CLINICAL RESEARCH

Treatment of hypertension with ketanserin, a new selective 5-HT₂ receptor antagonist

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Abstract

The new selective 5-HT₂ receptor blocking agent ketanserin was given in a dose of 10 mg intravenously to 12 patients with essential hypertension. It caused a distinct fall in supine systemic arterial, right atrial, pulmonary artery, and pulmonary capillary "wedge" pressures. Cardiac output, renal blood flow, and glomerular filtration rate showed no persistent changes. Thus 5-HT₂ receptor blockade caused dilatation of both the resistance and capacitance vessels and of the renal vascular bed. Heart rate and plasma concentrations of renin and noradrenaline rose after ketanserin.

These data suggest that 5-HT may have a role in maintaining high blood pressure.

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) has long been recognised as a potent vasoactive agent.¹ It appears to act mainly as an amplifier of other vasoconstricting agents such as noradrenaline and angiotensin II.² 5-HT may be implicated in the pathogenesis of hypertension, but its role is obscured by its multifaceted actions in healthy individuals.¹ Furthermore, the lack of specific antagonists has hampered the precise delineation of 5-HT's role in blood pressure regulation. Recently Peroutka and Snyder, using radioligand studies, distinguished two distinct 5-HT receptors.³ Binding to the 5-HT₁ receptor has so far not been related to any effect of 5-HT, but binding to the 5-HT₂ receptor correlates with both in-vitro and in-vivo pharmacological and physiological effects of 5-HT.^{3,4} A specific 5-HT₂ receptor antagonist, ketanserin, is now available which in therapeutic doses does not block the effect of amines other than 5-HT. It appears to be free of the central side effects associated with less

specific 5-HT antagonists.⁵ This has prompted us to investigate the haemodynamic effects of this new compound in patients with essential hypertension.

Patients and methods

Twelve patients were studied, eight men and four women, aged 59 ± (SEM) 4 years (range 40 to 77 years). The diagnosis of essential hypertension was established by routine screening, including intravenous urography. Antihypertensive treatment, if any, was stopped three weeks before the study. The use of a new, intravenous antihypertensive agent was explained to the patients, who all gave their informed consent to the study.

They were admitted to a metabolic ward and received a diet with a constant sodium (40-50 mmol/day) and potassium (70-100 mmol/day) content. When blood pressure and sodium balance were stable the patients were investigated in the cardiovascular laboratory after an overnight fast. A Swan-Ganz catheter was introduced percutaneously in an antecubital vein and positioned in the pulmonary artery. A short polyethylene catheter was placed in a radial artery. A peripheral vein in the opposite arm was cannulated for renal function studies. Baseline haemodynamic measurements and blood sampling were started at least 90 minutes later. Ketanserin, 10 mg in 20 ml of saline, was infused in the right atrium in three minutes and the effects were followed for two hours. Right atrial pressure, pulmonary artery pressure, arterial pressure, and heart rate were continuously monitored and recorded. Mean pressures were obtained by electronic integration, and the mid-axillary line was defined as the zero-pressure reference level. The patients remained supine throughout the study. Cardiac output and mean pulmonary capillary "wedge" pressure were measured before, five minutes after the end of the ketanserin infusion, and then every 30 minutes. Triplicate measurements of cardiac output using the thermodilution technique (10 ml 5% dextrose in water at 1-2°C) were averaged. The following haemodynamic values were derived: total peripheral vascular resistance = (mean arterial pressure - right atrial pressure)/cardiac output (kPa/s/l); pulmonary vascular resistance = (mean pulmonary artery pressure - mean pulmonary capillary wedge pressure)/cardiac output (kPa/s/l). Using a continuous infusion technique⁶ we estimated the effective renal plasma flow and glomerular filtration rate by clearance of ¹³¹I-hippuran and ¹²⁵I-thalamate respectively. Renal blood flow was calculated using the venous packed cell volume and assuming 75% renal extraction of hippuran. Renal vascular resistance was calculated as the mean arterial pressure/renal blood flow (kPa/s/l). Well-established methods were used to measure plasma concentrations of active renin⁷ and noradrenaline.⁸ Statistical analyses were performed using Student's *t* test for paired data.

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Results

Systolic and diastolic pressures fell from $188 \pm 6/89 \pm 5$ mm Hg to $159 \pm 9/75 \pm 6$ mm Hg five minutes after the end of the infusion of ketanserin (fig 1). Arterial pressure remained significantly below baseline level during the two-hour observation period. One patient had symptomatic hypotension; his arterial pressure fell from 177/85 mm Hg to 82/43 mm Hg within five minutes, but by 30 minutes it had risen

FIG 1—Effects of ketanserin on arterial pressure, heart rate, plasma noradrenaline, cardiac output, and total peripheral vascular resistance in 12 patients with essential hypertension. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Conversion: SI to traditional units—Vascular resistance: 1 kPa/s/l $\approx$ 10 dyn/s/cm⁵.

vascular resistance fell significantly, but there were no major changes in effective renal plasma flow and glomerular filtration rate. Although basal active renin concentration was low it rose significantly.

Discussion

5-HT is released by aggregating platelets during clotting and it contributes to local vasoconstriction.² It is also released by enterochromaffin cells, where it increases blood flow to exocrine glands of the gut.⁹ Apart from such local actions endogenous 5-HT has not been thought to have systemic haemodynamic effects.¹ This view, however, is now being challenged by preliminary results with ketanserin, a newly developed specific 5-HT₂ receptor antagonist.¹⁰

Our data show that ketanserin exerted its hypotensive action

FIG 2—Effects of ketanserin on pulmonary artery pressure, wedge pressure, right atrial pressure, and pulmonary vascular resistance in 12 patients with essential hypertension. ** $p < 0.01$; *** $p < 0.001$. Conversion: SI to traditional units—Vascular resistance: 1 kPa/s/l $\approx$ 10 dyn/s/cm⁵.

Effects of ketanserin on mean arterial pressure and renal function in 12 patients with essential hypertension

	Baseline	After ketanserin infusion			
		1 h	p Value	2 h	p Value
Mean arterial pressure (mm Hg)	121 $\pm$ 5	102 $\pm$ 7	< 0.001	106 $\pm$ 7	< 0.001
Glomerular filtration rate (ml/min)	90 $\pm$ 5	92 $\pm$ 5	NS	90 $\pm$ 5	NS
Effective renal plasma flow (ml/min)	302 $\pm$ 18	290 $\pm$ 17	NS	296 $\pm$ 21	NS
Renal vascular resistance (kPa/s/l)	1368 $\pm$ 102	1202 $\pm$ 97	< 0.05	1284 $\pm$ 110	NS
Plasma active renin (mU/l)*	9.5 $\pm$ 2.0	14.9 $\pm$ 3.4	< 0.01	15.3 $\pm$ 2.8	< 0.01

*Normal range 15-45 mU/l.
Conversion: SI to traditional units—Vascular resistance: 1 kPa/s/l $\approx$ 10 dyn/s/cm⁵.

to 105/57 mm Hg. Both the initial and the sustained fall in arterial pressure were due to a drop in total peripheral vascular resistance. Heart rate and cardiac output rose, but in contrast to heart rate, the cardiac output increased only transiently (fig 1). The rise in heart rate was accompanied by an increase in plasma noradrenaline concentration. Ketanserin caused a fall in the filling pressures of both ventricles (fig 2). Pulmonary artery pressure also fell, but this was probably not due to a direct vasodilating effect of ketanserin on the pulmonary vascular bed, as pulmonary vascular resistance did not change. The effects of ketanserin on renal function are shown in the table. Renal

by lowering total peripheral vascular resistance. The fall in right atrial pressure suggested that it also had an effect on venous tone. The responses of the heart rate and plasma noradrenaline concentrations were probably baroreflex-mediated. Reflex sympathetic stimulation may also have caused the transient rise in cardiac output. This effect might have been overruled by the fall in venous return and the reduction of preload. Vasodilatation also occurred within the kidneys, and, despite a fall in arterial pressure, the glomerular filtration rate did not diminish. The anti-

hypertensive action of ketanserin is thus characterised by a favourable haemodynamic profile. The observation that ketanserin lowered not only systemic arterial pressure but also cardiac filling pressures suggests that this balanced vasodilatation may be of particular interest for the treatment of congestive heart failure. Indeed, a favourable response to ketanserin in this condition has been reported recently.¹¹

5-HT not only acts as a direct vasoconstrictor, but it also amplifies the vasoconstrictor responses to agents such as noradrenaline and angiotensin II.² 5-HT is released by aggregating platelets in atherosclerotic arteries, which are abnormally responsive to this amine.¹² Ketanserin antagonises not only the direct vasoconstrictor effect of 5-HT but also its amplifying effects on other vasoactive substances.⁵ These mechanisms may all be implicated in the haemodynamic effects of 5-HT₂ receptor blockade by ketanserin. This compound is thus a new therapeutic tool for investigating the role of 5-HT in the pathogenesis of various forms of hypertension. Experience so far warrants further assessment of its place in the management of hypertension.

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Sodium-potassium cotransport activity as genetic marker in essential hypertension

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Abstract

Sodium-potassium cotransport activity is thought to be defective in essential hypertension and could be a useful genetic marker for susceptibility to essential hypertension. In this study cotransport activity in subjects with hypertension was compared with that in normotensive controls. The effects of ethnic differences, environment, and antihypertensive drugs were also studied. Mean cotransport activity was lower in hypertensive subjects than in controls of the same ethnic groups. There was, however, a large overlap between controls and hypertensive subjects. No ethnic or environmental influences were found.

The large overlap found suggests that sodium-potassium cotransport activity is not a useful genetic marker in essential hypertension.

Introduction

The sodium-potassium cotransport system in human erythrocytes was characterised by Wiley and Cooper in 1974.¹ This cotransport system is distinct from the sodium-potassium adenosine triphosphatase pump; is specifically inhibited by the diuretic frusemide; and transports sodium and potassium ions in the same direction, in a 1:1 ratio, either into or out of the cell depending on the prevailing concentration gradients of sodium and potassium.¹ Several reports have suggested that the sodium-potassium cotransport system is defective in essential hypertension²⁻⁴ and that this is a useful genetic marker for susceptibility to essential hypertension, low cotransport activity being inherited as a single autosomal dominant gene.⁵

We compared cotransport activity in patients with essential hypertension and in normotensive controls, and assessed the effect of antihypertensive drug treatment on cotransport activity in different ethnic groups and in identical twins.

Subjects and methods

Sodium-potassium cotransport was assayed in sodium-loaded red cells by measuring frusemide-sensitive sodium and potassium efflux in the presence of ouabain, according to the method of Dagher and Garay.⁶ The only modification we made to this method was in the sodium-loading medium, which contained 50 mmol (mEq)/l sodium, 150 or 170 mmol/l (0.12 or 0.14 mg/100 ml) choline, and 0.015 mmol/l p-chloromercuribenzenesulphonate. This was necessary to achieve intracellular sodium concentrations as close as possible to 25 mmol

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