Effects of Intravenous Infusion of Dopamine in Cirrhotics (36770)

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Functional renal failure continues to be a major unsolved problem in patients with chronic liver disease. It is defined as any recent elevation of blood urea nitrogen or creatinine concentration in the presence of liver disease with ascites. The "hepatorenal syndrome" has become the popular synonym however, "funcational renal failure" (1) is preferable because it emphasizes the purely functional nature of the renal lesion. The kidneys appear normal at necropsy and when transplanted into noncirrhotic recipients regain their lost function (2). It is generally agreed that renal blood flow is reduced in functional renal failure but the cause of this reduction remains an enigma (3, 4). A number of pharmacological agents (5) have failed to reverse completely the basic pathophysiological defects in hepatorenal syndrome.

It has been demonstrated that intravenously infused dopamine increases renal blood flow in both dogs (6) and human subjects (7). Barnardo, Baldus and Maher (8) demonstrated a consistent increase in effective renal plasma flow after dopamine infusion in patients with cirrhosis with various degrees of impairment of renal function. This study suggested potential beneficial effects of dopamine in hepatorenal syndrome. The purpose of our study was to investigate the responses of cirrhotic patients to a 24 hr infusion of a therapeutic dose of dopamine.

Patients and Methods. Ten patients with histologically proven cirrhosis of the liver were studied. Cirrhosis was associated with hepatitis in three, chronic alcoholism in four and uncertain etiologies in three. There were seven females and three males, with ages ranging from 39 to 78 with a mean of 55. None of the patients gave a history of renal disease; all had normal urinalysis, blood urea nitrogen, and serum creatinine, except patient No. 10. One patient (No. 1) died with renal insufficiency 2 mo after the study. No postmortem study was obtained. Six of these patients had severe ascites (Nos. 1, 2, 3, 4, 9, 10). Ascites was classified into mild or severe. The studies were carried out on these patients while the patients were on a 1 g sodium diet with constant fluid intake (1000 ml/day) and furosemide (Lasix) 40 mg twice a day. Serum bilirubin, SGOT, LDH, albumin, BUN, creatinine, serum electrolytes, serum and urine osmolarity, 24 hr urine volume, urinary electrolytes and creatinine were measured before, during and after infusion of dopamine. After 3 day equilibration period, a 3 day study period was begun. A dose of dopamine (3,4-dihydroxyphenylethylamine) 2 μg/kg/min in 5% dextrose in water (20 ml/hr) was infused on Day 2. Plain 5% dextrose solution was given (20 ml/hr) on the first and the third days as control. Hourly blood pressure measurements were obtained during the infusion period by the use of a sphygmomanometer. Data obtained were evaluated statistically by the means of Student's *t* test for paired observations.

Results. A summary of the clinical and biochemical features of the patients is shown in Table I. Adverse reactions were not noted during the administration of dopamine in these patients. There were no significant changes in blood pressure and pulse rate befor, during and after dopamine infusion. Likewise, there were no changes in the serum bilirubin, albumin, SGOT, and LDH during the entire study period. Results of the renal func-

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TABLE I. Clinical Characteristics and Liver Function Test.

No.	Age	Sex	Diagnosis	Ascites	Bilirubin (mg/100 ml)	SGOT (units)	Albumin (g/100 ml)	PT (sec)
1	67	M	Laennec's cirrhosis, alcoholic	4+	3.4	95	2.6	13/12
2	57	F	Postnecrotic cirrhosis	3+	7.2	50	2.6	13/13
3	49	M	Laennec's cirrhosis, alcoholic	4+	1.4	45	4.21	14/12
4	70	F	Postnecrotic cirrhosis	4+	1.4	50	3.5	13/12
5	54	F	Laennec's cirrhosis, alcoholic	—	4.05	50	3.1	15/13
6	39	F	Laennec's cirrhosis, alcoholic	—	0.48	52	3.4	14/13
7	50	F	Postnecrotic cirrhosis	—	0.8	197	3.8	14/13
8	66	F	Postnecrotic cirrhosis	—	1.4	165	4.5	14/13
9	65	M	Postnecrotic cirrhosis	4+	1.9	28	3.4	13/12
10	77	F	Postnecrotic cirrhosis	4+	0.2	30	3.7	12/13

tion tests are outlined in Table IIA and B. As shown in Table IIA, there was no significant differences in the values for blood urea nitrogen, serum creatinine, sodium and potassium before, during and after infusion of dopamine. A typical response as shown in Fig. 1 is represented by patient No. 7.

Creatinine clearance. Control values varied widely within the group being less than 100 ml/min in 7 of 10 patients. Infusion of dopamine was accompanied by a decrease in creatinine clearance from a mean control value of 58.6 to 44.5 ml/min ($p < .05$; Table IIB). After infusion of dopamine, there was an increase in the creatinine clearance to 54.7 ml/min ($p < 0.05$) approximating the control value. The values were lower in the patients with ascites than those without, but this was

TABLE II. Tests Before, During and After Dopamine Infusion.[a]

	BUN (mg/100 ml)	Creatinine (mg/100 ml)	Sodium (mEq/liter)	Potassium (mEq/liter)	Serum osmolarity (mOsm/liter)
	A. Biochemical profile of patients				
Predopamine	22.9 ± 5.0	1.08 ± 0.15	136.0 ± 1.2	4.88 ± 0.41	288.4 ± 5.33
Dopamine	23.7 ± 5.3	1.13 ± 0.15	137.0 ± 1.3	4.38 ± 0.14	285.8 ± 3.81
Postdopamine	23.1 ± 4.6	1.06 ± 0.14	137.5 ± 1.8	4.46 ± 0.14	288.0 ± 2.50

Urine values	Predopamine	Dopamine	Postdopamine
	B. 24 hr urinary values		
Volume (ml/24 hr)	1164.5 ± 138	1469 ± 282.60	1249.7 ± 231.30
Osmolarity (mOsm/liter)	398.4 ± 38.10	344.5 ± 25.88[c]	411.8 ± 36.60[b]
Sodium (mEq)	47.9 ± 10.35	85.52 ± 26.50[c]	33.6 ± 9.60
Potassium (mEq)	43.7 ± 7.05	56.7 ± 11.60	48.3 ± 9.20
Creatinine (g/24 hr)	0.75 ± 0.08	0.56 ± 0.50	0.75 ± 0.09
Creatinine (ml/clearance min)	58.6 ± 9.75	44.5 ± 6.40[b]	54.7 ± 11.70[b]

[a] Values are mean ± SE.
[b] $p < .05$.
[c] $(0.05 < p < 0.1)$.

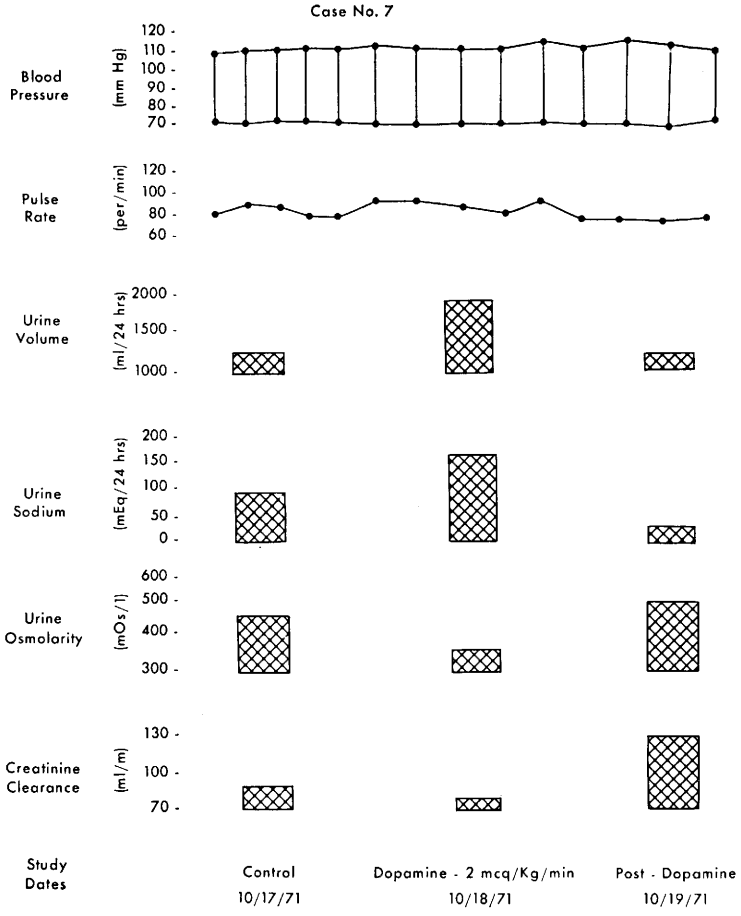

FIG. 1. Renal response in subject No. 7; 50 year old white female with postnecrotic cirrhosis. Note the decrease in GFR and urine osmolarity, and increase in urine volume and sodium excretion during dopamine infusion.

not of statistic significance and no difference in responses to dopamine infusion was observed among patients with and without ascites.

Plasma and urine osmolarity. The mean preinfusion values for serum and urinary osmolarity were 288.4 and 398.4 mOsm/liter, respectively. During infusion of dopamine, serum and urine osmolarity decreased to 285.8 and 344.5 mOsm/liter, respectively. After stopping the drug infusion, urine osmolarity increased to 411.8 mOsm/liter; this increase was significant ($p < .05$, Table IIB).

Urinary excretion of sodium, potassium and water. An increase in the 24 hr urinary sodium was observed during the administration of dopamine (85.5 $\pm$ 26.5 mEq) compared to the control value (47.9 $\pm$ 10.35 mEq). This was of borderline significance. The mean urinary sodium excretion was 85.6 on the patients without ascites as compared to 85 in the ascitic patients. Dopamine also caused an increase in urinary potassium, from a mean of 44 to 57 mEq ($p < .05$). Likewise, the 24 hr urine volume increased from a mean control value of 1164.5 to 1469.8 ml during dopamine infusion. This increase in urine volume, hower was not statistically significant. No significant differences in the response of sodium and potassium excretion and urinary volume were noted between the patients receiving and those not receiving diuretic therapy.

Discussion. It is generally agreed that the renal blood flow in cirrhotics is reduced. It has also been established that these patients have reduced renal perfusion (3) associated with increased renal vascular resistance, (4) a redistribution of blood flow away from the cortex (4, 9) and a fall in glomerular filtration rate (3, 4). These studies were undertaken when a high blood urea had already been established. Using ^{133}Xe washout technique, Kew, *et al.* (10) demonstrated diminished renal blood flow and shunting of blood from cortex to medulla in cirrhotic patients even with normal blood urea levels.

Dopamine has been shown to dilate the renal vascular bed (6), thus diminishing renal vascular resistance. This direct renal vasodilator effect may therefore explain the increase in effective renal plasma flow during dopamine infusion in patients with renal failure and cirrhosis (8). Similar increases in renal plasma flow had been shown in both normal subjects and in patients with congestive heart failure (7, 12).

Barnardo, Baldus and Maher (8) showed that dopamine caused a consistent increase in effective renal plasma flow (ERPF) with little change in glomerular filtration or rates of sodium and water excretion. Their study was however, only observed over a brief period of dopamine infusion. A moderate pressor response was later induced in four instances without further change in either GFR or ERPF and during more prolonged infusions there was no augmentation of the effect observed in the initial 60 to 90 min (8).

Contrary to the results reported by Barnardo, Baldus and Maher (8) the glomerular filtration rate, as measured by the 24 hr creatinine clearance in all our patients, decreased during infusion of dopamine. Our results would indicate that dopamine does not abolish the functional abnormality responsible for the renal circulatory disturbance ("shunting") in the cirrhotics. Although renal blood flow was not determined in this study, we felt that this reduction in creatinine clearance could be explained on the basis of the accentuation of the abnormal renal hemodynamics that are frequently seen in cirrhotics. Normally the renal cortex takes the greatest part of the blood entering the kidney, and a fairly good correlation between renal and cortical blood flow and impairment of renal function as assessed by creatinine clearance has previously been reported (9, 10). Based on these and other studies, it is therefore reasonable to explain the decreased creatinine clearance in our patients during infusion of dopamine on basis of decreased cortical perfusion. Although there was a definite decrease in creatinine clearance in our patients, the 24 hr urine volume and the urinary sodium excretion actually increased during the drug infusion period. An increase in medullary flow should result in diminished tubular reabsorption of sodium and medullary osmotic concentration causing increases in urinary sodium and volume excretion (11). This mechanism may explain the renal responses in the patients we studied. The prompt onset of natriuresis and the lack of reciprocal changes in potassium excretion in our patients suggest that dopamine was not exerting its action by inhibiting the effects of excessive aldosterone on renal tubules.

Thus our results suggest that dopamine may have accentuated the "shunting" of blood from the cortex to medulla in cirrhotics, and that this effect of dopamine on renal function was completely reversible. In contrast to Barnardo, Baldus and Maher's study (8), the above effects were observed after prolonged infusion of dopamine. Since there is marked autonomic instability in cirrhotics, the effects of therapeutic agents on renal function in our opinion would be better evaluated if studies were carried out over a prolonged period of time. Also, the basic renal derangement represents a somewhat permanent alteration in the renal physiology which can not be expected to reverse in a matter of hours. Our data would thus suggest that dopamine has little or no beneficial effect on renal function in cirrhotics.

Summary. The effects of 24 hr intravenous infusion of dopamine in 9 cirrhotic patients without azotemia and one patient with mildly elevated BUN were studied. Dopamine (3, 4-dihydroxyphenylethylamine) 2 μg/kg/min produced statistically significant decrease in

creatinine clearance and urine osmolarity, and an increase in urinary sodium excretion of borderline significance. These could be attributed to "shunting" of blood from the renal cortex to the medulla brought about by dopamine. This effect was reversible when the drug infusion was discontinued. The therapeutic value of dopamine in hepatorenal syndrome is therefore being questioned.

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Received June 21, 1972. P.S.E.B.M., 1972, Vol. 141.