EFFECT ON EXERCISE TOLERANCE AND PHARMACOKINETICS OF CONVENTIONAL AND SUSTAINED RELEASE PREPARATIONS OF PROPRANOLOL IN PATIENTS WITH ANGINA PECTORIS

— A Double-blind Cross-over Study —

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Ten patients with effort angina were studied in a randomized double-blind cross-over trial in order to investigate the effect of sustained release propranolol (LA) and conventional propranolol (Prop) formulations on exercise tolerance. LA was given once daily and Prop three times daily. Treadmill exercise tests were performed using the Bruce protocol and the plasma propranolol levels were measured. The following results were obtained:

1) LA proved to have an anti-anginal effect similar to Prop. No adverse reactions were observed after administration of either of the drugs.
2) Similar suppressive effect of the heart rate, blood pressure and double product at rest and on exercise was seen after LA and Prop while the exercise capacity was increased.
3) The plasma level of propranolol was higher at 2 hours after Prop than LA administration, but there was no difference between LA and Prop at 4 and 24 hours after administration.
4) The plasma propranolol level at 4 hours after LA correlated with the percent reduction in exercise heart rate and with the percent reduction in the double product.

Our study suggested that once-a-day administration of LA could improve patients’ compliance and adds another choice to the list of clinically useful β-blockers for the treatment of angina pectoris on effort.

Many β-adrenoceptor blockers (β-blockers) have been developed since propranolol (‘Inderal’) was first introduced to the market for the treatment of angina pectoris, especially for effort angina in 1966. At present β-blockers are widely used for the treatment of not only angina but also hypertension and arrhythmias.

Propranolol was the first β-blocker introduced into the clinical practice. The useful daily dosage of propranolol in Japan is 30–120 mg, which is usually administered in 3 to 4 divided doses due to the relatively short elimination half-life. As long-term therapy is required for cardiovascular diseases, a simpler regimen will be more desirable.

Key Words:
Sustained-release propranolol
Conventional propranolol
Angina pectoris
Exercise tolerance

(Received December 11, 1983; accepted June 4, 1984)
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**Abbreviations:** RCA = right coronary artery; LMT = left main trunk artery; LAD = left anterior descending artery; LCX = left circumflex artery
in order to improve the patients' compliance.\textsuperscript{2}
McAinsh et al.\textsuperscript{3} has demonstrated that the therapeutic blood level can be maintained over 24 hours after administration of long-acting propranolol. The results of our open trial\textsuperscript{4} also revealed that the sustained release propranolol is useful for the treatment of angina pectoris.

This study was conducted in a double-blind cross-over method using treadmill exercise tests in order to compare the effect of sustained release propranolol\textsuperscript{*} and of conventional propranolol on effort angina, and to study the pharmacokinetics of both preparations of propranolol by measurement of the plasma propranolol levels.

METHODS

Patient Population (Table I)

Ten patients who were seen for chest pain between December, 1981 and December, 1982 were admitted into the trial. They were eight males and two females, whose age ranged between 47 and 69 years. Four of them were outpatients and the other six were inpatients. They all had angina on effort, although four of them had angina at rest. At entry four patients had a history of angina for less than six months; three for 1-5 years and the remaining three for more than 5 years. Only one patient had a history of old myocardial infarction. Coronary arteriography was performed in eight patients, and was confirmed to have significant stenosis of more than 75% luminal narrowing in diameter at least in one of the three major coronary arteries. Informed consent was obtained from each patient prior to this trial.

Test Drugs and Administration Procedures

A two-week placebo run-in period preceded the four-week treatment period. One group received 60 mg sustained release propranolol (LA) once daily (taken at 8.00 a.m.) for the first two weeks (Treatment I) while the other group was treated with 20 mg conventional propranolol (Prop) t.i.d. (taken at 8.00 a.m., noon and 6.00 p.m.). These treatments were crossed over in the latter two weeks (Treatment II). The study was conducted in a double-blind cross-over fashion.

The run-in placebo was distinguishable from LA and Prop. In each treatment period the identical-looking placebo to Prop was used with active LA capsule, or vice versa. Nitroglycerin was allowed to be used sublingually as needed for anginal attacks, but was instructed not to be used for the prophylactic purpose.

Exercise Test and Examination Parameters

The patients underwent a stepwise treadmill exercise test using the Bruce protocol. During the run-in period the test was repeated at least twice before obtaining the control level. The hospitalized patients performed the test at noon on the last day and 8.00 a.m. on the following morning (i.e. 4 and 24 hours after the last morning dose, respectively) of Treatment I and II. The ambulatory patients, however, performed the exercise test just before and 4 hours after the last morning dose (i.e. 8.00 a.m. and noon, respectively). During the exercise test electrocardiographic changes in ST-segment were monitored in leads aVF, V2, and V5, and blood pressure and heart rate were examined every minute. The exercise was ended when anginal pain or leg fatigue occurred.

Blood samples were taken to assay plasma propranolol levels before and 2, 4 and 24 hours after the last morning dose at the end of Treatment I and II. The specimens were centrifuged and the plasma was stored in a freezer. A third party\textsuperscript{†} determined the plasma propranolol level by radio-immuno-assay.

Analyses of Data Obtained

The background data of the patients and the usefulness of the test drugs were assessed by $\chi^2$-test, t-test and U-test while the heart rate and blood pressure were compared with the baseline values obtained during the run-in period using t-test. LA and Prop are identical when absorbed into blood, although the formulation and the speed of absorption are different. The exercise tolerance test and the blood sampling for plasma propranolol level were carried out at the end of each two-week Treatment I and II. Therefore, it was considered that very little effect was carried over from Treatment I when the subsequent test and sampling were made at the end of Treatment II. The overall assessment was made after taking all parameters into consideration.

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* Supplied from ICI-Pharma Ltd.
† The determination was made by SRL. The detectable limit by this method is 0.4 ng/ml. Each sample was double checked and the reproducibility was confirmed.
Fig. 1. Effect on heart rate, blood pressure and double product at rest.

The heart rate, blood pressure and double product before and 4 hours after the drug administration after two-week treatment are compared with the run-in values, the results of which are shown as mean ± S.D.

□ = LA treatment; ■ = Prop treatment; * = p < 0.05; ** = p < 0.01

Fig. 2. Results of case No.10 during the treadmill exercise tests.

From left to right, the changes of heart rate, double product and plasma level of propranolol in the 48-year-old male patient who suffered from effort angina with RCA and LCX narrowing. Following LA and Prop, the exercise tolerance capacity increased and the double product decreased. It is considered that the 4-hr values being superior to the 0-hr values is consistent with the plasma levels of propranolol.

□ = Control; ■ = LA treatment; ○ = Prop treatment; — = 0 hr; --- = 4 hr

RESULTS

Four of the ten patients began with LA, followed by Prop, while the remaining six received Prop preceding LA administration. Background parameters such as sex, age, diagnosis and concurrent diseases did not differ significantly between the two groups (Table I). Exercise data were analysed in 8 patients because exercise tests were not performed at 0 hour during the treatment period in two patients.

1. Effects on HR, BP and DP at Rest

As illustrated in Fig. 1, the heart rate (HR)
and double product (DP), systolic blood pressure (BP) × HR, significantly decreased following LA and Prop administration when compared with the run-in values, but did not alter much between 0 and 4 hour value during the treatment period. The BP was significantly lower only at 4 hours after the drug administration when compared with the run-in values. However, there was no significant difference between LA and Prop in either HR, BP or DP.

2. Effects on HR, BP and DP with Exercise

Figure 2 illustrates the changes in HR and DP during the treadmill exercise tests before and 4 hours after the drug administration as well as plasma level of propranolol in one patient (Case No. 10). An increase in exercise capacity from the baseline was seen. The exercise DP was attenuated before the treatment but the reduction became more significant at 4 hours after administration.
Table II shows the average changes in exercise capacity of eight patients. When compared with the run-in values, the exercise capacity increased at 0 and 4 hours following the treatment with LA and Prop, but there was no significant difference between both drugs. The exercise HR, BP and DP were compared at the equivalent levels of exercise workload between the run-in and treatment period (Fig. 3). The exercise heart rate was changed from 114.5 ± 16.3 (mean ± SD) beats/min to 91.9 ± 15.0 at 0 hour and 90.9 ± 12.9 at 4 hours in the LA group, and to 89.3 ± 17.0 at 0 hour and 92.8 ± 11.8 at 4 hours in the Prop group. Thus, significant suppression of exercise heart rate was observed following both treatments (p < 0.01); the increase in systolic BP with exercise was also suppressed; accordingly, DP was also attenuated significantly (p < 0.01). There were no significant differences between LA and Prop in exercise HR, BP and DP at 0 and 4 hours after drug administration.

3. Plasma Propranolol Level
The changes in plasma propranolol levels which were determined by radio-immuno-assay are shown in Fig. 4. The plasma propranolol level after LA varied between 19 and 26 ng/ml during the treatment period. On the other hand, the highest mean plasma propranolol level after Prop was 40 ng/ml. However, in the chronic administration, the minimum steady-state plasma propranolol level after LA was quite consistent with that after Prop.

The correlation of the plasma propranolol level with HR, BP and DP was also studied. The plasma propranolol level at 4 hours after LA correlated with the percent reduction in exercise HR (γ = 0.643) and with the percent reduction in exercise DP (γ = 0.730), but did not correlate with either parameter at 0 hour after LA and at 0
or 4 hours after Prop.

4. Anti-anginal Effect

Figure 5 shows the changes in the frequency of anginal episodes and the consumption of nitroglycerin tablets. The anginal episodes significantly decreased at Treatment I in both groups when compared with the run-in period. No significant change was observed in either of the groups after the procedure was crossed. The nitroglycerin consumption was also reduced during the treatment period but such reduction was not significant. Both LA and Prop were equally effective in patients with classical effort angina as well as with combined effort and rest angina.

No harmful side effect was noted throughout the trial period.

DISCUSSION

β-blockers have been used widely for the treatment of effort angina. Since Prop has normally to be taken three or four times a day, many patients fail to maintain a regular schedule. Sustained form, LA, will be of benefit because of its simplicity of regimen. Although this study was not aimed to investigate the effectiveness of the drugs regarding the decrease in angina attacks and nitroglycerin consumption, the results obtained showed that both Prop and LA produce a significant reduction of anginal episodes and a tendency of decrease in nitroglycerin consumption when compared with the run-in periods. Therefore, it was suggested that LA and Prop were equally effective for the treatment of angina and that LA would be useful in clinical practice. Details of our findings with regards to the anti-anginal action of LA has been separately reported.

The anti-anginal effect of propranolol is to suppress the myocardial oxygen consumption during exercise. The myocardial oxygen consumption is affected mainly by LV wall stress, HR and cardiac contractility. The DP, which is the multiplication of HR by systolic BP, two major factors of the oxygen consumption, is often used in clinical practice as a simple index, since DP well correlates with myocardial oxygen consumption. Propranolol significantly decreased BP, DP and particularly HR at rest. For the evaluation of β-blocking effects on effort angina various exercise tests are generally performed. A stepwise increment of workload to reach the anginal threshold within 3–6 minutes is considered to be appropriate for the assessment of anginal attacks. In this study, the Bruce protocol was used and the test was finished within 10 minutes. Therefore, no residual fatigue was carried over at the time of the second exercise test at 4 hours after administration. Prior to the trial inclusion, the patients tried the same exercise test at least twice so that they were familiar with the test method to avoid any possible effect of a patient's inexperience.

There was a little concern about a 'warm-up' phenomenon induced by the repetition of exercise tests within a short period or a 'training' effect at the end, but the repetition was minimal in this study. Following Prop and LA administration exercise capacity was increased. Exercise HR, systolic BP and DP at the equivalent levels of workload were significantly decreased. These may indicate that the exercise capacity was increased due to reduction of myocardial oxygen consumption. This action of the drug is said to be correlated with the plasma propranolol level. The mean plasma propranolol level after Prop ranged between 19 and 40 ng/ml, and a constant level of 19–26 ng/ml was maintained after LA. The plasma propranolol levels at 0 hour were similar after the chronic dosing with LA and Prop. The plasma propranolol level correlated with the percent reduction in exercise HR and in the DP only at 4 hours after LA. Although the β-blocking effect of propranolol is said to be dose-related, we could not find a good dose-effect relationship at 0 hour in LA, and 0 and 4 hours in Prop. This is probably due to the small number of study population, various metabolic rates of propranolol and different intrinsic sympathetic activity from patient to patient, especially during the exercise.

In conclusion, once-a-day administration of LA is equally valuable as thrice-a-day administration of Prop, and is helpful for an improvement of patient's compliance. The optimum dosage should be clinically evaluated in the future.

Acknowledgement

We thank Professor Ryouhei Hori of Department of Pharmacetics, Kyoto University Hospital for his assistance as a controller, and also Mr. Shigeru Kubo for his technical assistance at the exercise test.

Japanese Circulation Journal Vol. 48, October 1984
REFERENCES


