Single-dose effects of ibopamine hydrochloride on renal function in patients with congestive heart failure

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To examine the renal effects of ibopamine HCl we evaluated 15 patients with New York Heart Association Class II–III congestive heart failure and mild renal insufficiency (creatinine clearance [CL_{cr}] = 45–85 ml min⁻¹). Diuretics and vasodilators were withheld and a sodium (Na⁺)-restricted diet was initiated. All patients exhibited positive Na⁺ balance at the time of evaluation. Hourly urine volumes, urine chemistries, serum chemistries, PAH and inulin/iothalamate clearances were determined 2 h pre and 4 h post a single 200 mg oral dose of ibopamine. Effective renal plasma flow, creatinine clearance, filtration fraction, and the fractional excretion of sodium and potassium were not significantly altered postdose. A significant increase in urine output and decrease in urine osmolality were seen at all time points postdose. A significant reduction in serum potassium (2 and 3 h) and blood urea nitrogen (1, 3 and 4 h) concentrations occurred. Measurements of glomerular filtration rate by inulin or [¹²⁵I]-iothalamate produced differing results in the patient groups studied. We conclude that a single dose of ibopamine does not produce significant improvements in renal function in patients with congestive heart failure, mild renal insufficiency and positive sodium balance.

Keywords ibopamine congestive heart failure renal insufficiency renal plasma flow creatinine clearance

Introduction

Ibopamine HCl is an orally active diisobutyric ester of *N*-methyldopamine undergoing clinical evaluation in the management of symptomatic congestive heart failure (Dei Cas *et al.*, 1980; Leier *et al.*, 1986; Reffo *et al.*, 1984; Ren *et al.*, 1983, 1984). Pharmacologically, ibopamine and its metabolites possess unique dopaminergic, α - and β -adrenoceptor agonist properties (Dei Cas *et al.*, 1982, 1983). In theory, activation of these receptors augments cardiac inotropy and

renal blood flow. Stefoni and associates (1981) have previously demonstrated that ibopamine causes a dramatic increase in creatinine clearance in normal subjects and in patients with varying degrees of chronic renal failure. The objective of the present investigation was to characterize the effects of a single 200 mg dose of ibopamine on renal function in patients with congestive heart failure, mild renal insufficiency and positive sodium balance.

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Methods

The trial group was comprised of 15 subjects (fourteen male and one female) with New York Heart Association Functional Class II-III congestive heart failure and mild renal insufficiency (creatinine clearance 45–85 ml min⁻¹). The age range was from 54 to 74 years (mean = 62.8 years).

Vasodilators, β -adrenoceptor blocking agents and dopamine antagonists were discontinued 72 h prior to the trial to determine creatinine clearance and sodium balance. Patients were then admitted to the research unit for 2 days prior to the study day and placed on a 4 g NaCl/day diet and daily 24 h urine collections were obtained. On the study day, an intravenous catheter was placed in an arm vein for the administration of *p*-aminohippurate (PAH) (Merck, Sharp & Dohme; West Point, PA) and inulin (American Critical Care; McGraw Park, IL) (University Hospitals of Cleveland) or PAH and [¹²⁵I]-iothalamate (Isotex; Friendswood, TX) (Loma Linda, CA). Then, a water load of 10 ml kg⁻¹ over 45 min was administered. All urinary water losses thereafter were replaced ml for ml. Priming doses of PAH (8 mg kg⁻¹) and inulin (50 mg kg⁻¹) or [¹²⁵I]-iothalamate (10–20 μ Ci) were administered and followed by a main-

tenance infusion based on estimated glomerular filtration rate or effective renal plasma flow. Hourly urine volumes, urine chemistries, serum chemistries, PAH and inulin/iothalamate clearances were determined for 2 h before and 4 h after a single oral 200 mg (conventional) dose of ibopamine.

The plasma and urine concentrations of PAH and inulin were determined using methods previously described by Smith (1976). [¹²⁵I]-iothalamate concentrations were determined by gamma counting (Beckman Gamma Counter 8200, San Ramon, CA). Renal clearances, filtration fraction, and fractional excretion rates were calculated and expressed per 1.73 m² body surface area. The resultant data was statistically analyzed by Student's *t*-test for paired data and analysis of variance, with each time point post-dose being compared separately to the baseline value. A *P* value < 0.05 was considered to be statistically significant.

Results

Urine data (Tables 1 and 2).

A rapid rise in urine output occurred immediately after ibopamine administration. The volume

Table 1 Urine and blood changes occurring after single dose of ibopamine

	Baseline=	Time after ibopamine administration* (h)			
		1	2	3	4
<i>Urine</i>					
Volume (ml h ⁻¹)	307 $\pm$ 186	414 $\pm$ 203*	384 $\pm$ 178*	387 $\pm$ 164*	369 $\pm$ 164*
Osmolality (mmol kg ⁻¹)	146 $\pm$ 82	102 $\pm$ 47†	129 $\pm$ 99*	101 $\pm$ 47†	105 $\pm$ 46*
<i>Blood</i>					
Osmolality (mmol kg ⁻¹)	284 $\pm$ 6	281 $\pm$ 10*	283 $\pm$ 6*	281 $\pm$ 6†	281 $\pm$ 6*
Sodium (mmol l ⁻¹)	135 $\pm$ 3	136 $\pm$ 3	136 $\pm$ 3	136 $\pm$ 3	136 $\pm$ 3
Potassium (mmol l ⁻¹)	4.1 $\pm$ 0.5	4.1 $\pm$ 0.5	3.9 $\pm$ 0.5*	3.9 $\pm$ 0.4*	4.0 $\pm$ 0.6*
Creatinine (mg dl ⁻¹)	1.2 $\pm$ 0.3	1.2 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3
Urea nitrogen (mg dl ⁻¹)	17.2 $\pm$ 9.1	16.6 $\pm$ 9.1*	16.6 $\pm$ 8.8*	16.3 $\pm$ 8.9*	16.2 $\pm$ 9.1*

Values are mean $\pm$ s.d. for 15 samples.

= Baseline values are mean $\pm$ s.d. of data at -2 and -1 h before ibopamine administration (30 samples).

* *P* < 0.01 by ANOVA

† *P* < 0.05 by ANOVA

Table 2 Calculated renal function parameters

	Baseline=	Time after ibopamine administration* (h)			
		1	2	3	4
Creatinine clearance (ml min ⁻¹)	48 ± 19	47 ± 13	46 ± 15	45 ± 14	48 ± 13
Renal plasma flow (ml min ⁻¹)	107 ± 58	104 ± 47	103 ± 41	112 ± 56	111 ± 48
Gomerular filtration rate (ml min ⁻¹)					
Inulin	44 ± 14	42 ± 12	34 ± 7†	38 ± 12	42 ± 12
Iothalamate	32 ± 16	37 ± 14	44 ± 18	42 ± 12	42 ± 18
Filtration fraction					
Inulin	0.38 ± 0.09	0.38 ± 0.21	0.36 ± 0.23	0.31 ± 0.09*	0.33 ± 0.12
Iothalamate	0.43 ± 0.20	0.59 ± 0.32	0.58 ± 0.34	0.60 ± 0.30	0.57 ± 0.27
Fractional excretion of sodium (%)					
Inulin	1.1 ± 0.8	1.2 ± 0.9	1.4 ± 0.7	1.2 ± 0.7	1.1 ± 0.6
Iothalamate	0.5 ± 0.6	0.4 ± 0.5	0.4 ± 0.4	0.4 ± 0.6	0.3 ± 0.3
Fractional excretion of potassium (%)					
Inulin	21 ± 9	20 ± 9	20 ± 9	17 ± 6	16 ± 4
Iothalamate	17 ± 11	17 ± 9	18 ± 11	16 ± 10	14 ± 7

Postdose values are mean ± s.d. for 15 samples; except where broken down into individual variables for inulin (*n* = 8) and iothalamate (*n* = 7).

= Baseline values are mean ± s.d. of data at -2 and -1 h before ibopamine administration (30 samples)

* *P* < 0.01 by ANOVA

† *P* < 0.05 by ANOVA

measured increased from a mean baseline 307 ± 186 ml h⁻¹ to a peak of 414 ± 203 ml h⁻¹ (+ 35%) within 1 h. Thereafter, all urine outputs steadily declined to 384 ± 178 ml h⁻¹ (+ 25% over baseline) to 387 ± 164 ml h⁻¹ (+ 26%) to 369 ± 164 ml h⁻¹ (+ 20%) at 2, 3 and 4 h postdose, respectively. All values were shown to be statistically significant (*P* < 0.01) postdose.

Urine osmolality was low during all collection intervals and remained relatively stable at this level throughout. Osmolality declined from a mean baseline of 146 ± 82 mmol kg⁻¹ to 102 ± 47 mmol kg⁻¹ within 1 h and reached a trough at 101 ± 47 mmol kg⁻¹ water by 3 h. All values postdose were statistically significant.

Renal function parameters

Creatinine clearance and effective renal plasma flow showed no statistically significant change at any time point after ibopamine administration. Measurement of glomerular filtration rate pro-

duced conflicting results. Since inulin and [¹²⁵I]-iothalamate were used (at different study centers) to assess this variable, both sets of values are reported. Inulin demonstrated a drop in glomerular filtration rate to a trough (-22.5%) at 2 h postdose and a return to baseline by 4 h postdose. Conversely, [¹²⁵I]-iothalamate demonstrated a rise in glomerular filtration rate to a peak (+ 37.7%) at 2 h postdose and a much slower return to baseline.

Blood data

Overall, serum chemistries were normal throughout the study period. However, potassium and blood urea nitrogen concentrations fell significantly after ibopamine administration. Potassium concentrations declined from 4.1 ± 0.5 mmol l⁻¹ to 3.9 ± 0.4 mmol l⁻¹ at 2 and 3 h postdose (*P* < 0.01). Blood urea nitrogen concentrations fell from 17.2 ± 9.1 mg dl⁻¹ to 16.2 ± 9.1 mg dl⁻¹ (*P* < 0.01) at 4 h postdose.

Discussion

In the present study, ibopamine failed to demonstrate a significant improvement in renal function parameters, namely creatinine clearance, effective renal plasma flow or glomerular filtration rate. These results may reflect the initial water loading of 10 ml kg^{-1} , and their subsequent ml for ml replacement (mean water load 767 ml/subject). Patients were maintained at this initial level of hydration for 3 h prior to dosing, in a steady state manner.

The expected effects from the absorption of a large fluid volume should be a decrease in the extracellular fluid osmolality. Osmoreceptors continually monitoring concentration changes reflexly inhibit arginine vasopressin secretion. The arginine vasopressin reduction decreases water permeability in the distal segments of the nephron. Sodium is therefore reabsorbed normally but water is unable to follow. Thus, a large volume of dilute urine is excreted.

The above theory closely mirrors the findings in this investigation. Urine output dramatically increased for several hours post ibopamine administration. Also, urine osmolality and electrolyte concentrations were significantly reduced. No saluresis or kaliuresis was shown to occur. Creatinine clearance and effective renal plasma flow were relatively unaltered or shown to improve marginally. Unfortunately, no serum ibopamine or epinine concentrations were measured to aid in further validating actual pharmacologic intervention. The increase in urine output may be drug induced, however, the possibility that the diuresis seen was purely a result of water loading cannot be excluded as this trial contained no control phase which could be used for comparative purposes.

The effects of ibopamine on glomerular filtration rate in the population studied is unclear. Measurements were made on this variable by the administration of inulin ($n = 8$) or [^{125}I]-iothalamate ($n = 7$). In each instance though, a considerably different result was reported. In the inulin group, glomerular filtration rate declined after ibopamine administration and eventually returned to baseline. The [^{125}I]-

iothalamate group, glomerular filtration rate rose over time and remained elevated. However, in both groups, glomerular filtration rate was similar by the fourth h. Close analysis of the differences (age, gender, aetiology and severity of congestive heart failure, incidence of hypertension, incidence of coronary artery disease and renal function) between the study populations at both sites showed only that a slight difference in renal function existed. The group which received inulin had a mean creatinine clearance of 55 ml min^{-1} whereas the group receiving [^{125}I]-iothalamate had a mean creatinine clearance of 40 ml min^{-1} . Thus, it is possible that ibopamine might have had a more beneficial effect on glomerular filtration rate in the group with poorer renal function. There is indirect evidence, that patients with severe renal impairment show delayed renal decline for 6–12 months post ibopamine chronic administration (Docci *et al.*, 1986; Stefoni, 1982). However, we feel that further investigation into ibopamine's effect on this variable is needed as the subgroup sample sizes are much too small to warrant such a firm conclusion.

Conclusion

In conclusion, we find that a single oral 200 mg dose of ibopamine did not produce a significant improvement in renal function parameters in patients with congestive heart failure, mild renal insufficiency and positive sodium balance. A statistically significant increase in urine volume and decrease in urine osmolality, serum potassium and urea nitrogen concentrations were seen following ibopamine administration. Some of these may be artifacts due to water loading. Further investigation into the effects of ibopamine on glomerular filtration rate are warranted.

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