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Effect of β-adrenoceptor antagonists on the decline of the chronotropic response to isoprenaline

T. FENYVESI, C. F. GEORGE AND C. T. DOLLERY

*M.R.C. Clinical Pharmacology Research Group, Royal Postgraduate Medical School, London, W.*12, *U.K.*

The effect of three β-adrenoceptor antagonists (propranolol, practolol and H 35/25*) have been investigated on the decline of the tachycardia produced by intravenous doses of isoprenaline. Propranolol (0·5 mg/kg *laevo*-isomer) caused a significant increase in the rate of decline from 17·2 to 36·5 beats/min. Practolol (2 mg/kg), H 35/25 (2 mg/kg) and the combination of the two did not influence the rate of decline. Only propranolol caused a change in the slope of the isoprenaline heart rate dose-response curve; the observed increase of this slope is the probable cause of the change in rate of decline of the heart rate response.

During previous studies on propranolol in which isoprenaline was used to assess the degree of β-adrenoceptor blockade, we noticed that the duration of the chronotropic response to rapid intravenous doses was reduced. We have therefore undertaken further studies on the time course of isoprenaline-induced tachycardia in anaesthetized dogs treated with propranolol, practolol and H 35/25. Propranolol affects β-adrenoceptors in heart and vascular smooth muscle to a similar degree, but in addition has membrane stabilizing activity (Black, Duncan & Shanks, 1965; Morales-Aguilera & Vaughan Williams, 1965). Practolol was chosen because it acts selectively on cardiac β-adrenoceptors but lacks membrane stabilizing activity (Barrett, Crowther & others, 1968; Dunlop & Shanks, 1968). H 35/25 produces selective blockade of β_2-adrenoceptors (Levy & Wilkenfeld, 1969).

METHODS

Anaesthesia was induced in 13 mongrel dogs using thiopentone sodium (20 mg/kg) and maintained with pentobarbitone. Two PE 160 catheters were inserted in one cephalic vein to a distance of 15 cm. A single PE 160 catheter was inserted via the right femoral artery into the abdominal aorta. The arterial blood pressure was monitored through this using a consolidated electrodynamics transducer and charted on a Devices M4 Recorder. Heart rate was measured with a Neilson instantaneous ratemeter triggered by the R-wave of the ecg. Isoprenaline was injected in slug doses intravenously, each dose being diluted in 1 ml of saline. Isoprenaline dose-response curves were constructed in the control state and after the administration of β-adrenoceptor antagonists. These were analysed by calculating regressions for changes in heart rate and for diastolic blood pressure on log dose of isoprenaline and dose ratios were computed. The time course of the isoprenaline-induced tachycardia was calculated from readings off the continuous recording at 0·1 min intervals. Since

* (±)-1-(4′-Methylphenyl)-2-isopropylaminopropanol HCl.

the decline of the heart rate effect proved to be linear with time it has been expressed as beats per minute change.

The β-adrenoceptor blocking agents were infused intravenously, using a Harvard pump, at doses of 0·5 mg/kg (−)-propranolol hydrochloride, 2 mg/kg practolol and 2 mg/kg H 35/25, [(±)-1-(4′-methylphenyl)-2-isopropylamino-propanol hydrochloride: Hassle]; these were chosen on the basis of previous work in this laboratory and that of Levy & Wilkenfeld (1969). In one experiment 0·06 mg/kg atropine and 2 mg/kg lignocaine were infused after practolol; the former to block the parasympathetic and the latter to provide membrane stabilizing activity at least equivalent to that of propranolol 0·5 mg/kg. In two experiments, we compared the rate of disappearance of tritiated isoprenaline from plasma both before and after propranolol administration. For this the labelled drug (specific activity: 1·82 mCi/U mol), was injected intravenously and the disintegrations per min/ml were measured in arterial blood sampled by a fraction collector over 12 s periods for 3 min. The measurements were made in a Packard Tricarb Liquid Scintillation Spectrometer.

RESULTS

An estimate of the selectivity of β-adrenoceptor blockade was derived by comparing the dose ratios obtained for diastolic blood pressure and heart rate. After practolol there was evidence of selective blockade of the cardiac β-adrenoceptors, the ratio for blockade of the diastolic blood pressure responses (DBP) to heart rate responses (HR) being 0·072 ± 0·022. In contrast after H 35/25 alone the ratio for DBP:HR was 9·04 ± 3·10, indicating a selective blockage of β-adrenoceptors in vascular smooth muscle. After the combination of practolol and H 35/25 the ratio for DBP:HR was 0·83 ± 0·24.

The rate of decline of the heart rate response

The rate of decline of the chronotropic effect of isoprenaline increased in all eight dogs after propranolol. The mean rate of decline in 40 control administrations of isoprenaline was 17·2 ± 1·3 beats/min and 36·5 ± 1·3 in 77 administrations after propranolol ($P < 0·001$). Practolol treatment in three dogs did not cause a

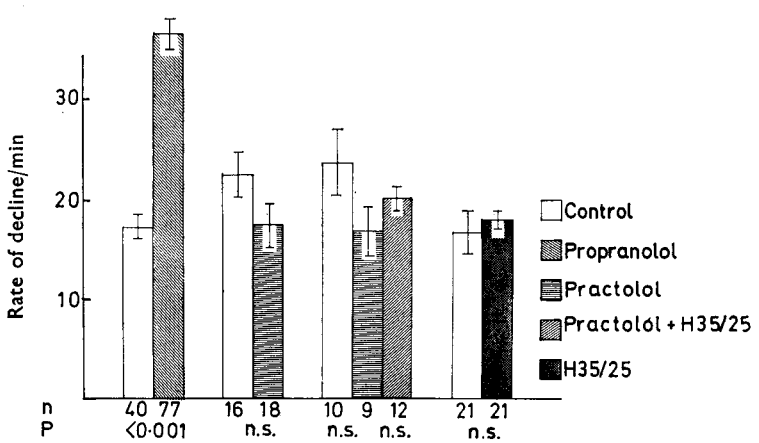

FIG. 1. Rate of decline of the chronotropic response to isoprenaline before and after β-adrenoceptor blockade. The numbers of observations made are indicated beneath each histogram together with the level of significance achieved.

significant change in the rate of decline of the tachycardia produced by isoprenaline. The mean rate of decline in 16 control administrations was 22·4 ± 2·2 and in 18 administrations 17·4 ± 2·2 beats/min after practolol. In two of these dogs H 35/25 was administered after practolol following which the rate of decline was 20·1 ± 1·2 beats/min. H 35/25 was given alone in two further experiments but did not cause any change in the rate of decline in the heart rate response to isoprenaline (Fig. 1). Neither atropine nor lignocaine added after practolol changed the rate of decline. There was, however, a significant correlation between the maximal achieved increase in heart rate and the rate of decline, $P = <0{\cdot}01$, but because a very large change in

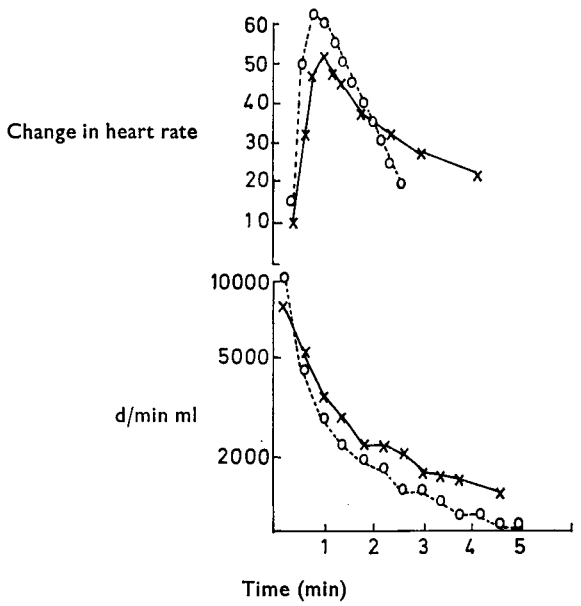

FIG. 2. Rate of decline of the chronotropic response and plasma disappearance of [^{3}H]isoprenaline before and after propranolol. ×—× Control, $T_{\frac{1}{2}}$ = 99·5 s; rate of decline = 18·5 beats/min. ○—○ Propranol, $T_{\frac{1}{2}}$ = 91·4 s; rate of decline = 48·4 beats/min.

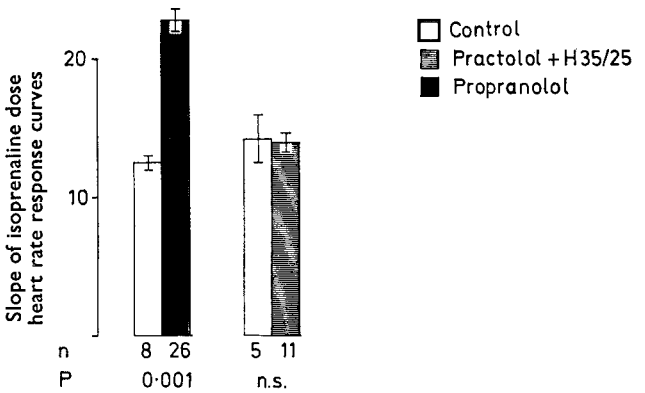

FIG. 3. Slopes of the isoprenaline heart rate dose response curves before and after β-adrenoceptor blockade. The numbers of dose response curves constructed are indicated beneath each histogram together with the level of significance achieved.

the maximal effect caused only a slight increase in the rate of decline these data were analysed independently of the actual heart rate effect.

Plasma half-life of [^{3}H]labelled isoprenaline

In two experiments the estimated plasma half-life of isoprenaline was 114·9 and 99·5 s in control and 137·0 and 91·4 s after propranolol treatment. The simultaneous change in the decline of the heart rate effect is shown in Fig. 2.

Effect of β-adrenoceptor blocking agents on the slope of isoprenaline dose heart rate response curves

Treatment with propranolol caused a significant increase in the slope of isoprenaline heart rate response curves from 12·5 ± 0·55 to 22·71 ± 0·86 ($P < 0·001$). Practolol and H 35/25 did not change these slopes, the control mean slope in this group was 14·29 ± 1·81, and the mean values after the two treatments being 13·95 ± 0·59 (Fig. 3). (The slopes are expressed in change of heart rate by increasing the isoprenaline dose by one natural logarithmic unit.)

DISCUSSION

These results show that whereas propranolol increases the rate of decline of the chronotropic response to isoprenaline in anaesthetized dogs, practolol does not. Adding H 35/25, a selective β_2-adrenoceptor blocking agent (Levy & Wilkenfeld, 1969) to practolol enabled us to mimic the non-selective β-adrenoceptor blocking properties of propranolol. Nevertheless, this combination did not cause any change in the rate of decline of the heart rate response to isoprenaline. Thus, the difference cannot be attributed to the reflex effect evoked by the unopposed vasodilator action of isoprenaline after practolol. Further evidence against this possibility is derived from the single experiment in which atropine was administered after practolol but did not alter the rate of decline. An alternative explanation could be that the membrane stabilizing effect of propranolol is responsible. This explanation has been rejected on the grounds that the combination of practolol and lignocaine failed to cause an increase in the rate of decline of the chronotropic effect of isoprenaline.

Levy (1966) has shown that the rate of decline of drug action can be expressed by the formula $(K \times M)/2·3$ where K is the apparent first order rate constant of drug elimination and M is the slope of the dose-response curve. In our experiments, the rate of elimination of [^{3}H]isoprenaline from plasma was not changed by treatment with propranolol. We have, however, found that the slope of the dose-response curve is increased significantly by propranolol. Furthermore, we have demonstrated a significant correlation between the rate of decline of the heart response and the slope of the dose-response curve. As the observed values for change in the rate of decline fall within the 95% confidence limits predicted from the change in slope after propranolol, we consider that this is the most likely explanation for the observed increase in the rate of decline.

Most workers including Black & others (1965) have reported parallel, rightward displacement of the dose-response curve for isoprenaline after the administration of propranolol. However, Blinks (1967) has shown that the curve is slightly steeper in the presence of propranolol and our results in anaesthetized dogs confirm this finding. The explanation for the change in slope of the dose-response curve after

propranolol is not known. It cannot be due to a change in uptake of isoprenaline to the receptors in the presence of larger doses necessitated by shift of the dose-response curve (Langer & Trendelenberg, 1969), as practolol, especially in combination with H 35/25, caused the same shift to the right without altering the slope of the dose-response curves.

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