I. J. Med. Sc.
Eighth Series. Vol. 3. No. 3.
March, 1970

BETA ADRENERGIC BLOCKING PROPERTIES OF D AND DL PROPRANOLOL IN MAN

By

I. BRICK, K. J. HUTCHINSON and I. C. RODDIE

Department of Physiology, The Queen's University of Belfast.

RACEMIC (DL) propranolol is a beta adrenergic receptor antagonist (Black *et al.* 1964). In a study of the optical isomers of propranolol Howe & Shanks (1966) have shown that D propranolol had about 1/60-1/100 the activity of DL propranolol in blocking the effects of isoprenaline in dogs and cats. In the present experiments the potency of D and DL propranolol in antagonizing the response to intra-arterial and intravenous infusions of isoprenaline in man was compared.

Methods

Two series of experiments were performed on healthy male subjects who lay supine on a couch in a laboratory maintained at a temperature between 20° and 22°C. All recordings were made on a Beckman Type R Dynograph. Forearm blood flow was measured using water filled plethysmographs. The volume changes were converted using a Statham pressure transducer (P23 BB) as described by Hyman & Windsor (1966). Arterial blood pressure was recorded intermittently through a catheter in the left brachial artery using a Statham pressure transducer (P23 AA). The length of the catheter was adjusted to give approximately 64% critical damping (Cliffe, 1966). Instantaneous heart rate was recorded using a cardiotachometer triggered by the R wave of the electrocardiogram. The output from the cardiotrachometer was integrated to give an average reading every 30 sec. Respiration was recorded using two stethographs, one around the chest and the other around the abdomen connected to a pressure transducer (Statham P23 BB).

Dilutions of drugs were prepared in ascorbic acid (0.003%) saline (0.9%) mixture. Isoprenaline was given as DL isoprenaline sulphate (Boots), acetylcholine as acetylcholine chloride (Labs, Lamatte et Boinot), and D and DL propranolol as the hydrochloride (Imperial Chemical Industries).

In the first series of experiments the drugs were infused intra-arterially and the forearm blood flow response to intra-arterial acetylcholine and intra-arterial isoprenaline before and after D or DL propranolol was studied.

In the second series of experiments the heart rate, forearm blood flow and arterial pressure responses to intravenous isoprenaline before and after intravenous D or DL propranolol were studied.

Results

Intra-arterial infusions

Figure I shows plethysmograms from two experiments of the intra-arterial series. In the upper panel the effect of DL propranolol on the re-

sponses to intra-arterial acetylcholine and isoprenaline is shown. Acetylcholine, 2.5 μg/min, infused into the left brachial artery caused a large increase in left forearm blood flow as shown by the increase in slope of the plethysmograms during the 3 min. infusion period. Similarly a large increase in blood flow was caused by the intra-arterial infusion of isoprenaline, 0.25 μg/min. There was no change in blood flow in the right forearm in either experiment. The left forearm was then treated with DL propranolol, 25 μg/min., for 5 min. as a loading dose; the infusion of propranolol was continued at this rate throughout the rest of the run. The response to a further 3 min. infusion of acetylcholine was reduced while that to a further infusion of isoprenaline was abolished.

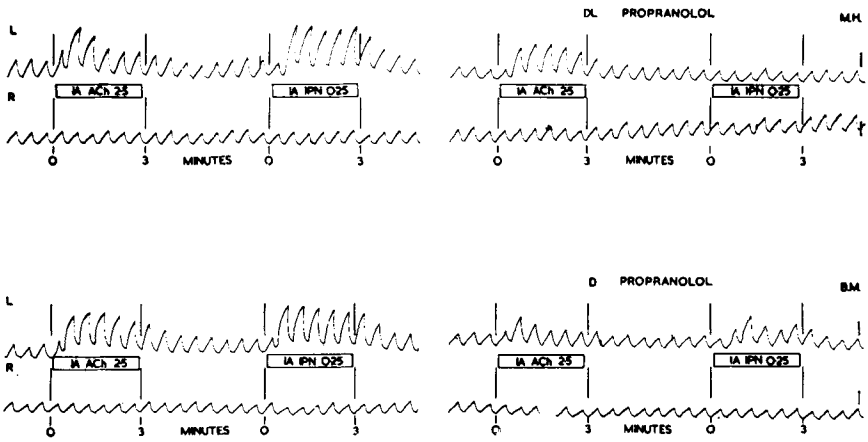

Fig. 1—Plethysmograms of left (L) and right (R) forearm blood flow before and after treatment with DL propranolol (upper traces) and D propranolol (lower traces). Acetylcholine (ACh), 2.5 μg/min, and isoprenaline (IPN), 0.25 μg/min were infused into the left brachial artery during the periods represented by the open rectangles.

In the lower panel of Fig. 1 the effect of D propranolol on the effects of similar infusions of acetylcholine and isoprenaline in a different subject is shown. Before treatment with D propranolol intra-arterial acetylcholine, 2.5 μg/min., and isoprenaline, 0.25 μg/min., again caused large increases in left forearm blood flow. The left forearm was then treated with D propranolol in the same dose as DL propranolol in the experiment shown in the upper panel; that is, 25 μg/min. for 5 min. before and throughout the run. While the responses to the repeat infusions of acetylcholine and isoprenaline were both reduced by D propranolol the response to isoprenaline was not abolished. Similar results were obtained in a further two experiments of each type and the averaged results of the three sets of experiments are shown in Fig. 2. Though DL and D propranolol were about equally effective in reducing the vasodilator response to intra-arterial acetylcholine DL propranolol was much more effective than D propranolol in reducing the vasodilator response to isoprenaline.

The effects of three rates of infusion of D and DL propranolol, 1.0, 5.0 and 25.0 μg/min., on the response of forearm blood flow to intra-arterial isoprenaline were examined. The results are summarized in Fig. 3. The mean increase in forearm blood flow during the 3 min. infusion

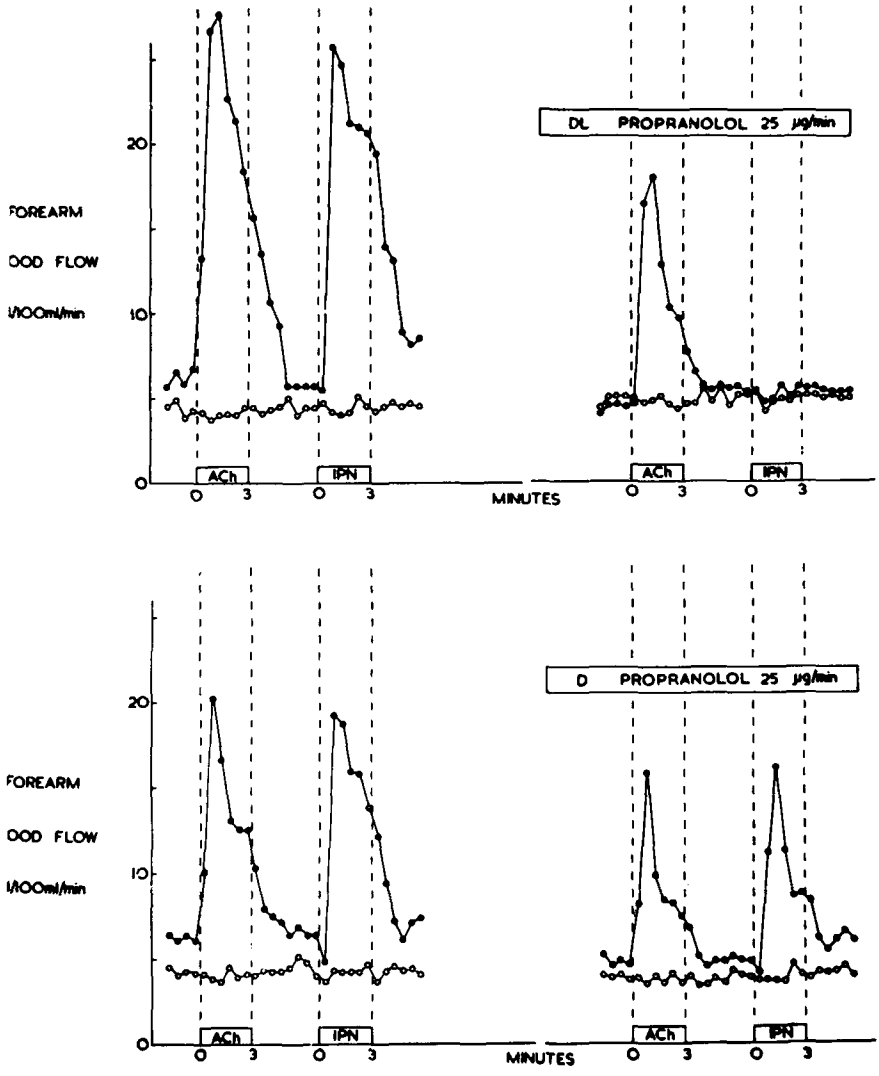

Fig. 2—The effect of DL propranolol (upper panel) and D propranolol (lower panel) on the blood flow responses in the forearm to infusion of acetylcholine (ACh), 2.5 µg/min and isoprenaline (IPN), 0.25 µg/min, into the left brachial artery. ● left forearm blood flow; O right forearm blood flow. The results show the average of three experiments.

of acetylcholine or isoprenaline before treatment with D or DL propranolol has been expressed as 100%. The mean increases in blood flow after treatment with D or DL propranolol have then been expressed as a percentage of this control change. It can be seen that both forms of propranolol reduced the response to acetylcholine. At the lower dose levels DL propranolol was much more effective than the D form. At the dose level of 25.0 µg/min. both forms of propranolol significantly reduced the response to acetylcholine to the same level ($p<0.05$). Using isoprenaline

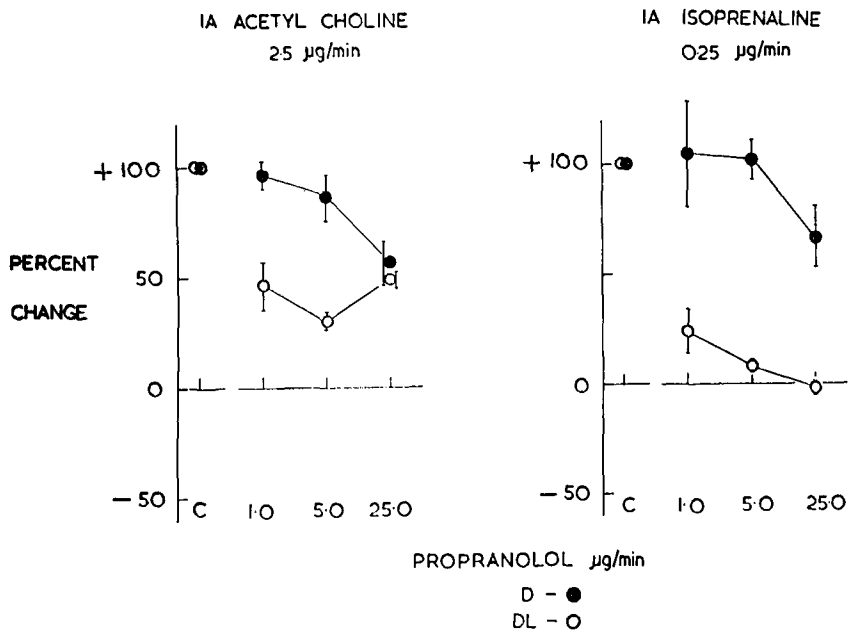

Fig. 3—The effect of D and DL propranolol of the responses of forearm blood flow to intra-arterial acetylcholine (left panel) and isoprenaline (right panel). The symbols show the responses before (C) and after the treatment of the foearm with 1.0, 5.0 and 25.0 µg/min D propranolol (●) and DL propranolol (O). Each symbol is the mean of observations on three subjects. The standard error of the mean is indicated by the vertical lines (|)

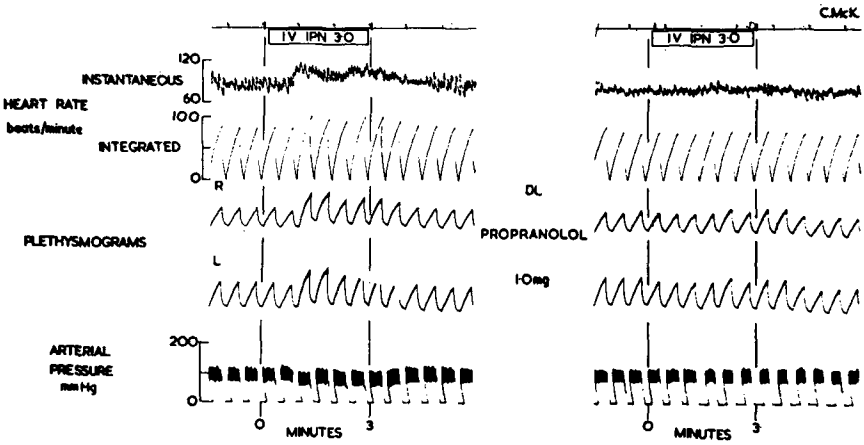

Fig. 4—The effect of intravenous infusion of isoprenaline (IPN), 3.0 µg/min, before (left panel) and after (right panel the intravenous injection of 1 mg DL propranolol in one subject. Records (from above downwards) are of minute time trace, instantaneous heart rate, integrated heart rate, right forearm blood flow, left forearm blood flow and arterial pressure.

there was a marked difference in the effect of the two forms of propranolol at all dose levels. DL propranolol caused much greater reductions in the responses than did equivalent doses of the D form.

Intravenous infusions

The effect of intravenous administration of D and DL propranolol on the responses to intravenous isoprenaline was studied in a further series of experiments. Figure 4 shows a typical experiment from a series using DL propranolol. It can be seen that isoprenaline, 3.0 μg/min., caused an increase in heart rate, an increase in forearm blood flow and a fall in diastolic pressure. After 1.0 mg. of DL propranolol given intravenously over 5 min. the isoprenaline infusion was repeated and this time the responses were abolished. Figure 5 shows a typical experiment from a series using D propranolol. It can be seen that the responses to isoprenaline, 3.0 μg/min. intravenously, were similar before and after the administration of D

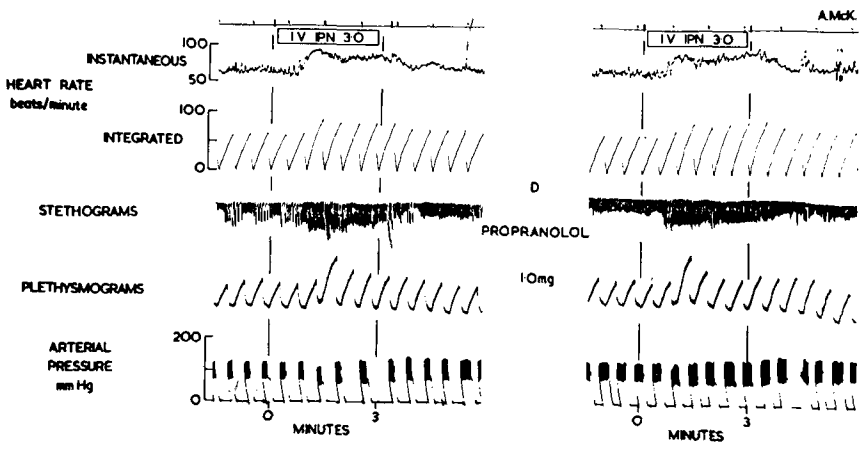

Fig. 5—The effect of intravenous infusion of isoprenaline (IPN). 3.0 μg/min, before (left panel) and after (right panel) the intravenous injection of 1 mg D propranolol, in one subject. Records (from above downwards) are of minute time trace, instantaneous heart rate, integrated heart rate, respiratory stethograms, right forearm blood flow and arterial pressure.

propranolol, 1.0 mg. intravenously. Figure 6 shows, in the upper panel, the average responses to isoprenaline in three subjects before and after DL propranolol and, in the lower panel, the average responses of three different subjects before and after D propranolol. In both series there was an increase in heart rate, a fall in diastolic pressure and an increase in forearm blood flow in response to isoprenaline, 3.0 μg/min. intravenously before treatment with propranolol. After treatment with DL propranolol the responses were abolished. After treatment with D propranolol there was little or no change in the responses.

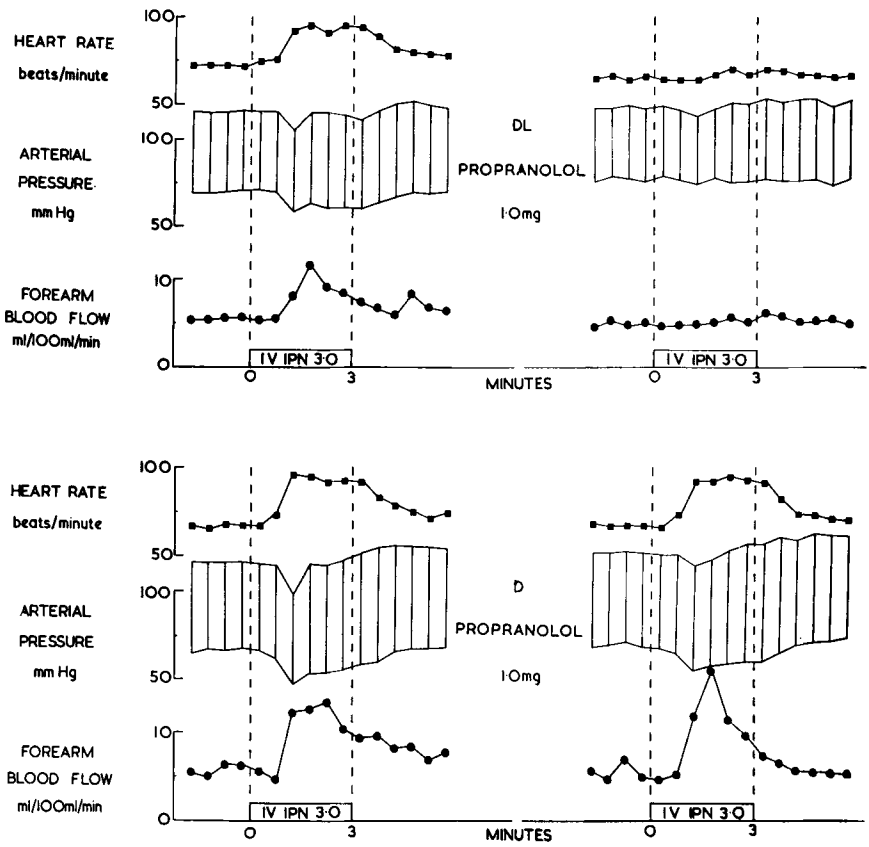

Fig. 6—The effect of DL propranolol (upper panel) and D propranolol (lower panel) on heart rate, arterial pressure and forearm blood flow responses to the intravenous infusion of isoprenaline (IPN), 3.0 μg/min. heart rate; ||||| systolic and diastolic pressure; ● forearm blood flow. In the upper panel the symbols represent the averaged results from three subjects while in the lower panel they represent the lower panel they represent the averaged results from three different subjects.

In order to assess the relative potency of the two forms of propranolol two doses of each were used and the results are shown in Fig. 7. As in the intra-arterial experiments the response to isoprenaline before propranolol has been expressed as 100% and the responses obtained after propranolol as a percentage of this control change. In the three experiments with D propranolol 1.0 and 10.0 mg. of the drug were used and in the three experiments with DL propranolol 0.1 and 1.0 mg. were used. It can be seen that DL propranolol was much more effective than D propranolol in reducing the three responses to isoprenaline 3.0 μg/min. The reduction in response obtained after DL propranolol, 0.1 mg., is roughly equivalent to that obtained after D propranolol, 10.0 mg. This suggests that DL propranolol is approximately 100 times as potent as the D form.

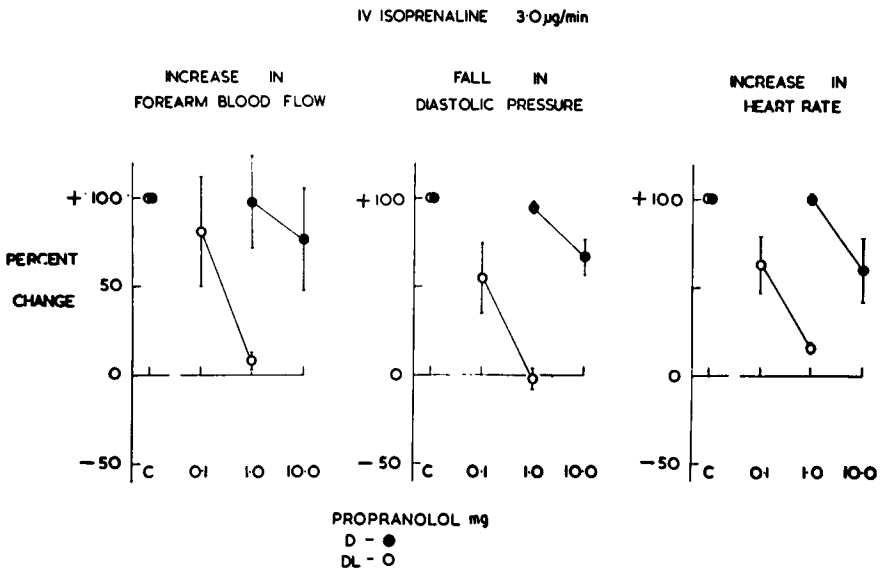

Fig. 7—The effect of D and DL propranolol on the responses of forearm blood flow (left panel), diastolic blood pressure (centre panel) and heart rate (right panel) to the intravenous administration of D propranolol (●) 1.0 and 10.0 mg and DL propranolol (O) 0.1 and 1.0 mg. The standard error of the mean is indicated by the vertical lines (|)

Discussion

These experiments show that beta adrenergic receptor activation with isoprenaline can be antagonized by both D and DL propranolol. However, in the intra-arterial experiments DL propranolol was found to be more than 25 times more potent than D propranolol and in the intravenous experiments 100 times as potent as the D form. This is in agreement with the findings of Howe & Shanks (1966) in cats and dogs.

A more surprising finding was that both forms of propranolol antagonized the vasodilator response to acetylcholine in the forearm. Though DL propranolol was more effective at low doses, at the dose level of 25 μg/min. D and DL propranolol caused similar reduction in this response.

Antagonism of the action of acetylcholine by local anaesthetics such as procaine, cocaine, amethocaine and nupercaine, has been demonstrated on various smooth muscle preparations (de Elio, 1948; Bucknell & Whitney, 1964). DL propranolol is 2 to 3 times more active than procaine as a local anaesthetic (Morales-Aguilera & Vaughn-Williams, 1965). Shanks (personal communication) has shown that the local anaesthetic properties of D and DL propranolol are similar. This would suggest that the acetylcholine antagonism of the two forms of propranolol is related to their actions as local anaesthetics and separate from their actions as beta adrenergic receptor antagonists.

Summary

1. The beta adrenergic blocking activity of D and DL propranolol was compared in healthy male subjects.

2. On intra-arterial administration, DL propranolol was more than 25 times as potent as D propranolol in antagonizing the forearm blood flow response to intra-arterial isoprenaline.

3. On intravenous administration DL propranolol was about 100 times as potent as D propanolol in antagonising the heart rate, forearm blood flow and diastolic blood pressure response to intravenous isoprenaline.

4. Intra-arterial D and DL propranolol also antagonised the forearm blood flow response to intra-arterial acetylcholine. It is suggested that the acetylcholine antagonism of the two forms of propranolol is related to their actions as local anaesthetics and separate from their actions as beta adrenergic receptor antagonists.

References

Black, J. W., Crowther, A. F., Shanks, R. G., Smith, L. H. and Dornhorst, A. C. (1964). A new adrenergic beta receptor antagonist. Lancet, i, 1080-1081.

Bucknell, Anne and Whitney, B,. (1964). A preliminary investigation of the pharmacology of the human taenia coli preparation. Brit, J. Pharmac. Chemother., 23, 164-175.

Cliffe, P. (1966). Engineering techniques in clnical medicine. Bio-med. Engineering, 1, 356-365.

De Elio, F. J. (1948). Acetylcholine antagonists : a comparison of their action in different tissues. Brit. J. Pharmac. Chemother., 3, 108-112.

Howe, R. and Shanks, R. G. (1966). Optical isomers of propranolol. Nature, 210, 1336-1338.

Human, C. and Windsor, T. (1966). An electric volume transducing system for plethysmographic recording. J. Appl. Physiol., 21, 1403-1404.

Morales-Aguilera, A. and Vaughan Williams, E. M. (1965). The effects on cardiac muscle of beta receptor antagonists in relation to their activity as local anaesthetics. Brit. J. Pharmac. Chemother., 24, 332-338.

Received for publication January 27th, 1970.