Responses of the systemic circulation and of the renin-angiotensin-aldosterone system to ketanserin at rest and exercise in normal man

ROBERT FAGARD, ANNE CATTAERT, PAUL LUNEN, JAN STAESSEN, LUC VANHEES, EMMANUEL MOERMAN* AND ANTOON AMERY

Hypertension and Cardiovascular Rehabilitation Unit, Department of Pathophysiology, University of Leuven, Leuven, and *Heymans Institute of Pharmacology, University of Ghent, Ghent, Belgium

(Received 4 January/1 June 1983; accepted 18 July 1983)

Summary

1. The systemic circulation at rest and during exercise was studied in ten normal male volunteers, after placebo on one occasion and after acute intravenous administration of the serotonergic antagonist ketanserin on another occasion. The effects of ketanserin on the components of the renin-angiotensin-aldosterone system, on plasma catecholamines and on exercise capacity for graded uninterrupted exercise were also investigated.

2. At rest in recumbency rapid intravenous injection of 10 mg of ketanserin, followed by a continuous infusion of 2 mg/h, produced an acute but transient fall in mean intra-arterial pressure of 6 mmHg compared with placebo. After 15 min the mean arterial pressure with ketanserin was within 2 mmHg of the mean pressure with placebo. In the sitting position both at rest and up to 30% of maximal work rate, the mean arterial pressure during ketanserin did not differ from the pressure on placebo. However, at higher levels of physical activity the rise in mean arterial pressure was lower with ketanserin; the pressure achieved with placebo was 7.5 mmHg higher at maximal work rate. Heart rate and cardiac output were significantly higher during ketanserin.

3. When the subjects were lying down and resting, plasma noradrenaline and adrenaline levels, plasma renin activity and angiotensin I concentration were not affected by ketanserin; however, these values were higher in the sitting position both at rest and during exercise. Plasma aldosterone was reduced by ketanserin during exercise and also when the subject was resting in the recumbent position.

4. Exercise capacity as measured by peak oxygen uptake was similar during ketanserin (3.09 ± SE 0.12 litres/min) and during placebo (3.11 ± 0.13).

5. The data suggest that 5-hydroxytryptamine can have only a small role, if any, in pressure homoeostasis in sodium replete man at rest in recumbency. At moderate and heavy levels of exercise, the results are compatible with a role for 5-hydroxytryptamine in pressure regulation. Activation of the sympathetic nervous system by ketanserin is suggested by increases of plasma catecholamines, heart rate, cardiac output and plasma renin. The suppression of plasma aldosterone suggests that 5-hydroxytryptamine may have a role in the regulation of aldosterone secretion which is independent of angiotensin II.

Key words: aldosterone, angiotensin, blood pressure, catecholamines, haemodynamics, 5-hydroxytryptamine, ketanserin, renin, serotonin.

Introduction

The effects of 5-hydroxytryptamine (serotonin) on the cardiovascular system are 'uniquely complex' [1]. There is a substantial evidence that serotonergic neurons in the central nervous system are involved in the maintenance of vascular tone [2]. Furthermore, 5-hydroxytryptamine may have a peripheral role through direct vasoconstrictive
actions [3, 4] and through potentiation of the effects of noradrenaline and of angiotensin II [5, 6]. 5-Hydroxytryptamine may also produce arterial dilatation [7-11]. Peripheral infusion of 5-hydroxytryptamine in the conscious normal rabbit, however, does not significantly alter mean arterial pressure [12], whereas blood pressure decreases in the unanaesthetized rat [13]. In patients with carcinoid tumours flushes are usually associated with a falling or an unchanged blood pressure [14]. Therefore the function of endogenous 5-hydroxytryptamine in cardiovascular homoeostasis is not well understood.

Peroutka & Snyder [15] described two distinct populations of 5-hydroxytryptamine binding sites, but only the serotonin type 2 receptor appeared to be important for the vascular effects of the compound. Recently a serotonin antagonist became available which is reported to be selective and specific for serotonin type 2 receptors, and devoid of intrinsic serotonin-like activity and of central effects (3-{2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl}-2,4(1H,3H)-quinazolininedione: ketanserin; R41 468 Janssen Pharmaceutica, Beerse, Belgium) [16]. The agent is effective in curtailing the direct and indirect vasoconstrictor properties of 5-hydroxytryptamine but does not seem to interfere with the vasodilatations that 5-hydroxytryptamine can cause through its direct effects on resistance vessels or to prejunctional inhibition of adrenergic neurotransmission [17, 18]. α1-Receptor blocking properties have been described in the rat [19-21]. In man, acute administration of ketanserin does inhibit serotonin induced platelet aggregation [22] whereas reports on its α1-antagonistic properties are conflicting [23-25].

We report on the acute haemodynamic effects of ketanserin in sodium-replete normotensive subjects at rest and during exercise to elucidate the possible role of 5-hydroxytryptamine in cardiovascular homoeostasis in these conditions. Also its role on the components of the renin-angiotensin-aldosterone system and on plasma catecholamines is evaluated.

Materials and methods

Subjects

Ten normal male volunteer subjects, aged 24 ± 1 years, with a weight of 69.5 ± 3.3 kg and a height of 176 ± 2 cm, agreed to participate in the study after the procedure had been explained and their written consent was obtained. They remained on their regular diet. Their urinary sodium excretion averaged 124 ± 14 mmol/24 h, and potassium excretion was 64 ± 4 mmol/24 h. At the pretest (see the Experimental protocol) peak oxygen uptake during graded uninterrupted exercise averaged 49.9 ± 2.0 ml/min⁻¹ kg⁻¹, and the highest work rate was 269 ± 10 W.

Experimental protocol

The tests were performed in the laboratory where room temperature was 18-22°C and humidity 40-60%. The protocol is summarized in Fig. 1. The subjects performed three uninterrupted graded exercise tests on the bicycle ergometer in the sitting position, until exhaustion. The first test (pretest) was meant to assess the subject’s peak exercise capacity and preceded the actual experiments by 1-4 weeks. The initial external work load of 10 W was increased by 10 W every minute. Peak VO₂ was noted as well as the external work loads at which 30% and 60% of peak VO₂ was reached. For the second and third tests, which were 2 weeks apart, the subjects arrived in the laboratory at 08.30-09.00 hours. They had eaten a light breakfast at home without coffee or tea. After introduction of a small catheter into an antecubital vein (Abbocath-T, 18-G), and one in the brachial artery (Vygon, 115.09) for measuring intra-arterial pressure and for sampling of arterial blood, the subjects were allowed to rest in the recumbent position for 30 min while sodium chloride solution (154 mmol/l: saline) was infused intravenously (period RRcon). Then either 10 mg of ketanserin (2 ml) or vehicle alone (placebo) was

![Fig. 1. Protocol of the study. The arrows labelled I denote the points of intravenous injection of either placebo or ketanserin. See the Materials and methods section for explanation.](image-url)
Effects of ketanserin in normal man

rapidly injected intravenously (5 s) in a randomized double-blind manner; subjects nos. 1, 2, 4, 8 and 10 received ketanserin at the second test and subjects nos. 3, 5, 6, 7 and 9 received ketanserin at the third test. The rapid injection of ketanserin or placebo was followed by a continuous infusion of ketanserin at a rate of 2 mg/h (10 ml/h) or of placebo for the total duration of the test. The subjects remained recumbent for 16 min more (period RRexp). The subjects then assumed the sitting position on the ergometer bicycle for 15 min (period RS). The exercise test was started at a work load of 10 W for 1 min and the load was increased by 10 W/min until exhaustion; however, at 30% and 60% of peak VO2 the external work load was maintained for 7 min to allow steady-state haemodynamic measurements and sampling of arterial blood. The subjects were not informed on the results of any of the tests.

Methods

Respiratory and haemodynamic variables

Intra-arterial pressure was measured through an indwelling catheter in the brachial artery with an electronic transducer (Elema Schönander EMT 34) and recorded continuously on a Mingograph 81 recorder. Mean arterial pressure was obtained by electrical damping.

Expired gas was collected in a mixing box by using an open-circuit method. Oxygen uptake (VO2) and carbon dioxide output (VCO2) were continuously calculated from the volume of the expired gas and its O2 and CO2 concentrations, analysed by electronic gas analysers which were previously calibrated with test gases of known composition (Siregnost FD, Siemens). VO2 and VCO2 were reduced to volumes at STPD.

Cardiac output expressed in l/min was estimated by the CO2 rebreathing method as described and validated in our laboratory [26]. Cardiac output was not measured at RR and was determined in duplicate at RS, at 30 and 60% of peak work rate; cardiac output was not measured at higher work rates since the CO2 rebreathing procedure could affect peak exercise performance. Systemic vascular resistance was calculated by dividing mean arterial pressure by cardiac output. Heart rate was continuously recorded from the electrocardiogram. Stroke volume was calculated from cardiac output and heart rate.

Biochemical variables

Plasma renin activity (PRA) was measured by the method of Fyhrquist & Puutula [27], plasma angiotensin II (ANG II) and plasma aldosterone concentration (PAC) as described by Lijnen et al. [28, 29], and plasma lactate by an enzymatic method [30]. Plasma catecholamines were measured by the method of Da Prada & Zurcher [31]. Plasma levels of ketanserin were determined by an h.p.l.c. method by Janssen Pharmaceutica (unpublished work).

Statistical analysis

Statistical methods used are paired Student’s t-test (2P) and three-way analysis of variance. In the latter analysis we considered (a) levels of physical activity (or time), (b) subjects, and (c) treatment, and their interactions as sources of variation. Only the effects of treatment and interactions between treatment and levels of physical activity (or with time) are discussed. When an interaction was present the significance of the difference between ketanserin and placebo data at a given level of activity or at a given time was assessed by using the residual mean square from the analysis of variance.

For plasma renin activity, plasma ANG II, plasma aldosterone concentration and plasma catecholamines the statistical analysis was performed on the log values since their distribution was closer to Gaussian; the geometric mean and range is therefore reported. Other values are given as means ± SE.

Results

Haemodynamic and respiratory data

Effects of ketanserin on arterial pressure and heart rate at rest recumbent. Fig. 2 illustrates the data of heart rate and of systolic, diastolic and mean arterial pressures at rest recumbent. Before the injection of ketanserin or placebo there was no significant difference between the observations on the 2 different days (tests 2 and 3) for any of the variables. Before placebo injection mean arterial pressure averaged 81 ± 2 mmHg and heart rate 67 ± 4 beats/min. After the injection of ketanserin, heart rate was significantly higher and systolic, diastolic and mean arterial pressures were significantly lower than after placebo (F > 39; P < 0.001). However, the interactions between the effect of treatment and time were significant and Fig. 2 indicates at which time intervals the effect of treatment was significant. Ketanserin induced an increase of heart rate of 19 ± 6 beats/min 2 min after the injection but the difference in heart rate was reduced to approximately 4 beats/min after about 5 min. Also the effect on arterial pressure was greatest immediately after the injection. At
FIG. 2. Heart rate and systolic, diastolic and mean intra-arterial pressures during the control period RRcon (○, before placebo; ■, before ketanserin) and during the experimental period RRexp (○, during placebo; ■, during ketanserin). Differences between ○ and ■, and between ○ and ■, are analysed by three-way ANOVA. Values during placebo and during ketanserin are significantly different for all values ($F \geq 39; P < 0.001$ for all); because of the significant interactions between treatment effects and time, significant differences are given at various times ($**P < 0.05$; $**P < 0.01$). There are no significant differences for values before placebo and before ketanserin.

2 min the difference between the ketanserin and placebo study was 6 mmHg for systolic arterial pressure, 5 mmHg for the diastolic pressure, and 6 mmHg for mean arterial pressure; at 14–16 min these values were 2.5, 2.5 and 2 mmHg respectively.

Effects of ketanserin on haemodynamic and respiratory variables in the sitting position, at rest and during exercise. Fig. 3 illustrates the data for systolic, diastolic and mean arterial pressures in the sitting position at rest (RS) and during exercise expressed as percentage (per 10%) of the peak work rate during placebo and ketanserin treatment. The effect of treatment was significant for each variable ($F \geq 23; P < 0.001$) and so was the interaction between the effect of treatment and the level of activity. At rest in the sitting position, systolic arterial pressure during ketanserin was 6 mmHg lower ($P < 0.01$) than during placebo but diastolic and mean arterial pressures were not significantly different. During exercise systolic, diastolic and mean arterial pressures were not different at the lower work rates of 10–30%, but

FIG. 3. Systolic, diastolic and mean intra-arterial pressures during placebo (○) and during ketanserin (■) in subjects in the sitting position at rest (RS) and during exercise (per 10% of peak work rate). Values during placebo and during ketanserin are significantly different for all variables ($F \geq 23; P < 0.001$ for all); because of the significant interactions between treatment effect and levels of activity, significant differences are indicated at various levels of activity ($*P < 0.05$; $**P < 0.01$).

FIG. 4. Heart rate during placebo (○) and during ketanserin (■) for subjects in the sitting position at rest (RS) and during exercise (per 10% of peak work rate). Values during placebo and during ketanserin are significantly different ($F = 101; P < 0.001$); because of the significant interaction between treatment effect and levels of activity, significant differences are indicated at various levels of activity ($*P < 0.05$; $**P < 0.01$).
the exercise-induced rise of arterial pressure was less pronounced during ketanserin than during placebo treatment. At the highest work rate the difference was $15 \pm 3$ mmHg for systolic arterial pressure, $5 \pm 2$ mmHg for diastolic arterial pressure and $7.5 \pm 2$ mmHg for mean arterial pressure. Heart rate was slightly but significantly higher during ketanserin at lower work rates (Fig. 4). The difference reached a maximal value of $12 \pm 2$ beats/min at 60% of peak work rate. At peak work rate the heart rate was similar for both treatment regimens. Fig. 5 summarizes the haemodynamic data in the sitting position at rest and at 30% and 60% of peak work rate. Cardiac output was significantly

![Graph](image]

**Fig. 5.** Cardiac output and systemic vascular resistance during placebo (○) and during ketanserin (●) in subjects in the sitting position at rest (RS) and at 30 and 60% of peak work rate. Values are means ± SE. (a) $F$ (the effect of treatment) = 4.7 ($P < 0.05$); (b) $F = 1.3$ (N.S.); there are no significant interactions between the effects of treatment and levels of activity.

<table>
<thead>
<tr>
<th>TABLE 1. Respiratory variables and arterial pH and plasma lactate with subjects in the sitting position at rest and during exercise at 30, 60 and 100% of peak oxygen uptake</th>
<th>30%</th>
<th>60%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen uptake ($\dot{V}O_2$, ml/min)</td>
<td>Placebo 276 ± 12</td>
<td>1137 ± 36</td>
<td>2104 ± 98</td>
</tr>
<tr>
<td>Ketanserin 269 ± 12</td>
<td>1142 ± 36</td>
<td>2119 ± 90</td>
<td>3094 ± 123</td>
</tr>
<tr>
<td>Respiratory gas exchange ratio</td>
<td>Placebo 0.84 ± 0.02</td>
<td>0.85 ± 0.01</td>
<td>0.95 ± 0.01</td>
</tr>
<tr>
<td>Ketanserin 0.84 ± 0.05</td>
<td>0.84 ± 0.01</td>
<td>0.95 ± 0.01</td>
<td>1.09 ± 0.02</td>
</tr>
<tr>
<td>Ventilation ($V_E$, l/min)</td>
<td>Placebo 8.4 ± 0.5</td>
<td>26.6 ± 1.0</td>
<td>50.9 ± 2.0</td>
</tr>
<tr>
<td>Ketanserin 8.9 ± 1.0</td>
<td>27.4 ± 1.6</td>
<td>53.1 ± 2.5</td>
<td>102.5 ± 5.3</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>Placebo 11.7 ± 1.4</td>
<td>21.3 ± 1.0</td>
<td>24.5 ± 1.7</td>
</tr>
<tr>
<td>Ketanserin 11.0 ± 1.3</td>
<td>20.6 ± 1.0</td>
<td>26.4 ± 1.3</td>
<td>38.7 ± 2.5</td>
</tr>
<tr>
<td>pH</td>
<td>Placebo 7.41 ± 0.01</td>
<td>7.39 ± 0.01</td>
<td>7.36 ± 0.01</td>
</tr>
<tr>
<td>Ketanserin 7.40 ± 0.01</td>
<td>7.39 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.29 ± 0.01</td>
</tr>
<tr>
<td>Plasma lactate (mg/dl)</td>
<td>Placebo 17.5 ± 2.4</td>
<td>20.4 ± 2.0</td>
<td>32.8 ± 2.7</td>
</tr>
<tr>
<td>Ketanserin 17.9 ± 2.8</td>
<td>28.4 ± 7.1</td>
<td>40.8 ± 6.4</td>
<td>103 ± 11</td>
</tr>
</tbody>
</table>

*Values for plasma lactate at 1, 3 and 5 min after interruption of exercise.
higher during ketanserin, by an average of 0.7 litre/min \((F = 4.7; \ P < 0.05)\), without significant interaction between treatment and levels of activity; stroke volume was not affected \((F = 0.0\); not significant). Systemic vascular resistance, calculated from mean arterial pressure and cardiac output, tended to be lower during ketanserin, but the difference was not significant; systemic vascular resistance could, however, not be calculated at peak work rate when the greatest difference in pressure was observed, since cardiac output was not measured at this very peak.

Oxygen uptake, respiratory gas exchange ratio, minute ventilation, the respiratory equivalent for oxygen and respiratory rate were not significantly affected by ketanserin \((F = 0.0\); not significant). Systemic vascular resistance, calculated from mean arterial pressure and cardiac output, tended to be lower during ketanserin, but the difference was not significant; systemic vascular resistance could, however, not be calculated at peak work rate when the greatest difference in pressure was observed, since cardiac output was not measured at this very peak.

**Data on the renin-angiotensin-aldosterone system and on plasma catecholamines**

Table 2 summarizes the effect of ketanserin on plasma renin activity, plasma ANG II, plasma aldosterone concentration and on plasma catecholamines at recumbent rest, 16 min after the injection. Placebo had no effect on any of the variables. Ketanserin did not affect plasma renin activity and plasma ANG II concentration, but significantly lowered plasma aldosterone concentration by 18±4\% \((P<0.01)\). Plasma noradrenaline and adrenaline were not affected.

The data for subjects in the sitting position are shown in Figs. 6 and 7. Compared with the data during placebo ketanserin increased plasma renin activity \((F = 7.7; \ P < 0.01)\) and plasma ANG II concentration \((F = 4.4; \ P < 0.05)\) but plasma aldosterone concentration dropped significantly \((F = 7.1; \ P < 0.01)\); none of the interactions between treatment and levels of activity was significant (Fig. 6). In the sitting position at rest and during exercise both plasma noradrenaline \((F = 63; \ P < 0.001)\) and plasma adrenaline \((F = 41; \ P < 0.001)\) were significantly higher during ketanserin without significant interactions with the levels of activity (Fig. 7).

**Plasma levels of ketanserin**

Sixteen minutes after the start of ketanserin administration the plasma level of the drug averaged 82±9 ng/ml. At rest in the sitting position and at 30%, 60% and 100% of the final work rate these values were 71±8, 65±8, 67±9 and 61±8 ng/ml.

**Discussion**

The purpose of the present study was (1) to determine the acute haemodynamic response to ketanserin in sodium-replete normotensive man at rest and during exercise, (2) to study the effects on the renin-angiotensin-aldosterone system and on plasma catecholamines, and (3) to evaluate possible changes in peak oxygen uptake.

The results may shed light on the physiological role of 5-hydroxytryptamine, since ketanserin has
Effects of ketanserin in normal man

been shown to have antiserotonergic properties after acute administration in man [22]. However, α₁-antagonistic effects, which have been found in rats [19-21] and in man [25] cannot be excluded, though they could not be demonstrated in two other studies in man [23,24].

The rapid intravenous injection of ketanserin acutely lowered mean intra-arterial pressure by 6 mmHg, which was associated with an increase of heart rate. This haemodynamic effect is compatible with α₁ blocking properties of high plasma concentrations of the drug. Indeed rapid intravenous injection of 10 mg produces an average drug level of 0.2 µg/ml after 1 min (J. Symoens, personal communication). After 16 min plasma ketanserin averaged 82 ng/ml in our study, and the acute effect on blood pressure and heart rate had diminished, leaving only a 2 mmHg lower mean arterial pressure in comparison with placebo. At that time plasma levels of noradrenaline and of adrenaline had not changed, suggesting that the sympathetic nervous system was not activated. Our data indicate that peripheral serotonin can have only a small role, if any, in pressure homoeostasis in supine young normotensive sodium-replete man. This is in agreement with other studies which demonstrated that the serotonin-antagonists mianserin [32] and cyproheptadine [33] did not alter

\[ F = 63.1, P < 0.001 \]

\[ F = 41.5, P < 0.001 \]

FIG. 6. Plasma renin activity, plasma angiotensin II and plasma aldosterone concentration during placebo (○) and during ketanserin (●) in subjects in the sitting position at rest (RS) and at 30, 60 and 100% of peak work rate. Values are means ± se. (a) $F$ (the effect of treatment) = 7.70 ($P<0.01$); (b) $F = 4.41 (P<0.05); (c) F = 7.10 (P<0.01); there are no significant interactions between the effects of treatment and levels of activity.

FIG. 7. Plasma noradrenaline and plasma adrenaline concentrations during placebo (○, ○) and during ketanserin (●, ●) in subjects in the sitting position at rest and at 30, 60 and 100% of peak work rate. Values are means ± se. $F$ refers to the effect of treatment; there are no significant interactions between the effects of treatment and levels of activity.
arterial pressure in the normal human. On the other hand, after sodium depletion, ketanserin produced a 17/15 mmHg decrease of arterial pressure 10 min after intravenous injection [24], but cyproheptadine did not alter arterial pressure in sodium depleted normal man [34].

In subjects in the sitting position on the bicycle ergometer ketanserin did not affect arterial pressure at rest and at low levels of activity, except for a slight but significant decrease of systolic pressure at rest. With greater activity ketanserin did reduce the increase of arterial pressure. Cardiac output had slightly but significantly risen during ketanserin administration. The increases of heart rate, cardiac output and of plasma catecholamines are compatible with activation of the sympathetic nervous system in these circumstances. Since cardiac output was only measured at rest sitting and at sub-maximal work rates, systemic vascular resistance could be calculated only when pressure was not or only slightly affected. Although the tendency of systemic vascular resistance to decrease was not significant, the increased cardiac output suggests that the hypotensive effect of ketanserin is caused by arteriolar dilatation. This would be in agreement with studies in hypertensive patients [35] and in patients with heart failure [36]. The findings suggest that 5-hydroxytryptamine could have a role in pressure regulation during exercise. One can only speculate on the mechanisms involved. Because ketanserin does not cross the blood-brain barrier at the doses used, blockade of central serotonergic mechanisms cannot be invoked. Also ketanserin does not block the vasoconstricting effects of serotonin on resistance vessels [17]. Dynamic physical activity induces vasoconstriction in the non-working vascular beds, in contrast to the marked dilatation in the working muscles. It is tempting to speculate that 5-hydroxytryptamine is physiologically operative at higher levels of dynamic physical activity. It could contribute to the vasoconstriction in the non-working vascular beds, either through a direct action or through potentiation of the effects of a stimulated sympathetic nervous system [37] and renin-angiotensin system [38, 39].

Ketanserin significantly decreased plasma aldosterone concentration. This effect was dissociated from the behaviour of renin and of ANG II, a well-known stimulus of aldosterone secretion. Renin and ANG II remained unchanged at recumbent rest, but the exercise induced increase was greater during the test with ketanserin. The rise of renin may be explained by activation of the renal baroreceptors and/or to sympathetic nervous system stimulation, of which the slight tachycardia and the rise of plasma catecholamines are indicative. The suppression of plasma aldosterone, while plasma ANG II remained unchanged (at rest) or even increased (during exercise), suggests that 5-hydroxytryptamine may have a role in the regulation of aldosterone, provided it does not increase its degradation or clearance, by e.g. an increase in hepatic flow. 5-Hydroxytryptamine has been shown to be a potent stimulus to aldosterone production by isolated zona glomerulosa cells of the rat adrenal cortex [40, 41]. Cyproheptadine did reduce plasma aldosterone in patients with hyperaldosteronism without tumour (hyperplasia); however, the drug did not affect plasma aldosterone in patients with an aldosterone-producing adenoma, nor in five sodium-depleted normal subjects [34]. The mechanism of the effect of ketanserin on plasma aldosterone remains to be elucidated.

Finally, ketanserin and the haemodynamic changes it induced did not alter peak oxygen uptake, nor anaerobic metabolism.

Acknowledgments
The authors gratefully acknowledge the assistance of L. Lommelen, H. Vervaet, J. Boogaert, R. Nuyts, L. Jans, G. Melotte, C. Willems, L. Cockx, J. Delsupehe, J. Huysecom and J. Romont. Ketanserin was generously supplied by Janssen Pharmaceutica, Beerse, Belgium. We thank Dr J. Symoens for his valuable advice.

References
Effects of ketanserin in normal man


