β -Adrenoceptor Blocking Drugs at Maximum β -Blockade in Relation to Dose and Plasma Concentration

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β -Adrenoceptor-blocking drugs play a dominant role in the treatment of hypertension, angina pectoris and cardiac arrhythmias (1, 5). In addition, these drugs are applied in a number of non-cardiological disorders without definite explanation of their mode of action, such as hyperthyroid disease, psychotic disorders, essential tremor, migraine prophylaxis and glaucoma. It has never been clearly defined to what extent the differing pharmacological properties of β -blockers are of significance for all these treatment indications. It was the aim of the present work to study three different types of β -receptor-blocking drugs, i.e. drugs with clearly differing pharmacological properties, in an intrasubject comparison by use of standard tests for measuring β -blockade and by determination of the plasma level of the β -blockers.

Methods

The drugs used in the study were metoprolol, pindolol and propranolol. The pharmacological profile of these β -blockers is shown in table I. By definition, all three drugs have the β -blocking activity in common; differences only exist with respect to potency per weight. Metoprolol is a β_1 -specific (cardioselective) blocker. Pindolol possesses intrinsic activity. All three compounds have some negative inotropic effect. The membrane-stabilizing (quinidine-like) activity is considered to be negligible in therapeutic doses.

9 healthy subjects participated in the study after giving informed consent. They were 6 male and 3 female, age range 21–30 years, weight range 53–81 kg. The study was planned using a randomized, cross-over design. Each subject received each β -blocker at increasing doses until maximum β -blockade was achieved (maximum β -blockade is defined below).

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Table I. Pharmacological properties of β -adrenoceptor-blocking drugs

β -Blocker

β -Blocking potency (propranolol =

1.0)

Intrinsic activity

β_1 -Selectivity

Membrane stabilizing activity

Metoprolol

Pindolol

Propranolol

1 6

1

++

+

+ ++

Each dose was administered in a three times daily regimen over 2 days. In the control period and at the end of every 2-day treatment period (4 h after final dose), an exercise test on a treadmill was performed using the treadmill load which in the control tests had increased the heart rate above 150 beats per minute (bpm). In addition, after each treatment period a blood sample was obtained for determination of the actual plasma concentration. Maximum β -blockade was assumed when, by the subsequent dose increase of the β -blocker, no further reduction of exercise tachycardia was observed. Single doses used were 25, 50, 75, 100, 150 mg metoprolol, 2.5, 5, 7.5, 10, 15 mg pindolol, and 20, 40, 80, 120 mg propranolol.

In the pretreatment period and at maximum α -blockade with all drugs isoprenaline stimulation was carried out with increasing doses of isoprenaline administered as intravenous bolus injections (4) up to a dose that produced an increase in heart rate by 30 bpm. Metoprolol, pindolol and propranolol plasma concentrations were determined by the use of gas liquid chromatographic and fluorometric assay procedures (2, 3, 6).

Results and Discussion

Resting Heart Rate

Metoprolol and propranolol caused a reduction of resting heart rate at each dose tested. The reduction was, however, significant only with the 80-mg dose (t.i.d.) of propranolol (64.5 vs. 73.2 bpm), but also with the 50-mg (66.1 bpm) and the 75-mg (59.3 bpm) dose of metoprolol. Even at maximum β -blockade the resting heart rate was never significantly below 60 bpm. Under no dose of pindolol did a significant reduction of resting heart rate occur, which is due to pindolol possessing intrinsic activity.

Exercise Heart Rate

Mean exercise heart rate was 163 bpm in the control period, but was reduced with each β -blocker at all doses tested to a minimum level of 116 bpm (80 mg propranolol), 127 bpm (7.5 mg pindolol), and 120 bpm (80 mg meto-

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250 -

200-

e:

en

C. 150 -

0 50- 7/8 3/8 7/8 SS S SSS 3/8

is : 5/8 w 1/8 w p 7/8 S 1/8 1/8;

2 0J K...V...1 F,,,,:;! L...viv-!-J

Metoprolol Pindolol Propranolol

SD 42% 45% 57%

Fig. 1. Mean plasma concentrations of metoprolol, pindolol and propranolol (+ SD) at maximum β -blockade.

prolol). Thus, propranolol produced the greatest reduction in exercise heart rate, and pindolol had the slightest effect, although differences between β -blockers were small.

Exercise heart rate at maximum β -blockade was reduced from 163 ± 6 bpm in the control period to 116 ± 10 bpm with propranolol, 128 ± 7 bpm with pindolol, and 120 ± 9 bpm with metoprolol. Maximum β -blockade was found at different β -blocker doses for each subject, so that the mean values given for maximum blockade are not identical with the values for one specific dose.

β -Blocker Doses

When the doses of the β -blockers that produced maximum β -blockade were compared, it was found that daily doses of 234 ± 96 mg propranolol, 21.6 ± 6.0 mg pindolol and 249 ± 99 mg metoprolol had equipotent effects with respect to inhibition of exercise tachycardia in this group of healthy subjects. This potency ratio of 10:1:10 (propranolol:pindolol:metoprolol) is in disagreement with data from the literature showing equipotent doses at a 6:1:6 ratio (7). The differences might be due to the test used to determine potency or the fact that potency commonly is evaluated after single doses, while we studied the multiple dose situation.

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Fig. 2. Dose response curves for isoprenaline stimulation before treatment and at maximum β -blockade with metoprolol, propranolol and pindolol in one subject. CO = Control; ME = metoprolol; PR = propranolol; PI = pindolol.

β -Blocker Plasma Concentrations

Plasma concentrations of the β -blocking drugs determined at maximum β -blockade are shown in figure 1. Equipotency in terms of plasma concentration is given at a ratio of 7:1:7 (propranolol:pindolol:metoprolol). From these data it may tentatively be concluded that the upper level of the range of therapeutic plasma concentrations is 160 ng/ml for propranolol, 25 ng/ml for pindolol, and 160 ng/ml for metoprolol.

Isoprenaline Stimulation

The dose response relationship for the isoprenaline stimulation before treatment and at maximum β -blockade with all three β -blockers is shown for one subject in figure 2. The pattern of changes is identical in all subjects. All curves appear to run parallel to each other. The β -blocker curves are shifted to the right, as is to be expected. The control (pretreatment) curve is always at the left side of the graph, next to it is the metoprolol curve, the propranolol curve is shifted even more to the right, but the highest isoprenaline doses are always needed to suppress maximum β -blockade with pindolol.

For each isoprenaline test the dose needed to produce a 30-bpm increase in heart rate was determined. Mean isoprenaline doses were 3.8 ± 3.0 μ g in the control period, 22 ± 9 μ g for metoprolol, 200 ± 140 μ g for propranolol and 458

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± 199 μ g for pindolol. The ratio of isoprenaline doses for all three β -blockers was 1:9:21. It is obvious that the β -blockers show a completely different behavior at the exercise test and at the isoprenaline test. At exercise pindolol has a somewhat lower capacity to reduce heart rate, due to its intrinsic activity. In the isoprenaline test, however, the greatest β -blockade is seen under pindolol, whereas metoprolol exhibits β -blockade considerably less, and propranolol is situated between the two.

Conclusions

The present study shows that inhibition of exercise tachycardia and inhibition of isoprenaline-induced tachycardia are two completely different and non-comparable tests to measure β -blockade.

It needs to be discussed whether the results in the isoprenaline test are due to differences in ratio of the β_1/β_2 -receptor-blocking activity of the three β -blockers. If a β -blocker is cardioselective, i.e. the β_1/β_2 -blocking capacity is high, then a low dose of isoprenaline may be sufficient to abolish the β_1 -blocking effect (metoprolol). Conversely, if the β_1/β_2 ratio is low (pindolol) a high isoprenaline dose may be needed to suppress the β -blocking effect.

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