Renal and neurohumoral effects of ibopamine and metoclopramide in normal man

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The effects of 100 mg ibopamine, an orally active nonselective dopamine agonist on renal haemodynamics, sodium excretion, blood pressure (BP), heart rate (HR) and neurohumoral parameters were investigated in 10 healthy volunteers, with and without metoclopramide pretreatment. A small and temporary rise of glomerular filtration rate (GFR) was found after ibopamine without but not with metoclopramide pretreatment. No differences in effective renal plasma flow (ERPF) but a small rise in sodium excretion were observed comparing ibopamine with control. Metoclopramide induced a fall in sodium excretion which was not reversed by ibopamine. Ibopamine failed to affect BP and HR and no changes of PRA or plasma aldosterone concentration (PAC) were found. Metoclopramide induced a pronounced increase of PAC which was blunted by ibopamine. Plasma and urinary catecholamines were unchanged for all study days. We conclude that ibopamine induces natriuresis probably not by the observed small and temporary renal haemodynamic effects but by direct stimulation of DA₁ dopamine receptors in the proximal tubule.

Keywords ibopamine metoclopramide renal function dopaminergic agent

Introduction

Dopamine induces renal vasodilation and natriuresis (Cavero *et al.*, 1987; Smit *et al.*, 1988). The need for parenteral administration limits its application. Ibopamine is de-esterified to epinine (methyl-dopamine) after oral administration. Epinine is known to stimulate dopamine receptors and to a lesser degree adrenergic receptors (Nichols *et al.*, 1987; Rajfer *et al.*, 1986). Ibopamine is mainly used in patients with congestive heart failure (Ghirardi *et al.*, 1985; Van Veldhuisen *et al.*, 1989). In healthy volunteers no renal function studies have been performed with simultaneous measurements of GFR and ERPF. In the present study we assessed the effects of ibopamine on GFR and ERPF and sodium excretion, with and without pretreatment of the aspecific dopamine antagonist metoclopramide.

Methods

Ten healthy volunteers, four males and six females, mean age 27 years, (range 18–48) were studied. All gave written informed consent and the study was approved by the hospital ethics committee. All volunteers were in-

structed to adhere to a 150 mmol sodium/day diet for at least 4 days before the studies. At the start of each study day a water load of 300 ml was given and throughout the studies 300 ml h⁻¹ of water. Glucose 5% 100 ml h⁻¹ was infused intravenously. Three renal function studies were performed in random order, being separated by at least 3 days each. On study day A only vehicle was infused. On study day B after two baseline values 100 mg ibopamine was administered orally. On study day C, after two baseline values, metoclopramide was infused: 10 mg 30 min⁻¹, followed by 10 mg h⁻¹ for the rest of the study. Ibopamine was given 2 h after the start of metoclopramide.

GFR and ERPF were measured hourly using [¹²⁵I]-iothalamate and [¹³¹I]-hippurate, respectively (Donker *et al.*, 1977). Ibopamine tablets 100 mg were provided by Zambon Laboratories. Hourly urine portions were examined for electrolytes. Blood samples for plasma renin activity (PRA) and PAC and catecholamines were withdrawn at the end of the baseline period and 2 and 4 h (for C also 6 h) later. PRA and PAC were determined by radioimmunoassay. Urine dopamine and plasma dopamine, adrenaline and noradrenaline were determined by h.p.l.c. Heart rate and blood pressure were

recorded every 15 min using an automatic noninvasive device (Oxford Accutracker). All data unless otherwise mentioned, are given as mean $\pm$ s.d. and/or 95% confidence intervals. In the figures data are given as mean $\pm$ s.e. mean. All the values for ERPF and GFR were corrected for a body surface of 1.73 m². Paired *t* statistics were calculated for differences at specific time points on study day A compared with B and C with corrections for multiple comparisons according to Duncan. Analysis of variance was employed to demonstrate differences among groups over time. Differences were considered statistically significant at the 5% level.

Results

Effects on blood pressure and heart rate

No changes were found in blood pressure and heart rate during the study days or between the different study days. Overall blood pressure and heart rate averaged 115/70 mm Hg and 65 beats min⁻¹, respectively.

Effects on renal haemodynamics (Table 1)

No differences between the study days were found except a significant increase of GFR on study day B 1 h after ingestion of ibopamine: GFR was 111 $\pm$ 19 for A, vs 122 $\pm$ 18 ml min⁻¹ for B. No significant changes in ERPF were found both during and between all study days. Filtration fraction increased for all study days when compared with baseline values. However, no significant differences between the study days were found.

Effects on sodium and potassium excretion (Figure 1)

Baseline sodium excretion was comparable on all study days.

In a comparison of differences at matched time points an increase in hourly sodium excretion after ibopamine administration was observed which did not reach significance. However, cumulative sodium excretion increased significantly after ibopamine administration.

Metoclopramide resulted in a significant fall in sodium excretion which was not reversed by subsequent ibopamine administration.

Figure 1 Natriuresis is shown both as hourly absolute and fractional excretion. A trend of increased sodium excretion is noticed, which did not reach significance for hourly values. However, cumulative natriuresis (during 4 h) showed a significant increase due to ibopamine. Ibopamine did not reverse the decrease in sodium excretion due to metoclopramide. An asterisk indicates a significant difference compared with the control study ($P < 0.05$). Mean and s.e. mean are shown for a) and b) and 95% CI for c). Δ control, $\square$ ibopamine, ∇ ibopamine plus metoclopramide (mcp).

Table 1 Effects on GFR and ERPF (ml min⁻¹ 1.73 m⁻²); 95% confidence intervals are given. Ibopamine induces a small transient 10% increase of GFR, 1 h after ibopamine ingestion. An asterisk indicates a significant difference compared with the control study ($P < 0.05$)

	<i>Baseline</i>	<i>Baseline</i>	<i>1 h</i>	<i>2 h</i>	<i>3 h</i>	<i>4 h</i>		
<i>A (control study)</i>								
ERPF	408–566	399–574	385–545	402–573	427–568	425–576		
GFR	97–123	99–128	97–125	102–134	107–137	110–142		
<i>B (ibopamine)</i>								
ERPF	406–550	401–538	425–550	400–516	429–543	420–548		
GFR	99–124	100–129	109–134*	107–129	110–143	108–136		
	<i>Baseline</i>	<i>Baseline</i>	<i>Mcp</i>	<i>Mcp</i>	<i>1 h</i>	<i>2 h</i>	<i>3 h</i>	<i>4 h</i>
<i>C (ibo + mcp)</i>								
ERPF	396–553	401–545	393–511	388–547	406–557	409–522	397–526	407–548
GFR	98–120	101–122	100–120	102–128	106–130	105–121	106–125	107–129

Identical results were found for absolute and fractional sodium excretion. For potassium excretion all baseline values were comparable and no significant differences between the study days existed.

Effects on PRA and PAC

No significant differences in baseline values for both PRA and PAC were found. No significant changes in PRA occurred on any study days. No changes in PAC were found during study day A and B. During study day C PAC rose significantly during metoclopramide infusion from 0.22 ± 0.21 to 0.92 ± 0.42 nmol l⁻¹. After subsequent ibopamine administration PAC fell significantly compared to the value during metoclopramide alone to 0.52 ± 0.23 nmol l⁻¹ but remained above baseline and control study values.

Effects on catecholamines

Baseline values for plasma and urinary catecholamines were comparable on all study days and no changes occurred during the study days. This applied to noradrenaline, adrenaline and dopamine.

Discussion

In healthy volunteers renal haemodynamic effects of ibopamine have been assessed only by calculation of endogenous creatinine clearances (Harvey *et al.*, 1984; Incerti *et al.*, 1986; Stefoni *et al.*, 1981), with the exception of a small study by Britton who measured ERPF (Britton *et al.*, 1986). A pronounced increase in creatinine clearance with a dose of 50 mg was found in an acute open study by Incerti *et al.* (1986). In contrast, in a controlled study by Harvey *et al.* (1984) 150 and 600 mg ibopamine caused no changes in creatinine clearances. Britton *et al.* (1986) unexpectedly found a fall in ERPF after 200 or 600 mg ibopamine. In an experimental study in dogs intravenous ibopamine resulted in a dose-dependent increase in renal blood flow (Nichols *et al.*, 1987). Our results show no changes of ERPF and a small and temporary 10% rise of GFR after administration of 100 mg ibopamine which was not present during simultaneous infusion of the asselective dopamine antagonist metoclopramide. This suggests a dopamine-receptor mediated mechanism for this ibopamine-induced rise in GFR. On the one hand the lack of increase of ERPF might be the result of a balance between the expected DA₁ dopamine receptor induced renal vasodilation,

reversed by α -adrenoceptor agonist properties of ibopamine. On the other hand one might argue that only weak DA₁-receptor stimulation is present after oral ibopamine. However, ibopamine did induce a small but significant rise in cumulative sodium excretion. This may be due to direct stimulation of DA₁ receptors in the proximal tubule (Felder *et al.*, 1984). In open uncontrolled studies a pronounced natriuretic effect was found in normals and in patients with liver cirrhosis (Incerti *et al.*, 1986; Salerno *et al.*, 1990; Stefoni *et al.*, 1981). In controlled studies the results are conflicting. Melloni *et al.* (1981) report a marked natriuresis due to ibopamine 50 mg twice daily, while Harvey *et al.* (1984) did not observe any effects on natriuresis in an acute study with 150 and 600 mg ibopamine. Metoclopramide alone induced a fall in natriuresis, which was not reversed by ibopamine. In earlier studies from our institution intravenous dopamine, in doses ranging from 0.5 to 8.0 μ g kg⁻¹ min⁻¹ was capable of reversing this effect of metoclopramide (Smit *et al.*, 1988). We conclude that renal dopaminergic effects of ibopamine in the dose used in our study are moderate in healthy volunteers.

In an acute uncontrolled study ibopamine decreased PAC in patients with severe congestive heart failure (Nakano *et al.*, 1986). PAC is elevated in patients with congestive heart failure. In our volunteers, with unstimulated aldosterone secretion, no changes in PAC were seen after ibopamine alone. This is probably due to tonic suppression of aldosterone secretion by endogenous dopamine which is also illustrated by the rise of PAC during metoclopramide (Noth *et al.*, 1980). The suppression of metoclopramide-induced increases in PAC by ibopamine may be due to DA₂ dopamine receptor stimulation by ibopamine. Since we did not perform infusions of only metoclopramide lasting longer than 2 h, one might argue that the lowering of aldosterone is a time-related effect, and not due to ibopamine. However, Gordon *et al.* (1983) found no evidence for such a time-related effect during a 240 min infusion of metoclopramide.

In patients with congestive heart failure ibopamine lowered noradrenaline levels (Rajfer *et al.*, 1986; Van Veldhuisen *et al.*, 1989). In our volunteers no changes in plasma noradrenaline were seen. Possibly, DA₂ receptor stimulation by ibopamine has no role in suppression of noradrenaline release in the unstimulated orthosympathetic nervous system, but is relevant during sympathetic-adrenal stimulation in congestive heart failure, as suggested earlier by Mannelli *et al.* (1988).

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