IBOPAMINE (SB 7505) IN NORMAL SUBJECTS AND IN CHRONIC RENAL FAILURE: A Preliminary Report

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1 Pharmacological and experimental studies have shown that ibopamine (SB 7505, di-isobutyric ester of *N*-methyldopamine) is capable of increasing renal blood flow, diuresis, urinary sodium, potassium and creatinine excretion.

2 SB 7505 was given to twelve volunteer patients, six of whom had normal renal function and six with various degrees of chronic renal impairment.

3 In both groups the drug yielded a prompt increase in urinary excretion of water, sodium and potassium, while creatinine clearance was also seen to increase.

4 Heart rate and arterial pressure were unaffected by SB 7505 in all patients.

5 Results seem encouraging and call for further study on the proper use of the drug in clinical nephrology.

Introduction

Few if any drugs are capable of increasing renal circulation and hence being of use in the clinical management of patients suffering from acute or chronic renal failure. This prompted us to investigate the effects on the kidney of a new substance, SB 7505, the di-isobutyric ester of *N*-methyldopamine (ibopamine hydrochloride, manufactured by Simes S.p.A.—Milan).

Preliminary experiments with this drug have shown it to be capable of increasing renal blood flow and urinary excretion of water, creatinine and electrolytes (Merlo, Brusoni & Ghirardi, 1979; Melloni, Minoja, Lureti, Bagliani, Brusoni, Pamparana & Ghirardi, 1979; Cicchetti, Bruni, Loreti, Pamparana & Ghirardi, 1980).

This paper reports the results of a clinical and functional short term study on the action of SB 7505 in subjects with normal or reduced glomerular filtration rate.

Methods

The study was performed on two groups of ambulant in-patients, the first (G1) with normal renal function and the second (G2) with various degrees of reduction in renal function (Table 1). Patients were treated with SB 7505 50 mg *per os* twice a day (08.00 h and 18.00 h) for 7 days, this dose being chosen on the basis of our previous pilot experience (unpublished data) and the data of other authors (Melloni *et al.*, 1979;

Dei Cas, Manca, Vasini, Mansour, Bernardini & Visioli, 1980).

A nurse was present when the drug was taken. Treatment with other drugs was stopped 5–7 days before starting the experiment with SB 7505.

Three days before and every day during treatment the following parameters were assessed: systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), body weight, 24 h diuresis, plasma creatinine, creatinine clearance (C_{cr}) (Henry, 1968), urinary Na^+ and K^+ excretion (Na_u^+ , K_u^+). Plasma Na^+ and K^+ (Na_p^+ , K_p^+) were measured before treatment and on the third and seventh days. In addition electrocardiogram (ECG), blood glucose, blood urea nitrogen (BUN), serum glutamic oxalacetic and pyruvic transaminase (SGOT and SGPT), gamma glutamyl transferase (γ GT) (Persijn & Van Der Slik, 1976), alkaline phosphatase, bilirubin and plasma proteins were recorded before and after treatment in order to assess the drug tolerance.

Daily urinary excretion of the two enzymes lysozyme (Prockop & Davidson, 1964) and γ GT (Persijn & Van der Slik, 1976) was measured as a check on possible kidney damage deriving from the drug according to Stefoni, Prandini, Campieri, Fatone, Borgnino & Coli (1979) and Harrison, Parker and de Silva (1973). In addition the urine was microscopically examined for cells and casts.

Careful clinical evaluation was kept up throughout treatment. Patients with normal renal function followed a free diet. Patients with renal impairment

Table 1 Characteristics of the patients (G1 and G2) treated orally with 100 mg SB 7505 for 7 days.

Subjects	Sex	Age (years)	Diagnosis	C (mg/100 ml)		C _{cr} (ml/min)	
				Before	After	Before	After
Group 1							
1	F	25	Normal subject	0.8	0.6	97	123
2	M	33	Hereditary nephropathy	1.0	0.7	128	133
3	F	21	Normal subject	0.8	0.6	120	136
4	F	30	Normal subject	0.8	0.7	105	101
5	F	47	Single kidney (acquired)	1.0	0.6	80	105
6	M	24	Acute glomerulonephritis	0.8	0.6	98	140
Group 2							
7	M	39	Chronic interstitial nephritis	8.9	8.2	9	13
8	M	60	Chronic pyelonephritis	2.4	2.0	38	47
9	M	24	Hereditary nephropathy	2.6	2.3	35	43
10	F	41	Hereditary nephropathy	6.0	5.3	13	16
11	M	65	Chronic interstitial nephritis	6.0	5.4	12	17
12	M	52	Chronic glomerulonephritis	4.3	3.9	18	17

C = plasma creatinine

C_{cr} = creatinine clearance

had a protein intake reduced according to the degree of residual renal function. Care was taken in all cases to make no changes in diet compared with the days leading up to treatment. Sodium and fluid intake were carefully controlled in each case. Caffeine-containing beverages and smoking were excluded.

Both trial groups consisted of volunteers from our Nephrology and Dialysis Department. The aim and methods of the experiment were explained to patients at the outset. The permission for the study was obtained from the local ethical committee.

All the data obtained were computerized and statistical evaluation was performed by Student's *t*-test for paired samples comparing the data recorded the day before starting the treatment and that recorded on the last day of treatment.

Results

Treatment with SB 7505 led (Figure 1) to an immediate progressive increase in diuresis in both groups of patients: 53.6% in G1 ($P < 0.05$) and 14.9% in G2 ($P < 0.10$).

Plasma concentration of creatinine decreased by 25.9% in G1 and 13.5% in G2, while creatinine clearance significantly increased in both groups, respectively by 18.3% and 25.6%.

Figure 2 shows the behaviour of plasma Na⁺ and K⁺ which decreased slightly in G1 and marginally, though not to any statistically significant degree, in G2.

The urinary excretion of sodium and potassium increased in both groups. In G1 Na_u⁺ and K_u⁺ increased by 82.2% and 82.6% respectively, while in G2 the increase was less marked (18.2% and 61.2%). Body weight, heart rate, systolic blood pressure and

diastolic blood pressure did not change significantly in either group (Table 2). The clinical tolerance of the drug throughout treatment was good. No side-effects or changes in the haematological parameters were

Figure 1 Behaviour of diuresis, plasma creatinine and creatinine clearance in two groups of patients (a) normal and (b) impaired renal function) treated orally with SB 7505 (100 mg/day for 7 days).

observed. No variation was detected in the daily urinary excretion of lysozyme and γ GT, as well as in the urinary microscopic test for cells and casts.

Figure 2 Behaviour of plasma concentration and urinary excretion of Na^+ and K^+ in two groups of patients (a) normal and (b) impaired renal function) treated orally with SB 7505 (100 mg/day for 7 days).

Table 2 Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and body weight before and after treatment with SB 7505: mean values $\pm$ s.e. mean. No statistical difference was observed after Student's *t*-test for paired samples.

	Group 1		Group 2	
	Before	After	Before	After
HR (beats/min)	75.3 $\pm$ 1.9	76.3 $\pm$ 1.5	72.4 $\pm$ 1.3	73.7 $\pm$ 1.2
SBP (mmHg)	116.7 $\pm$ 5.7	119.2 $\pm$ 5.5	135.2 $\pm$ 4.0	137.6 $\pm$ 5.0
DBP (mmHg)	71.7 $\pm$ 3.8	72.5 $\pm$ 4.2	88.5 $\pm$ 3.2	89.3 $\pm$ 3.4
Body weight (kg)	60.3 $\pm$ 6.8	60.1 $\pm$ 6.9	71.7 $\pm$ 6.0	71.4 $\pm$ 5.7

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Discussion

Our results confirm that the action of SB 7505 extends to the human kidney. It proved to be active, albeit to a differing degree, in patients with normal and impaired renal function.

SB 7505 is structurally related to dopamine and its pharmacological action is probably due to this structural similarity. Studies on intravenously administered dopamine (Breckenridge, Orme & Dollery, 1971; Goldberg, 1974; Wilson, 1977; Baglin, Goupil, Domart & Fritel, 1979) show physiological and functional effects on the kidney similar to those we obtained with oral administration of SB 7505.

In patients with normal renal function the drug induces a marked and prompt increase in urinary excretion of water, sodium and potassium. At the same time the decrease in plasma values of the last two electrolytes does not give rise to any variations detectable clinically or by ECG. Diuresis increases even in patients with renal impairment, though less than in normal subjects. Here, too, there is an increase in urinary excretion of sodium and potassium, although to a lesser degree. As far as plasma creatinine and creatinine clearance are concerned, both groups show a decrease in the former and an increase in the latter.

Lastly the absence of variations in the daily urinary excretion of lysozyme and γ GT rules out any direct nephrotoxic action deriving from SB 7505.

The results of this preliminary study seem encouraging and further studies are called for to investigate the most appropriate clinical employment on renal impairment of this promising drug.

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