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Sensitivity of residual nephrons to high dose furosemide described by diuretic efficiency

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Abstract Ten haemodialysis (HD) patients with a median residual creatinine clearance (CL_{CR}) of 1.9 ml · min^{-1} · 1.73 m^{-2} (range 0.6–5.3) were treated with oral furosemide (F) 2.0 g. Overall-efficiency (O-E, daily sodium excretion/total urinary F) and total-efficiency (Δ-E, increase in daily sodium excretion/total urinary F) were measured on the last 24 hours of each interdialysis interval. In addition, O-E was measured during the complete interdialysis interval in 10 HD patients with a median CL_{CR} of 5.6 ml · min^{-1} · 1.73 m^{-2} (range 0.7–6.8) treated for 1 year with a fixed oral dose of F between 250–1000 mg (median 625 mg).

In the short study the median O-E was 10.6 mmol · mg^{-1} (range 1.9–22.0) and Δ-E 6.2 mmol · mg^{-1} (range 1.3–11.2). The fractional excretion of sodium FE_{Na} was significantly increased from 9.6 % (range 4.1–22.9) to 27 % (range 14.6–56.2) during F treatment. A positive correlation was found between the basal FE_{Na} and Δ-E. In the long-term study median O-E was 6.4 mmol · mg^{-1}. O-E and FE_{Na} showed no change over time although median RCC decreased from 5.6 to 1.9 ml · min^{-1} · 1.73 m^{-2} and median F excretion from 11.8 to 7.5 mg per day.

It can be concluded that diuretic efficiency in haemodialysis patients is dependent on FE_{Na} and the state of hydration during the interdialysis interval.

Key words Furosemide, Haemodialysis; creatinine clearance, renal excretion, diuretic efficiency

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Furosemide is known to be effective in patients with end stage renal failure [1]. Previous studies have demonstrated that loop diuretics in high doses are even effective in chronic haemodialysis patients with residual renal function [2–6]. The diuretic response in relation to the excretion of furosemide has not been determined in these patients. The pharmacodynamics of loop diuretics are best assessed by relating the urinary excretion of the loop diuretic to the response, since it is the diuretic in the tubular urine that blocks electrolyte reabsorption in the loop of Henle [7, 8]. This diuretic response can be quantified in several ways, including urine volume, sodium excretion, fractional excretion of sodium (FE_{Na}) and chloride excretion [8]. Recently, the concept of the ratio of the sodium to furosemide excretion rate has been proposed to describe the efficiency of the drug [7, 9, 10]. When measured in patients with moderate renal insufficiency, the relationship between the urinary excretion rate of furosemide and FE_{Na} is comparable to that in normals [11, 12]. The upper plateau of response amounts to a FE_{Na} of 20–25 % [13]. However, so far no data have been published about the response of loop diuretics quantified as diuretic efficiency and FE_{Na} in chronic haemodialysis patients still producing some urine. Urine volume in haemodialysis patients with residual renal function decreases just after dialysis and increases during the interdialysis interval. A clearer understanding of the pharmacodynamics of furosemide in end stage renal disease would aid in the diuretic management of haemodialysis patients.

The aim of this study was to determine the diuretic efficiency and FE_{Na} during the last day of the interdialysis interval after treatment with high dose furosemide. The second objective was to determine the efficiency of the diuretic on separate days in the interdialysis interval during long term follow-up. Therefore, a short study was carried out in which haemodialysis patients were treated daily with oral furosemide 2.0 g. A long-term study was then done in which patients were treated with a fixed dose of furosemide of 250–1000 mg daily.

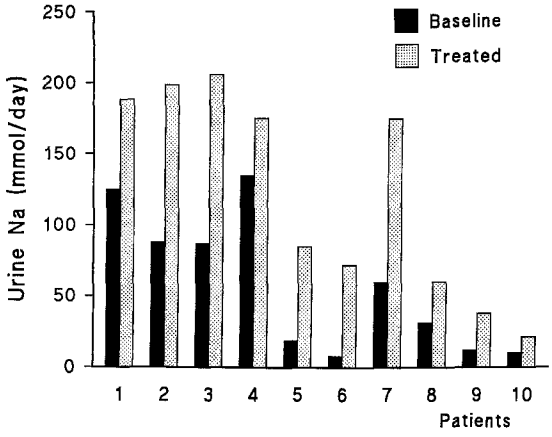

Fig. 1 Short study: mean sodium excretion by 10 patients during the control period (baseline) and during therapy with furosemide 1 g bd (treated). The dose of furosemide had to be reduced to 500 mg daily in Patients 1 and 2 because of signs of dehydration. Then numbers of the patients correspond to Table 1

Patients and methods

Informed consent was obtained from all patients, after approval by the local hospital Committee on Medical Ethics. The study was done simultaneously with investigations of the pharmacodynamic actions and adverse effects of high dose furosemide in chronic haemodialysis patients. Those results have already been published [6].

Short study

Ten haemodialysis patients (4 females) with a mean residual creatinine clearance of 1.9 ml · min^{-1} · 1.73 m^{-2} (range 0.6–5.3) and a urine production of at least 100 ml per day were studied. Their primary renal diseases were tubulointerstitial nephritis (4), chronic glomerulonephritis (2), renal vascular disease (2), adult polycystic kidney disease (1) and lupus nephritis (1). Their mean age was 64 years (range 49–79 y). Participants were in a stable condition with a median time on haemodialysis of 30 months (range 5–103 months). All patients were able to collect urine accurately. In all patients voiding took place by spontaneous emptying of the bladder. Urine was collected in opaque containers. After a control period of one week the patients were treated with orally 1 g furosemide (Lasix Forte^{P} P 500 mg, Hoechst twice daily) for 1 week. The patients were instructed to keep to a diet containing 60 mmol sodium and 40 mmol potassium. Fluid intake was restricted to daily volume of urine produced. These dietary restrictions were started from the commencement of the haemodialysis treatment, and were stable for each patient. Urine volume, sodium and furosemide were measured in the last 24 h collection of the interdialysis interval during the control period and when they were treated with furosemide. The urine values represent the mean of the two collection days in each period. Urine sodium was measured by Autoanalyser and urinary furosemide concentration was determined by an HPLC method [14]. Diuretic response was expressed as daily sodium excretion, or as FE_{Na}, defined as:

$$FE_{Na}(\%) = \frac{U_{Na} \times P_{CR}}{P_{Na} \times_{CR}} \times 100 \quad (1)$$

where U_{Na} is urine sodium concentration (mmol/l), U_{Cr} is urine creatinine concentration (mmol · l^{-1}), P_{Na} is plasma sodium concentration (mmol · l^{-1}) and P_{Cr} is the plasma creatinine concentration (mmol/l).

Long-term study

Thirteen haemodialysis patients with a residual creatinine clearance of 4.9 ml · min^{-1} · 1.73 m^{-2} (range 0.7–6.8) were studied for one year. Their primary renal diseases were tubulointerstitial nephritis (4), chronic glomerulonephritis (2), renal vascular disease (4), lupus nephritis (1), and unkown (2). Their mean age was 66 years (range 50–77 y). They had been on chronic haemodialysis for a median of 15 months (range 4–88 months). Dependent on their diuretic response in a period of dose finding, they were treated with a fixed oral dose of furosemide 250–1000 mg each day. Three patients received 250 mg, another three 500 mg, one 750 mg, and six 1000 mg furosemide daily. Furosemide 250 mg was given once a day, and the higher doses were divided into 2 equal doses given in the morning and the afternoon. The patients were instructed to keep to a diet containing 60 mmol sodium and 40 mmol potassium, and fluid intake was restricted to mean daily volume of urine producted. Urine was collected in opaque containers by spontaneous voiding, in three 24-hour collection periods during the longest dialysis-free interval. After a control period of one interdialysis interval, urine volume, sodium, creatinine and furosemide excretion were measured at monthly intervals during the first 3 months, and 3-monthly in the next period. Residual renal function was determined by calculating endogenous creatinine clearance using the mean urinary creatinine excretion from the 24-hour collections during the complete interdialysis interval and the mean plasma creatinine values at the end and the beginning of the dialysis on each side of the urine collection period [14].

Efficiency of furosemide

Efficiency represents how much effect is obtained per unit of stimulus as a function of stimulus (C) [10]. The concept of efficiency can be derived from the sigmoid E_{max} model (the Hill equation; [7, 10, 16, 17]). Diuretic efficiency (Eff) can be calculated as:

$$Eff = \frac{E - E_0}{C} = \frac{E_{max} \cdot C^{S-1}}{C_{50\%}^{S} + C^{S}} \quad (2)$$

in which E is the diuretic effect on sodium excretion, E_0 is the basal sodium excretion, E_{max} is the maximum drug-induced sodium excretion, C represents the urinary furosemide excretion rate, $C_{50\%}$ is the furosemide excretion rate associated with half-maximal induced diuresis, and S is a fitting parameter known as slope factor [18]. A total or time-averaged diuretic efficiency can be calculated from:

$$Total\text{-}Eff = \frac{\int_0^{24} (E - E_0)\, dt}{\int_0^{24} Cdt} = \frac{total\ induced\ diuresis\ (24\,h)}{total\ furosemide\ excretion\ (24\,h)} \quad (3)$$

The ratio between the total excretion of sodium, and that of furosemide was used to describe the overall diuretic efficiency [7]:

$$Overall\text{-}Eff = \frac{\int_0^{24} (E + E_0)\, dt}{\int_0^{24} Cdt} = \frac{total\ diuresis\ (24\,h)}{total\ furosemide\ excretion\ (24\,h)} \quad (4)$$

The total-Eff and overall-Eff were used in the short study. Only overall-Eff was used in the long-term study because E_0 could not be followed over the one year period of furosemide treatment.

Statistical analysis

The nonparametric two-sided Wilcoxon and Spearman test were used to analyse urine parameters in the short and long-term studies because the data in this population were not normally distributed. Values on the three individual days of the interdialysis interval in the long-term study of each patient are expressed as mean (SD). Differences between the days of the dialysis-free interval were examined with the paired Student's *t* test.

Table 1 Short study: underlying renal disease, residual creatinine clearance (CL_{CR}), median urinary furosemide excretion (mg/day, percentage of the oral dose), fractional sodium excretion (FE_{Na}) during control period (C) and during exposure to furosemide (E), overall and Δ-efficiency during exposure to furosemide (2000 mg/day)
RVD, renal vascular disease; TIN, tubulointerstitial nephritis; CGN, chronic glomerulonephritis; APKD, adult polycystic kidney disease; LE, lupus nephritis

Patient	Disease	CL_{CR} ml · min^{-1} · 1.73m^{-2}	Urine F		FE_{Na}(%)		Efficiency (mmol · mg^{-1})	
			mg per day	%	C	E	overall	total
1[a]	RVD	5.3	13	1.2	9.5	26.7	14.5	7.3
2[a]	TIN	5.2	19	1.5	9.6	14.6	11.8	7.0
3	TIN	3.6	18	0.9	13.3	27.2	9.4	5.4
4	TIN	2.8	20	1.0	5.6	23.9	5.7	4.6
5	CGN	1.9	16	0.8	5.5	21.3	5.2	4.0
6	RVD	1.8	39	2.0	4.1	15.9	1.9	1.6
7	TIN	1.7	10	0.5	22.9	56.2	22.0	11.2
8	APKD	0.9	4	0.2	14.6	37.4	14.8	6.9
9	CGN	0.6	4	0.2	15.8	36.2	11.8	8.2
10	LE	0.6	6	0.3	8.5	40.9	2.6	1.3
Median		1.9	14.5	1.0	9.6	27.0*	10.6	6.2

$P < 0.005$; [a] Dose of F had to be reduced from 2000 mg to 500 mg/day

Table 2 Long-term study ($n = 10$): residual creatinine clearance (CL_{CR}), urinary volume, cumulative (Na) and fractional sodium (FE_{Na}) excretion, furosemide excretion, and overall-efficiency (O-E) during the pretreatment period and during 12 months with fixed-dose furosemide (250–1000 mg); median (range) compared with pretreatment levels, furosemide excretion and O-E compared with 1 month of treatment

Months	CL_{CR} ml · min^{-1} · 1.73m^{-2}	Volume ml per day	Na mmol per day	FE_{Na} [%]	Furosemide mg per day	O-E mmol · mg^{-1}
0	5.6 (0.7–6.8)	750 (120–1290)	37 (6–68)	6.2 (1.7–24.0)		
1	5.7 (0.8–7.0)	1110*(220–1580)	64*(22–143)	12.2**(6.1–37.6)	11.8 (3.0–61.3)	5.1 (2.0–16.0)
2	6.0 (1.0–6.8)	1050* (200–1500)	66* (17–132)	12.0** (6.2–31.6)	15.0 (1.3–31.6)	5.4 (2.1–20.6)
3	4.5**(0.6–6.4)	1250*(200–1840)	75*(16–115)	13.1** (4.3–31.7)	11.9 (2.1–33.4)	6.3 (1.9–15.6)
6	4.3**(0.6–6.3)	960*(180–1580)	54*(12–142)	13.5**(4.6–31.9)	8.9**(1.9–26.8)	5.5 (2.1–17.9)
9	3.2**(0.5–6.0)	630 (140–1580)	40 (9–155)	12.7**(4.5–30.6)	7.9*(1.4–26.6)	7.0 (1.1–17.9)
12	1.9**(0.5–5.9)	710 (180–1820)	41 (9–153)	11.1**(3.4–34.1)	7.5*(1.1–27.2)	6.2 (1.1–22.4)

* $P < 0.005$, ** $P < 0.02$

Results

Short study

All patients showed greater natriuresis during furosemide treatment (Fig. 1). The dose of furosemide had to be reduced to 500 mg in the two patients with the highest creatinine clearance (5.3 and 5.2 ml · min^{-1} · 1.73 m^{-2}) because of signs of dehydration. The median increase in sodium excretion was 64 mmol/day (range 11–140) and in urinary volume it was 560 ml per day (range 140–1030 ml per day). Individual baseline sodium excretion rates varied in relation to the residual creatinine clearance (r 0.73, $P < 0.02$). As shown in Table 1, the median urine furosemide excretion was 14.5 mg per day (range 4–39 mg per day) and median total efficiency was 6.2 mmol · mg^{-1} (range 1.3–11.3 mmol · mg^{-1}). The median FE_{Na} increased from 9.6 % (range 4.1–22.9 %) in the control period to 27.0 % (range 14.6–56.2 %) during furosemide treatment ($P < 0.005$). Six patients had an FE_{Na} above 25 % during furosemide treatment. A positive correlation was found between basal FE_{Na} and the total-efficiency (r 0.81, $P < 0.01$) and the overall-efficiency (r 0.85, $P < 0.01$). No relationship was found between the efficiency of furosemide and creatinine clearance, basal sodium excretion, underlying renal disease or furosemide excretion. A positive correlation was found between furosemide excretion, expressed as percentage of the oral dose, and the residual creatinine clearance (r 0.76, $P < 0.05$). No relation was found between furosemide excretion and the underlying renal disease.

Long-term study

Ten of the 13 patients were followed for 1 year. The study was discontinued in 3 patients because of kidney transplantation (1), cerebrovascular accident (1) and bullous dermatosis (1). The effect of furosemide administration on median urinary volume, sodium and furosemide excretions, and overall efficiency are shown in Table 2. An initial rise in urine production and sodium excretion during the first 3 months was followed by a gradual reduction. The FE_{Na} increased from 6.2 % (range 1.7–24.0) to 12.2 % (range 6.1–37.6) after 1 month of treatment with furosemide and remained stable during the 12 months follow up. The overall efficiency did not change with time, although the median creatinine clearance and furosemide excretion both decreased. A positive correlation was found between the basal FE_{Na} and the overall efficiency at 1 month (r 0.66, $P < 0.05$), and between the residual creatinine clearance and furosemide excretion expressed as a per-

Table 3 Long-term study: residual creatinine clearance (CL_{CR}) from the start (S) and the end (E) of follow up period during 12 months, underlying renal disease (D), and furosemide dose; mean values of urinary furosemide concentration ([F]), urinary furosemide excretion (F), and overall-efficiency (O-E) during the first (A), second (B) and third (C) day of all interdialysis intervals during the 12 months follow up. Mean (SD), days B and C were compared with A

Pt	CL_{CR}		D	F dose	A			B			C		
	S	E		mg per day	[F] mg · l^{-1}	F mg per day	O-E mmol · mg^{-1}	[F] mg · l^{-1}	F mg per day	O-E mmol · mg^{-1}	[F] mg · l^{-1}	F mg · day^{-1}	O-E mmol · mg^{-1}
1	6.6	5.9	UK	250	12.0 (7.1)	13.5 (4.5)	4.2 (1.7)	9.0 (5.6)	11.5 (6.0)	7.6 (4.0)	7.1 (2.3)	12.4 (7.3)	10.4 (4.2)
2	5.9	5.0	TIN	250	8.5 (4.8)	9.4 (4.1)	8.6 (5.1)	8.2 (3.9)	11.0 (5.1)	10.7 (6.0)	7.2 (3.6)	11.0 (4.7)	12.4 (7.1)
3	4.2	1.6	CGN	500	18.3 (5.1)	10.6 (3.0)	1.8 (1.0)	12.3 (3.0)	11.8 (1.8)	4.1 (2.1)	8.9 (3.4)	9.3 (4.0)	5.8 (1.8)
4	6.8	2.2	RVD	500	28.0 (2.9)	22.1 (9.2)	1.4 (0.5)	29.5 (6.2)	28.3 (9.1)	1.9 (0.7)	27.6 (9.8)	25.0 (6.3)	1.9 (0.9)
5	6.8	5.0	RVD	500	19.3 (1.7)	19.9 (5.3)	4.1 (1.0)	15.4 (1.9)	18.8 (2.7)	5.8 (0.9)	12.8 (2.6)	19.5 (6.8)	6.5 (1.4)
6	5.2	1.7	TIN	1000	14.5 (2.7)	12.9 (7.2)	4.6 (0.7)	12.3 (4.3)	12.3 (8.4)	7.2 (2.5)	9.3 (2.3)	10.3 (4.1)	9.5 (3.1)
7	0.7	0.5	CGN	1000	12.3 (8.3)	4.0 (3.0)	10.2 (4.6)	9.3 (4.7)	3.3 (2.1)	12.4 (6.7)	10.1 (7.1)	3.7 (3.3)	15.3 (9.2)
8	1.4	0.8	RVD	1000	8.2 (3.1)	1.8 (0.6)	12.5 (5.7)	5.1 (1.5)	1.6 (0.9)	20.2 (4.0)	4.4 (0.9)	1.9 (0.5)	23.8 (5.6)
9	0.9	0.5	TIN	1000	17.1 (7.8)	3.1 (1.9)	4.1 (1.7)	12.6 (9.8)	2.5 (2.5)	9.0 (3.6)	12.9 (11.3)	2.8 (3.3)	6.5 (2.5)
10	5.9	5.4	UK	1000	23.2 (12.9)	23.8 (13.8)	4.6 (1.6)	20.1 (9.3)	31.5 (23.0)	5.4 (1.5)	20.7 (8.4)	32.2 (16.3)	5.2 (1.3)
Mean					16.1	12.1	5.6	13.4*	13.3	8.4*	12.1#	12.8	9.7*
SD					6.3	7.9	3.6	7.0	10.3	5.2	7.0	10.0	6.3

* $P < 0.005$, ** $P < 0.001$

RVD, Renal vascular disease; CGN, chronic glomerulonephritis; TIN, tubulointerstitial nephritis; UK, unkown

centage of the oral dose (r 0.83, $P < 0.01$). The mean urinary furosemide concentration, furosemide excretion and overall efficiency on the three days of all the interdialysis intervals during the 12 month follow up of the patients are shown in Table 3. During the interdialysis interval the mean urinary furosemide concentration decreased from 16.1 (6.3) to 12.1 (7.0) $\mu g \cdot ml^{-1}$ ($P < 0.05$). However, the daily furosemide excretion remained stable, due to an increase in urine volume on the second and third days of the interdialysis interval. The mean daily overall efficiency increased from 5.6 (3.6) to 9.7 (6.3) mg/mmol ($P < 0.05$) due to an increase in sodium excretion and unchanged excretion of furosemide.

Discussion

The main findings in the short study were that urine volume and sodium excretion during the interdialysis interval were increased by high dose furosemide. A strong positive correlation was found between diuretic efficiency and basal FE_{Na}, but the converse relationship was found between diuretic efficiency and the basal diuresis and sodium excretion, creatinine clearance, and cumulative furosemide excretion. Thus, the patient with the highest basal FE_{Na} had the highest diuretic efficiency (Patient 7, Table 1) but with moderate cumulative excretion of furosemide. On the other hand, the patient with the lowest basal FE_{Na} had very low diuretic efficiency and the highest cumulative excretion of furosemide.

The 'efficiency' of furosemide describes the relationship between the diuretic effect and excretion of the drug. This diuretic parameter is dependent on time, different modes of administration, and is strongly influenced by the state of hydration [19–21]. Our results seem to indicate that the efficiency of furosemide in end-stage renal disease is mainly related to basal FE_{Na} rather than cumulative furosemide excretion, although the rate profile of furosemide excretion could not be determined in this study. Unfortunately, different fluid replacement patterns and urinary collection periods in the different studies make comparison of diuretic efffficiency between studies unreliable [9].

The FE_{Na} increased above 25 % in six patients, and even up to 56.2 % in one patient. The high FE_{Na} may indicate that the remaining tubules were subject to an extremely large solute load, causing high fluid pressure in the tubules. Such functional adaptations occur in surviving nephrons as chronic renal disease advances. They are called the "magnification phenomenon" and may be responsible for the hypertrophy and hyperplasia of the proximal convoluted tubules in end stage renal disease [22, 23].

The long-term study showed that the overall efficiency and FE_{Na} remained stable, even though the urine volume, sodium and furosemide excretion decreased during the one year follow up. The slow decrease with time

of the diuretic response to the fixed dose of furosemide appears to be fully explained by the measured decrease in renal function caused by progression of the underlying renal disease. Earlier investigations in hypertensive patients without renal disease showed an impaired natriuretic response to furosemide during prolonged diuretic therapy [24]. Adaptation at the distal convoluted tubule and beyond could account for the reduced effect during diuretic therapy [20]. We assume that the distal convoluted tubule is unable to adapt to furosemide therapy in patients with end stage renal disease.

Adequate hydration by sodium and fluid replacement in healthy volunteers resulted in a greater diuretic response to furosemide than in volunteers with sodium depletion [20]. The last day of the interdialysis interval is usually a time of slight overhydration. As a consequence, the overall efficiency increased during the interdialysis interval due to the increase in sodium excretion.

Furosemide is a weak acid and is secreted by the anionic secretory pathway in the proximal tubules [25]. Competition for this pathway with exogenous organic acids in normals, and with endogenous organic acids in renal insufficiency, may lead to diuretic resistance [26, 27]. The positive correlation between residual creatinine clearance and furosemide excretion in the urine as a percentage of the oral dose in the short and long-term studies illustrates the relationship between the proximal tubular secretion of organic acids and residual renal function. Accumulation of organic acids during the interdialysis interval should result in a decrease in the secretion of furosemide. In this study, however, the total daily urinary furosemide excretion at the end of the interdialysis interval did not change during the study.

In conclusion, the study has shown that the functioning nephrons in end stage renal disease remain sensitive to furosemide reaching the tubules. The fractional sodium excretion by the residual nephrons and the state of hydration during the interdialysis interval are the main determinants of diuretic efficiency in patients on chronic haemodialysis.

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