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Effect of Ketanserin on Hemodynamics, Plasma-Catecholamine Concentrations, and Serotonin Uptake by Platelets in Volunteers and Patients with Congestive Heart Failure

H. Grobecker, I. Gessler, *W. Delius, P. Dominiak, and F. Kees

*Department of Pharmacology, University of Regensburg, Regensburg, and *Department of Cardiology, Bogenhausen Hospital, Munich, Federal Republic of Germany*

Summary: Ketanserin, which preferentially blocks 5-HT_2-serotonergic receptors, was injected intravenously (i.v.) to patients with congestive heart failure in a bolus dose of 10 mg, followed by an i.v. infusion of 3 mg/h over a period of 4 h. The drug caused a decrease in total peripheral resistance and, conversely, an increase in stroke volume. Right atrial and pulmonary artery pressures were decreased. Plasma noradrenaline rose twofold over the basal levels shortly after injection, but showed a distinct fall 2 h after beginning of the treatment. The concentrations of ketanserin in plasma after bolus injection approximated 100–150 ng/ml. The sympathoneuronal and sympathoadrenal reaction during tilting were increased after i.v. injection of 10 mg ketanserin in volunteers. The noradrenaline and adrenaline levels in plasma rose significantly more when compared with values before the injection of the drug. In vitro as well as in vivo ketanserin exerts a concentration-dependent inhibitory effect on the active transport of serotonin and catecholamines (dopamine, noradrenaline, adrenaline) into human platelets. Considering platelets as a model of the sympathetic neurons, the inhibition of reuptake of catecholamines by ketanserin could contribute to the observed increase in circulating catecholamines after injection of the drug. **Key Words:** Ketanserin hemodynamics—Congestive heart failure—Volunteers—Plasma catecholamines—Blood platelets.

Ketanserin is a quinazoline derivative that blocks vasoconstriction induced by serotonin in various animal models (1). Binding to 5-HT_2-serotonergic receptors correlates both in vitro and in vivo with the peripheral pharmacological and physiological effects of serotonin (2). As ketanserin is used for the treatment of hypertension (3), it was of interest to investigate the hemodynamic effects of the drug both in patients with congestive heart failure and in healthy volunteers. In addition, investigations on uptake of biogenic amines in human platelets, as a model of sympathetic neurons, has been performed. Our data show that ketanserin is capable of lowering total peripheral resistance, increasing stroke volume, and inhibiting active uptake of serotonin and catecholamines by platelets.

PATIENTS, VOLUNTEERS, AND METHODS

Twenty patients were studied, nine men and 11 women [mean age, 64 years (range 47–80 years)] (New York Heart Association, stage III–IV). The diagnosis of congestive heart failure was established by routine screening. Measurement of cardiac output was performed with thermodilution. Right atrial and pulmonary artery pressures were measured. Total peripheral resistance was calculated. Heart rate and blood pressure were determined continuously. Ten milligrams of ketanserin was injected i.v. as a bolus within 15 min. Subsequently the drug was infused intravenously (i.v.) 3 mg/h over a period of 4 h. Blood samples for radioenzymatic determination of catecholamines (4) were obtained from a cubital vein. Six healthy volunteers, ages 25–35 years, were investigated. Blood platelets were prepared and incubated before and after injection of 10 mg ketanserin i.v. as described previously (5). Tilting was performed on an automatic table moving the volunteers from the horizontal to the vertical plane (45°).

RESULTS

In patients with congestive heart failure, the i.v. injection of ketanserin caused a significant fall in total peripheral resistance and a significant increase in cir-

Address correspondence and reprint requests to Dr. H. Grobecker, at Lehrstuhl für Pharmakologie, der Universität Regensburg, Universitätsstraße 31, D-8400 Regensburg, Federal Republic of Germany.

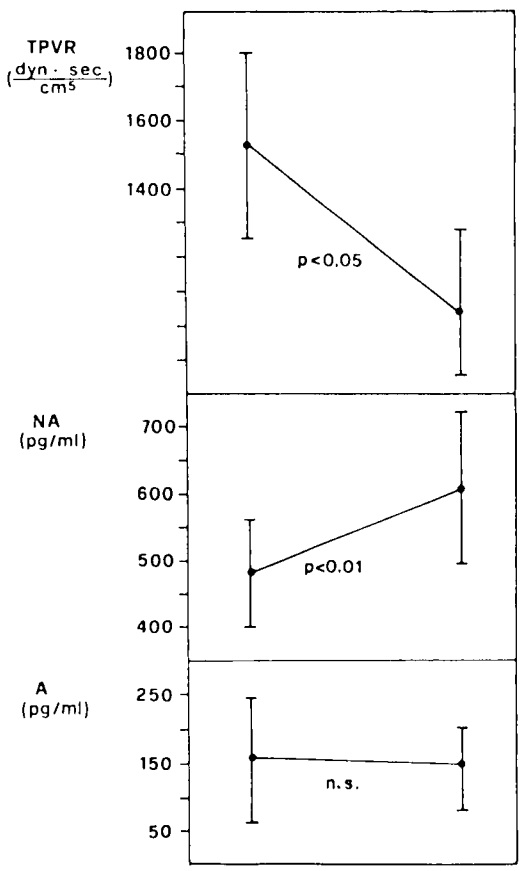

FIG. 1. Significance of changes in circulating plasma catecholamines and total peripheral resistance after intravenous injection of 10 mg ketanserin in patients with congestive heart failure. For details see Methods and Results sections. A, adrenaline; NA, noradrenaline; TPVR, total peripheral vascular resistance.

culating noradrenaline, whereas plasma adrenaline did not change (Fig. 1). Concomitantly with the fall in total peripheral resistance, an increase in stroke volume (from 54 ± 6 to 64 ± 4 ml; $p < 0.01$) occurred. Plasma levels of ketanserin (6) were 105 ± 10 ng/100 ml. In volunteers, ketanserin (bolus of 10 mg i.v.) induced a small decrease in systolic blood pressure during supine position. Heart rate did not change. Tilting before administration of ketanserin resulted in an increase of circulating noradrenaline from 250 ± 20 to 560 ± 60 pg/ml ($p < 0.01$ SEM). Adrenaline levels were not changed. After injection of ketanserin and subsequent tilting, noradrenaline levels rose to 1,400 ± 200 pg/ml and adrenaline levels rose from 50 ± 15 (controls in supine position) to 105 ± 18 pg/ml ($p < 0.01$). Circulating dopamine did not change before and after administration of ketanserin.

In vitro uptake of [^{14}C]serotonin by human platelets was inhibited by increasing concentrations of ketanserin ($IC_{50} = 5 \times 10^{-5} M$; incubation time: 5 min). In addition, uptake of catecholamines by platelets was blocked by ketanserin, as shown in Table 1. Also, uptake of serotonin by platelets obtained from blood samples of a contralateral vein 1 or 5 min after i.v. injection of 10 mg ketanserin was considerably diminished (control: 40×10^{-2} cpm/[^{14}C]serotonin/10^8 platelets; 1 min after injection of ketanserin: 8×10^{-2} cpm/[^{14}C]serotonin/10^8 platelets; incubation time 5 min).

DISCUSSION

The results of this study in humans confirm experimental observations that ketanserin is able to induce vasodilatation possibly by blockade of 5-HT_2 receptors, thereby diminishing enhanced peripheral resistance, e.g., in patients with congestive heart failure. Reducing the afterload of the impaired heart resulted in an increased stroke volume. This might have therapeutic implications in the treatment of congestive heart failure. Considering the mechanism of vasodilatation, a blockade of peripheral postsynaptic α_1-adrenoceptors by ketanserin cannot be excluded, as the concentrations of ketanserin in plasma reached values more than 100 pg/ml. In line with this assumption is the impaired sympathetic counter-regulation in volunteers during tilting under the influence of ketanserin. In this context, it is also of interest that, in animal experiments, a stimulation of central α_1-adrenoceptors by ketanserin resulted in inhibition of total peripheral sympathetic outflow (7).

In vitro as well as in vivo ketanserin exerted a concentration /dose–dependent inhibition of uptake of serotonin and catecholamines (dopamine, noradrenaline, adrenaline) by platelets (Table 1). However, the concentrations of ketanserin for half-maximum inhibition are

TABLE 1. *Effect of ketanserin on active uptake of catecholamines by human platelets in plasma in vitro*

Concentration of ketanserin (*M*)	Inhibition of CA uptake (%)		
	DA	NA	A
10^{-6}	40	40	20
10^{-5}	60	58	49
10^{-4}	75	70	69
Incubation 60 min at 37°C	IC_{50}(*M*) $3 \times 10^{-6} M$	$4 \times 10^{-6} M$	$1 \times 10^{-5} M$

CA, catecholamine; DA, dopamine; NA, noradrenaline; A, adrenaline

higher than those needed for blockade of either peripheral postsynaptic α_1-adrenoceptors or serotoninergic (S_2) receptors. Considering platelets as a model of the sympathetic neuron, however, inhibition of reuptake of catecholamines by ketanserin could possibly contribute to the observed increase in circulating catecholamines shortly after injection of the drug.

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