The urinary sodium : potassium ratio and response to diuretics in resistant oedema

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Summary

Nineteen patients with severe oedema due to either cirrhosis of the liver or to congestive cardiac failure, who had failed to respond to previous diuretic therapy, were treated with either increasing doses of frusemide (Group A), or with frusemide in a fixed dose of 80 mg daily and increasing doses of spironolactone (Group B). In Group A there was an inverse correlation between the baseline 24-hr urinary sodium:potassium (Na : K) ratio and the 24-hr urinary potassium excretion during diuresis, and a direct correlation between the urinary Na : K ratio before and after diuresis. Thus, in patients of this group during diuresis, there was a significantly higher urinary potassium excretion in those with a baseline urinary Na : K ratio of <1 , as compared with those with a ratio of >1 . In Group B a satisfactory diuresis was achieved without marked urinary potassium loss in those patients with a baseline urinary Na : K ratio of <1 , whereas no diuresis was obtained in the two patients with a baseline urinary Na : K ratio of >1 . These results suggest that the measurement of the baseline urinary Na : K ratio is of help in determining the potential value of spironolactone in patients with resistant oedema.

Introduction

The treatment of patients with sodium retention has been greatly improved since the introduction of powerful 'loop' diuretics such as frusemide (Stason *et al.*, 1966; Verel *et al.*, 1964). However, there is a wide variation in response between subjects and it is not uncommon to find patients who do not sustain

a satisfactory diuresis with standard doses of frusemide. Higher doses of the drug may produce electrolyte imbalance, notably hypokalaemia which is of particular significance in patients with liver disease (Read *et al.*, 1954) and those patients receiving digoxin (Kleiger, Vitale and Brown, 1965). One important factor which determines the variability of the response to diuretics is the level of endogenous mineralocorticoid secretion. The urinary potassium content and sodium : potassium (Na : K) ratio of normal subjects given a thiazide diuretic has been found to reflect exogenous or endogenous mineralocorticoid activity (Edmonds and Wilson, 1960): when such activity was elevated, the subjects had a low urinary Na : K ratio with a poor natriuresis and considerable urinary potassium losses; when mineralocorticoid activity was low the urinary Na : K ratio was elevated and the subjects sustained a good natriuresis with little increase in urinary potassium loss. Similar results have been obtained when the response of oedematous patients to thiazide diuretics was studied (Edmonds, 1960).

The object of the present study was to assess whether measurement of the urinary Na : K ratio in oedematous patients, unresponsive to their current therapy, was of value in predicting their response to either increasing doses of frusemide or to the combination of frusemide and spironolactone.

Patients and methods

Patients (Table 1)

Patients in hospital with marked fluid retention and a plasma creatinine below $150 \mu\text{mol/l}$ were studied over an initial 3-day period during which their treatment remained unchanged. If they failed to achieve a satisfactory diuresis, defined as a weight-loss $>0.5 \text{ kg/day}$ maintained for 48 hr, they were randomly allocated to one of two treatment regimes (see below), and the initial 3-day period used as a baseline. Nineteen patients were studied, four on more than one occasion.

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Treatment

(i) *Group A.* Patients received frusemide 80 mg given once daily, increasing to 160 mg/day and then to 250 mg/day at 3-day intervals, unless a satisfactory diuresis was achieved. Patients in this group also received 3.6 g KCl as 'Slow K' daily (48 mEq K).

(ii) *Group B.* Patients received 80 mg frusemide given once daily and spironolactone in an initial dose of 100 mg b.d. increasing to 200 mg b.d. if a satisfactory diuresis was not achieved within 3 days.

All patients received a normal ward diet without added salt.

Investigations

Daily fluid intake and urinary volume were recorded by the nursing staff. Patients were weighed daily by one of the authors at the same time each day. Blood for estimation of sodium and potassium was collected on alternate days. Twenty-four hour urinary sodium and potassium were measured daily. Sodium and potassium were measured by flame photometry by the routine chemical pathology laboratory. The results of the mean of each 3-day period are presented in Fig. 1.

Results

All patients in Group A responded to increasing doses of frusemide, only two requiring more than 160 mg daily (Table 1). In Group B, all except two patients responded to the combination of frusemide and spironolactone, the majority with a dose of spironolactone 200 mg daily, although two patients required 400 mg daily. The two who failed to respond to this regime subsequently responded to frusemide alone in a dose of 160 mg daily (Table 1). The

variation in sodium excretion produced by the different diuretic regimes was wide (Fig. 1).

In Group A patients there was an inverse correlation between the baseline urinary Na : K ratio and the mean 24-hr urinary potassium excretion during diuresis ($r = -0.715$; $P < 0.01$), and a positive correlation between the Na : K ratio before and after satisfactory diuresis ($r = 0.73$; $P < 0.01$) (Fig. 2). No such correlations were found in Group B (Fig. 3). The two patients in this group who did not sustain a diuresis were the only two who had urinary Na : K ratios > 1.0 (2.2 and 3.9).

FIG. 1. 24-hr urinary sodium levels (mean of 3 days) before and after effective diuretic therapy.

FIG. 2. Relationships between the mean baseline urinary Na : K ratio and the mean 24-hr urinary potassium excretion and Na : K ratio during diuresis in Group A patients. Frusemide; ●—●, cardiac failure; ×—×, chronic liver disease.

TABLE 1. Clinical details of patients studied and their response to therapy

Group	Age of patient (years)	Sex	Diagnosis	Initial therapy	Ultimate effective diuretic therapy	Weight loss during diuresis (kg/day)	
A	47	M	Cirrhosis	F 40 mg+Slow K 2.4 g	F 80 mg+Slow K 3.6 g	1.0	
	52	F	CCF	Digoxin 0.25 mg	F 80 mg+Slow K 3.6 g	1.0	
	51	F*	CCF	F 120 mg+Slow K 3.6 g	F 250 mg+Slow K 3.6 g	0.5	
	60	M*	Cirrhosis	F 80 mg+Slow K 1.8 g	F 160 mg+Slow K 3.6 g	0.5	
	54	F	Cirrhosis	F 80 mg+Slow K 3.6 g	F 160 mg+Slow K 3.6 g	0.5	
	86	M	CCF	B 5 mg+Slow K 3.6 g	F 80 mg+Slow K 3.6 g	0.75	
	64	F	Cirrhosis	F 80 mg+Slow K 3.6 g	F 160 mg+Slow K 3.6 g	0.75	
	65	F	CCF	F 80 mg+Slow K 3.6 g	F 160 mg+Slow K 3.6 g	0.8	
	60	M	CCF	F 80 mg+Slow K 3.6 g	F 160 mg+Slow K 3.6 g	0.5	
	64	F	CCF	F 80 mg+Slow K 3.6 g	F 160 mg+Slow K 3.6 g	0.75	
	60	M	CCF	F 80 mg+Slow K 3.6 g	F 250 mg+Slow K 3.6 g	0.8	
	64	M	Cirrhosis	F 80 mg+Slow K 3.6 g	F 160 mg+Slow K 3.6 g	1.0	
	B	41	M	Cirrhosis	F 80 mg+Slow K 3.6 g	F 80+SL 400mg	0.75
		49	M	CCF	F 80 mg+Slow K 3.6 g	F 80+SL 200 mg	0.8
51		F*	CCF	F 80 mg+Slow K 3.6 g	F 80+SL 200 mg	1.0	
51		F	CCF	F 120 mg+Slow K 3.6 g	F 80+SL 400 mg	0.5	
60		M*	Cirrhosis	F 80 mg+Slow K 1.8 g	F 80+SL 200 mg	0.6	
60		M	CCF	F 80 mg+Slow K 1.8 g	F 80+SL 200 mg	0.5	
70		F	CCF	F 80 mg+Slow K 3.6 g	F 80+SL 200 mg	0.75	
52		M	Cirrhosis	F 80 mg+Slow K 3.6 g	F 80+SL 200 mg	0.5	
63		M	CCF	F 160 mg+Slow K 3.6 g	F 80+SL 200 mg	0.8	
†		60	M	CCF	F 80 mg+Slow K 3.6 g	No response	—
†		64	M	Cirrhosis	F 80 mg+Slow K 3.6 g	No response	—

* Patients studied on two separate occasions.

B, Bendroflumethiazide.

F, Frusemide.

SL, Spironolactone.

CCF, Congestive cardiac failure.

† For ultimate effective therapy see Group A.

FIG. 3. Relationships between the mean baseline urinary Na : K ratio and the mean 24-hr urinary potassium and Na : K ratio during diuretic therapy in Group B patients. Frusemide + spironolactone; ●—●, cardiac failure; ×—×, chronic liver disease.

In Group A, both baseline urinary potassium excretion and urinary Na excretion achieved during diuresis were unrelated to the baseline urinary Na : K ratio. Patients with an initially low urinary Na : K ratio showed a considerably increased urinary potassium loss during diuresis ($P<0.001$) as compared with their baseline levels. Patients with an

initial Na : K ratio >1.0 showed a lesser though still significant increase ($P<0.05$) in urinary potassium excretion. The difference in urinary potassium levels during diuresis between these two groups of patients was highly significant ($P<0.003$) (Table 2).

The initial urinary sodium and potassium levels and the urinary sodium content achieved during

TABLE 2. Comparison of the mean 24-hr urinary sodium and potassium levels of patients with baseline urinary Na : K ratios < 1.0 with those > 1.0 after treatment with frusemide alone (Group A)

Baseline urinary Na : K ratio	Mean daily urinary sodium (mEq/24 hr)		Mean daily urinary potassium (mEq/24 hr)	
	Baseline ($\pm$ s.d.)	During diuresis ($\pm$ s.d.)	Baseline ($\pm$ s.d.)	During diuresis ($\pm$ s.d.)
< 1 ($n=7$)	28 ($\pm$ 24)	153 ($\pm$ 42)	42 ($\pm$ 19)	95 ($\pm$ 18)
> 1 ($n=5$)	81 ($\pm$ 19)	163 ($\pm$ 43)	38 ($\pm$ 7)	53 ($\pm$ 9)

* Matched pairs *t*-test.

TABLE 3. Comparison of the mean 24-hr urinary sodium and potassium levels before and after treatment with increasing doses of frusemide (Group A) or the combination of frusemide and spironolactone (Group B) in patients with baseline urinary Na : K ratios < 1.0

Treatment group	Mean daily urinary sodium (mEq/24 hr)		Mean daily urinary potassium (mEq/24 hr)	
	Baseline ($\pm$ s.d.)	During diuresis ($\pm$ s.d.)	Baseline ($\pm$ s.d.)	During diuresis ($\pm$ s.d.)
A ($n=7$)	28 ($\pm$ 24)	153 ($\pm$ 42)	42 ($\pm$ 19)	95 ($\pm$ 18)
B ($n=9$)	25 ($\pm$ 21)	156 ($\pm$ 65)	44 ($\pm$ 19)	59 ($\pm$ 21)

* Matched pairs *t*-test.

diuresis were similar when patients with a baseline urinary Na : K ratio < 1.0 in Group A were compared to those with a baseline Na : K ratio < 1.0 in Group B. There was, however, a significant difference in urinary potassium levels during diuresis between the two groups ($P < 0.001$) (Table 3). It must be remembered, however, that all patients in Group A, but not those in Group B, were receiving potassium supplements of 48 mEq daily. No significant changes were observed in serum Na or K in any patient during the study.

Discussion

With the introduction of potent oral diuretics, the problem of treating patients with fluid retention resistant to therapy is becoming less common. However, diuretic therapy of patients who fail to respond to thiazide or low dose frusemide therapy is potentially hazardous owing to the risk of inducing excessive losses of potassium with higher doses. The rationale for giving spironolactone to such patients is to counteract secondary hyperaldosteronism. Direct measurement of plasma aldosterone and aldosterone secretion rates in oedematous patients with congestive cardiac failure has not produced consistent results. Aldosterone activity has not been found to be consistently raised and neither has any correlation been found between aldosterone activity and the response of patients to spironolactone (Thomas and Bartter, 1961); Sanders and Melby, 1964; Bartter, 1964). We studied the 24-hr urinary Na : K ratio because it has been considered to be useful as an indirect assessment of mineralocorticoid activity (Adamson and Jamieson,

1972; Milly, Thomas and Williamson, 1961) and is a simple and inexpensive measurement within the scope of any chemical pathology department.

In the patients receiving incremental doses of frusemide, the baseline urinary Na : K ratio correlated positively with the Na : K ratio and negatively with the urinary potassium excretion once diuresis had been achieved. Thus a high urinary potassium loss could have been predicted in those with a baseline Na : K ratio of < 1.0. It was of interest, in this relatively small series, that patients with oedema due to cirrhosis of the liver and those with congestive cardiac failure appeared to respond similarly to frusemide. In contrast, it has previously been suggested that the diuretic response of patients with hepatic disease may be closely related to the level of endogenous mineralocorticoid secretion (Eggert, 1970), whereas this is less important in patients with oedema due to cardiac failure (Thomas and Bartter, 1961; Sanders and Melby, 1964; Bartter, 1964).

The baseline urinary Na : K ratio was also of help in assessing the response of patients treated with frusemide and spironolactone. Thus, all the patients treated with a possible increased endogenous mineralocorticoid secretion, as indicated by a baseline Na : K ratio of < 1.0, sustained a satisfactory diuresis on this regime. The two patients with a high Na : K ratio did not respond to this combination of diuretic drugs, although they subsequently responded to high doses of frusemide alone. There was no correlation in patients receiving spironolactone and frusemide together between the baseline urinary Na : K ratio and the urinary

potassium levels and the Na : K ratio during diuresis.

In conclusion, it is suggested that the measurement of a 24-hr urinary Na : K ratio provides a rapid and easily measured index with which to modify a diuretic regime which is not effective. If the urinary Na : K ratio is <1.0 , the addition of spironolactone to the pre-existing therapy should be the treatment of choice. It is effective and prevents the excessive urinary potassium loss that occurs if such patients are given larger doses of frusemide. In patients with baseline urinary Na : K ratios >1.0 , spironolactone may be ineffective and higher doses of frusemide produce a satisfactory diuresis without excessive urinary potassium loss.

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