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Synergetic Effects of Dopamine and High-Dose Bumetanide in Patients with Oliguria

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Abstract The effects of a combination of dopamine and bumetanide were studied in eight patients with oliguria not responsive to conventional treatment. Dopamine was infused at a rate of 3 μg/kg/min and bumetanide was given as a 0.05-0.1 mg/kg bolus every 2 hours intravenously. Administration continued for 3 to 15 days. Urine output, blood urea nitrogen, serum creatinine, the ratio of urine to plasma osmolarity, free water clearance, and serum electrolytes were measured before, during, and after the administration period. Six of the eight patients responded with an increase in urine output and improvement of the other variables ; the other two did not. We conclude that the combination of dopamine and high-dose bumetanide is effective in increasing diuresis in critically ill patients in the early stages of oliguria.

Key Words : Dopamine, bumetanide, oliguria, synergetic effect.

Introduction

The pathophysiology of nonspecific acute renal failure is not completely understood[1]. It is essential in critically ill patients with oliguria to stimulate diuresis as soon as possible. High doses of diuretics are conventionally given. However, if renal vasoconstriction is the principal cause of the acute oliguria, the use of diuretics alone is often ineffective. Lindner et al.[2] found in dogs that a combination of dopamine and furosemide produced renal vasodilatation, a high rate of urine flow, and improvement of the impaired renal function. Talley et al.[3] reported that administration of dopamine with diuretics may reverse acute renal failure in humans. In this study, we gave patients with acute oliguria both dopamine and high dose bumetanide, which is 30 times as potent as furosemide in enhancing sodium excretion[4,5].

Materials and Methods

Our subjects were eight critically ill patients with acute oliguria. Patient characteristics are summarized in Table 1. One of the eight patients

Case	Age	Sex	Diagnosis	Therapy				Outcome
				Dopamine (mg/hour)	Bumetanide (mg/2 hours)	Duration (days)	Effective	
1	72	M	Trauma	17	4.2	4	Yes	Recovered
2	72	F	Septic shock	5-7	1.3-2.5	13	Yes	Recovered
3	65	F	Acute cholangitis	8-15	3.3	15	No	Died
4	75	F	Brain abscess	8	7.5	5	No	Unchanged
5	52	M	Septic shock	8	0.4-1.7	8	Yes	Recovered
6	43	M	After operation for esophageal varix	10	0.8-2.5	7	Yes	Recovered
7	74	M	Pulmonary edema	10	0.4-3.3	4	Yes	Died
8	66	F	Acute pneumonia +COPD *	12	0.8-1.3	3	Yes	Recovered

Table 1 Patient characteristics and dopamine-bumetanide therapy.
* COPD=chronic obstructive pulmonary disease.

was transferred to our intensive care unit (ICU) from another hospital with the diagnosis of acute renal failure following trauma. The other seven patients entered the oliguric state during their stay in the ICU. Dopamine-bumetanide therapy was started when urine output was less than 100 ml in 6 hours despite conventional treatment including fluid loading, and administration of mannitol, furosemide, or ethacrinic acid. Mechanical ventilatory support, antibiotics, digitalis and vasopressor agents (norepinephrine plus phentolamine) were used as needed. Hypovolemia as judged by pulmonary artery pressure or wedge pressure using a Swan-Ganz catheter, or by central venous pressure, was corrected by infusion of lactated Ringer's solution or whole blood. Dopamine was diluted in 5 % dextrose to a concentration of [0.6 x kg of body weight] mg/100 ml. Usually, the infusion was begun at a rate of 3 μg/kg/min, and then gradually increased to a maximum of 6 μg/kg/min, or decreased to a minimum of 1 μg/kg/min, according to the changes in urine output. The heart rate and mean arterial pressure did not change with the dopamine infusion in any patients. Bumetanide was given intravenously as bolus injection at a dose of up to 0.1 mg/kg every 2 hours. This administration continued for three to 15 days. Urine volume was measured hourly as the primary index of the response to this therapy. Urine output, blood urea nitrogen (BUN), serum creatinine (Cr), the ratio of urine to plasma osmolarity (Uosm/Posm), free water clearance (C_{H_2O}), and plasma electrolytes were measured before, during and after therapy. The volumes obtained 6 to 12 hours before therapy were considered control values. Peritoneal dialysis was done in two patients (Cases 1 and 4) for 8 or 11 days. In the patients who responded, the paired Student's t-test was used to calculate significance.

Results

Table 1 demonstrates the efficacy of the therapy. The doses of dopamine and bumetanide used during each 24-hour pereod were averaged separately and the units of mg/24 hours were converted to mg/hour for dopamine and mg/2 hours for bumetanide. When the mean values were widely different from day to day, the doses are indicated as ranges. In six of the eight patients (Cases 1, 2, 5, 6, 7, and 8), urine output increased within 3 hours after the start of the therapy ; in the other two patients (Cases 3 and 4), urine output either did not change, or decreased.

Figure 1 shows the variables we measured for one patient (Case 2) throughout the therapy. Bumetanide alone did not cause diuresis or improve renal function, but the two drugs given together did. (Fig. 1) Mean values for renal function before the start of

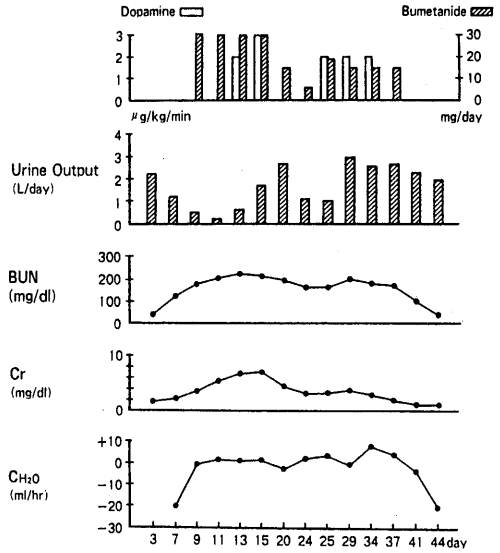

Fig. 1 Effects of bumetanide and of dopamine given with bumetanide on urine output, BUN, Cr, and free water clearance (C_{H_2O}) in case 2.

the therapy (control values) and at the end in the patients who responded are listed in Table 2 and those in the patients, who did not responde, in the Table 3. In the patients who responded, the mean urine output and Uosm/Posm increased signigicantly, and the mean BUN, Cr levels, and C_{H_2O} decreased, but not significantly. Plasma Na significantly increased, though the values of the plasma electrolytes were, in most patients, within the normal range. In patients who did not respond, all of the values became worse (Case 3) or remained unchanged (Case 4) despite the therapy. Endogenous creatinine clearance (Ccr) and Na excretion, calculated before and after therapy, in some of the patients who responded, improved. Ccr changed from 3.3±3.0 ml/min (mean±SE, n=6) to 32.7±6.2 ml/min and Na excretion from 14.6±9.6 to 97.9±32.5 Eq/min (n=4).

		Before	After
Urine output	(ml/hour)	13±5	91±37 *
BUN	(mg/dl)	91±37	60±17
Cr	(mg/dl)	3.8±1.3	1.9±0.8
Uosm/Posm		1.01±0.03	1.24±0.07 *
C_{H_2O}	(ml/hour)	−0.3±0.6	−22.6±8.7
Plasma Na	(mEq/l)	135±3	147±5 *
Plasma K	(mEq/l)	4.4±0.5	4.1±0.4
Plasma Cl	(mEq/l)	97±1	103±4

Table 2 Mean renal function before and immediately after therapy in the patients who responded.
Mean ± SE (n=6)
* significantly different from control ($p<0.05$)

		Case 3		Case 4	
		Before	After	Before	After
Urine Output	(ml/hour)	45	1	4	12
BUN	(mg/dl)	80	350	70	72
Cr	(mg/dl)	3.6	8.7	4.4	4.1
Uosm/Posm		1.08	0.78	1.01	1.03
C_{H_2O}	(ml/hour)	4.0	0.2	0.4	−0.3
Plasma Na	(mEq/l)	143	135	136	146
Plasma K	(mEq/l)	3.0	6.8	5.5	4.0
Plasma Cl	(mEq/l)	96	79	−	−

Table 3 Renal functions before and after therapy in the two patients showing no response

Discussion

We found that using both dopamine and a large dose of bumetanide prevents a further decrease in urine output in critically ill patients in the initial phases of acute oliguria. Use of bumetanide alone neither caused diuresis nor improved renal function, but the addition of dopamine did both. Dopamine improved renal function when administered intravenously at a rate of 2.6 to 7.1 μg/kg/min[6].

Bumetanide in doses up to 0.1 mg/kg causes dose-dependent diuresis[4] and is excreted with a plasma half-life of 1.5 hours[5]. The infusion of dopamine and the intervals between and doses of bumetanide would therefore seem to be suitable in this study.

In the six out of eight patients who improved with administration of these drugs, the decrease in BUN and Cr suggested an improvement of glomerular function and effective excretion of these substances. The increases in Uosm/Posm and C_{H_2O} indicated an improvement in distal tubular function. The increase in Ccr and Na excretion seen in some patients who responded to the therapy reflects an increase in the glomerular filtration rate and renal blood flow. In the patients who did not respond to the therapy, we think that renal function had already progressed to tubular necrosis. No doubt several factors cause oliguria in renal failure. However, there is evidence suggesting that the tubulo-glomerular feedback mechanism is particularly important in development of acute renal failure.

Mason[7] stated that impaired tubular reabsorption results in a rise in the NaCl concentration in the macula densa, and this produces a rise in the renin activity of the juxtaglomerular apparatus of the nephron which, mediated by the renin-angiotensin system, constricts glomerular vessels and reduces the glomerular filtration rate. Bumetanide acts mainly of the ascending limb of Henle's loop[8] and causes an increase in urine flow and Na excretion, a decrease in Na absorption, and alterations in the glomerular filtration rate[4]. Dopamine dilates the renal vasculature or redistributes the intracortical blood flow by specific action on the dopaminergic receptor[9] ; it also increases renal blood flow, inulin clearance, and Na excretion[6]. Therefore, we think that dopamine acts on the renal vasculature and bumetanide in the tubules synergistically, blocking the tubuloglomerular feedback mechanism. The decrease in BUN and Cr, and the increase in urine output, Uosm/Posm, C_{H_2O}, Cr, and Na excretion seen in this study probably result from the blockade of this feedback mechanism.

We think that this therapy should be useful in stimulating diuresis in critically ill patients with oliguria unresponsive to conventional therapy. Perhaps organic and non-organic renal failure could be distinguished by the response to such therapy.

References

1) Levinsky, N. G. : Pathophysiology of acute renal failure. *N. Engl. J. Med.*, **296** : 1453-1458, 1977.
2) Linder, A., Cutler, R. E. and Goodman, W. G. : Synergism of dopamine plus furosemide in preventing acute renal failure in the dog. *Kindney Int.*, **16** : 158-166, 1979.
3) Talley, R. C., Forland, M. and Beller, B. : Reversal of acute renal failure with a combination of intravenous dopamine and diuretics. *Clin. Res.*, **18** : 518, 1970.
4) Cohen, M. R., Hinsch, E., Vergana, R., Ryan, J., Kolis, S. T. and Schwartz, M. A. : A comparative diuretic and tissue distribution study of bumetanide and furosemide in the dog. *J. Pharmacol. Exp. Ther.*, **197** : 697-702, 1976.
5) Halladay, S. C., Sipes, I. G. and Carter, D. E. : Diuretic effect and metabolism of bumetanide in man. *Clin. Pharmacol. Ther.*, **22** : 179-187, 1978.
6) MacDonald, R. H. Jr., Goldberg, L. I., McNay, J. L. and Tuttle, E. P. Jr. : Effects of dopamine in man : Augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. *J. Clin. Invest.*, **43** : 1116-1124, 1964.
7) Mason, J. : Tubulo-glomerular feedback in the early stage of experimental acute renal failure. *Kidney Int.*, **10** : s106-s114, 1976.
8) Bourke, E., Asbury, M. J. A., O'Sullivan, S. and Gatenby, P. B. B. : The site of action of bumetanide in man. *Eur. J. Pharmacol.*, **23** : 283-289, 1973.
9) Hardaker, W. T. Jr. and Wechsler, A. S. : Redistribution of renal intracortical blood flow