Proc EDTA (1982) Vol 19

DOPAMINE-FRUSEMIDE THERAPY IN ACUTE RENAL FAILURE

G Graziani, S Casati, **A Cantaluppi**, A Citterio, A Aroldi, A Scalamogna, D Brancaccio*, C Ponticelli

Ospedale Maggiore Policlinico, and
**Ospedale San Paolo, Milano, Italy*

Summary

In 16 patients with ARF and in three with hepatorenal syndrome we infused dopamine (3μg/kg/min) and frusemide (10–15mg/kg/day) for 6–24 hours. This treatment produced in all patients a significant diuresis and natriuresis without any modification of blood pressure, pulse rate, and central venous pressure. In three patients with hepatorenal syndrome diuresis was established during dopamine and frusemide infusion, but severe oliguria again reappeared when drug infusion was stopped. This experience suggests that this therapy may avoid fluid overload and hyperkalaemia in oliguric patients reducing the need for dialysis. It is also the first successful approach in the treatment of hepatorenal syndrome although its effect is transient.

Introduction

Experimental studies have shown that dopamine in subpharmacological doses interacts with specific dopaminergic intrarenal receptors causing a reduction in renal vascular resistance and improvement of cortical vasculature [1]. On the other hand, frusemide produces intrarenal vasodilating prostaglandin synthesis with consequent redistribution of blood flow from the medulla to the cortex in hypoperfused kidneys [2–4]. Therefore, dopamine in low dose combined with frusemide seems to be a rational prophylactic measure whenever oliguria occurs. Indeed the combination of the two drugs is able to prevent anuria in dogs intoxicated with uranyl nitrate [5]. Extensive experience is still lacking in man. Talley et al [6] reported five patients in whom combined dopamine and diuretic therapy was used; more recently Henderson et al [7] obtained a diuresis in 11 oliguric patients, unresponsive to mannitol and frusemide, after low dose dopamine infusion.

We report here our experience with the association of low dose dopamine and frusemide in 19 anuric patients: 15 with post-operative oligoanuria, one with

post-partum oliguria, and three with hepatorenal syndrome. All these patients did not respond to hypertonic mannitol and high dose frusemide infusion.

Patients and methods

Nineteen oliguric patients were investigated: in one patient oliguria occurred after delivery, in 15 after surgical operation and three cirrhotic patients developed progressive oliguria with urinary sodium excretion less than 10mmol/L.

In no patient was anuria due to water-electrolyte imbalances. Twenty per cent mannitol (200ml) and frusemide (400–800mg) were administered intravenously in all cases, but failed to improve diuresis in any patient. After a period of documented oliguria (less than 30ml/hr) ranging from 6 to 36 hours, dopamine (1–3 μg/kg/min) and frusemide (10–15mg/kg/day) were infused from 6 up to 24 hours.

Fluid administration was regulated in order to keep central venous pressure between 5 and 10cmH_2O.

The mean and standard deviation (SD) values of urine output, central venous pressure (CVP), blood pressure (BP) and urinary sodium excretion, measured every hour for six hours before and 12 hours after therapy, were recorded. The statistical analysis was performed by Student's t-test for paired observations.

Results

The infusion of dopamine and frusemide produced a significant diuresis (from 12.2 ± 8.8 to 100.4 ± 28.1ml/hr; $p < 0.001$) and natriuresis (from 30.5 ± 13.2 to 81.8 ± 27.4mmol/L; $p < 0.001$) without any variation in systolic BP, CVP, and pulse rate (Table I). It is important to stress that in patients with post-operative and post-partum oliguria the withdrawal of therapy was not followed by a failure of diuresis. The three patients with hepatorenal syndrome showed a dopamine-frusemide dependence, since oliguria immediately recurred after stopping the infusion (Figure 1). Of interest was the observation that in all these cases, the restarting of dopamine-frusemide administration was accompanied by restoration of diuresis and natriuresis, during the period of infusion, and again oliguria reappeared after withdrawal of treatment.

Five out of 16 patients with post-operative and post-partum oligoanuria required dialysis, in spite of persistent polyuria. Six patients died from complications unrelated to acute renal failure (ARF). Two out of three patients with hepatorenal syndrome died because of hepatic coma, and the other one died because of bleeding oesophageal varices a few days later.

Discussion

Patients with hypoperfused kidneys who are oliguric after correction of hypovolaemia and infusion of hypertonic mannitol or frusemide are candidates for dialysis. Our results show that the association of high dose frusemide and low dose dopamine may still promote a diuresis in these cases. Indeed, in 19 patients

TABLE I. Clinical details and response to treatment of 15 post-operative oliguric patients and one post-partum ARF

Number	Age (years)	Surgical operation	Diuresis ml/hr B	Diuresis ml/hr A	Urinary Na mmol/L B	Urinary Na mmol/L A	Systolic blood pressure mmHg B	Systolic blood pressure mmHg A	CVP cm H_2O B	CVP cm H_2O A	Pulse rate beat/min B	Pulse rate beat/min A	Dialysis	Outcome
1	56	Splenorenal shunt	20	130	30	113	140	130	2	3	112	108	–	Alive
2	65	Aortic graft	14	80	–	62	100	105	9	9	96	100	PD	Alive
3	58	Colectomy	20	122	44	68	75	100	7	8	102	104	HD	†Septic shock
4	49	Colectomy	16	87	39	78	100	110	8	8	104	98	–	Alive
5	44	Aortic graft	15	110	36	78	90	120	5	7	98	124	PD	†Septic shock
6	57	Aortic graft	30	120	33	90	90	120	9	9	140	124	–	Alive
7	43	Pancreatectomy	1	70	46	90	160	160	–	–	92	96	–	Alive
8	45	Renal auto TX	4	66	41	102	105	100	5	5	98	98	–	Alive
9	65	Colectomy	1	100	9	75	120	125	2	2	120	116	–	†Sepsis
10	77	Gastrectomy	15	80	29	74	130	105	5	5	118	88	–	Alive
11	62	Aortic graft	0	150	–	–	80	100	10	9	120	112	–	Alive
12	53	Hepatectomy	1	90	48	90	105	110	3	3	96	96	HD	†Sepsis
13	68	Colectomy	10	140	10	70	130	130	10	11	100	102	–	Alive
14	72	Colectomy	15	90	12	82	120	125	11	10	98	96	–	†Septic shock
15	63	Hepatectomy	18	120	20	94	140	135	5	5	84	80	–	†Peritonitis
16	26	Post-partum ARF	17	52	31	126	105	110	–	–	76	84	PD	Alive
MEAN			12	100	31	82	112	118	6	7	101	102		10/16 Alive
STANDARD DEVIATION			9	28	13	27	24	16	3	3	21	13		
p			< 0.001		< 0.001		NS		NS		NS			

B = before therapy; A = after therapy; TX = transplantation; ARF = acute renal failure; CVP = central venous pressure; PD = peritoneal dialysis; HD = haemodialysis; † = dead

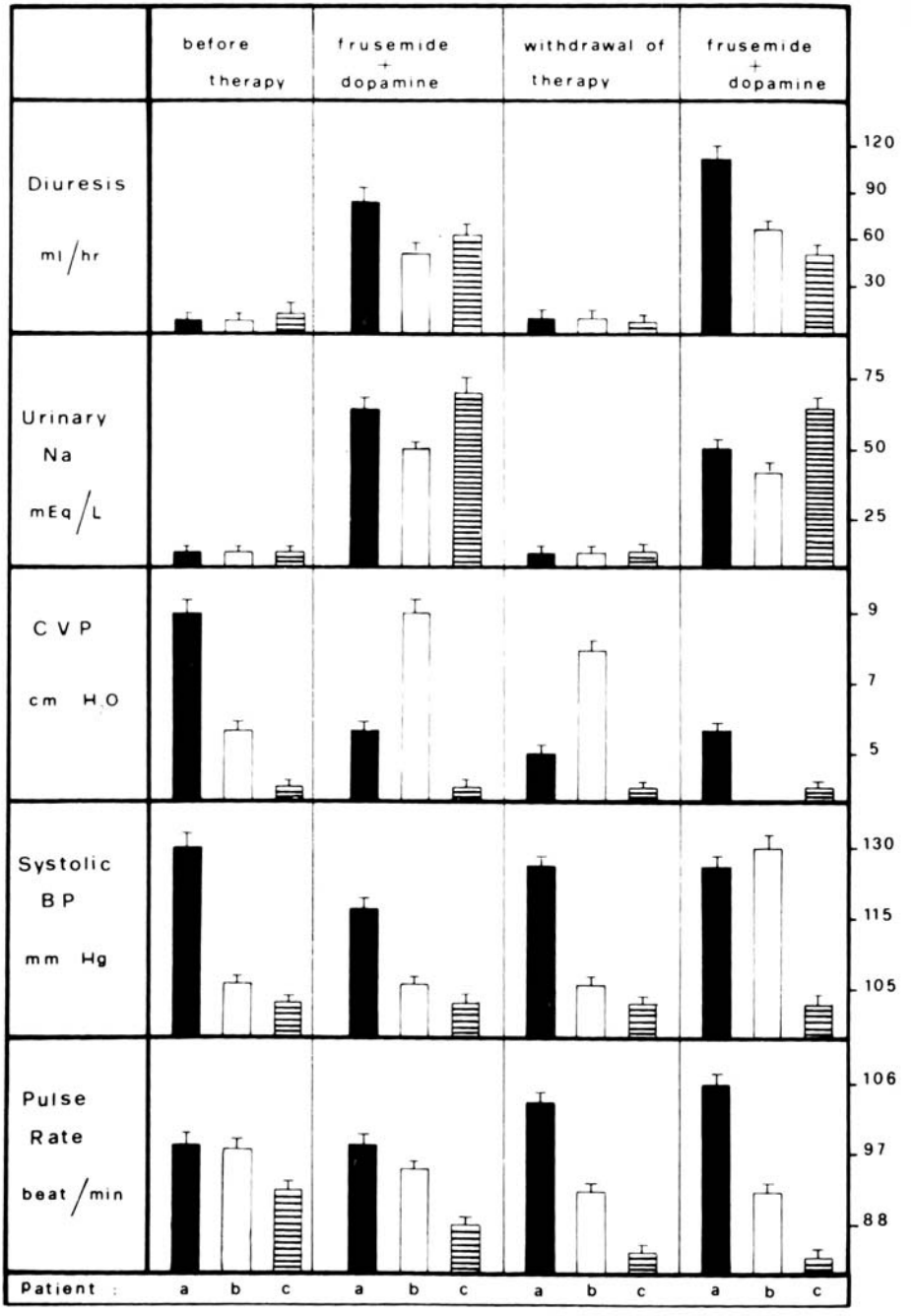

Figure 1. Diuresis, urinary sodium excretion, central venous pressure (CVP), systolic blood pressure (BP) and pulse rate in three patients with hepatorenal syndrome. Bars represent the mean value ± SD of each follow-up period (24–36 hours)

with anuria refractory to classical therapeutic measures, diuresis was restored after dopamine and frusemide administration, and the answer was not dependent on the rate of urinary sodium excretion. Moreover diuresis was also obtained, although only transiently, in three patients with hepatorenal syndrome in which oliguria is usually resistant to any treatment. Whether the reversal of oliguria in our patients could be attributed to dopamine or to its synergism with frusemide, still remains unsettled. Henderson et al [7] emphasised the role of dopamine since they observed restoration of diuresis in 11 patients resistant to frusemide only after administration of subpharmacological doses of dopamine. However in this experience, dopamine was administered one to three hours after high doses of frusemide. In normal subjects the plasma half-life of frusemide is about 30 minutes, and as the drug is mainly excreted by the kidney, an increased plasma half-life probably occurred in the oliguric patients reported by Henderson [8, 9]. Thus it is impossible to separate the effects of dopamine per se from those due to the association dopamine-frusemide in Henderson's series. On the other hand the combination of the two drugs might theoretically be synergistic. Dopamine at subpharmacological doses stimulates intrarenal dopaminergic receptors and causes marked vasodilation both of afferent and efferent arterioles [10]. This effect allows the transport of frusemide to the loop of Henle and increases salt and water excretion and urine flow rate to the macula densa, blocking in turn the renin-angiotensin axis [11]. The interruption of angiotensin-mediated afferent vasoconstriction increases tubular flow in Henle's loop and enhances medullary prostaglandin PGE_2 migration to the macula densa [12].

In ARF there is no clear evidence that non-oliguric patients have a better prognosis than oliguric ones. Anderson et al [13] reported a reduced mortality in non-oliguric patients, while Brown et al [14] failed to demonstrate a difference between the two groups in duration of renal failure, dialysis requirements and mortality. Nevertheless there is a general agreement that the onset of diuresis can prevent the risk of fluid overload, hyperkalaemia and dialytic emergency in patients with ARF. Our results suggest that in patients, unresponsive to mannitol and frusemide treatment, the association of frusemide and dopamine at low doses was not only effective in promoting diuresis but also avoided dialysis in 11 out of 16 cases of ARF. This therapy was almost free of side effects.

The hepatorenal syndrome is considered a functional nephropathy without any histological evidence of an intrinsic renal lesion. In this syndrome, the vasoconstriction and the redistribution of cortical blood flow toward the medulla, seems to play a major role in the pathogenesis of severe oliguria, with a low urinary sodium concentration. In our patients the infusion of dopamine and frusemide was accompanied by increased diuresis and natriuresis, suggesting that the drug association produced both reduction in intrarenal vascular resistance and improvement in cortical blood flow. Unfortunately the effects were limited to the period of infusion, since the withdrawal of therapy, was rapidly followed by reduction of diuresis and natriuresis to pretreatment values.

Although the therapeutic benefits were transient in our patients, nevertheless in our experience the association of dopamine and frusemide was the only way of restoring diuresis in patients with hepatorenal syndrome. We think that further investigation of the use of this therapy in such catastrophic conditions should be undertaken.

References

1 Goldberg LI. *Pharm Reviews 1972; 24:* 1
2 Williamson HE, Marchand GR, Bourland WA. *Kidney Int 1976; 10:* 113A
3 Patak R, Rosenblatt S, Fadem S et al. *Abstracts VIIth Int Congr Nephrol 1978;* R-12
4 Ciabattoni G, Pugliese F, Cinotti GA et al. *Europ J Pharmacol 1979; 60:* 181
5 Lindner A, Cutler RE, Goodman WG et al. *Kidney Int 1979; 16:* 158
6 Talley RC, Forland M, Beller B. *Abstracts Clin Res 1970; 18:* 518
7 Henderson IS, Beattie TJ, Kennedy AC. *Lancet 1980; ii:* 827
8 Brun-Buisson C, Le Gall JR. *Lancet 1980; ii:* 1301
9 Graziani G, Cairo G, Tarantino F et al. *Lancet 1980; ii:* 1301
10 Andreucci VE, Dal Canton A, Corradi A et al. *Kidney Int 1976; 9:* 475
11 Thurau K, Boylan JW. *Am J Med 1976; 61:* 308
12 Andreucci VE. *Proc EDTA 1977; 14:* 115
13 Anderson RJ, Linas SL, Berns AS et al. *N Engl J Med 1977; 296:* 1134
14 Brown CB, Ogg CS, Cameron JS. *Clin Nephrol 1981; 15:* 90

Address for correspondence: A Cantaluppi, Division of Nephrology and Dialysis, Ospedale Maggiore Policlinico, Milano, Italy