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WHY DIURETIC TREATMENT INCREASES AZOTAEMIA IN PATIENTS WITH CHRONIC GLOMERULONEPHRITIS

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Summary

The mechanism of diuretic-induced increased azotaemia was studied in three groups of patients with chronic glomerulonephritis and renal failure (GFR = 10–40ml/min), that were treated with frusemide (F), 50–250mg/day, for six days. *Group 1:* Nine patients, clearance of creatinine (C_{cr}) and of urea (C_{urea}), filtered urea ($Urea_F$), urinary urea excretion ($Urea_E$) and body urea nitrogen appearance (UNA) were measured daily, before and after frusemide. *Group 2:* 10 patients, C_{cr}, C_{urea} and osmolar clearance were measured before frusemide, in the last day of frusemide and three days after its interruption, during maximal water diuresis, to calculate proximal tubular reabsorption (R_{prox}). *Group 3:* seven patients were studied as in Group 1, but extracellular fluid volume depletion was prevented by daily oral replacement of Na^+ excreted in urine. In Group 1, frusemide raised plasma urea concentration from a mean control value of 126.3mg/100ml to 190.5mg/100ml in the last day of treatment ($p < 0.0005$). C_{urea} fell more than C_{cr}. $Urea_E$ decreased rapidly in the first three days of treatment and remained low thereafter, even if $Urea_F$ rose progressively throughout the treatment period. UNA was significantly increased in the first day of treatment. In Group 2, C_{urea} was markedly reduced in the last day of treatment, when R_{prox} was significantly decreased. In Group 3, none of the changes of Group 1 was observed. These results show that the rise in azotaemia is not due to a fall in GFR (as commonly believed), but to increased tubular reabsorption of urea in the distal part of the nephron. This effect depends on body fluid volume depletion.

Introduction

Diuretic therapy often increases azotaemia in patients with chronic renal failure. This phenomenon is currently believed to be the warning signal of a further reduction in GFR, secondary to extracellular fluid volume depletion.

We have noticed, however, that frequently this rise in azotaemia is not associated with a proportional increase in serum creatinine concentration. This

observation has prompted us to investigate the mechanisms of the diuretic-dependent increased azotaemia in patients with advanced renal disease.

Methods

Studies were carried out in 26 patients in which renal failure (GFR, 10–40ml/min) was secondary to chronic glomerulonephritis. All patients were moderately hypertensive. None had nephrotic syndrome, nor cardiac failure. In all patients, medication was discontinued and a period of stabilisation allowed. This was considered satisfactory when body weight and plasma urea concentration were constant for five consecutive days. Then, frusemide was administered for six days, daily dosage being adjusted in each patient to achieve a clinically evident diuresis, judged by a rise in urine volume and salt excretion. The dose used ranged from 50–250mg/day.

Patients were divided in three groups. *Group 1:* nine patients, clearance of creatinine (C_{cr}) and of urea (C_{urea}), urea filtration rate ($Urea_F$), urinary urea excretion ($Urea_E$) and body urea nitrogen appearance (UNA) were measured daily before and during frusemide administration. UNA was calculated according to Walser [1], as the sum of urea nitrogen in urine and the change in body urea nitrogen. The urea compartment was estimated as 60 per cent of body weight. *Group 2:* In 10 patients, C_{urea}, C_{cr} and osmolar clearance were measured before frusemide, in the last day of treatment, and three days after stopping, during maximal water diuresis. Water diuresis was induced by oral administration of 20ml/kg body wt of water in one hour, and was maintained by administration of an amount of water equal to urine flow plus 1ml/min to replace insensible losses [2]. After a steady state of urine flow had been obtained, two to three clearance studies (each 30 minutes long) were carried out. In water diuresis, fractional proximal tubular reabsorption (R_{prox}) could be calculated [3]:

$$R_{prox} = [(C_{cr} - V)/C_{cr}] \times 100$$

where V is urinary volume (in ml/min). *Group 3:* Seven patients were studied as in Group 1, but extracellular fluid volume depletion was prevented by careful daily replacement of urinary sodium losses.

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

Results

Group 1 Frusemide caused a rise in plasma urea concentration, from a mean basal value of 126.3 ± 46.7mg/100ml to 190.5 ± 64.8mg/100ml (mean ± SD) in the last day of treatment ($p<0.0005$). The effects of frusemide on creatinine clearance and renal handling of urea are shown in Table I. Both C_{cr} and C_{urea} were significantly lowered by diuretic treatment. The reduction in C_{urea}, however, was much more marked than C_{cr}, as shown by a significant fall in the ratio C_{urea}/C_{cr}. Urinary urea excretion decreased progressively in the first three days of treatment, remaining low thereafter. The amount of filtered urea rose progressively during frusemide administration. UNA was significantly increased from 7.45 ± 3.05 to 10.21 ± 4.43g/24h ($p < 0.025$) in the first day of treatment, but returned to control values in the following days.

TABLE I. Effects of frusemide on creatinine clearance and renal handling of urea

	Control	Days of treatment					
		1	2	3	4	5	6
C_{cr} (ml/min)	19.7 ±5.8	19.0 ±4.7	18.6* ±5.5	17.9* ±5.2	17.2** ±5.2	17.1** ±5.3	17.4** ±4.3
C_{urea} (ml/min)	10.0 ±4.0	8.4** ±4.2	6.7** ±1.9	5.2** ±1.3	4.9** ±1.1	5.5*** ±2.0	5.2*** ±1.5
C_{urea}/C_{cr}	0.46	0.42	0.36	0.32	0.31*	0.33***	0.30***
$Urea_E$ g/24h	17.4 ±6.8	14.6 ±6.0	13.5** ±3.9	11.4* ±2.2	11.5** ±2.6	13.7* ±5.3	13.6* ±4.7
$Urea_F$ g/24h	33.6 ±8.9	34.6 ±11.7	37.5* ±12.2	39.6* ±13.7	40.3 ±14.4	41.8*** ±11.5	45.7*** ±14.1

Values are mean ± SD
* $p < 0.05$; ** $p < 0.025$; *** $p < 0.01$

Group 2 The results of water diuresis studies are shown in Table II. Fractional reabsorption of water was significantly reduced in the last day of treatment, when C_{urea} was also markedly decreased. No significant change in R_{prox} was observed three days after interruption of treatment, while C_{urea} was still significantly lower than control.

TABLE II. Effects of frusemide on fractional proximal tubular reabsorption and urea clearance in water diuresis

	R_{prox} (%)	C_{urea} (ml/min)
Control	84.4 ± 6.2	16.5 ± 7.4
Last day of treatment	77.8 ± 7.5*	11.3 ± 5.3**
Three days after interruption	89.3 ± 4.1	13.6 ± 6.8*

Values are mean ± SD. * $p < 0.05$; ** $p < 0.01$
R_{prox} = fractional reabsorption of water in proximal tubule

Group 3 The results of this study are shown in Table III. In this Group, treatment with frusemide did not modify C_{cr}, C_{urea}, $Urea_E$, $Urea_F$ nor UNA. Plasma urea concentration remained unchanged too, averaging 107.9 ± 42.5mg/100ml in control condition and 108.4 ± 43.0mg/100ml in the last day of treatment.

TABLE III. Effects of frusemide on creatinine clearance and renal handling of urea in patients receiving a daily amount of Na^+ equal to that excreted in urine

	Control	Days of treatment					
		1	2	3	4	5	6
C_{cr} (ml/min)	22.3 ±8.1	25.9 ±13.3	23.5 ±9.9	23.1 ±10.6	26.0 ±9.7	26.3 ±13.5	23.6 ±10.9
C_{urea} (ml/min)	12.8 ±6.0	12.0 ±5.0	10.9 ±4.8	11.4 ±6.0	13.5 ±4.5	14.2 ±8.0	12.9 ±6.9
$Urea_E$ g/24h	17.4 ±3.3	17.7 ±2.8	16.7 ±4.7	16.6 ±4.1	19.2 ±4.9	18.9 ±5.8	16.7 ±3.2
$Urea_F$ g/24h	30.9 ±4.1	37.4 ±8.3	35.2 ±7.8	33.6 ±6.6	36.1 ±8.7	34.5 ±12.7	30.3 ±4.1

Values are mean ± SD

Discussion

This study confirms that diuretic treatment increases plasma urea concentration in patients with chronic renal failure. Group 1 studies clearly indicate that this increase in azotaemia is mainly secondary to a fall in urinary excretion of urea. This, however, is not due (as commonly believed) to a fall in GFR, since it occurs even if the amount of filtered urea is increased. Therefore, increased tubular reabsorption of urea must account for the phenomenon. In addition to this mechanism, a transitory increase in UNA may contribute to the rise in azotaemia.

Group 2 studies were undertaken to obtain information about which segment of the nephron is the site of increased tubular reabsorption of urea. Clearance studies in water diuresis were used for this purpose, assuming that 1) in this condition proximal reabsorption of water can be calculated [3] and 2) in the proximal tubule the rate of urea reabsorption is proportional to that of water [4]. The results show that proximal water reabsorption is impaired during diuretic treatment, and thus suggest that also proximal reabsorption of urea is decreased. Therefore, the marked reduction in C_{urea} taking place during therapy with frusemide should depend upon increased reabsorption (or reduced excretion) of urea in the distal part of the nephron.

Group 3 studies exclude that changes in tubular handling of urea are the consequence of a direct, pharmacologic action of frusemide on the tubule. The fall in urea excretion, in fact, did not occur in patients treated with frusemide, in which extracellular fluid volume depletion was prevented by salt administration.

The mechanism by which volume depletion increases urea reabsorption (or reduces urea excretion) in the distal nephron is not apparent from the present study. Animal studies, however, have shown that the principal site of tubular regulation of urea excretion is the collecting duct [5]. In this tubular segment, urea reabsorption should be passive and mainly secondary to that of water. Therefore, a rise in salt and water reabsorption in collecting duct, caused by extracellular volume depletion [6], might also increase urea reabsorption.

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