Amiloride prevents amphotericin B related hypokalaemia in neutropenic patients

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SUMMARY Twenty neutropenic patients with various haematological disorders were randomised prospectively to receive either intravenous amphotericin B alone or amphotericin B and oral amiloride 5 mg twice a day for treatment of confirmed or suspected fungal infection. Patients receiving amiloride had a significantly higher plasma potassium ($p < 0.01$), a significantly lower urinary potassium loss ($p < 0.01$), and required significantly less potassium chloride supplementation to maintain their plasma potassium within the normal range ($p < 0.001$). Amiloride was well tolerated, had no clinically important side effects, and provided effective control of plasma potassium in patients treated with amphotericin B.

Invasive fungal infections are an important cause of morbidity and mortality in neutropenic patients. Amphotericin B is the most effective drug currently available for the management of systemic fungal infections in such patients, but nephrotoxicity is a major limiting factor in its use.¹ The nephrotoxic effects of amphotericin B are due to combined actions on both the glomeruli and renal tubules. In particular, selective distal tubular epithelial toxicity seems to be, at least in part, responsible for the profound potassium wasting which is a major clinical side effect of treatment with amphotericin B.²⁻⁴

Recent studies have also shown that amphotericin B also affects sodium flux in both the distal and transverse human colon, suggesting a further site of changed sodium/potassium exchange in patients treated with this agent.⁵

The management of potassium wasting induced by amphotericin B may be difficult, and even large intravenous doses of potassium chloride may not be fully effective in correcting the hypokalaemia. As a consequence, clinical problems, especially muscle weakness and cardiac arrhythmias, are seen in a proportion of patients.

Amiloride, a pyrazine derivative, is a potassium sparing diuretic widely used in clinical practice. It increases urinary excretion of sodium and bicarbonate while decreasing urinary potassium excretion by the distal convoluted tubule.⁶ Amiloride also has actions outside the kidney and inhibits sodium absorption

from the distal colon. Furthermore, the action of amiloride on this site potentially antagonises the effects of amphotericin B.⁵

The aim of this study was to determine whether amiloride could prevent the hypokalaemia associated with treatment with amphotericin B.

Patients and methods

Twenty consecutive neutropenic (absolute neutrophil count $< 0.5 \times 10^9/l$) patients with various haematological disorders were entered into the study over six months. The study was approved by the appropriate local ethical committees and all patients gave informed written consent. The indications for amphotericin B treatment were either evidence of invasive fungal infection diagnosed by biopsy and culture, or fever unresponsive to five days of broad spectrum antibiotics in the presence of continuing neutropenia.⁷

On entry into the study patients were randomised to receive either amphotericin B alone intravenously or amphotericin B intravenously with oral amiloride 5 mg twice a day. Both groups received identical combinations of broad spectrum antibiotics before entry into the study, and there was no difference in aminoglycoside administration between the two groups. Broad spectrum antibiotics were continued throughout amphotericin B treatment in all but two patients. All patients received a standard hospital diet containing 40 mmol potassium/day except one patient (case 9) in the group taking amphotericin alone who required parenteral feeding.

Patients with an initial serum creatinine concentration of $> 200 \mu\text{mol/l}$ and those taking cyclosporin A for graft versus host disease after allogeneic bone marrow transplantation were excluded from entry into the study.

DRUG ADMINISTRATION

Amphotericin B was administered by slow intravenous injection in 5% dextrose over six hours. On day 1 a 1 mg test dose was given intravenously over two hours followed by 4 mg intravenously over the next four hours. On day 2 the dose of amphotericin B given was increased to 0.25 mg/kg, again given over six hours. On day 3 and thereafter the dose was maintained at 0.5 mg/kg body weight a day. Amiloride (5 mg) was administered orally at 9.00 am, one hour before amphotericin B administration and at 9.00 pm five hours after amphotericin B administration had been completed.

ELECTROLYTE MEASUREMENTS

Plasma potassium, sodium, and creatinine were measured daily on a sequential multiple analysis/computer (Technicon). Daily 24 hour urinary potassium was measured using a flame photometric method. (Instrumentation laboratories 143). Serum magnesium was measured using an atomic absorption spectrophotometer.

Plasma potassium, total oral, and intravenous potassium supplementation per day and 24 hour urinary potassium losses were measured for patients in both groups.

POTASSIUM SUPPLEMENTATION

Group taking amphotericin alone

Oral potassium chloride was given if plasma potassium fell below 3.5 mmol/l. Initially 48 mmol of oral potassium chloride were given every 24 hours and this

was increased to 96 mmol after 24 hours if plasma potassium remained below 3.5 mmol/l.

Group taking amphotericin and amiloride

Potassium chloride (48 mmol) was given at the start of amphotericin treatment if the plasma potassium was 3 mmol/l or lower. During treatment with amphotericin, oral supplements were given to maintain the plasma potassium at 3.5 mmol/l, or if the observed trend in plasma potassium predicted a fall below 3.5 mmol/l.

If oral supplementation was inadequate or poorly tolerated in either group then intravenous potassium chloride was given and requirements titrated to maintain a plasma potassium above 3.5 mmol/l.

Amphotericin B treatment was discontinued when a full course of treatment had been completed for documented fungal infection or when neutrophil recovery and defervescence of fever had occurred in those patients treated on an empirical basis.

Results were analysed statistically using the Mann-Witney U test.

Results

The two patient groups studied were broadly similar in terms of age, underlying haematological diagnosis, and duration of amphotericin B treatment (tables 1 and 2).

Plasma potassium, urinary potassium losses, and daily potassium requirements for the patients receiving amphotericin B alone and patients receiving amphotericin B with amiloride are shown in tables 1 and 2, respectively. Plasma potassium was significantly higher in the group receiving amiloride. ($p < 0.01$), while potassium supplementation was significantly higher in the group receiving amphotericin alone ($p < 0.001$).

Table 1 *Patient characteristics of group taking amphotericin alone*

Case No	Age (years)	Diagnosis	Plasma potassium (mmol/l)					Mean 24 hour urinary excretion/day
			Days on amphotericin B treatment at 0.5 mg/kg/day	Range of plasma	Mean plasma	Range of daily supplements/day	Mean daily supplements/day	
1	39	ALL	13	3.0-4.8	3.70	0-124	71	54.1
2	60	AML	12	2.9-4.8	3.58	32-153	94	69.3
3	61	AML	11	2.5-3.5	3.09	217-358	243	111.0
4	56	AML	8	3.3-4.7	3.98	48-96	90	106.9
5	49	AML	14	2.4-4.9	3.57	60-180	106	90.8
6	43	AML	11	3.1-3.8	3.40	88-144	113	137.2
7	47	AML	7	1.8-2.3	2.12	80-360	194	56.4
8	56	AML	5	2.5-3.7	3.14	40-240	113	92.0
9	74	HD	4	2.9-3.6	3.32	96-150	109	
10	18	ALL	15	2.5-4.7	3.58	100-280	169	120.8

ALL = Acute lymphoid leukaemia

AML = Acute myeloid leukaemia

HD = Hodgkin's disease

Table 2 Patient characteristics of group taking amphotericin and amiloride

Plasma potassium (mmol/l)								
Case No	Age (years)	Diagnosis	Days on amphotericin B treatment at 0.5 mg/kg/day	Range of plasma	Mean plasma	Range of daily supplements/day	Mean daily supplements/day	Mean 24 hour urinary excretion/day
1	19	ALL	8	1.9-3.8	2.78	48-96	88	64.0
2	62	AML	4	3.1-4.6	3.80	0	0	38.3
3	66	AML	3	2.8-4.6	3.73	16-48	26.6	42.0
4	18	ALL	7	4.0-5.1	4.62	0	0	100.3
5	55	MDS	21	3.1-5.3	4.25	0	0	17.1
6	61	CLL	3	3.6-4.8	4.20	0-32	10.6	38.3
7	65	AML	8	3.9-5.2	4.47	0	0	49.2
8	35	AML	9	3.2-4.3	3.77	16-64	41.7	65.1
9	57	MM	5	3.5-4.4	3.80	0-52	18.4	48.0
10	56	AML	11	2.9-3.8	3.43	0-48	32	30.0

ALL = Acute lymphoid leukaemia
AML = Acute myeloid leukaemia
MDS = Myelodysplastic syndrome
CLL = Chronic lymphatic leukaemia
MM = Multiple myeloma

Four patients receiving amiloride required no potassium supplementation during amphotericin B treatment and of the six remaining patients, only two required intravenous potassium supplementation. In contrast, all patients receiving amphotericin B alone required potassium supplementation with nine patients requiring intravenous potassium. Urinary losses of potassium were significantly higher in patients treated with amphotericin B alone when compared with patients receiving additional amiloride ($p < 0.01$). Observed ranges in plasma potassium, 24 hour urinary potassium losses, and daily potassium

supplementation for each group are summarised in the figure.

Daily potassium balance was calculated for the two groups from measurements of daily potassium intake and daily urinary potassium losses. Patients receiving amphotericin alone showed an apparent mean daily positive potassium balance of 79.3 mmol (range +23 mmol to +172 mmol) while the group receiving additional amiloride showed a paradoxically smaller daily gain of 13.6 mmol (range -60 mmol to +66 mmol).

SIDE EFFECTS

There was no clinically important side effects in the group receiving additional amiloride. Four patients developed clinically unimportant hyponatraemia with the lowest recorded plasma sodium in the range 128-125 mmol/l. Three patients in each group had a minor rise in serum creatinine which did not lead to suspension of treatment. Hypomagnesaemia requiring correction with intravenous magnesium developed in two patients receiving amphotericin B alone and in one patient receiving amphotericin B and amiloride.

Discussion

Severe hypokalaemia is the most serious side effect of amphotericin B treatment.³ The correction of hypokalaemia is difficult and may require up to 300 mmol of potassium chloride replacement a day. Oral potassium chloride supplementation in high doses is often poorly tolerated in neutropenic patients due to associated mucositis, and large intravenous doses of potassium chloride requiring careful monitoring are therefore necessary. An agent that safely decreases potassium requirements in this group of patients would thus be clinically useful. This study has shown

Figure Median and range of plasma potassium, 24 hour urinary potassium excretion, and daily potassium supplements for both groups.

that amiloride significantly reduces the potassium supplementation required in patients receiving short or prolonged periods of treatment with amphotericin B.

Amiloride seems to act on transport proteins affecting the active movement of ions across cell membranes. The potassium sparing effect of amiloride on renal excretion is thought to be due to blockage of sodium reabsorption in the distal renal tubule rather than to a direct effect on potassium secretion.⁶ Although not specifically addressed in the present study, this distal tubular effect is probably responsible for the reduction by amiloride of urinary potassium losses in subjects treated with amphotericin B.

The well recognised renal action of amiloride does not, however, provide a complete explanation of our data. In particular, patients receiving amphotericin B alone seem to be in gross positive potassium balance, using only urinary losses to calculate daily potassium balance. Potassium retention at this level seems unlikely in the face of the low plasma potassium concentrations observed. A more likely explanation is that potassium loss from the gastrointestinal tract in neutropenic patients is significant even in the absence of gastrointestinal symptoms. In support of this contention is the recent demonstration that amphotericin B affects ion exchange in the colon in man and that this action is potentially antagonised by amiloride. We are currently investigating the effects of amphotericin B and amiloride on gastrointestinal potassium excretion in both neutropenic patients and in a non-neutropenic control group.

The predicted effects of amiloride on plasma sodium were, mild and did not result in clinically important hyponatraemia. Renal magnesium wasting also occurs in patients treated with amphotericin B and the associated clinical problems are well recognised.^{8,9} Amiloride has been shown to decrease renal magnesium excretion in studies on animals,¹⁰ and our preliminary data suggest that amiloride may also

reduce the urinary magnesium losses seen with treatment amphotericin B in man.

Amiloride was well tolerated by all patients and produced no clinically important side effects. Oral amiloride therefore provides a safe alternative to high dose intravenous potassium replacement in patients undergoing treatment with amphotericin B.

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