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Suppression of Plasma Renin Activity by Propranolol: Correlation with Plasma Propranolol Levels[1] (38141)

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Propranolol has been used widely as an anti-hypertensive agent. The mechanism of its blood pressure lowering action is not fully understood. After acute administration cardiac output falls but following chronic administration decreased peripheral resistance possibly due to a fall in plasma renin activity is the predominant feature (1–3).

Human and animal studies have shown that propranolol can lower plasma renin activity (PRA) and blunt the increase in PRA in response to such stimuli as renal nerve stimulation (4), posture and diuretics (5) and hypoglycemia (6). In preliminary experiments we were unable to find a persistent suppression of PRA in rabbits receiving twice daily intramuscular injections of propranolol for 4–6 weeks. Since propranolol's effect on heart rate is related to the blood level of the antagonist (7, 8), we examined the relationship of PRA to plasma propranolol levels in rabbits. Not all reports in the literature relate the biological effects of propranolol to the time of the administration of the last dose and hence indirectly to the blood level of the drug (3).

Methods. Nineteen female New Zealand white rabbits were used in 2 experiments. Mean weight was 2.95 kg ± 0.46 kg. All rabbits were placed in wooden restraining cages for periods up to 6 hr until they became acclimated to the confinement and rested quietly (average time, 16 hr). Five ml of blood were collected from a marginal ear vein by nicking the vein with a sharp razor blade after vasodilatation induced by topical xylene. The blood was collected into chilled test tubes containing sodium EDTA, centrifuged at 4° and plasma stored at −20°. Plasma propranolol levels were kindly performed by Ayerst Research Laboratories, Montreal, Canada, using the flurometric method of Shand *et al.* (9). Plasma renin activity was determined by radioimmunoassay (10).

Experiment #1. Three rabbits received 6 mg of propranolol in 0.2 ml sterile water intramuscularly (im). Blood samples were collected before and 1, 2, 3 and 4 hr after the propranolol administration. Four rabbits received twice daily injections of propranolol 2 mg/kg im for 3 mo. On the day of study these rabbits received 6 mg im and blood samples were collected as described above.

Experiment #2. Eight rabbits were randomly divided into 2 groups of 4. After con-

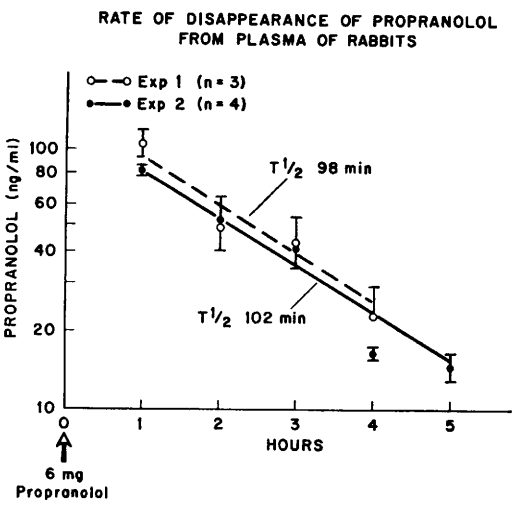

FIG. 1. The plasma half-life of intramuscular propranolol: plot of log of propranolol concentration on ordinate and time on abscissa. Experiment #1 indicates the disappearance rate in first experiment, and Experiment #2 from the second experiment.

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trol blood samples were collected, one group received 6 mg propranolol im while the other group, the vehicle, 0.2 ml sterile water. Blood samples were collected at hourly intervals for 5 hr. Immediately after the 4 hr collection, the vehicle treated rabbits were given 6 mg of propranolol im, while propranolol treated animals received the vehicle.

Experiment #3. Heart rates were recorded on an electrocardiograph in 6 control rabbits before and 2 min after intravenous injection of 2 μg of isoproterenol. Two additional rabbits received 6 mg of propranolol intramuscularly after control heart rates were recorded. The response of the heart rate to intravenous isoproterenol was measured as in the control rabbits at hourly intervals for 5 hr.

Results. The half-life of propranolol administered im to New Zealand white rabbits is 98 min in Experiment #1 and 102 min in Experiment #2 (Fig. 1).

Figures 2 and 3 shows the inverse relationship between PRA and plasma propranolol levels. As the propranolol level decreases, PRA rises. However, it was possible that the rising PRA was due to repeated blood sampling and the stress of confinement.

Figure 4 illustrates that for 3 hr and after 4 blood collections PRA is not significantly altered in a control group of rabbits while PRA is significantly lowered by propranolol in the treated rabbits when the sum of points A, B and C are compared with the sum of points A′, B′ and C′ ($P < .01$). At the time of the fifth blood sample at 4 hr, PRA does rise spontaneously in the control as well as the propranolol treated rabbits. Although the experiment is continued for one more hour im propranolol still lowers PRA significantly in the control rabbits ($P < .01$).

The mean heart rate of the six control rabbits before and after isoproterenol was 219 ± 9 S.E.M. and 337 ± 46 respectively, a significant increase of 117 beats/min ($P < .01$). In the 2 rabbits that received 6 mg propranolol im, there was a mean decrease in basal heart rate of 18 beats/min and inhibition of the isoproterenol induced increase for 4 hr. At 5 hr, there was an increased heart rate of 50 and 70 beats/min after isoproterenol, indicating a waning of the propranolol block. In Fig. 4, it can be seen that at 4 and 5 hr plasma renin levels rose spontaneously in both

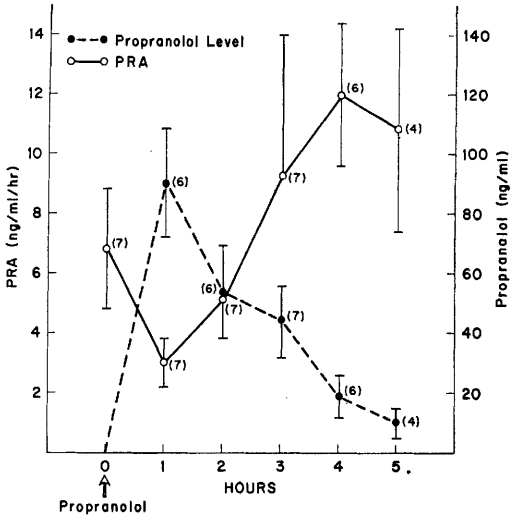

FIG. 2. The time course of PRA and plasma propranolol levels after im propranolol administered immediately after 0 time blood collection. Data from experiment #1 and #2 are averaged. The numbers in parentheses indicate the number of measurements at that time.

the control and propranolol treated rabbits.

Discussion. The disappearance rate of propranolol from rabbit plasma after acute administration is quite rapid with a $T_{\frac{1}{2}}$ of approximately 100 min. In our unpublished studies in the spontaneously hypertensive rat, we found the $T_{\frac{1}{2}}$ to be 78 min. Chronic administration of propranolol in the rabbit does not alter its half life. A relationship between plasma levels of propranolol and β-adrenergic blocking effects has been shown in man (7, 8). In the present experiments, we show an inverse correlation between the plasma concentration of propranolol and the peripheral plasma renin activity. It is possible that the inverse relationship between PRA and plasma propranolol levels is a fortuitous one. The stress of the experiment may have raised the PRA as the propranolol level was falling. However, the control rabbits undergoing the same procedure showed little change in PRA for the first 3 hr (Fig. 4), while the propranolol treated rabbits had persistently lower PRA which appeared to rise with time.

The heart rate response to isoproterenol seemed to be blocked for about the same length of time after administration of propranolol. The plasma renin activity is prob-

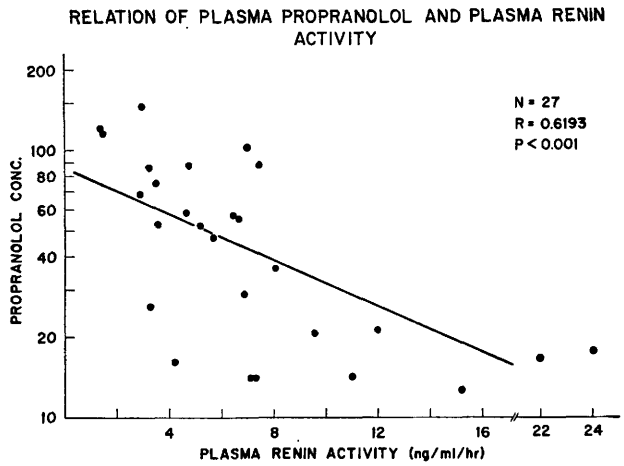

FIG. 3. Inverse correlation of plasma propranolol concentration and PRA. Regression line and coefficient are shown.

ably a reflection of renin secretion by the kidney although changes in renin disappearance rate cannot be excluded.

In relating the decreased peripheral resistance after chronic propranolol administration to its PRA lowering action it is important to note the relationship of the blood letting to the time of drug administration and to plasma levels of the drug.

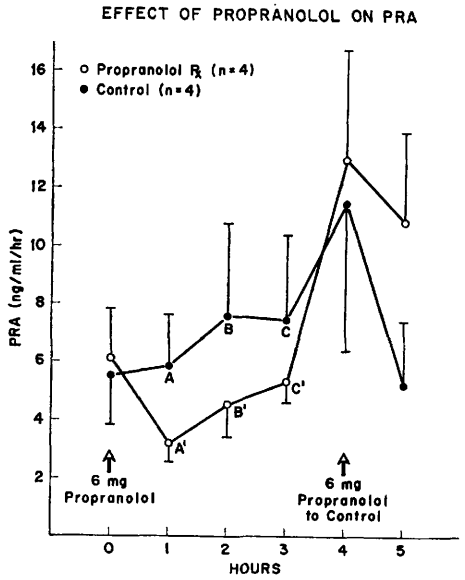

FIG. 4. The effect of propranolol and time on PRA. PRA is significantly lowered by propranolol when the sum of points A, B and C are compared to the sum of points A′, B′ and C′ ($P < 0.01$). After 3 hr, PRA rises in both control and propranolol treated rabbits. PRA is significantly lowered by propranolol administration to control rabbits ($P < 0.01$).

Summary. The plasma half-life of propranolol after intramuscular injection is 100 min in the New Zealand female rabbit. After the administration of a single dose of propranolol, there is a lowering of plasma renin activity (PRA) and an inverse correlation between PRA and plasma propranolol. It appears that the effect of propranolol on PRA is related to the plasma level of the drug which directly relates to the time of the last administration of the drug.

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