platelet count of 220×10^9/l, and an erythrocyte sedimentation rate of 60 mm in the first hour. Cytotoxic leucocyte antibodies were present. A Coombs test gave a negative result.

Within two days no neutrophils were present on peripheral blood films. The total white cell count was $0·5 \times 10^9$/l. On bone marrow aspiration the cellularity was normal but there was evidence of nuclear lysis. The granulocyte precursors were greatly diminished. There was a pronounced reversal of the myeloerythroid ratio. Occasional granulocyte cells with ingested lysed nuclear material could be seen (see figure). The erythropoietic cells showed features of dyserythropoiesis. Stainable iron was absent. Megakaryocytes were present and there was a mild increase in marrow lymphocytes.

Prednisone treatment (1 mg/kg body weight/day) was started. Her only