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A Randomized Comparison of Metoclopramide and Domperidone on Plasma Aldosterone Concentration and on Spironolactone-Induced Diuresis in Ascitic Cirrhotic Patients

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The effect of metoclopramide and domperidone, two dopamine antagonists, administered to cirrhotic patients with ascites and secondary hyperaldosteronism, was examined to evaluate the changes in plasma aldosterone levels and in spironolactone-induced diuresis.

In 15 patients with ascites and secondry hyperaldosteronism, the intravenous administration of 10 mg metoclopramide significantly increased plasma aldosterone levels (23%, $p < 0.01$). This effect was observed when an equivalent dose of domperidone was administered.

In 20 ascitic patients treated with spironolactone (300 mg per day), the administration of metoclopramide (20 mg) significantly reduced urinary output (24%, $p < 0.001$) and urinary sodium (35%, $p < 0.001$) while simultaneously increasing urinary potassium (24%, $p < 0.001$) and plasma aldosterone (40%, $p < 0.001$). This effect was not observed with domperidone in an equivalent dose.

Therefore, it is recommended that metoclopramide should be avoided during diuretic therapy in cirrhotic patients with ascites. In these circumstances, domperidone is preferred.

Metoclopramide, a dopamine antagonist, stimulates aldosterone production in man (1). In contrast, domperidone, which is also a dopamine antagonist, does not stimulate aldosterone secretion; whether or not this is due to its inability to penetrate the blood-brain barrier, is unknown (2).

Although aldosterone does not appear to be the primary determinant of impaired sodium excretion in cirrhosis, hyperaldosteronism plays an important role in formation of ascites (3, 4). The present study was designed to investigate whether metoclopramide or domperidone influence plasma aldosterone levels and whether metoclopramide or domperidone influenced the diuretic effect of spironolactone in nonazotemic cirrhotics with ascites.

PATIENTS AND METHODS

The investigation was performed in 35 patients with cirrhosis admitted to our unit for treatment of ascites (Table 1). The diagnosis in 27 of 35 patients was based on peritoneoscopy with liver biopsy. In the other patients, peritoneoscopy was not possible because of severe thrombocitopeny, and the diagnosis was based on clinical and biochemical findings.

To investigate an etiologically homogenous group of cirrhotic patients, we included only HBsAg-positive patients who represent about 25% of cirrhotics at our institution. Twelve patients were also HBeAg-positive. No patient had a history of chronic alcoholism. Further criteria for inclusion were ascites, absence of jaundice, gastrointestinal bleeding or hepatic encephalopathy and normal renal function.

The protocols were explained to potential subjects and informed consent was obtained. No subject refused to participate. No drop-outs occurred during the study. There were no side effects of medications during the study.

Student's t test for paired data was used for all statistical comparisons. Data are presented as the mean ± S.D.

The study was divided into two protocols.

Protocol I. The aim was to investigate the effects of

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TABLE 1. DEMOGRAPHIC AND BIOCHEMICAL CHARACTERISTICS OF THE 35 CIRRHOTIC PATIENTS (MEAN ± S.D.)

	Protocol I	Protocol II	
		Metoclopramide	Domperidone
Total cases	15	10	10
Male/female	10/5	7/3	6/4
Age	52 ± 14	50 ± 11[a]	48 ± 9[a]
HBsAg-positive	15	10	10
HBeAg-positive	6	2	4
Esophageal varices[b]	15	10	10
SGPT (mU/ml)	49 ± 10	54 ± 10[a]	59 ± 18[a]
Serum γ-globulin (gm/dl)	1.7 ± 0.2	2 ± 0.5[a]	1.9 ± 0.4[a]
Serum bilirubin (mg/dl)	1.7 ± 0.5	2.2 ± 0.7[a]	1.9 ± 0.7[a]
Serum albumin (gm/dl)	3.2 ± 0.3	3.1 ± 0.3[a]	3 ± 0.3[a]
Prothrombin time (%)	62 ± 5	58 ± 10[a]	60 ± 7[a]
Serum creatinine (mg/dl)	1.1 ± 0.1	1.3 ± 0.2[a]	1.2 ± 0.2[a]
Creatinine clearance (ml/min)	97 ± 4	98 ± 9[a]	95 ± 3[a]
Serum Na^+ (mEq/liter)	131 ± 3	132 ± 4[a]	134 ± 3[a]
Serum K^+ (mEq/liter)	3.5 ± 0.1	3.6 ± 0.2[a]	3.5 ± 0.2[a]
Blood urea nitrogen (mg/dl)	47 ± 5	42 ± 4[a]	45 ± 5[a]
Ascites proteins (gm/dl)	1.9 ± 0.3	1.7 ± 0.4[a]	2 ± 0.3[a]

[a] p is not significant for differences between the two values.
[b] Endoscopically assessed.

intravenous administration of 10 mg of metoclopramide and 10 mg of domperidone on plasma levels of aldosterone in 15 cirrhotics who were supine for 12 hr. All patients had ascites elevated plasma levels of aldosterone. Each patient received metoclopramide and domperidone in random order with an interval of at least 4 days between the two drugs. Seven days before the study, diuretic agents were discontinued and patients received a daily diet containing 50 mEq sodium, 100 mEq potassium and 800 to 1,000 ml water. Venous blood samples were obtained at 10, 20, 30, 60 and 90 min after metoclopramide or domperidone administration.

Plasma aldosterone was measured by the direct radioimmunoassay of Williams (5). Reagents were obtained from Sorin Biomedica, (Saluggia, Italy). All samples were drawn in duplicate. Assay sensitivity was 10.5 ± 2.2 pg per ml. The coefficient of variation (CV) was calculated to determine intraassay and interassay variability: intraassay CV was 7.5% and interassay CV was 11%. Normal values were < 160 pg per ml.

Plasma renin activity (PRA) was determined using the radioimmunoassay method of angiotensin I developed by Freedlender (6). Reagents were obtained from Sorin Biomedica. PRA samples were drawn in duplicate and had assay sensitivity of 0.18 ± 0.04 ng per ml. Intraassay CV was 5.8% and interassay CV was 16.5%. Normal values were 0.2 to 2.7 ng per ml per hr.

Protocol II. The aim of the second protocol was to investigate the effects of intravenous administration of metoclopramide or domperidone on spironolactone-induced diuresis in 20 patients with cirrhosis and ascites. As shown in Table 1, no significant difference in liver function tests was present between the two groups of patients.

Ten patients received metoclopramide (Group A), and ten were given domperidone (Group B). Patients were randomized to receive either domperidone (10 mg) or metoclopramide (10 mg). Patients but not the clinicians were blinded to treatment.

Before the study, all subjects were hospitalized and placed on a 50 mEq sodium and 100 mEq potassium diet. Diuretic drugs were withheld for 6 days. During this period, mean urinary sodium excretion was 28 mEq per day (range: 14 to 87).

On the seventh day, patients in both groups were given spironolactone (300 mg daily) for 1 week prior to the test, in an attempt to attain a consistent diuretic action. The natriuretic response to spironolactone was assessed in 24-hr urine samples collected from 8 a.m. to 8 a.m. on three consecutive days. On Day 1 of the study, patients received only spironolactone. On Day 2, patients received spironolactone plus 10 mg of intravenous metoclopramide (Group A) or domperidone (Group B) at 9 a.m. and again at 6 p.m. Each drug was administered as a bolus. On Day 3, patients received only spironolactone. Twenty-four hour urine samples were analyzed for volume, creatinine (7), sodium and potassium content. Venous blood samples for aldosterone and PRA determination were obtained at 8 a.m. of Day 1 and Day 2 and at 60 min after metoclopramide or domperidone administration.

RESULTS

As shown in Figure 1, in response to administration of 10 mg of metoclopramide, plasma aldosterone increased from the basal value of 288 ± 74 to 354 ± 90 pg per ml at 60 min ($p < 0.01$). After domperidone administration, no significant change was observed in plasma aldosterone levels which decreased slightly from the basal value of 293 ± 67 to 272 ± 71 pg per ml at 60 min.

No significant modification in PRA was observed during the test period.

Table 2 summarizes the changes in urinary output, urinary sodium, urinary potassium, urinary creatinine, PRA and plasma aldosterone levels in the 20 patients of the study. Urinary creatinine excretion was constant, suggesting that urine collection was complete.

Between Days 1 and 2 after metoclopramide, there were significant decreases in natriuresis [35 ± 7% (10/

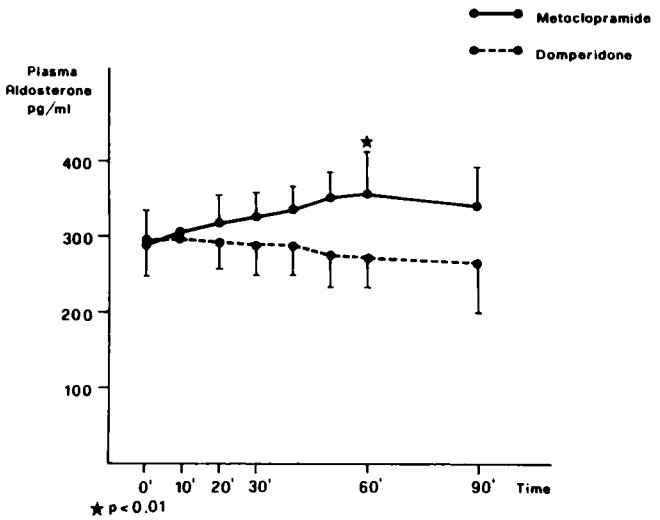

FIG. 1. Plasma aldosterone concentration after 10 mg i.v. metoclopramide or domperidone administration.

TABLE 2. URINE OUTPUT, URINE SODIUM, URINE POTASSIUM, URINE CREATININE, PLASMA ALDOSTERONE AND PRA IN DAY 1 (A CONTROL DAY), DAY 2 (AFTER METOCLOPRAMIDE OR DOMPERIDONE ADMINISTRATION) AND DAY 3 (A SECOND CONTROL DAY) IN 20 CIRRHOTIC PATIENTS WITH ASCITES

		Metoclopramide			Domperidone		
Day		1	2	3	1	2	3
Urine output (ml/24 hr)	X[a]	1,295	980	1,240	1,250	1,200	1,260
	S.D.	±70	±115	±99	±60	±70	±60
	P	<0.001	<0.001		NS[b]	NS	
Urine sodium (mEq/24 hr)	X	136.1	88.4	116.3	138.3	133.5	136.7
	S.D.	±11.9	±16.6	±20.7	±10.7	±11.2	±9.8
	P	<0.001	<0.001		NS	NS	
Urine potassium (mEq/24 hr)	X	36.8	45.2	35.3	38	39	32
	S.D.	±6	±4.9	±6.9	±4	±7	±7
	P	<0.001	<0.001		NS	NS	
Urine creatinine (mg/24 hr)	X	1,836	1,812	1,771	1,547	1,514	1,488
	S.D.	±320	±316	±275	±179	±197	±207
	P	NS	NS		NS	NS	
Plasma aldosterone (pg/ml)	X	199	279	212	189	192	190
	S.D.	±78	±98	±55	±80	±70	±82
	P	<0.001	<0.001		NS	NS	
PRA (ng/ml/hr)	X	0.73	0.84	0.82	0.92	0.93	0.89
	S.D.	±0.7	±0.3	±0.3	±0.5	±0.6	±0.4
	P	NS	NS		NS	NS	

[a] X, mean.
[b] NS, not significant ($p > 0.05$).

10 patients, $p < 0.001$)] and urine output [24 ± 7% (10/10 patients, $p < 0.001$)] and a significant rise in urinary potassium [24 ± 7% (10/10 patients, $p < 0.001$)]. Urinary sodium on Day 1 correlated inversely with the decrease in sodium excretion from Days 1 to 2: the lower the urinary sodium excretion on spironolactone, the greater the fall in sodium excretion with metoclopramide (Figure 2). The increase in plasma aldosterone levels from Days 1 to 2 correlated with the decrease in sodium excretion occurring in the same period (Figure 3): the greater the rise of plasma aldosterone levels, the greater the fall in sodium excretion. All changes returned toward baseline on Day 3.

After domperidone, urinary sodium and potassium excretion, urine output and plasma aldosterone levels did not change (Table 2).

No modification was observed in plasma or urinary creatinine and PRA with either metoclopramide or domperidone administration.

DISCUSSION

Metoclopramide increases plasma aldosterone levels in normal man (1). Domperidone, another dopamine antagonist, does not stimulate aldosterone secretion (2). Our study confirms and extends these findings to patients with cirrhosis, secondary hyperaldosteronism and

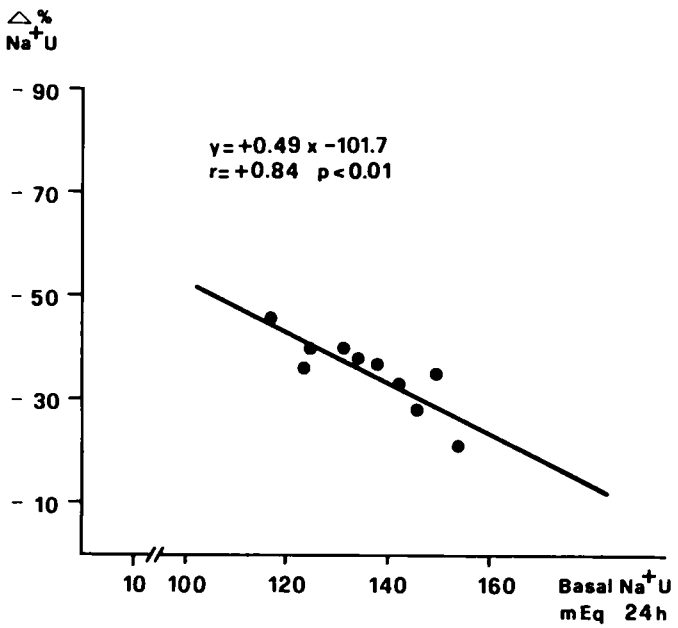

FIG. 2. Correlation between basal urine Na^+ output (mEq per 24 hr) and Na^+U per cent decrease (Δ% Day 2 to Day 1) in 10 patients with cirrhosis and ascites before and after metoclopramide administration.

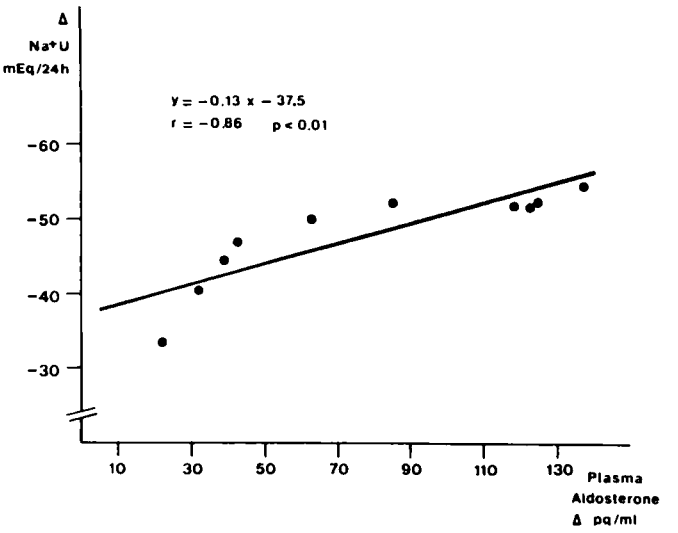

FIG. 3. Correlation between plasma aldosterone increase (Δ pg per ml) and Na^+U decrease (Δ mEq per 24 hr) after metoclopramide administration in 10 cirrhotic patients with ascites.

ascites. In such patients, intravenous metoclopramide further increased plasma concentration of aldosterone; domperidone did not. (Mazzacca, G. et al., *Annals of Internal Medicine* 1983; 98:1024–1025, Correspondence).

Several investigators have challenged the traditional viewpoint that aldosterone is the major determinant of sodium retention in cirrhosis (8). Even if hyperaldosteronism is not the primary factor, it plays a permissive role in formation of ascitic fluid (4). Therefore, drugs which further increase plasma concentrations of aldosterone might adversely affect diuresis induced by an aldosterone inhibitor in cirrhotic patients. Our study supports this concept. In our patients with cirrhosis and ascites, metoclopramide blunted the natriuretic response to spironolactone by 35% ($p < 0.001$), whereas domperidone did not cause any significant change in the spirono-

lactone-induced diuresis. Patients with the smallest natriuretic response to spironolactone on Day 1 tended to have the greatest blunting with metoclopramide. Furthermore, the antinatriuretic response with metoclopramide paralleled its aldosterone-stimulating effect: a highly significant negative correlation was found between per cent change in plasma aldosterone levels and urinary excretion. Our findings support the importance of hyperaldosteronism in formation of ascitic fluid in liver cirrhosis and suggest that the adverse action of metoclopramide on spironolactone-induced natriuresis may be related to the increase in plasma concentration of aldosterone.

Regardless of the mechanism for its antinatriuretic effect, metoclopramide should be avoided during diuretic therapy in cirrhotic patients with ascites. In these circumstances domperidone is preferred.

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