BETA-ADRENERGIC BLOCKADE IN ISCHAEMIC HEART DISEASE

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1. On the evaluation of the therapeutic effects of anti-anginal agents.

It is widely accepted opinion that the double blind method is indispensable for evaluation of clinical effect of anti-anginal agents. Multicentrial controlled double blind study is a standard method in many countries at present. However, it is inefficient to investigate the effect of newly developed antianginal agents by multicentrial controlled method without preliminary studies.

In this regard we usually use the sequential analysis of Armitage for preliminary evaluation. In this analysis, the drug to be tested and its placebo are given in the way of cross-over and double blind, and their effects are compared in individual cases. In our design the required probabilities of successful treatment are set at 80% for the drug and 30% for placebo, two-sided significance level at $2a = 0.05$, and power of the test at $1 - \beta = 0.95$. The probability of 30% for placebo was determined according to Beecher's investigation and our own experiences. By this design, a decision is made by use of the cases equal to or less than 19, in which either of the drug or placebo is more effective. Frequency, severity and duration of anginal attacks, exercise tolerance measured by treadmill, and number of the consumed nitroglycerin tablets were selected as parameters for evaluation and proper points were given to each item according to the grade of improvement. The effectiveness of the drug is evaluated by comparing the scores, i.e. sums of the obtained points in each case.

Various antianginal agents have been investigated by this method. Among them, propranolol was evaluated as effective, because better scores were obtained in 7 out of 9 cases by this drug than placebo. Isosorbide dinitrate and nifedipine, a newly developed antianginal agent, were also judged as effective, because scores were better in 9 out of 13 cases in the former and in 9 out of 16 cases in the latter. Required probability of effectiveness of 80% in our design is a considerably high value, so that the above-mentioned drugs were concluded to have an excellent effect on angina pectoris.

2. The difference in antianginal effects of the beta-blockers.

Although the effectiveness of beta-blockers in angina pectoris has been widely confirmed, some of the beta-blockers were not regarded effective by our design of sequential analysis. For example, little difference was present between the effects of pindolol and its inactive placebo.

Various reasons may explain this result, but following explanation were considered most likely. It has been observed that pindolol has an effect to suppress max dp/dt at the small dose, but this effect is not distinct at the larger dose. Because max dp/dt is regarded as an index of myocardial O_2 consumption, the results may indicate that the dose of pindolol used in our study was too large for the Japanese to suppress the O_2 consumption. In this trial we used pindolol of daily dose of 15 mg divided in 3 times, based on our clinical experience in the treatment of arrhythmias. Because max dp/dt was not determined in our study, however, this may be mere supposition. At any rate the pharmacological effects of beta-blockers are not always same. Accordingly the dose to be used should be carefully determined.

3. The effects of antianginal agents on left ventricular function.

According to the recent concepts Vmax is regarded more reliable indicator for myocardial O_2 consumption than max dp/dt.

Although Vmax cannot be directly measured, formulae for its approximate determination using the left ventricular pressure curve clinically obtained by left heart catheterization have been proposed by Hugenholtz et al and Mason et al. We have employed the Hugenholtz's formula modified for computer use by Ushiyama, a staff of our department, and his colleagues at Hahnemann Medical College in Philadelphia. In some cases a simple index, max dp/dt/IP, was employed, which was proved by us to be highly correlated with Vmax (calculated by above-stated formula) with a correlation rate of 0.92.

In order to examine the effects of antianginal agents on the left ventricular function during anginal attack, it is necessary to study them before administration of the drug. According to the results obtained by Ushiyama at the Hahnemann Medical College with his colleagues using left ventricular catheterization, max dp/dt was observed to increase in all of 8 normal controls and 20 cases with ischaemic heart disease, when heart rate was increased by intra-atrial pacing. On the other hand, Vmax decreased in healthy controls and 10 cases in which anginal pain or ST depression was not induced by increasing the heart rate up to 150 to 160/min., while it increased in 10 cases with induced angina pectoris or ST depression, indicating the essential difference between the patients with and without anginal attack. Cardiac output showed similar changes with Vmax.

Then we studied the effects of propranolol on the changes of left ventricular function caused by exercise in 5 cases with exertional angina using left ventricular catheterization. The hemodynamics examined in this study were heart rate, mean brachial arterial pressure, left ventricular systolic and end-diastolic pressure, TTI, max dp/dt, stroke volume, cardiac index, left ventricular stroke work index and Vmax.

After the hemodynamics were determined at rest without administration of the drug, the patients were made to exercise with the aid of supine type bicycle ergometer, until the ST depression appeared under telemetric monitoring of ECG. At the end of exercise hemodynamic determination was made again.

Fifteen minutes later the same procedures were performed with administration of the drug. The hemodynamics were determined at rest 5 to 10 minutes after intravenous injection of prapranolol of 2 or 5 mg, and immediately after, the same amount of exercise was started.

Comparing the changes of the parameters by exercise between before and after administration of the drug, the increase of heart rate, left ventricular systolic pressure, cardiac output, max dp/dt and Vmax induced by exercise were observed to be suppressed by the drug with significant differences. These findings confirm the current concepts that beta-blockers improve angina pectoris by reducing the myocardial O_2 consumption.

For comparison, similar experiments were made on nifedipine in 9 cases with exertional angina, which does not belong to the beta-blockers. The results showed tendencies to suppress the changes of the most parameters induced by exercise, but much less distinct in comparison with the effects of propranolol. Accordingly the mode of the action of nifedipine was not appreciated by this experiment, but it was noted that the elevation of end-diastolic pressure produced by exercise was eliminated after the use of the drug. Further investigation is required as to the mode of the anti-anginal action of this drug.

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