BM 12.434, a novel compound with vasodilating and β-adrenoceptor-blocking activities

E. VON MÖLLENDORFF, C. HUSCHKA, E. SCHRÖTER AND U. ABSHAGEN
Boehringer Mannheim GmbH, Clinical Pharmacology, Mannheim, FRG

Summary

1. BM 12.434 was compared with a known β-adrenoceptor-blocking agent, metipranolol, and a combination of metipranolol and isosorbide-5-mononitrate in healthy volunteers. BM 12.434 and metipranolol were given in equi-effective β-adrenoceptor-blocking doses (reduction of exercise-increased pulse-pressure product).

2. Responses of the cardiovascular system were determined by non-invasive methods.

3. BM 12.434 increased the peripheral resistance less than metipranolol.

4. After BM 12.434, in contrast to metipranolol, both arterial flow and the venous capacity showed significant increase.

5. The combination of isosorbide-5-mononitrate and metipranolol differed from metipranolol alone mainly by the effect on venous capacity, which showed a slight increase.

6. BM 12.434 is a β-adrenoceptor-blocking agent whose additional actions on the veins and arteries are potentially useful for the treatment of both coronary heart disease and of arterial hypertension.

Key words: β-adrenoceptor blockade, BM 12.434, isosorbide-5-mononitrate, metipranolol, vasodilatation.

Abbreviations: M, metipranolol; IS-5-MN, isosorbide-5-mononitrate.

Introduction

BM 12.434 [4-(2-hydroxy-3-{4-(phenoxy-methyl)piperidino}propoxy)indole] is a new compound which has been shown in animals to combine β-adrenoceptor-blocking and vasodilating activities. The purpose of the present study was to determine, in humans, if there is a difference with respect to the action on peripheral circulation between BM 12.434 and metipranolol, a β-adrenoceptor-blocking agent without partial agonist activity and β₁-specificity.

Preliminary results revealed a tendency for BM 12.434 to dilate arteries and veins. The combination of isosorbide-5-mononitrate and metipranolol was chosen for comparison because the pharmacodynamics and pharmacokinetics of its constituents [1-3] could be expected to match best those of BM 12.434. In an unpublished investigation in six healthy volunteers the β-adrenoceptor-blocking effect of 80 mg of BM 12.434 in a bicycle exercise test was about equal to that of 5 mg of metipranolol.

Methods

In the present investigation, 12 male healthy volunteers (age 21–28, \(x = 24.5\) years) received by mouth, in a random cross-over and double-blind fashion, 80 mg of BM 12.434, 5 mg of metipranolol, and 20 mg of isosorbide-5-mononitrate + 5 mg of metipranolol. Apart from heart rate, blood pressure and cardiac output (impedance cardiography) were measured before and at 1, 2 and 3 h after administration in order to determine total peripheral resistance, and in addition the pressure in a peripheral vein. Arterial flow of the arm and venous capacity were determined by venous occlusion plethysmography, using for the determination of venous capacity an occlusion pressure of 40 mmHg, which was built up within 60 s (mercury-in-rubber strain gauge, Whitney).

In a further experiment in healthy volunteers, the arterial pulsations of the finger were recorded (digital pneumoplethysmography) after 80 mg of BM 12.434 by mouth (\(n = 6\)) and placebo (\(n = 6\)). For statistical analysis the Wilcoxon’s matched pairs signed rank test was used. Significance has been assumed if \(2\alpha \leq 0.05\).
Results

Results are shown in Table 1.

Although the stroke volume fell in all treatment groups by only 3%, the cardiac output decreased by 12% after metipranolol and IS-5-MN + M but by 7% after BM 12.434. None of these changes was statistically significant. Mean systolic blood pressure fell by about 5 mmHg after BM 12.434 and metipranolol, but by 12 mmHg after IS-5-MN. Diastolic pressure fell by only 5 mmHg after IS-5-MN + M. Total peripheral resistance increased by 17% after metipranolol, by 9% after pranolol it showed a slight tendency to fall.

Arm blood flow increased only after the increase after metipranolol was statistically significant. Arm blood flow increased by 7% after BM 12.434. None of these changes were significant. Arm blood flow increased only after BM 12.434 from 3.96 ± 0.66 ml min⁻¹ 100 ml⁻¹ to 4.93 ± 0.82, an increase of 24%. After IS-5-MN the flow showed an unexpected decline but this did not achieve statistical significance.

Venous capacity of the arm rose significantly after BM 12.434 from 2.06 ± 0.19 to 2.44 ± 0.16 ml/100 ml, i.e. 18%. After IS-5-MN + M venous capacity showed a slight but insignificant increase by 0.28 ml/100 ml from 2.15 ± 0.19, i.e. 13%, whereas after metipranolol it showed a slight tendency to fall. Venous capacity of the finger showed an increase only after BM 12.434, +28% at 1 h post-administration. The time-independent maxima are significantly different from the pre-drug control (2σ < 0.01).

The values for the venous capacity as determined by volume changes of the arm together with those of the venous pressure were used to plot the volume–pressure diagrams for each treatment group before and at 1, 2 and 3 h after drug administration (not shown). If after treatment the same increase of pressure as before coincides with a larger increase of volume, the distensibility of the veins must have been augmented. After metipranolol the volume–pressure curves before and at different times after drug administration were superimposable. The curves before and 1 h after IS-5-MN + M were close together, but the 2 h curve and especially the 3 h curve lay above the pre-drug control curve. Curves 1 and 2 h after BM 12.434 were widely separated, whereas 3 h after administration there was no difference from the control curve. This indicates that venous capacity measured by invasive techniques corresponds well to data derived from occlusion plethysmography.

In the trial with pneumoplethysmography, the amplitude of the arterial pulsations of the finger increased up to about 170% of the pre-drug value after administration of BM 12.434, but there was no significant change after placebo.

| Systolic pressure (mmHg) | 119 ± 2 | 117 ± 2 | 119 ± 3 | 118 ± 2 | 121 ± 2 | 123 ± 2 |
| Diastolic pressure (mmHg) | 77 ± 2 | 77 ± 1 | 77 ± 2 | 79 ± 2 | 78 ± 1 | 77 ± 2 |
| Pulse rate (beats/min) | 63 ± 1 | 64 ± 1 | 62 ± 1 | 66 ± 1 | 66 ± 1 | 64 ± 1 |
| Total peripheral resistance | 1324 ± 39 | 1328 ± 40 | 1321 ± 37 | 1329 ± 36 | 1329 ± 36 | 1330 ± 37 |
| Venous capacity of the arm (ml/100 ml) | 2.06 ± 0.19 | 2.44 ± 0.16 | 2.42 ± 0.19 | 2.23 ± 0.29 | 2.40 ± 0.27 | 2.28 ± 0.18 |
| Venous capacity of the finger (ml/100 ml) | 0.98 ± 0.14 | 1.17 ± 0.12 | 1.20 ± 0.16 | 1.25 ± 0.14 | 1.02 ± 0.12 | 1.08 ± 0.13 |
Discussion
The results after the administration of metipranolol are in accordance with the known effects of \( \beta \)-adrenoceptor-blocking agents. IS-5-MN + M differed from metipranolol alone by causing a drop in systolic pressure, and by its effect on venous capacity, which showed the expected slight increase. BM 12.434 evidently differs from metipranolol in its effects on the peripheral circulation. Despite a decreased cardiac output, arterial flow through the arm increased. This finding correlates with the increased amplitude of the finger arterial pulsations, which were determined independently.

The consistent behaviour of the venous capacity and of the volume–pressure relationship indicates undoubtedly that BM 12.434 has, unlike metipranolol, a venodilating activity. The mechanism of the vasodilating action of BM 12.434 is unknown but is assumed to be a direct one on the blood vessel. However, results from animal experiments provide no evidence that the substance has partial agonist activity, an \( \alpha \)-adrenoceptor-blocking activity, ganglionic or a post-ganglionic blocking activity. According to the present study and in the light of unpublished results on the duration of the pulse–pressure product reduction under physical stress, the vasodilating action of 80 mg of BM 12.434 is shorter than the \( \beta \)-adrenoceptor-blocking activity. Thus we could demonstrate the former for only 3 h after oral administration, whereas the latter persisted for approx. 6 h.

In conclusion, BM 12.434 differs from the conventional \( \beta \)-adrenoceptor-blocking drug metipranolol by its dilating effects on both arterial and venous vessels. The activity on the venous system is similar to that of the organic nitrates and suggests possible therapeutic usefulness of BM 12.434 in coronary heart disease. Moreover, this dilating effect on capacitance vessels could be useful in the management of hypertension, in view of the reduction in venous as well as arterial compliance in essential hypertension [4].

References