Lack of effect of ibopamine, a dopamine pro-drug, on renal function in normal subjects

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1 The effects of two single oral doses of ibopamine (150 and 600 mg) on heart rate, blood pressure, urine flow, sodium, potassium and creatinine excretion were studied in normal volunteers.

2 No significant change was observed in urine flow, sodium, potassium or creatinine excretion at either dose.

3 No significant change was observed in heart rate or blood pressure except that systolic blood pressure was transiently elevated after the 600 mg dose ($P < 0.05$).

Keywords ibopamine renal dopamine diuresis natriuresis epinine

Introduction

Receptors for dopamine have been identified in many peripheral tissues (Goldberg, 1972) including the renal vasculature. Goldberg and co-workers have shown that the renal vascular dopamine receptor has highly specific structural requirements (Goldberg *et al.*, 1968, 1978a, 1978b) and that only substitutions at the *N*-position of the dopamine molecule retain agonist activity. Epinine (*N*-methyl dopamine, Figure 1)

was found to be an agonist of similar potency to dopamine as measured by its effect on renal blood flow in pentobarbitone anaesthetised dogs in the presence of phenoxybenzamine: the α -adrenoceptor activity of epinine was greater than that of dopamine (Goldberg *et al.*, 1968). Dopamine infusion in man produces a marked increase in glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and urinary

Figure 1 Structural formulae of dopamine, epinine and ibopamine.

sodium ($U_{Na}V$), with a slight increase in urinary potassium (U_KV) (McDonald *et al.*, 1964) but is of value only for intravenous use as a result of its short half-life. Recently, ibopamine (Simes S.p.A., Milan) the di-isobutryl ester of epinine (Figure 1) has become available for clinical trials. Ibopamine was expected to be well absorbed orally and to be de-esterified in the gut and liver to release epinine into the circulation. Randolph *et al.* (1983) have shown with studies in the rat, dog and man that orally administered ibopamine is de-esterified to give measurable circulating levels of epinine. When carbon-14 labelled ibopamine was given to dog and rat the plasma levels of epinine and its conjugates constituted 50% of total drug related material in the dog and greater than 75% in the rat. The dose given to the dog (5 mg/kg) was of the same order as the dose we have given to man, but the dose given to the rats was greater (180 mg/kg). The activity of the other drug related material they found is unknown but unchanged ibopamine would be inactive at the dopamine receptor owing to the butyryl moieties on the catechol ring (Goldberg *et al.*, 1968). Randolph *et al.* (1983) demonstrated that epinine undergoes substantial hepatic conjugation: in male subjects who received a 600 mg oral dose of ibopamine the area under the mean plasma concentration curve for epinine alone was less than 2% of that for epinine and epinine conjugates (from 0 to 6 h).

The effect of ibopamine on renal function in six normal subjects and six patients with chronic renal failure was studied by Stefoni *et al.* (1981) who, at a dose of 50 mg twice daily, showed a rise in urine volume, $U_{Na}V$, U_KV and creatinine clearance (with a fall in plasma creatinine) in both groups which increased progressively over the course of a week. All these results, with the exception of urine volume in the renal failure patients, attained statistical significance at a level of at least $P < 0.05$. If these impressive results could be confirmed the drug would clearly have a therapeutic role as a diuretic and might be of unique value in increasing the glomerular filtration rate in patients with chronic renal failure. The present study was designed to examine the acute effect of single doses of ibopamine in healthy volunteers.

Methods

All subjects were healthy male volunteers between the ages of 20 and 50 years who had given informed consent. They were studied in accordance with the Declarations of Helsinki and Tokyo. The ethical committee of the General Infirmary at Leeds gave its approval to the proto-

col. In the first part of the study 10 subjects, mean ($\pm$ s.e. mean) age 31.9 ($\pm$ 2.0) years, mean weight 71.0 ($\pm$ 3.1) kg were given 150 mg of ibopamine by mouth. In the second part a further six subjects, mean age 32.5 ($\pm$ 3.3) years, mean weight 71.3 ($\pm$ 3.7) kg were given 600 mg of the drug by mouth. All individuals were studied on two days separated by at least a week. On one day they received an active drug and on the other day placebo in double blind crossover fashion. Subjects were asked to take a light breakfast on the study days without salty food; xanthine-containing drinks (tea, coffee, cocoa, cola) were to be avoided for 12 h; and alcohol for 24 h before the study. The subjects remained seated during the period of the experiment from 10.00 h to 16.00 h, except when passing urine. Ibopamine (or placebo) was taken at midday (0 h) with the proceeding 2 h constituting a run-in period during which baseline measurements were made. In order to maintain an adequate urine volume subjects were hydrated with 500 ml of distilled water at -2, 0 and 2 h. The pulse rate was measured every 15 min and the blood pressure in duplicate ever 30 min during a Dinamap monitor (Critikon Ltd). Timed urine collections were made from -2 to 0; 0 to 2; and 2 to 4 h; and a further collection made overnight from 4 to 24 h. Aliquots from these collections were assayed by the Department of Chemical Pathology using standard techniques for sodium, potassium and creatinine content. The laboratory was not aware of the study design. Venous blood samples taken at -2, 0, 2, 4 and 24 h allowed calculation of the plasma creatinine at the mid-point of each urine collection period and therefore the creatinine clearance. Samples of venous blood for determination of plasma renin activity (PRA) were taken at 0, 2 and 4 h, into tubes containing dipotassium EDTA as an anticoagulant. These specimens were immediately centrifuged at 2000 rev/min at 4°C for 5 min and then the plasma removed for storage at -20°C. PRA was assayed at a later date by incubation to form angiotensin I and determination of the peptide by radioimmunoassay (Haber *et al.*, 1969). In order to detect any damage to bone marrow or liver, venous blood was taken for full blood count; differential white cell count; and liver enzymes (aspartate transaminase, alanine transaminase, alkaline phosphatase, lactic dehydrogenase and γ -glutamyl transferase) before and 24 h after, receiving ibopamine or placebo.

Statistical analysis of the results was carried out by repeated measures analysis of variance using the statistical package BMDP 2V (Dixon & Brown, 1979). Analysis of single means after analysis of variance was carried out by the Newman-Keuls test (Winer, 1971).

Results

In the subjects given 150 mg of ibopamine the mean urine flow rate showed a slight increase compared to the run-in period but no definite change when compared to placebo (Figure 2). The mean sodium and potassium excretion rates tended to fall slightly over the course of the experiment because the subjects received only distilled water during their 6 h in the laboratory. There was no significant difference between active drug and placebo groups in relation to electrolyte excretion. Estimates of mean creatinine clearance showed no change throughout the experiment in either ibopamine or control group. Those subjects given 600 mg of ibopamine did appear to show an increase from baseline values of mean urine flow rate, in the first 2 h after receiving the active drug (Figure 3). This apparent rise in urine flow was not significantly different from the effect of placebo and was not accompanied by any increase in sodium excretion. As in the 150 mg study the sodium and potassium excretion rates both fell during the course of the experiment. The fall was less

marked in those given ibopamine but not significantly so. The creatinine clearance again did not change during the course of the study.

Measurements of pulse and blood pressure by the automatic method showed no significant difference between the ibopamine and placebo treated groups at the lower dose level (Figure 4); but at the higher dose level (Figure 5) the response of the systolic blood pressure (SBP) was significantly different ($P < 0.05$) from placebo when compared by analysis of variance. There was a rise in SBP maximal 30 min after oral dosing (Figure 5); and when individual means were compared by the Newman-Keuls test this was significantly greater ($P < 0.05$) than the mean SBP at 30 and 90 min before administration of the drug. Two hours after taking ibopamine the SBP had fallen to a level significantly different ($P < 0.05$) from the peak SBP. Comparisons of other individual means did not achieve statistical significance. There was a transient fall in mean SBP 60 min after taking placebo, which was significant ($P < 0.05$, Newman-Keuls) when

Figure 2 The effect of ibopamine 150 mg (▨) vs placebo (□) on renal function. The histogram represents the mean; with the bars denoting s.e. mean. Ibopamine or placebo was taken at time 0.

Figure 3 The effect of ibopamine 600 mg (▨) vs placebo (□) on renal function. The histogram represents the mean; with the bars denoting s.e. mean. Ibopamine or placebo was taken at time 0.

Figure 4 The effect of ibopamine 150 mg (○—○) or placebo (●—●) on pulse rate, systolic and diastolic blood pressure ($n = 10$). Ibopamine or placebo was taken at time 0.

compared with other means after and immediately before oral dosing.

When ibopamine was given at the lower dose, and in the placebo groups also, there was a small rise in PRA after 2 h compared with a fall when subjects were given 600 mg (Table 1). The change in PRA after 600 mg of ibopamine was not significantly different from control.

No serious adverse reactions were encountered and there was no change in any of the haematological indices or liver function tests. After ibopamine 600 mg two subjects experienced mild nausea and two experienced loose stools. Much more severe nausea and vomiting has been observed following the administration of structurally related *N*-dialkyl dopamine derivatives (Fennell *et al.*, 1983).

Discussion

McDonald *et al.* (1964) showed that infused dopamine has a pronounced effect on renal function in normal man. In their study mean $U_{Na}V$ increased from 171 to 575 $\mu\text{Eq}/\text{min}$. A comparable study with epinine has not been

done although since it has similar dopaminergic agonist activity at the renal vascular dopamine receptor (Goldberg *et al.*, 1968, 1978b) epinine derived from oral ibopamine was expected to be an effective natriuretic agent.

In this study ibopamine at a dose of 150 mg orally had no acute effect on renal or cardiovascular function. The extensive conjugation of epinine in plasma reported by Randolph *et al.* (1983) suggests considerable first-pass hepatic metabolism of the compound. In order to try and saturate this mechanism we increased the dose substantially to 600 mg. This dose also lacked a significant effect on water and electrolyte excretion. Despite the difference in study design the impressive results of Stefoni *et al.* (1981) led us to anticipate a measurable effect on renal function from single doses of ibopamine. An important difference in the Italian study was the continued administration of ibopamine for a period of 7 days. This regimen could have progressively saturated the hepatic conjugating mechanism although in general the catecholamines are subject to the phenomenon of tachyphylaxis on continued administration (Aviado,

Figure 5 The effect of ibopamine 600 mg (○—○) or placebo (●—●) on pulse rate, systolic and diastolic blood pressure ($n = 6$). Comparisons a:a, b:b, c:c and d with all SBP except e were significant ($P < 0.05$, Newman-Keuls). Ibopamine or placebo was taken at time 0.

1970). The progressively increasing effect which Stefoni *et al.* (1981) demonstrate in normal subjects leading to a considerable cumulative sodium deficit is difficult to account for. However, their study was not double-blind or placebo-controlled.

If sufficient free epinephrine is available to the kidney, its α -adrenoceptor activity resulting in renal vasoconstriction may be responsible for the lack of effects seen in our study. Such an explanation would account for the small rise in SBP seen at the higher dose. It has not been

Table 1 Effect of ibopamine or placebo on plasma renin activity (ng AI ml⁻¹ h⁻¹).

	Ibopamine 150 mg			Placebo		
Mean ($n = 10$)	2.4	3.6	2.6	2.3	2.7	2.1
s.e. mean	0.5	0.8	0.6	0.4	0.6	0.6
	Ibopamine 600 mg			Placebo		
Mean ($n = 6$)	3.6	3.0	2.6	2.6	3.3	2.7
s.e. mean	0.9	0.5	0.6	0.7	0.9	0.8
Time (h)	0	2	4	0	2	4

Values immediately before taking the drug and at 2 and 4 h afterwards. Ibopamine or placebo was taken at time 0.

shown that there is any low plasma level of epinine at which dopaminergic effects predominate, as there is with dopamine itself. The small rise in SBP after 600 mg ibopamine just achieved statistical significance and is compatible with a modest α -adrenergic effect or an inotropic effect. Groups in Italy (Dei Cas *et al.*, 1983), Belgium (Col *et al.*, 1983) and the USA (Leier *et al.*, 1983) have shown oral ibopamine, in single doses ranging from 100 mg to 300 mg, to increase the cardiac output in patients with congestive heart failure; which argues against an α -adrenoceptor agonist effect under these circumstances. However, in pentobarbitone anaesthetized dogs an infusion of epinine ($6 \mu\text{g kg}^{-1} \text{ min}^{-1}$) produced a pressor response and an increase in renal vascular resistance due to its α -adrenergic receptor activity, although vasodilation due to dopaminergic and β_2 -adrenoceptor activity could be demonstrated in the presence of phenoxybenzamine (Itoh *et al.*, 1983). When subjects were given 600 mg of ibopamine we observed a small fall in PRA although this result was not statistically significant. Such a trend is compatible with renal vasoconstriction and raised systemic arterial pressure.

In conclusion the results of our studies with ibopamine on renal function in normal volunteers are disappointing. If sufficient epinine

derived from oral ibopamine does escape hepatic first pass metabolism an α -adrenergic effect seems likely. Further studies on the pharmacology of epinine in man are needed. New orally active compounds are becoming available which resist first pass metabolism to a greater degree than ibopamine and are more specific for the renal vascular dopamine receptor. Fenoldopam is such a compound and has been shown to be an effective renal vasodilator (Stote *et al.*, 1983).

The search for an orally administered renally specific dopamine agonist is more than the quest for yet another diuretic. Our group has identified a defect in renal mobilisation of dopamine in essential hypertension (Perkins *et al.*, 1980) and in chronic renal failure (Casson *et al.*, 1983). An effective renal dopaminergic drug may have a salutary effect on urine sodium output and blood pressure in these conditions.

We are grateful to Smith, Kline and French for financial support and supplies of ibopamine; we acknowledge the assistance of Dr A. D. Clayden with the statistical analysis, the Department of Chemical Pathology for routine assays and Miss K. M. Milner and Mrs M. E. Smith for valuable secretarial assistance.

J.N.H. is supported by the National Kidney Research Fund and D.P.W. is a Squibb Research Fellow.

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(Received November 10, 1983,
accepted February 25, 1984)