CLINICAL RESEARCH

Muzolimine: a new high-ceiling diuretic suitable for patients with advanced renal disease

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Abstract

Muzolimine was administered by mouth to 24 patients with creatinine clearances ranging from 4 to 28 ml/min to treat oedema or hypertension, or both. In four of these 24 patients muzolimine was given after intravenous high-dose frusemide had been unsuccessful. Muzolimine significantly increased urine volume and excretions of sodium, chloride, and potassium ions. Its diuretic efficacy was further shown by a mean reduction in body weight of 8% and by the disappearance of oedema in all affected patients, even those refractory to intravenous frusemide. No rebound phenomenon was observed after the drug was stopped. Mean blood pressure was reduced in all hypertensive patients. Blood pressure was restored to normal in five out of seven patients treated with muzolimine alone and 10 out of 11 in whom muzolimine had been added to previously unsatisfactory antihypertensive treatment. Muzolimine was well tolerated by all patients.

Muzolimine appears to be the diuretic of choice when treating patients with advanced renal disease.

Introduction

In advanced renal failure diuretic treatment is hampered by the great loss of functioning nephrons as well as by the difficulty in further decreasing tubular reabsorption of sodium (and water) in residual nephrons; in residual nephrons a "spontaneous" intensive diuresis already occurs due to extracellular volume expansion or the rise in osmotic load, or both.[1] Only high-ceiling diuretics, such as ethacrynic acid or frusemide, may stil be effective.[2] Disadvantages of these drugs, however, are the frequent need for intravenous administration of high, potentially toxic, doses; the short duration of action; and the so-called "rebound phenomenon," whereby urine flow and sodium output often drop below control values as soon as the diuretic effect is exhausted.[3 4]

Muzolimine is a new potent diuretic with no structural similarity to currently available diuretics.[5] Chemically it is 3-amino-l-(3, 4 dichlormethyl-benzyl)-2-pyrazolin-5-one (fig 1). Investigations in animals and man have located its site of action in the ascending limb of Henle's loop.[6] High-peak plasma concentrations may be obtained soon after oral administration; its long-lasting effect has been attributed to a prolonged half life.[7]

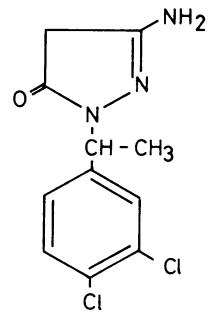

FIG 1—Structural formula of muzolimine.

The combination of high-ceiling activity with a long duration of action without the rebound phenomenon suggests that muzolimine may usefully be substituted for other potent diuretics in the treatment of salt retention in patients with renal failure.

This paper represents the first report on the use of muzolimine in patients with advanced renal failure.

Patients and methods

Our studies were performed in 24 patients with chronic renal failure (creatinine clearance below 30 ml/min) admitted to the nephrology unit. All patients required diuretic treatment because of oedema or hypertension, or both, and gave informed consent to the study.

EFFICACY OF MUZOLIMINE

The efficacy of muzolimine was studied in 20 patients; pertinent clinical data are summarised in table I. In each patient protein and sodium intakes were kept constant during the study. Before admin-

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TABLE I—*Clinical data on patients in whom efficacy of muzolimine was studied*

Case No	Sex	Age (years)	Renal disease	Creatinine clearance (ml/min)	Oedema*	Blood pressure (mm Hg)	Other conditions	Drugs
1	M	49	Amyloidosis	21	+	130/80	Light-chain disease	
2	M	49	Glomerulonephritis	13		190/100		
3	M	48	Glomerulonephritis	8	+ +	170/100	Cardiac failure	Digoxin, methyldopa
4	F	72	Pyelonephritis	6	+ +	200/100	Cardiac failure	Clonidine
5	F	69	Nephrolithiasis	19		140/100		
6	M	55	Glomerulonephritis with nephrotic syndrome	25	+ + +	260/120		Methyldopa
7	M	49	Malignant hypertension	13		200/130		Labetalol
8	M	52	Kimmelstiel-Wilson disease	9	+ + +	205/100	Cardiac failure	Digoxin, insulin
9	M	66	Glomerulonephritis with nephrotic syndrome	20	+ + +	160/80		Spironolactone
10	M	51	Glomerulonephritis with nephrotic syndrome	28	+ +	210/110		Clonidine, hydralazine
11	M	59	Nephrosclerosis	17	+	175/100	Diabetes, cardiac failure	Digoxin, clonidine, labetalol
12	M	58	Kimmelstiel-Wilson disease	27	+ + +	180/100		Insulin
13	M	68	Nephrosclerosis	22	+ +	180/120	Diabetes, cardiac failure	Digoxin
14	M	71	Glomerulonephritis with nephrotic syndrome	22	+ + +	130/70		Spironolactone
15	M	32	Malignant hypertension	25		185/100		Labetalol, minoxidil, propranolol
16	F	41	Chronic rejection	4	+ + +	160/100		Clonidine
17	M	56	Glomerulonephritis with nephrotic syndrome	25	+ + +	255/120	Cardiac failure	Hydralazine, digoxin, spironolactone
18	M	57	Malignant hypertension	5	+ +	190/130	Cardiac failure	Digoxin, propranolol, hydralazine
19	F	32	Glomerulonephritis	12	+	175/100		Timolol, hydralazine
20	M	49	Amyloidosis	7	+ + +	175/105	Myeloma, cardiac failure	Digoxin

* + = Suboedema. + + = Pitting oedema. + + + = Anasarca.

TABLE II—*Clinical data on patients in whom muzolimine was compared with frusemide*

Case No	Age (years)	Sex	Creatinine clearance (ml/min)	Renal disease	Associated conditions	Drugs
21	66	F	24	Nephrosclerosis	Diabetes, cardiac failure	Digoxin
22	18	F	19	Lupus nephritis	Cardiac failure, pleural effusion	Prednisone
23	59	F	11	Membranoproliferative glomerulonephritis	Cryoglobulinaemia, cardiac failure	Labetalol, prednisone, cyclophosphamide, digoxin
24	52	M	10	Kimmelstiel-Wilson disease	Cardiac failure, pleural effusion	Digoxin

TABLE III—*Effects of muzolimine on urinary excretory rates. (Figures are means ± SEM)*

	Basal value	With muzolimine
Urine volume (ml/day)	1040 ± 76	1936 ± 107*
Urinary excretion (mmol/day) of:		
Sodium	56·7 ± 6·7	154·3 ± 11·9*
Potassium	24·5 ± 3·2	43·4 ± 3·7*
Chloride	46·5 ± 5·9	139·1 ± 11·1*
Calcium	4·0 ± 0·2	4·1 ± 0·5
Hydrogen	10·3 ± 3·6	8·5 ± 2·2

*$p < 0.0005$, paired t test.
Conversion: SI to traditional units—Sodium, potassium, chloride, hydrogen: 1 mmol/day = 1 mEq/day. Calcium: 1 mmol/day = 2 mEq/day.

istration of muzolimine an appropriate period was allowed for stabilisation, which was considered to be satisfactory when body weight and plasma urea concentration were constant and the magnitude of changes in urinary sodium excretion did not exceed 20% in three consecutive days. In the last day of the stabilisation period basal 24-hour urine volume and urinary excretions of sodium, potassium, chloride, calcium, and hydrogen ions were measured. Plasma concentrations of sodium, potassium, chloride, and bicarbonate ions and urea, uric acid, and glucose were determined together with red and white blood cell counts and activities of aspartate and alanine transaminases. Body weight and supine blood pressure were measured and creatinine clearance calculated.

Muzolimine was started in a single daily dose given by mouth in the morning. Since this drug had not been used before in renal failure, the dosage was determined empirically for each patient using urine volume and salt excretion as guidelines. The initial dose was never lower than 1 mg/kg body weight; during treatment the dosage never exceeded 5 mg/kg body weight/day. Systemic blood pressure, body weight, and urinary excretory rates were monitored daily during treatment (experimental period) and for two days after the drug was stopped. Blood analyses and measurement of creatinine clearance were repeated at the end of the experimental period. In these studies any drug was stopped if this could be done without lessening medical care. Thus spironolactone was not stopped in some patients with nephrotic syndrome (cases 9, 14, and 17) and antihypertensive drugs were not stopped in cases of severe hypertension. These drugs, however, were maintained at the same dosage throughout the stabilisation and experimental periods.

COMPARISON BETWEEN MUZOLIMINE AND FRUSEMIDE

The effects of muzolimine and frusemide were compared in four patients (table II). All these patients required immediate and vigorous diuretic treatment because of severe fluid overload (anasarca) with respiratory distress due to cardiac failure or pleural effusion, or both. Thus high doses of intravenous frusemide were administered for one to two days. Since this treatment was unsuccessful, muzolimine was given in the hope of avoiding haemodialysis. Any drug treatment needed in addition to diuretics was continued unchanged during this study. Patients were maintained on a diet containing 20 mmol (mEq) sodium daily; 24-hour salt and water excretions were noted the day before and during treatment with both diuretics.

Student's paired t test was used for statistical analysis.

Results

EFFICACY OF MUZOLIMINE

Diuretic effects—In this study muzolimine was administered for a mean of 9·3 days. During treatment mean daily urinary output was about twice the basal value, excretions of sodium and chloride were almost three times the basal values, and potassium excretion was increased significantly, while only slight, non-significant changes were observed in calcium and hydrogen excretions (table III). The potency of the diuretic effect of muzolimine was further shown by the significant fall that occurred in mean body weight (from 73·3 ± SE 2·8 to 67·5 ± 2·5 kg, $p < 0.001$) and by the complete disappearance of oedema in all affected patients. The increases in urine volume and salt excretion on the first and last days of treatment were similar. No rebound phenomenon was observed in the first two days after the drug was stopped (fig 2).

Effects on blood pressure—Treatment with muzolimine was followed by a decrease in blood pressure in all hypertensive patients. Mean blood pressure was normalised in five out of seven hypertensive patients given muzolimine alone and in 10 out of 11 patients in whom muzolimine was added to their previous antihypertensive treatment (fig 3).

Effects on blood composition—Treatment with muzolimine caused a rise in both urea and uric acid concentrations, while the plasma creatinine concentration and creatinine clearance remained unchanged. Serum chloride concentration was significantly reduced, while serum concentrations of bicarbonate, sodium, potassium,

calcium, and glucose were not significantly modified (table IV). No pathological change occurred in red and white blood cell counts or serum transaminase activities.

Dosage—An inverse, though rough, correlation between dosage and creatinine clearance was found retrospectively. The mean daily dose was 1·8 mg/kg body weight in nine patients with creatinine clearances of 20-30 ml/min, 2·4 mg/kg body weight in five patients with creatinine clearances of 10-19 ml/min, and 4·6 mg/kg body weight in six patients with creatinine clearances below 10 ml/min.

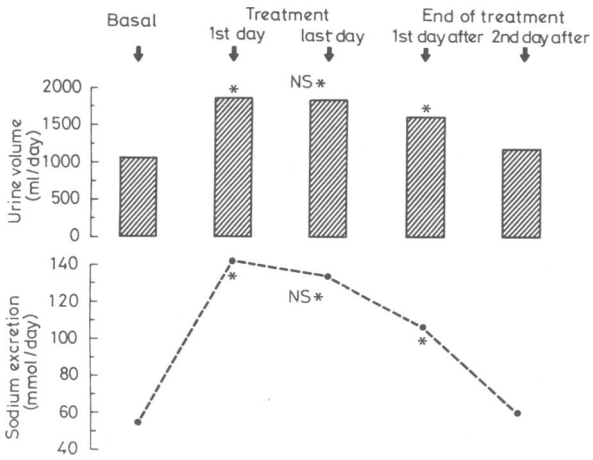

FIG 2—Mean urine volume and sodium excretion on first and last days of muzolimine administration and on first two days after end of treatment.
*p < 0·001 compared with basal value.
NS = Not significant when compared with result obtained on first day of treatment.
Conversion: SI to traditional units—Sodium: 1 mmol/day = 1 mEq/day.

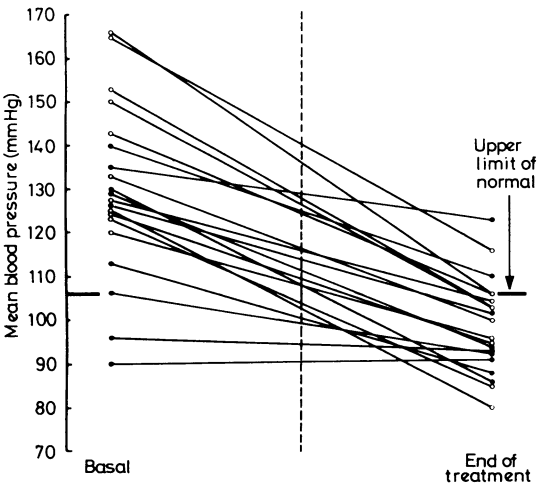

FIG 3—Effect of muzolimine on mean blood pressure.
● = Patients treated with only muzolimine. O = Patients treated with muzolimine and other antihypertensive agents.

TABLE IV—*Effects of muzolimine on plasma composition and creatinine clearance. (Figures are means ± SEM)*

	Basal values	Values at end of treatment
Urea (mmol/l)	25·1 ± 0·3	34·6 ± 0·3†
Uric acid (μmol/l)	452·1 ± 29·7	582·9 ± 23·7†
Sodium (mmol/l)	141·1 ± 0·8	139·6 ± 1·1
Potassium (mmol/l)	4·5 ± 0·2	4·1 ± 0·1
Chloride (mmol/l)	99·6 ± 0·8	95·4 ± 1·9*
Bicarbonate (mmol/l)	24·0 ± 1·4	24·5 ± 1·2
Calcium (mmol/l)	1·99 ± 0·75	2·06 ± 0·75
Glucose (mmol/l)	4·99 ± 0·33	5·55 ± 0·44
Creatinine (μmol/l)	698·4 ± 176·8	583·4 ± 79·6
Creatinine clearance (ml/min)	16·8 ± 1·5	15·8 ± 1·9

Significance of difference from basal values: *p < 0·05; †p < 0·001 (paired *t* test).
Conversion: SI to traditional units—Urea: 1 mmol/l ≈ 6 mg/100 ml. Uric acid: 1 μmol/l ≈ 16·8 μg/100 ml. Sodium, potassium, chloride, bicarbonate: 1 mmol/l = 1 mEq/l. Calcium: 1 mmol/l = 2 mEq/l. Glucose: 1 mmol/l ≈ 18 mg/100 ml. Creatinine: 1 μmol/l ≈ 11·3 μg/100 ml.

COMPARISON WITH FRUSEMIDE

Muzolimine raised sodium excretion and urine output in all four patients previously treated unsuccessfully with frusemide (fig 4). Sodium excretion was 45·0 ± SE 16·5 mmol/24 hours under basal conditions, 55·8 ± 18·4 mmol/24 hours during administration of frusemide ($p > 0·5$), but 178·0 ± 24·4 mmol/24 hours ($p < 0·05$) during treatment with muzolimine.

This rise in sodium and water excretion reversed respiratory distress and appreciably reduced peripheral oedema, so that haemodialysis was no longer necessary.

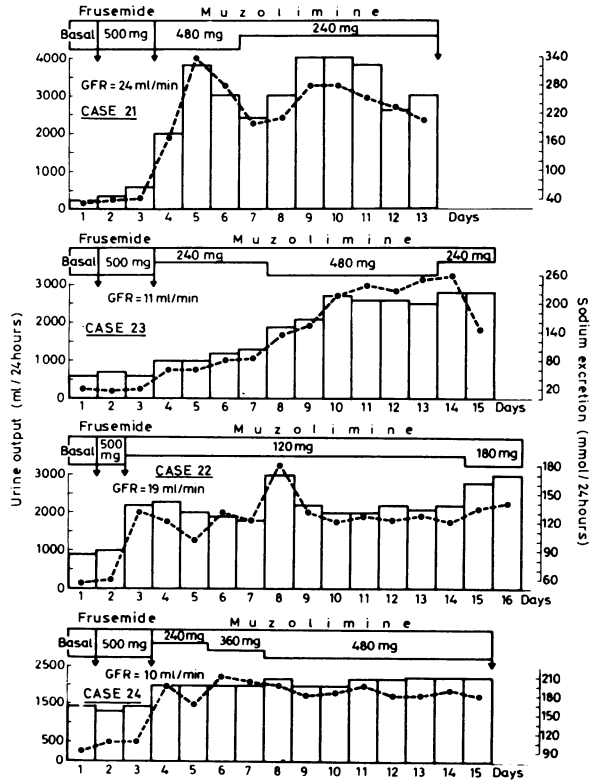

FIG 4—Effects of muzolimine on urine output and sodium excretion (● - - - ●) in four patients previously treated with intravenous frusemide.
GFR = Glomerular filtration rate.
Conversion: SI to traditional units—Sodium: 1 mmol/24 hours = 1 mEq/24 hours.

ADVERSE REACTIONS

Muscle cramps occurred in three patients (cases 2, 3, and 19) in the final days of treatment but disappeared soon after the drug was stopped. Fasting blood glucose concentration increased from 4·88 mmol/l (87·8 mg/100 ml) to 10·99 mmol/l (197·8 mg/100 ml) in a diabetic patient receiving insulin (case 12).

Discussion

It is widely accepted that salt retention and extracellular fluid volume expansion play a key part in the pathophysiology of hypertension secondary to chronic renal failure.[8 9] Hence the treatment of uraemic hypertension must rely on the correction of salt retention.

We normalised systemic blood pressure in our uraemic patients by increasing salt excretion with muzolimine; this occurred both in cases of previously untreated hypertension,

when muzolimine was given alone (cases 2, 5, 9, 12, and 20), and in cases of severe hypertension refractory to conventional antihypertensive agents, when muzolimine was added to the treatment already being given (cases 3, 4, 6, 7, 10, 11, 15, 16, 18, and 19).

Nephrotic syndrome, congestive heart failure (during the whole course of chronic renal failure), and the striking fall in urine output (in far-advanced chronic uraemia) are all responsible for salt retention and oedema requiring diuretic treatment. In all our uraemic patients with oedema administration of muzolimine resulted in complete resolution of the oedema; salt and water excretions increased considerably after adequate oral doses of the drug, despite creatinine clearances as low as 4 ml/min.

This favourable diuretic effect was obtained with single daily doses of the drug taken by mouth usually in the morning. No rebound phenomenon occurred at the end of the treatment. No adverse reactions were observed, apart from muscle cramps in three patients presumably secondary to excessive salt depletion.

The increase in potassium but not calcium excretion after administration of muzolimine appears particularly advantageous in patients with advanced uraemia because of their tendency to hyperkalaemia and hypocalcaemia. The significant fall in serum concentration of chloride observed at the end of treatment may reflect a primary effect of the drug on chloride reabsorption in Henle's loop.[10]

Renal function was not modified by muzolimine as shown by the constancy in creatinine clearance. Nevertheless, plasma concentrations of urea and uric acid were significantly increased, as is commonly observed after diuretic treatment in uraemic patients. This may be accounted for by a rise in tubular reabsorption of urea and uric acid secondary to the extracellular fluid volume contraction. A direct effect of the drug on tubular function, however, cannot be excluded.

These studies give convincing evidence that muzolimine is a potent diuretic extremely effective in treating salt retention in patients with advanced renal failure. It may even be preferable to other high-ceiling diuretics, such as frusemide: muzolimine given by mouth appeared to be effective in treating salt retention refractory to high intravenous doses of frusemide.

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Ipratropium bromide in acute asthma

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Abstract

Ipratropium bromide was given to patients admitted to hospital with acute asthma. A cumulative-dose-response technique in six patients showed that 500 μg given by nebuliser produced a maximal increase in peak expiratory flow rate. This dose of ipratropium bromide was included in a regimen in which it was given either two hours before or two hours after nebulised salbutamol to 22 patients. Ipratropium bromide given on admission was as effective as nebulised salbutamol. The two drugs in sequence produced greater bronchodilatation than either used alone, and the mean peak expiratory flow rate rose by 96% in four hours.

Thus giving ipratropium bromide in addition to salbutamol in severe asthma enhances the bronchodilator effect. Further studies are needed to determine whether the same effect may be obtained by giving two maximal doses of salbutamol two hours apart.

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Introduction

Inhaled atropine-like compounds are useful in treating airflow obstruction in chronic bronchitis and asthma. The latest preparation available is ipratropium bromide. It produces appreciable bronchodilatation but, on the whole, not as much as salbutamol. Ipratropium bromide and salbutamol in combination have an additive effect,[1] but some studies have failed to show this.[2 3] In these trials ipratropium bromide was given from a pressurised aerosol to patients with asthma, but not during an acute attack. Bronchodilators given from aerosol canisters are not particularly effective in severe asthma, but when given by nebuliser without positive pressure they are as effective as when given intravenously.[4 5] We studied the use of nebulised ipratropium bromide in acute asthma and compared it with nebulised salbutamol.

Patients and methods

We studied 28 patients (18 women and 10 men) aged 15-79 years admitted to hospital with an acute attack of asthma. Twenty-one were atopic. All had an arterial oxygen pressure of under 9·3 kPa (68 mm Hg) and a peak expiratory flow rate of less than 25% of the predicted value. Measurements of peak expiratory flow rate were made throughout with a Wright peak flow meter, the best of three readings being taken.

Selection of the dose of ipratropium bromide—A cumulative-dose