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# EVALUATION OF SYMPATHETIC BETA-RECEPTOR BLOCKADE BY RECORDING THE RATE OF VENTRICULAR PRESSURE RISE IN CATS

BY

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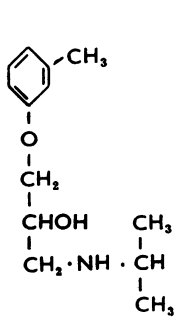
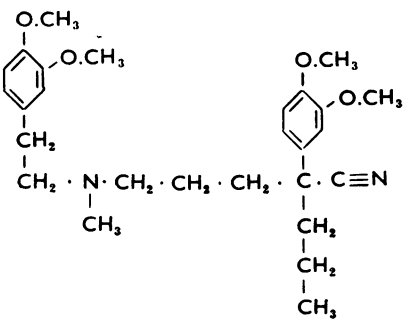
A characteristic property of β-receptor antagonists is the competitive inhibition of the cardiac action of isoprenaline. Typical β-receptor blocking drugs have myocardial depressant effects but will inhibit the action of isoprenaline in doses that do not depress the heart. Recently drugs with myocardial depressant properties have been claimed to be β-receptor antagonists—for example, iproveratril (Fleckenstein, 1964; Haas, 1964; Melville & Benfey, 1965). From results on the cat isolated papillary muscle, Melville & Benfey (1965) concluded that iproveratril is a competitive antagonist of noradrenaline. Concentrations of iproveratril had to be employed which reduced the amplitude of contraction.

It was of interest to repeat this study in the intact animal, using the maximal rate of rise in left ventricular pressure as an index to myocardial contractility. In doses that greatly reduced the rate of rise of ventricular pressure iproveratril inhibited the action of isoprenaline slightly, and procainamide and pentobarbitone had similar effects. In contrast, propranolol, Kö 592 (a close relative of propranolol), and pronethalol inhibited



Kö 592
(1-(3-Methylphenoxy)-2-hydroxy-3-isopropylaminopropane)



Iproveratril

the action of isoprenaline markedly. The method appeared to be useful also for the quantitative determination of isoprenaline antagonism and it was used to compare the potencies of propranolol and Kö 592.

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## METHODS

Cats were anaesthetized with pentobarbitone (35 mg/kg or more, intraperitoneally). The operating table was heated to maintain the normal body temperature, which was checked with a rectal thermometer. A tracheal cannula was inserted. Heparin (1,500 u.) was administered. The pressure in the left ventricle was measured with a Statham P 23 Db pressure transducer connected to a steel cannula which was 189 mm long. The cannula had an internal diameter of 0.8 mm, was open at the tip and had several small holes around the tip. It was inserted from the right carotid artery through the ascending aorta. At the end of the experiment the heart was opened and the position of the cannula and the condition of the heart valves were checked. The experiment was discarded if the valves were damaged. Ventricular pressure was recorded on a six-channel Hellige recorder,

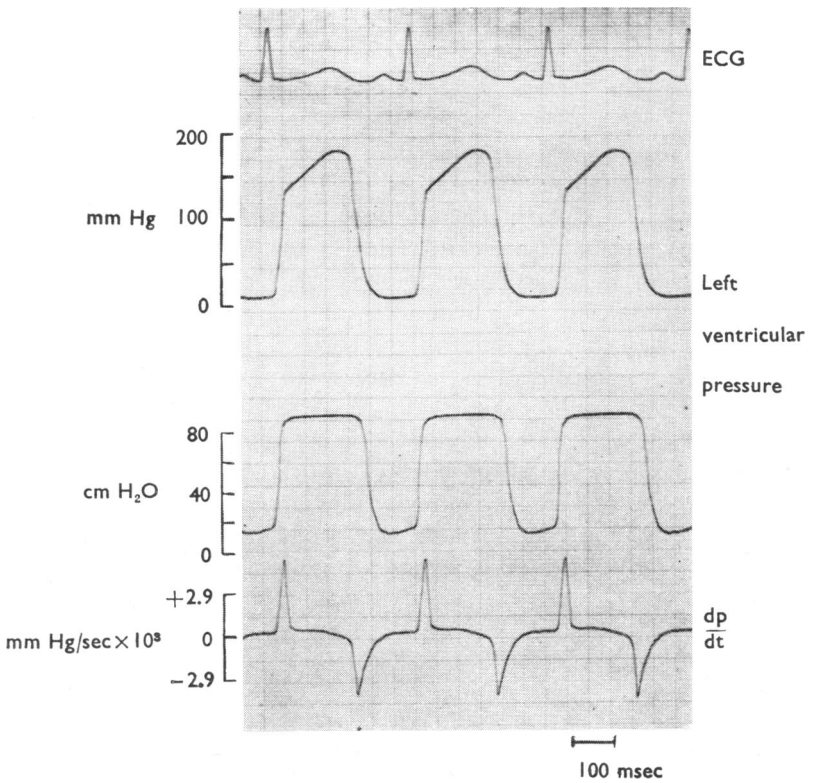


Fig. 1. Electrocardiogram (ECG), left ventricular pressure, left ventricular pressure cut off above 80 cm $H_2O$, and rate of change of ventricular pressure (dp/dt) in a cat anaesthetized with pentobarbitone sodium.

as shown in Fig. 1. To permit the accurate determination of end-diastolic pressure, the pressure record was cut off above approximately 80 cm $H_2O$ by two diodes and a magnified record was taken on an additional channel (Lutz, 1964). The rate of change of the ventricular pressure pulses (dp/dt) was continuously determined with an RC differentiating circuit consisting of a $10^4$ $\Omega$ resistor and a $10^{-8}$ farad condenser (Noble, 1953). The time constant of the circuit was $10^{-4}$ sec. The entire system of pressure recording maintained a uniform response to a sinusoidal frequency of 81 c/s (Heeg, unpublished).

The peripheral blood pressure was measured from the right femoral artery with a Statham P 23 Db pressure transducer on a short steel cannula. The electrocardiogram, taken from the right upper and left lower extremity, served to determine the heart rate.

For the quantitative determination of isoprenaline antagonism, 0.1 μg/kg isoprenaline was injected intravenously, followed 15 min later by the infusion of the antagonist. Six min later increasing doses of isoprenaline (0.3, 1, 3, 10, 30, and 100 μg/kg) were injected until the effect of the initial 0.1 μg/kg was reached. No dose was injected before dp/dt had returned to its control value before the previous dose. The injections of isoprenaline were completed in 19 min. The dose-ratio (dose of isoprenaline after the antagonist divided by that before the antagonist for equal changes in dp/dt) was determined graphically from dose-response curves.

Drugs were injected into the right femoral vein in a volume of 0.2 ml. of 0.9% saline, followed by 2 ml. of 0.9% saline, unless otherwise stated. The following drugs were used: isoprenaline sulphate, propranolol hydrochloride, pronethalol hydrochloride, Kö 592 (1-(3-methylphenoxy)-2-hydroxy-3-isopropylaminopropane hydrochloride, Boehringer, Ingelheim), iproveratril (Isoptin, Knoll), pentobarbitone sodium and procainamide. The amounts refer to the salts. The statistical calculations were made according to conventional procedures (Brownlee, 1957).

## RESULTS

### *Qualitative assessment of isoprenaline antagonism*

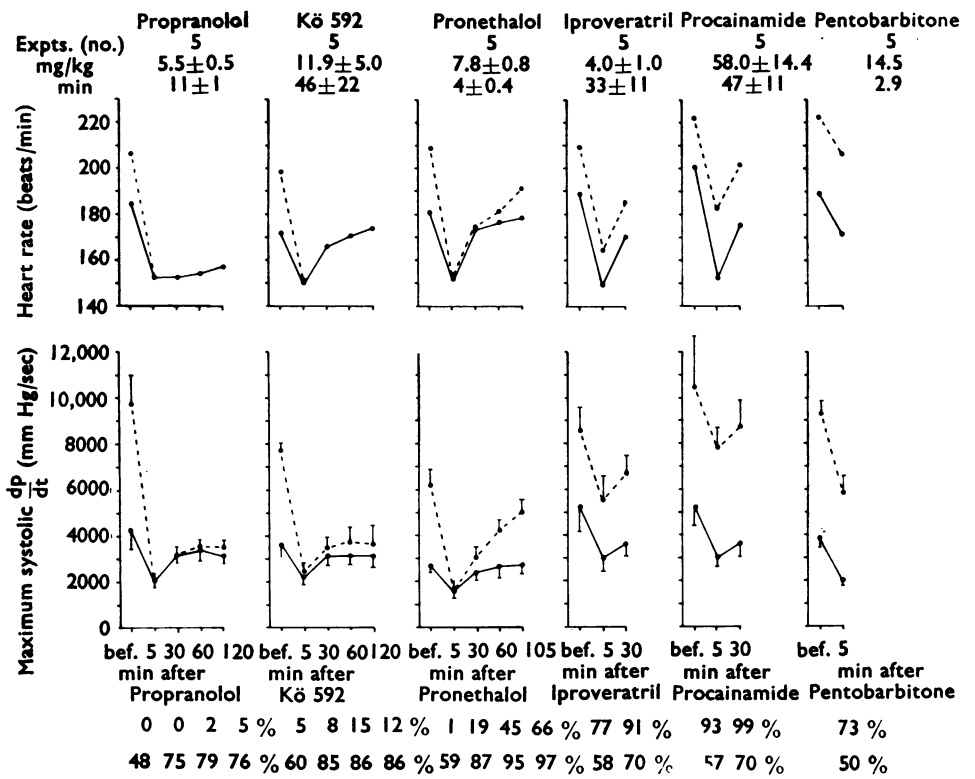


Fig. 2. Effect of isoprenaline (0.1 μg/kg, intravenously) on maximal rate of rise in left ventricular pressure (dp/dt) and heart rate in cats (pentobarbitone anaesthesia) before and after the infusion of drugs (mean doses in mg/kg ± standard error, mean time of infusion in min ± standard error). The solid lines refer to the controls, the broken lines to the effect of isoprenaline. The top numerals in the lower record refer to the effect of isoprenaline on dp/dt after the injection of antagonistic drugs as a percentage of that before their injection. The bottom numerals refer to the control dp/dt as a percentage of that before the injection of drugs.

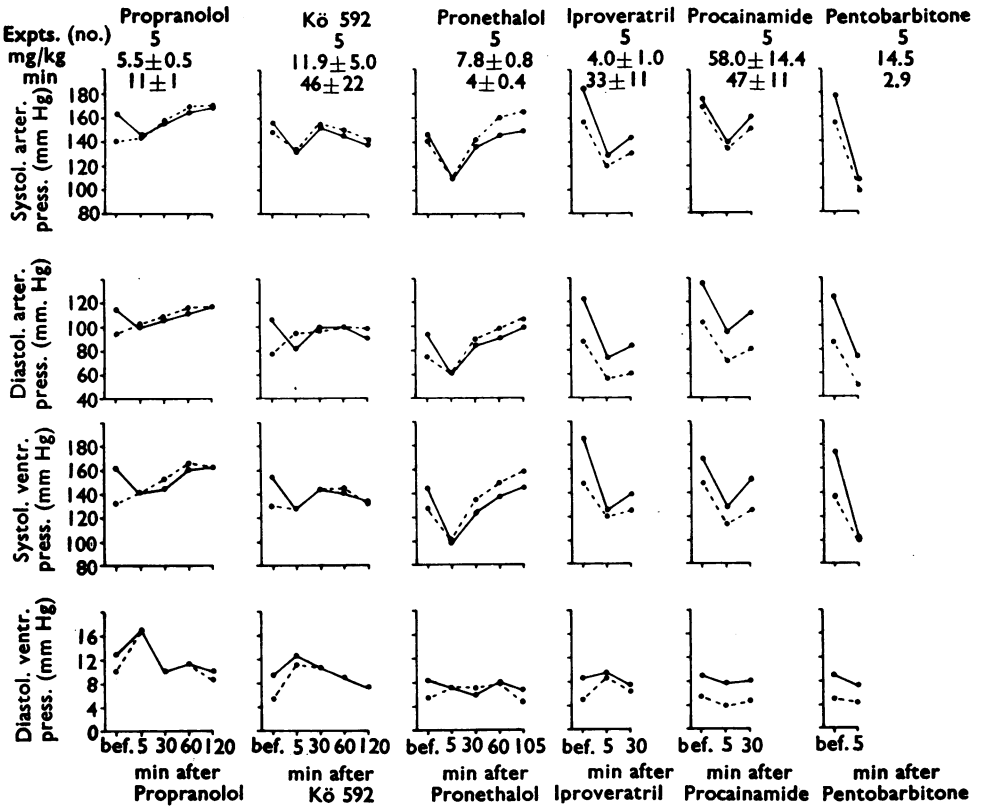


Fig. 3. Effect of isoprenaline (0.1 $\mu$g/kg, intravenously) on systolic and diastolic femoral arterial and left ventricular pressures in cats (pentobarbitone anaesthesia) before and after the infusion of drugs. The solid lines refer to the controls and the broken lines to the effect of isoprenaline.

Kö 592, which is chemically closely related to propranolol (Black, Crowther, Shanks, Smith & Dornhorst, 1964), and iproveratril, which has been claimed to be a competitive adrenaline antagonist on the heart (Fleckenstein, 1967; Haas, 1967; Melville & Benfey, 1965), were compared with two known $\beta$-receptor antagonists, propranolol and pronethalol (Black & Stephenson, 1962), and with two myocardial depressant drugs, procainamide and pentobarbitone. The experiments were begun with the injection of 0.1 $\mu$g/kg isoprenaline followed 15 min later by the infusion of the antagonistic drugs until dp/dt was approximately 50% depressed. Five, 15, 30, 45, 60, 75, 90, 105, and 120 min later the injection of 0.1 $\mu$g/kg isoprenaline was repeated.

The results are shown in Figs. 2 and 3. It is evident that propranolol, Kö 592 and pronethalol produced a profound inhibition of the action of isoprenaline on the heart rate, dp/dt and blood pressure, while iproveratril, procainamide, and pentobarbitone had small effects.

*Quantitative evaluation of isoprenaline antagonism*

Propranolol and Kö 592 were evaluated quantitatively as outlined in Methods. Figure 4 is a plot of the log dose-ratio of isoprenaline minus 1 against the log molar dose of

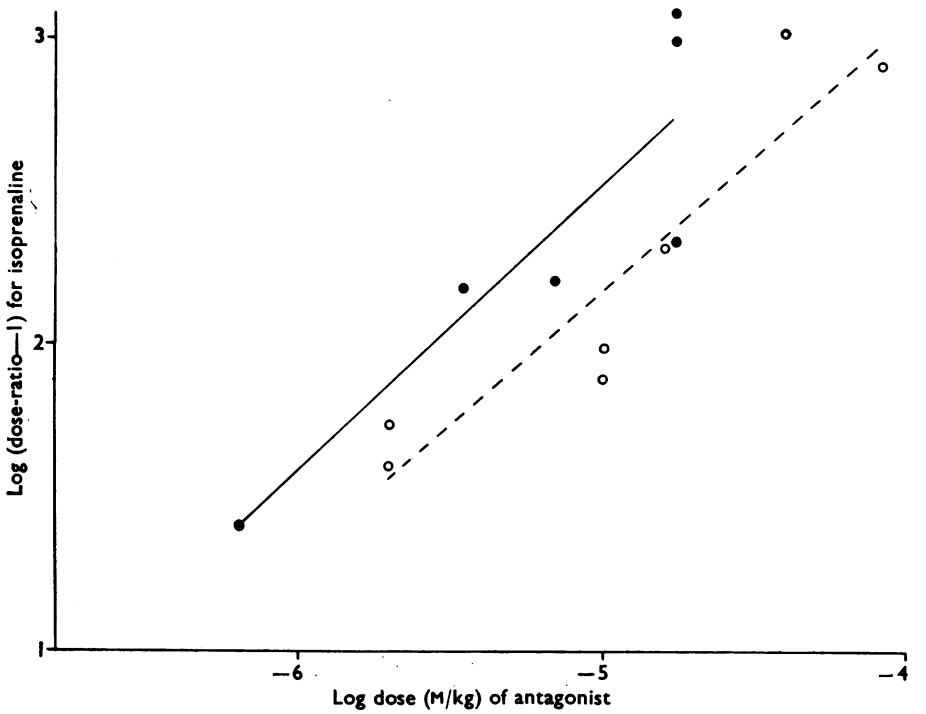


Fig. 4. Correlation of log (dose-ratio-1) for isoprenaline and log dose (M/kg) propranolol (dots) and Kö 592 (circles). The six results with propranolol were obtained in five experiments with cats (pentobarbitone anaesthesia, see Methods), and the seven results with Kö 592 in another five. The slope of the regression lines for propranolol (solid line) and Kö 592 (broken line) are 0.95 and 0.87 respectively.

propranolol and Kö 592. It is drawn according to Arunlakshana and Schild's (1959) method for the determination of $pA_{10}$, the negative logarithm of the molar concentration of an antagonist which increases the dose-ratio tenfold. One dose of propranolol (1, 2, 5 and 5 mg/kg) was infused in four experiments and the effect of 0.2 mg/kg was evaluated before that of an additional 4.8 mg/kg in the fifth experiment. One dose of Kö 592 (2.5, 2.5 and 21 mg/kg) was infused in three experiments and in two experiments the effect of 0.5 mg/kg was evaluated before that of an additional 3.5 and 9.5 mg/kg, respectively.

The regression lines for propranolol and Kö 592 had slopes of 0.95 and 0.87, respectively, which indicates a simple competitive antagonism. By extrapolation $pA_{10}$ values of 6.65 and 6.44 may be obtained for propranolol and Kö 592, respectively, showing propranolol to be 1.6 times more potent than Kö 592 on a molar basis and 1.9 times on a weight basis.

It is realized that $pA_{10}$ values refer to molar concentrations rather than doses. The $pA_{10}$ value of 6.65 for propranolol found in these experiments corresponds to a dose of 0.075 mg/kg causing 90% inhibition of the effect of isoprenaline on dp/dt. A dose of 0.15 mg/kg propranolol caused a 90% inhibition of the effect of isoprenaline on myocardial tension (measured with a strain-gauge arch sutured to the left ventricle) in

dogs anaesthetized with pentobarbitone sodium (Black *et al.*, 1964). This is in fair agreement with the present results. On the guinea-pig isolated atrium the $pA_{10}$ of propranolol with noradrenaline was 6.4 (Benfey & Varma, 1966).

## DISCUSSION

This study attempts to evaluate isoprenaline antagonism in the intact anaesthetized cat. Measurement of the maximal slope of the isometric contraction phase of the ventricular pulse (dp/dt), which has a highly significant correlation to myocardial contractility (Reeves, Hefner, Jones, Coghlan, Prieto and Carroll, 1960), permitted experiments without exposure of the heart for the attachment of a strain-gauge arch. Moreover, " increased ventricular contractility is expressed primarily by large changes in ' rates ' and small changes in quantities " of ventricular pressure rise (Rushmer, 1962).

Iproveratril is five to six times more potent than pronethalol in the intact guinea-pig (Fleckenstein, 1964), two times more potent than pronethalol in the guinea-pig isolated heart (Haas, 1964), and equal in potency on the cat isolated papillary muscle (Melville & Benfey, 1965). From the present results it appears that iproveratril has no adrenergic blocking action. The drug exerted a strong myocardial depressant action permitting the infusion of not more than 4 mg/kg in 33 min. While dp/dt was reduced to 58%, the isoprenaline effect was 77% of the control, and it was 91% 30 min after iproveratril when dp/dt had recovered to 70%. A similar reduction in the effect of isoprenaline (to 73%) occurred after pentobarbitone when dp/dt fell to 50%. In doses causing approximately 50% inhibition of dp/dt, halothane and ether also did not significantly inhibit the cardiac action of isoprenaline (Lennartz, Greeff & Heeg, 1966). No accurate determination of the potency of Kö 592 has been published. On the guinea-pig isolated atrium the drug was more potent than pronethalol (Kuschinsky & Rahn, 1965). In the present study the drug was only slightly less potent than its close relative, propranolol. As a local anaesthetic on the rabbit cornea, Kö 592 was three times less potent than propranolol and 1.6 times more potent than cocaine (Wagner, Greeff, Heeg & Pereira, 1966).

## SUMMARY

1. Isoprenaline antagonism was evaluated in cats, anaesthetized with pentobarbitone sodium, by recording the maximal rate of rise in left ventricular pressure (dp/dt) as an index to myocardial contractility.

2. In amounts that reduced dp/dt approximately 50% iproveratril, procainamide and pentobarbitone inhibited the effect of isoprenaline slightly, while under similar conditions propranolol, pronethalol and Kö 592 [1-(3-methylphenoxy)-2-hydroxy-3-isopropylamino-propane], a close relative of propranolol, inhibited the effect of isoprenaline greatly.

3. In a quantitative comparison propranolol had 1.6 times the potency of Kö 592.

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