Comparison of the effects of dopamine, dobutamine, and dopexamine upon renal blood flow: a study in normal healthy volunteers

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- 1 We compared the effects of dopexamine, dopamine and dobutamine on the heart rate, blood pressure and renal blood flow of six healthy volunteers in an open triple crossover trial.
- 2 The results suggest that at the dose ranges investigated dopamine was the most effective agent for increasing renal blood flow.

Keywords renal blood flow dopexamine

Introduction

Dopamine, an inotropic agent, is widely used to treat heart failure. At doses from $2\text{--}5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$, it has a selective effect on renal and mesenteric blood flow. This property is utilised to improve urine output by maintaining renal blood flow in low cardiac output states. At higher doses, this benefit is offset by α -adrenergic vasoconstriction.

Dobutamine on the other hand improves renal blood flow indirectly by increasing cardiac output and does not have any specific effect on renal artery calibre.

A structural analogue of dopamine has been developed, dopexamine hydrochloride (Fisons Pharmaceutical), which combines dopaminergic receptor agonist activity with a β -adrenoceptor agonist effect (Brown *et al.*, 1985b). Theoretically at least, this would improve renal blood flow in addition to reducing systemic vascular resistance and myocardial afterload.

This study compares the effects of dopexamine, dopamine and dobutamine on effective renal plasma flow (ERPF) and some cardiovascular parameters.

Methods

Six healthy, male, volunteers were studied. Written informed consent was obtained and the study was approved by the Hospital Ethics

Committee. Volunteers had a full medical examination, an ECG and haematological and biochemical profiles before inclusion. In addition all had refrained from alcohol and caffeine containing drinks for the previous 12 h but had been permitted to eat a light breakfast. Each volunteer was studied on three separate occasions, receiving a different drug (dopamine, dobutamine or dopexamine) in a randomised order. All drugs were mixed in 500 ml of normal saline. Incremental infusion rates of each drug were studied as follows: dopamine $2.5, 5, 10\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$; dobutamine $2.5, 5, 10\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$; and dopexamine $1, 2, 4\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$. These doses were chosen on the basis of previous pharmacological data (Fisons unpublished data).

Volunteers were semi-recumbent throughout the study. A 19 gauge cannula (Wallace Y-Can) was inserted, using local anaesthetic, into an antecubital vein and used for blood sampling. Another was inserted into a forearm vein of the other arm for the infusion of drugs and injection of isotopes.

The session was divided into five periods lasting 30 min each: a control period (without infusion of inotrope), followed by infusions of the low dose, intermediate dose, and high dose of the relevant agent, and then a recovery period. During the latter part of each period, measurements of pulse rate, blood pressure, and renal plasma flow were made. In addition blood

samples were taken at the end of both the control and recovery periods for haematological and biochemical estimations.

Measurements

ECG (lead II) was displayed throughout the study period. Blood pressure was measured by a semi-automatic auscultatory apparatus (Copal UA 251 electronic sphygmomanometer).

Renal plasma flow was estimated by measuring the clearance from plasma of sodium iodohippurate labelled with one of three isotopes of iodine. The labelled iodohippurate was injected 12 min after the start of each of the five periods and samples were taken 8, 13 and 18 min later for radioactivity measurements. ERPF was calculated from a semi-logarithmic plot of radioactive counts against time. The three points were joined using a least squares fit method. From this plot ERPF was calculated from the product of the volume of distribution (obtained by extrapolating the line back to time 0) and the gradient of the line. The method assumes that the radio-labelled iodohippurate is rapidly distributed and excreted, and the kinetics approximate to a single compartment model. Previous workers have demonstrated good correlation between this and direct measurements of renal plasma flow (Pritchard *et al.*, 1965; Tauxe *et al.*, 1971). In addition it has been shown that sampling at 9 and 18 min after injection of radioisotope is associated with the least estimation error when using a slope/intercept method for estimation of ERPF (Tauxe *et al.*, 1984).

Repeated measurements using tracers within a short period suffer from high background interference from previously injected radio-labelled material. This was overcome by using three different radiolabels (^{123}I , ^{125}I or ^{131}I) which are distinguished by different energy levels of radiation emission (Leach *et al.*, 1985). The fourth and fifth measurements used repeat in-

jections of the first two isotopes and there was therefore some loss of accuracy. However, hippuran clearance is rapid and this residual activity is relatively small so it can be largely obviated by using a quantitatively larger dose on the second and subsequent occasion. Background samples were taken for analysis before the fourth and fifth injections so that appropriate corrections could be applied.

Quantitative results were expressed as percentage change from the pre-infusion readings. The Wilcoxon matched pairs test was used for analysis of differences within treatment and between each treatment. Friedman two-way analysis of variance was applied to difference between the three treatments.

Results

The mean age, height and weight is shown in Table 1. During infusion of high dose dopamine one subject complained of severe nausea and the infusion had to be terminated before the ERPF estimate was completed. Another subject developed a bradycardia with first degree heart block at the end of the high dose dopamine infusion period. Otherwise the experiments were uneventful.

The initial values of heart rate, blood pressure and ERPF are presented in Table 2. The subsequent changes are expressed as percentages from these baseline values and are represented diagrammatically (Figure 1, 2 and 3).

Table 1 Biodata for the six volunteers

	Age (years)	Height (cm)	Weight (kg)
Mean	32	178.3	75.1
s.d.	3.9	6.3	6.7

Table 2 Group mean control values for heart rate, blood pressure and ERPF

	Heart rate (beats min ⁻¹)	Systolic BP (mmHg)	Diastolic BP (mmHg)	ERPF (ml min ⁻¹)
Dopamine	56 (2.7)	113 (4.2)	65 (1.9)	747 (41.1)
Dobutamine	57 (4.9)	118 (5.5)	65 (5.7)	781 (35.0)
Dopexamine	55 (6.5)	119 (5.7)	70 (3.4)	732 (37.2)

s.e. mean indicated in brackets.

Figure 1 Heart rate expressed as percentage of changes from baseline values after dopamine (●), dopexamine (○) and dobutamine (▲). (* $P < 0.05$; Bars are s.e. mean).

Figure 2 Systolic and diastolic blood pressure as expressed as percentage changes from baseline values after dopamine (●), dopexamine (○) and dobutamine (▲). (* $P < 0.05$; Bars are s.e. mean).

Figure 3 ERPF expressed as percentage changes from baseline values after dopamine (●), dopexamine (○) and dobutamine (▲). (* $P < 0.05$; Bars are s.e. mean).

Heart rate

Dopexamine caused a dose related increase in heart rate ($P < 0.05$) which reached a mean increase of 64.5% above the pre-infusion rate at the high dose. Dobutamine caused a significant rise in heart rate (mean rise of 23.9% above control) at the high dose only ($P < 0.05$). Dopamine had no effect on heart rate.

Blood pressure

Dopexamine caused a small rise systolic blood pressure (SBP) at all three doses ($P < 0.05$) but with no significant increase with increasing dose. Dobutamine caused a greater increase in SBP than dopexamine at the mid and high doses ($P < 0.05$). Dopamine caused a progressive rise in SBP which was significant at the mid and high doses ($P < 0.05$).

Mean diastolic blood pressure (DBP) fell progressively with all three drugs. However, for dopamine this fall was only significant at the high dose infusion with a mean fall of 35.2% below control ($P < 0.05$). In contrast all dose levels of dopexamine caused a progressive and compara-

tively greater fall in DBP ($P < 0.05$) with a mean fall of 38.1% of control at the high dose.

ERPF

Dopexamine caused a progressive rise in ERPF, significant at the mid and highest doses ($P < 0.05$). Dobutamine caused a small mean increase in ERPF at all dose levels none of which were significantly different from control. Dopamine caused a large rise in ERPF which was significant at all three dose levels ($P < 0.05$). The peak level occurred at the middle infusion rate ($5 \mu\text{g kg}^{-1} \text{min}^{-1}$) with a mean increase of 58.9% over the control. After administration of both dopamine and dopexamine infusions a persistently raised ERPF was still present 30 min later. However, this was only statistically significant for dopamine ($P < 0.05$).

Haematology and biochemistry

During the infusion with dopexamine there was a persistent fall in neutrophil and platelet counts (mean falls - 23.4% and 17.4% respectively; both significant at $P < 0.05$). One subject's

white cell count fell from 4.0/nl (54% neutrophils) to 2.5/nl (50% neutrophils) and his platelet count from 144,000/nl to 108,000/nl during the dopexamine infusion. A repeat estimate 3 days later was normal. There were no other effects on haematological or biochemical parameters.

Discussion

Our results suggest that dopexamine does have a specific effect on renal artery dopaminergic receptors, albeit to a lesser degree than dopamine. Work in dogs has demonstrated that dopexamine has a third of the potency of dopamine at dopaminergic type₁ receptors (DA₁), such as those found in mesenteric and renal vessels, and between a quarter and a sixth the potency at dopaminergic type₂ receptors (DA₂) (Brown *et al.*, 1984). The results of this study suggest a similar relationship in man.

The dose range of 1–4 µg kg⁻¹ min⁻¹ dopexamine which was chosen, does not enable us to determine whether dopexamine has the same efficacy as dopamine. There was no peak in ERPF which may occur at a higher dose. However the tachycardia caused by dopexamine appears to be dose-dependent and this would be a problem with using higher doses. Indeed one volunteer had a pulse rate of 132 beats min⁻¹ at the higher dose range. The cause of the tachycardia is probably a compensatory reflex due to a fall in peripheral vascular resistance secondary to β₂-adrenoceptor stimulation, although a slight β₁-adrenoceptor agonist effect may occur. This can be blocked with β-adrenoceptor blockers in dogs. In addition, further work in dogs anaesthetised with pentobarbitone (which suppresses this reflex) has demonstrated that there is a less of a tachycardia and a greater drop in blood pressure than seen in awake dogs (Brown *et al.*, 1985 b). Baroreceptor reflexes are reduced in patients with heart failure (Cohn & Franciosa,

1977) and thus dopexamine should produce less tachycardia in such patients (Brown *et al.*, 1985b). Indeed, there was less tachycardia in patients treated with dopexamine for chronic heart failure (Dawson *et al.*, 1985; Svenson *et al.*, 1986) than in our healthy volunteers.

All the drugs caused a rise in systolic blood pressure. For dopamine and dobutamine this appears to be dose related whereas for dopexamine this reaches a plateau at the low dose level. This agrees with previous experimental work which showed that a mild increase in contractility is achieved with dopexamine together with reduction in afterload (Jaski *et al.*, 1986).

Measurements of cardiac output would have been desirable and we had intended to use transcutaneous aortovelography for this purpose. Unfortunately, we were unable to get meaningful results at higher cardiac outputs, despite previous success in using this device in situations where cardiac output was near or lower than normal (in preparation). As the pulse became hyperdynamic aiming of the ultrasound beam became more difficult resulting in underreading of cardiac output. The consistent, small reductions in neutrophil and platelet counts were disconcerting. The speed at which the fall occurs suggests sequestration; there appear to be no long term ill effects, but as inotropes are generally used in sick patients whose white cell and platelet counts may already be low this effect should be further studied.

Although dopexamine increases ERPF at higher doses, this benefit appears to be outweighed by tachycardia at least in healthy volunteers with normal physiological responses. Dopexamine has been used with some success to treat patients with heart failure. The effect upon ERPF has not been established in these patients.

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References

- Brown, R. A., Farmer, J. B., Hall, J. C., Kasprzak, L., O'Connor, S. E., Smith, G. W. & Young, A. (1984). FPL 60278 (dopexamine): Actions at pre and postjunctional dopamine receptors and at alpha and beta-adrenoceptors. *Br. J. Pharmac.*, **81**, 120P.
- Brown, R. A., Brown, R. C., Hall, J. C., Dixon, J., Farmer, J. B., Foulds, R. A., Ince, F., O'Connor, S. E., Simpson, W. T., Smith, G. W., Springthorpe, B. & Tinker, A. C. (1985 a). Dopamine analogues in the treatment of heart failure. *3rd SCI-RSC Med. Chem. Symp.* 169–192.
- Brown, R. A., Farmer, J. B., Hall, J. C., Humphries, R. C., O'Connor, S. E. & Smith, G. W. (1985 b). The effects of dopexamine on the cardiovascular system of the dog. *Br. J. Pharmac.*, **85**, 609–619.
- Cohn, J. N. & Franciosa, J. A. (1977). Vasodilator therapy of cardiac failure (Second of two parts). *New Engl. J. Med.*, **297**, 254–258.
- Dawson, J. R., Thompson, D. S., Signy, M., Juul, S. M., Turnbull, P., Jenkins, B. S. & Webb-Peploe, M. M. (1985). Acute haemodynamic and metabolic effects of dopexamine, a new dopaminergic receptor agonist, in patients with chronic heart failure. *Br. Heart J.*, **54**, 313–320.

- Jaski, B. E., Wijns, O. W., Foulds, R. & Serruys, P. W. (1986). The haemodynamic and myocardial effects of dopexamine: a new β_2 -adrenoceptor and dopaminergic agonist. *Br. J. clin. Pharmacol.*, **21**, 393–400.
- Leach, K. G., Slowey, H. F., Rosen, M., & Asscher, A. W. (1985). Serial measurement of renal plasma flow. *Eur. J. nucl. Med.*, **11**, 33–35.
- Neale, M. G., Baker, P., Brown, K., Foulds, R. A. & Morris, D. A. (1986). Pharmacokinetics and metabolism of dopexamine in man. *Acta Pharmac. Tox.*, **59**, 69.
- Pritchard, W. H., Eckstein, R. W., MachIntyre, W. J. & Dabaj, E. (1965). Correlation of renal blood flow determined by the single injection of hippuran-I131 with direct measurements of flow. *Am. Heart J.*, **70**, 789–796.
- Svensson, G., Sjogren, A. & Erhardt, L. (1986). Short term haemodynamic effects of dopexamine in patients with chronic congestive failure. *Eur. Heart J.*, **7**, 697–703.
- Tauxe, W. N., Dubovsky, E. V. & Kidd, T. E. (1984). Comparison of measurement of effective renal plasma flow by single plasma sample and plasma disappearance slope/volume methods. *Eur. J. nucl. Med.*, **9**, 443–445.
- Tauxe, W. N., Maher, F. T. & Taylor, W. F. (1971). ERPF: estimation from theoretical volumes of distribution of intravenously injected I-131 orthoiodohippurate. *Mayo Clin. Proc.*, **46**, 524–531.

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