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Effect of New Type ß-Blocker, Tilisolol Hydrochloride, on the Cardiovascular System in Healthy Young Volunteers

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Abstract: The cardiovascular profile of tilisolol hydrochloride, a new type ß-blocking agent that induces vasorelaxation after opening the potassium channels, was examined and the results were compared with those of metoprolol and carteolol. Fifty-seven healthy young volunteers were entered into the current double-blind, placebo-controlled study. The double protocol of the Master's test was used for the exercise. Tilisolol (10 mg, p.o.) decreased pre- and post-exercise systolic blood pressure, pulse rate and double-product within 2 hr after the drug administration, and it also reduced the increment of double-product by exercise at 1 hr as well as at 2 hr, which could reflect myocardial oxygen consumption. Metoprolol (40 mg, p.o.) and carteolol (5 mg, p.o.) showed trends similar to those observed by tilisolol. Since tilisolol is well-tolerated and possesses a cardiovascular profile similar to those of clinically well-established ß-blockers, it may become a clinically useful drug.

Key words: tilisolol, metoprolol, carteolol, ß-blocker, myocardial oxygen consumption

INTRODUCTION

Tilisolol hydrochloride, 4-[3-(tert-buthylamino)-2-hydroxypropoxy]-N-methylisocarbostyril hydrochloride (N-696), is a new type ß-blocker with vasorelaxing effect through an opening of potassium channels[1,2]. It has been reported to be a non-selective agent without intrinsic sympathomimetic action (ISA) and membrane stabilizing action (MSA)[3]. However, there is a lack of data comparing tilisolol with clinically well-established ß-blocking agents in humans with regard to cardiovascular effects under the same experimental condition.

The present study was designed to investigate the effects of tilisolol on systolic blood pressure and pulse rate in the healthy young volunteers and the results were compared with those of metoprolol and carteolol. Metoprolol is a typical $ß_1$-selective agent without ISA and with MSA, while carteolol is a non-selective agent with ISA and without MSA[4].

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METHODS

The present study was carried out in Yamanashi Medical University as an experimental course of clinical pharmacology. Fifty-seven healthy young volunteers; age 22.4±0.2 years old, body weight 64.0±1.0 kg, male 55, female 2, participated in this double-blind, placebo-controlled study. The over-all purpose and design of the study were carefully explained to the subjects as a group. The study was performed in accordance with the principles of the Helsinki Declaration. The subjects were free to drop out of the study at any time. Before the study, the subject underwent a physical examination and electrocardiogram (ECG) recording with an electrocardiograph

(Nihon-Kohden, ECG-6303, Tokyo, Japan). Subjects demonstrating abnormal data on any examination were excluded from the study.

Systolic blood pressure (mmHg) was measured in a sitting position using an automatic pneumatic cuff manometer (Sharp, MB-304H, Tokyo, Japan). The pulse rate (beats/min) was counted by palpation of the pulses on the radial artery. The double-product (mmHg · beats/min) was calculated as the product of systolic blood pressure and pulse rate, which reflected myocardial oxygen consumption. The double protocol of the Master's test was used for the exercise[5]. The oxygen saving effect of drug was assessed by the reduction of the increment in double-product by exercise, as described previously[6–8]. The subjects were randomly assigned to 3 groups to assess 3 different ß-blocking drugs, namely, tilisolol group (active drug: n=10, placebo: n=9), metoprolol group (active drug: n=9, placebo: n=10) and carteolol group (active drug: n=10, placebo: n=9). First, the cardiovascular parameters were measured before and immediately after the Master's exercise to obtain control values. Then, the parameters were repeatedly measured before and after exercise 1 hr and 2 hr after either ß-blocker or placebo tablet was orally given. ECG at rest was recorded between 1–2 hr after the drug administration to assess the effects of drugs on PQ interval, QRS width and QTc.

The drugs used in this study were commercially-available tablets of tilisolol hydrochloride (10 mg, Toyama-kagaku, Tokyo, Japan), metoprolol tartrate (40 mg, Fujisawa, Tokyo, Japan) and carteolol hydrochloride (5 mg, Otsuka, Tokyo, Japan). The drugs were given in a single dose recommended for clinical use for the treatment of essential hypertension. The data were presented as mean±SE. Statistical differences were analyzed using paired or unpaired Students *t*-test. A p value less than 0.05 was considered significant.

Results

All volunteers were able to tolerate the protocol of the present study. Neither symptomatic hypotension nor proarrhythmic events was observed during any part of the study. There were no significant changes in PQ interval, QRS width or QTc on ECG recorded during the study.

Effects of ß-blockers on systolic blood pressure and pulse rate

Tilisolol significantly decreased the post-exercise systolic blood pressure and pulse rate at 1 hr compared to the respective control values, and decreased the pre- and post-exercise systolic blood pressure and pulse rate at 2 hr, as shown in Fig. 1A. No significant change was observed in the placebo group except that the post-exercise pulse rate significantly decreased compared to the control value at 2 hr. There was a significant difference between the tilisolol and placebo groups in pre-exercise pulse rate at 2 hr. However, no significant change was observed in the increment of pulse rate by exercise in tilisolol as well as placebo group, as shown in Fig. 1B.

Metoprolol significantly decreased post-exercise systolic blood pressure and pulse rate at 2 hr compared to the respective control values, as shown in Fig. 1A. No significant change was observed in the placebo group except for the decrease in post-exercise systolic blood pressure at 2 hr compared to the control value. The increment in pulse rate by exercise at 2 hr in the metoprolol group significantly decreased compared to the control value, while no significant change was observed in the placebo group. There was no significant difference in each parameter between the metoprolol and placebo groups.

Carteolol significantly decreased the pre-exercise systolic blood pressure at 1 hr and post-exercise systolic blood pressure at 2 hr compared to the respective control values, as shown in Fig. 1A. The drug significantly

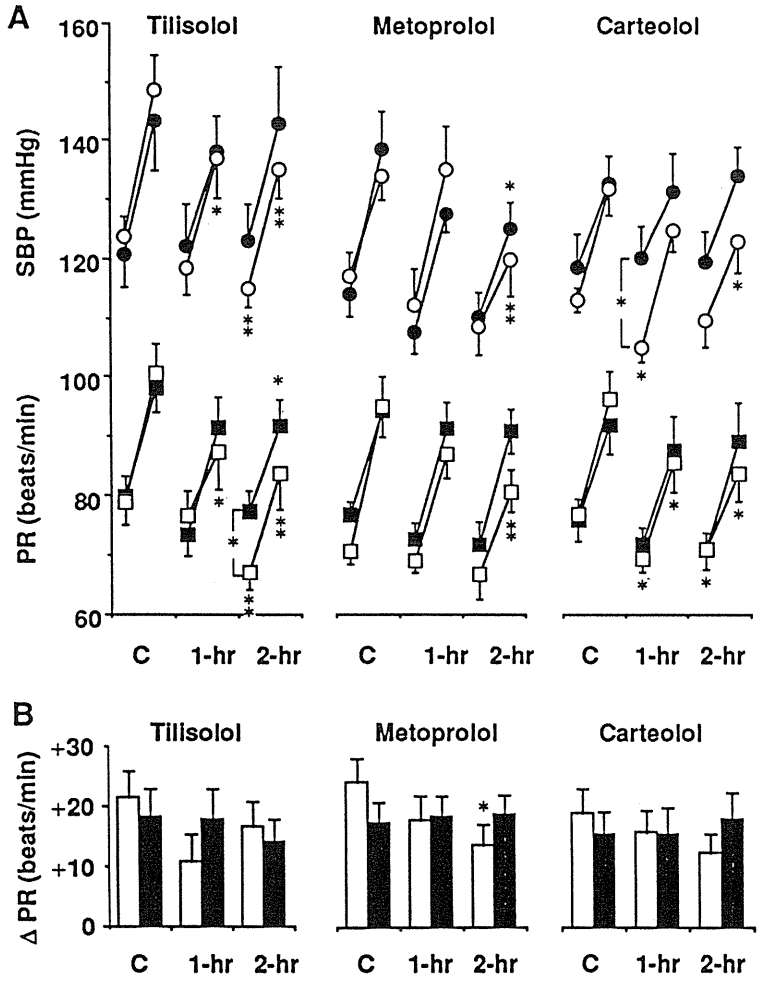

Fig. 1. A) Pre- and post-exercise systolic blood pressure (SBP) and pulse rate (PR) at control (C), 1-hr and 2-hr after the drug administration. B) Effects of drugs on the increment in pulse rate (Δ PR) by exercise in the control (C) compared to 1-hr and 2-hr after drug administration. Vertical bars represent SE. Open symbols represent the results of active drugs, while closed symbols represent those of placebo tablet. Asterisks represent significant changes from each control value, or significant differences between active drug and placebo groups. *$p<0.05$, **$p<0.01$.

decreased the pre- and post-exercise pulse rate compared to the respective control values at 1 hr as well as at 2 hr. There was no significant change in the placebo group. There was a significant difference between carteolol and the placebo group in the pre-exercise systolic blood pressure at 1 hr. On the other hand, no significant change was observed in the increment of the pulse rate by exercise in tilisolol as well as placebo group, as shown in Fig. 1B.

Effects of β-blockers on double-product

Tilisolol significantly decreased the post-exercise double-product at 1-hr, and also

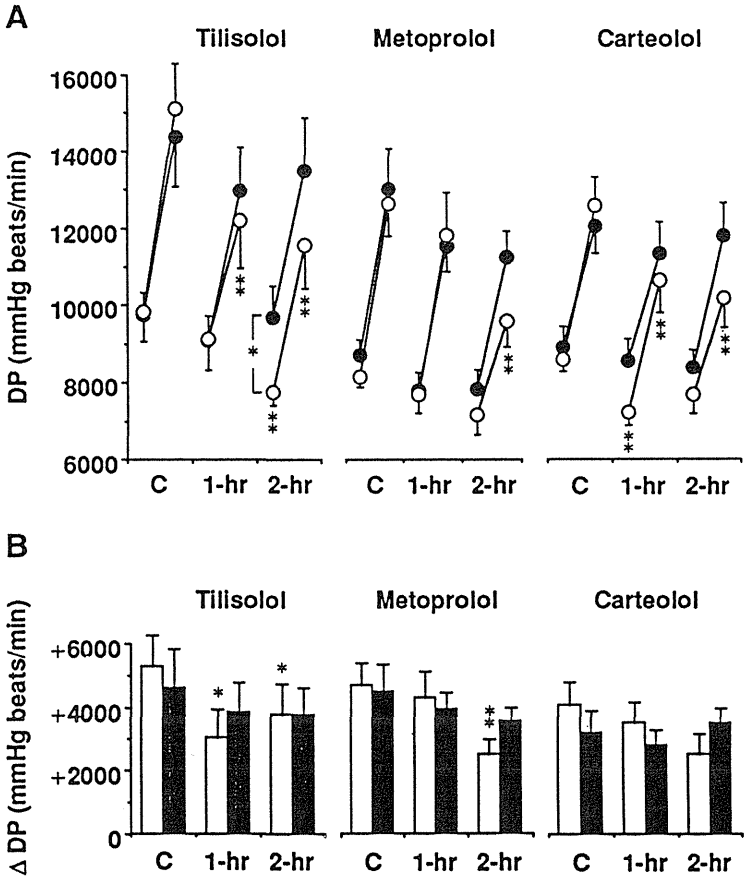

Fig. 2. A) Pre- and post-exercise double product (DP) in the control (C) compared to 1-hr and 2-hr after drug administration.
B) Effects of drugs on the increment in double product (Δ DP) by exercise in the control (C) compared to 1-hr and 2-hr after drug administration. Vertical bars represent SE. Open symbols represent the results of active drugs, while closed symbols represent those of placebo tablet. Asterisks represent significant differences from control values, or significant differences between the active drug and placebo groups. *$p<0.05$, **$p<0.01$.

decreased the pre- and post-exercise double-product at 2-hr, as shown in Fig. 2A. No significant change was observed in the placebo group. There was a significant difference between tilisolol and the placebo group in the pre-exercise double-product at 2 hr. However, tilisolol significantly decreased the increment of double-product by exercise at 1 hr as well as 2 hr compared to respective control values, but there was no significant change in the placebo group, as shown in Fig. 2B.

Metoprolol significantly decreased post-exercise double-product only at 2 hr compared to the control value, but there was no significant change in the placebo group, as shown in Fig. 2A. Metoprolol decreased the increment of double-product by exercise at 2 hr compared to the control value, but there was no significant change in the placebo group, as shown in Fig. 2B. There was no significant

difference in other parameters between the metoprolol and placebo groups.

Carteolol significantly decreased pre- and post-exercise double-product at 1 hr and post-exercise double-product at 2 hr compared to the respective control values, while no significant change was observed in the placebo group, as shown in Fig. 2A. However, there was no significant change in the increment of the double product by exercise in the carteolol or the placebo group, as shown in Fig. 2B. There was no significant difference in other parameters between the carteolol and placebo groups.

The reduction in the increment of double-product by exercise 1 hr after drug administration occurred in the order of tilisolol, carteolol and metoprolol, and that at 2 hr was in the order of metoprolol, tilisolol and carteolol.

Discussion

Given the pharmacological importance of comparative studies of new agents with clinically well-established drugs, we assessed the effects of tilisolol on the cardiovascular system in comparison with metoprolol and carteolol in 57 healthy young volunteers. The Master's exercise test was used to precisely assess the ß-blocking action of these drugs and the double-product was calculated to estimate the effects on oxygen consumption[6–8].

Tilisolol decreased pre- and post-exercise systolic blood pressure as well as pulse rate. Metoprolol and carteolol showed similar trends to those observed by tilisolol, suggesting that the ß-blocking actions of drugs were achieved in each medicated group. The doses of drugs used in this study differed on a mg basis, but their pharmacological efficacy for patients with essential hypertension was reported to be clinically similar[1–4,9]. Taken together, pharmacological properties, such as cardioselectivity, ISA, MSA and vasodilator action, seem to have little effect on the cardiovascular parameters assessed in the present study.

In some placebo groups, post-exercise systolic blood pressure at 2 hr, or post-exercise pulse rate at 2 hr significantly decreased compared with respective control values. Since the same exercise protocol was repeated, a conditioning mechanism might have affected the results 2 hr after drug administration.

A non-invasive approach was used to assess the oxygen-saving effect. The double-product is a well-documented clinical index of myocardial oxygen consumption[6–8]. In the present study, tilisolol decreased pre- and post-exercise double-product within 2 hr, while other ß-blockers used in this study showed a similar trend, but their potency and duration were somewhat different. For example, only tilisolol showed significant reductions in the increment of double-product by exercise both at 1 hr and at 2 hr. The combination of vasorelaxing effects with ß-blocking action might reduce oxygen consumption effectively[9–11], however, caution must be taken in interpreting the present results, which were obtained from a single dose drug study in healthy young subjects.

Since tilisolol is well-tolerated and possesses a cardiovascular profile similar to those of clinically well-established ß-blockers, it may become a clinically useful drug. The data shown in this study provide a convenient guideline for estimating the cardiovascular profile and oxygen saving-effect of new ß-blocking agents.

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