SOME EFFECTS OF KÖ 1313 IN ANIMALS AND MAN

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1 Kö 1313 competitively inhibited the increases in heart rate produced by isoprenaline in anaesthetized dogs.

2 Kö 1313 was 35 times more active than propranolol in blocking an isoprenaline induced tachycardia in anaesthetized dogs but only three times more active in blocking the increase in femoral blood flow produced by the injection of isoprenaline into the femoral artery. These observations suggest that Kö 1313 may have some cardio-selective activity.

3 When a series of doses of Kö 1313 was injected intravenously into anaesthetized dogs, the lower doses decreased heart rate while the larger doses increased heart rate. The same doses of propranolol reduced heart rate.

4 In lightly anaesthetized dogs, a series of doses of Kö 1313 progressively increased heart rate while propranolol produced little change. These observations indicate that Kö 1313 has slight intrinsic sympathomimetic activity.

5 The oral administration of Kö 1313 and propranolol had no effect on resting heart rate in man but reduced the increases produced by head-up tilt, standing and exercise.

Introduction

During recent years an increasing number of drugs which block β -adrenoceptors has been described (Fitzgerald, 1969). In addition to this property, these compounds may also possess intrinsic sympathomimetic activity or membrane stabilizing activity, and may have a selective blocking action (Fitzgerald, 1969; Shanks, 1969). The contribution of these properties to the therapeutic effect and adverse reactions produced by these drugs is still not clear. A new compound, Kö 1313 (2-nitrilo-*N*-isopropyl phenoxypropanolamine), which blocks β -adrenoceptors, possesses slight intrinsic sympathomimetic and local anaesthetic activity and in animals produced less cardiodepression than propranolol, has been described (Engelhardt & Traunecker, 1969).

In the present study we describe the effects of Kö 1313 and propranolol in anaesthetized dogs and in man.

Methods

Observations in dogs

Greyhounds of both sexes weighing 20-32 kg were anaesthetized either by the intravenous injection of pentobarbitone (30 mg/kg body weight) or by the intramuscular injection of morphine sulphate (0.5 mg/kg body weight) followed 1 h later by the

intravenous administration of pentobarbitone (20 mg/kg body weight). A cuffed endotracheal tube was inserted and positive pressure artificial respiration maintained with room air using a Palmer 'Ideal' Respiration Pump at 18 strokes/min and at a stroke volume of 13 ml/kg body weight. A polythene catheter was inserted into a limb vein for the injection of drugs. Arterial pressure was measured through a metal cannula inserted into the left carotid artery and attached to a pressure transducer (Consolidated Electrodynamics, Type 4-327-L221). The electrocardiogram was obtained from needle electrodes inserted under the skin. Heart rate, arterial pressure and the electrocardiogram (Lead II) were recorded on a Devices recorder (M4 or M8) and displayed continuously on a four-channel oscilloscope (Airmec). In eight dogs arterial blood flow to each hind limb was measured by means of electromagnetic flowmeters as described previously (Kofi Ekue, Shanks & Zaidi, 1971).

Observations in man

Observations were made in five healthy young male volunteers to whom the experimental procedure had been explained. The electrocardiogram (Lead II) was recorded on a direct writing electrocardiograph (Cardiomat, Siemens) at a paper speed of 25 mm/s. The heart rate was obtained by

Fig. 1 Dog: morphine and pentobarbitone anaesthesia, records of heart rate and arterial pressure. Responses to the intravenous injection of a series of cumulative doses of isoprenaline before (top records) and after the intravenous injection of 0.027 and 0.081 mg/kg Kö 1313 (at arrows, middle and bottom records respectively). The time of administration of isoprenaline is indicated at the top of each set of records. The doses of isoprenaline during the control period were 0.001, 0.003, 0.01, 0.03, 0.09, 0.27, 0.81 and 2.43 μ g/kg; additional doses after Kö 1313 (0.027 mg/kg) were 7.29, 21.87 and 65.61 μ g/kg and after Kö 1313 (0.081 mg/kg) were 196.83 μ g/kg. Time scale: 1 min intervals.

determining the time taken for five complete cardiac cycles. Exercise was performed by stepping on and off a box 40 cm high for 3 min at a rate of 32 times/minute.

Each subject rested supine on a tilt table until heart rate had been constant for at least 5 minutes. Heart rate was recorded before and at the end of a 3 min period of tilting to the 80° head-up position after which he was returned to the supine position. After 3 min in this position the subject stood upright for 3 min when heart rate was recorded. A 3 min period of exercise was performed. Heart rate was recorded before and within 4 s of completion of the exercise when the subject again lay down. These observations were made on two occasions, 30 min apart, before and 30 min, 1, 2, 3 and 4 h after the random administration of one of seven treatments on seven different days with at least five days between any two sets of observations. Each subject received a placebo, 20, 40 or 80 mg of Kö 1313, or propranolol by mouth. All subjects received all doses of both drugs.

Drugs

The following drugs were used: $\pm$ isoprenaline sulphate (Burroughs Wellcome); $\pm$ Kö 1313 hydrochloride (Boehringer Ingelheim) and $\pm$ propranolol hydrochloride (Imperial Chemical Industries Ltd.). The doses of isoprenaline are expressed as the base and those of propranolol and Kö 1313 are expressed as the salt.

Results

Observations in dogs

The effect of Kö 1313 on the responses to the intravenous injection of cumulative doses of isoprenaline. Observations were made in four dogs. Each dog received a series of increasing doses of isoprenaline by intravenous administration at 2 min intervals during continuous recording of the heart rate and arterial pressure. The dose of

isoprenaline was progressively increased until a dose was reached which produced no further increase in heart rate. The doses ranged from 0.001-1771.47 $\mu\text{g/kg}$ in a series of trebled increases although it was not always necessary to administer the last few doses. When the heart rate and arterial pressure had returned to new steady resting levels, Kö 1313, 0.027 mg/kg, was given by intravenous injection and, 10 min later, the series of doses of isoprenaline were repeated. The procedure was repeated after the intravenous administration of Kö 1313, 0.081 and 0.243 mg/kg.

Sample records, taken from one experiment to demonstrate the effect of Kö 1313 on the increases in heart rate and falls in diastolic arterial pressure produced by the series of doses of isoprenaline, are shown in Figure 1. During the control period increasing doses of isoprenaline produced progressive increases in heart rate reaching a maximum after the administration of 0.81 $\mu\text{g/kg}$ isoprenaline. The progressive falls in arterial diastolic pressure probably did not reach a maximum with the highest dose of isoprenaline. After the administration of Kö 1313, 0.027 and 0.081 mg/kg, larger doses of isoprenaline were required to increase heart rate and reduce diastolic pressure. After Kö 1313, 0.027 and 0.081 mg/kg, the maximum increases in heart rate were produced by isoprenaline, 21.87 $\mu\text{g/kg}$ and 65.61 $\mu\text{g/kg}$, respectively.

Figure 2 shows the mean increases in heart rate and mean decreases in diastolic arterial pressure produced by cumulative doses of isoprenaline before and after the series of doses of Kö 1313. Cumulative doses of isoprenaline before the administration of Kö 1313 increased the mean resting heart rate from 144.8 ± 10.3 beats/min to a maximum of 219.5 ± 11.3 beats/minute. The same doses of isoprenaline produced dose dependent decreases in diastolic arterial pressure from a

Fig. 2 The mean increases in heart rate and decreases in diastolic pressure produced by a series of increasing doses of isoprenaline, before ($\circ$) and after the intravenous injection of three doses of Kö 1313, 0.027 ($\bullet$), 0.081 ($\square$) and 0.243 mg/kg ($\blacksquare$).

Table 1 The doses of isoprenaline ($\mu\text{g/kg}$) that were calculated to produce 50% of the maximum increase in heart rate and fall in diastolic pressure during the control period and the same responses after three doses of Kö 1313. Values are derived from observations in Figure 2.

	Heart rate	Diastolic arterial pressure
Control	0.11	0.3
After Kö 1313 (0.027 mg/kg)	1.6	4.9
After Kö 1313 (0.081 mg/kg)	4.5	13.5
After Kö 1313 (0.243 mg/kg)	14.0	33.5

mean value of 145.3 ± 16.6 mmHg to 84.3 ± 16.2 mmHg. The dose response curves for isoprenaline were shifted to the right after the increasing doses of Kö 1313 but remained parallel to each other. The value for 50% of the maximum increase in heart rate produced by isoprenaline during the control period was determined. The doses of isoprenaline which produced this increase during the control period and after the three doses of Kö 1313 are given in Table 1. Similar observations were made for diastolic arterial pressure and the results are included in Table 1. The doses of isoprenaline which were required after Kö 1313, 0.027 mg/kg, to produce these responses for heart rate and diastolic pressure were respectively 15 and 16 times greater than those required during the control period. A three-fold increase in the dose of Kö 1313 required a similar increase in the dose of isoprenaline to produce the control responses to isoprenaline.

Fig. 3 Dog: morphine and pentobarbitone anaesthesia. Records of heart rate, arterial pressure, and femoral blood flow. Responses to the intravenous injection of isoprenaline ($0.5 \mu\text{g/kg}$) and intra-arterial injection of isoprenaline ($0.04 \mu\text{g/kg}$) at the times indicated before (a) and after the intravenous injection of Kö 1313, 0.003 (b), 0.027 (c) and 0.243 mg/kg (d). Time scale: 1 min intervals.

The effects of Kö 1313 and propranolol on the responses to intravenous and intra-arterial isoprenaline. Observations were made in eight dogs in which heart rate, arterial pressure and femoral blood flow were recorded. A series of increasing doses of isoprenaline were given by intravenous injection at 7 min intervals. A dose of isoprenaline which produced a near maximal increase in heart rate of between 28 and 60 beats/min was determined for each dog. This dose was usually $0.5 \mu\text{g/kg}$. Each dog was then given a series of increasing doses of isoprenaline by injection into the femoral artery at 7 min intervals. The dose of isoprenaline which produced the greatest increase in hind-limb blood flow with no effects on heart rate and systemic arterial pressure was determined for each dog. This dose was usually $0.04 \mu\text{g/kg}$. After determination of these test doses of isoprenaline for intravenous and intra-arterial administration, a series of doses of Kö 1313 or propranolol (0.001–0.729 mg/kg in a series of trebled increases) was administered by intravenous injection. Ten minutes after each dose the intra-

venous test dose of isoprenaline was administered and after the heart rate and arterial pressure had returned to steady levels, the intra-arterial dose of isoprenaline was given. Each drug was given to four dogs.

Sample records taken from one experiment are shown in Figure 3. During the control period, the intravenous injection of isoprenaline ($0.5 \mu\text{g/kg}$) increased heart rate and reduced diastolic arterial pressure; a small increase in femoral blood flow occurred. The intra-arterial injection of isoprenaline ($0.04 \mu\text{g/kg}$) increased femoral blood flow with little change in heart rate or arterial pressure. The increase in heart rate and fall in diastolic pressure produced by intravenous isoprenaline were reduced after the intravenous injection of Kö 1313, 0.003 mg/kg, and abolished after 0.027 and 0.243 mg/kg Kö 1313. The increase in femoral blood flow produced by intra-arterial isoprenaline was reduced after Kö 1313 (0.003 and 0.027 mg/kg) and abolished by 0.243 mg/kg. The averaged results from the four dogs are shown in Fig. 4, in which the responses to isoprenaline after

Fig. 4 Mean % change in the heart rate (○) and diastolic pressure (□) responses to the intravenous injection of isoprenaline (0.5 µg/kg) and the femoral flow (■) response to intra-arterial isoprenaline (0.04 µg/kg) after the intravenous injection of a series of increasing doses of Kö 1313 and propranolol. Each point is the mean ($\pm$ S.E.M.) of observations in four anaesthetized dogs.

each dose of Kö 1313 are expressed as a percentage of the initial control responses. There was a progressive reduction in all three responses after the administration of increasing doses of Kö 1313. Similar observations were made in four dogs in which isoprenaline was given by intravenous and intra-arterial injection before and after a series of increasing doses of propranolol. The averaged results are given in Figure 4. Increasing doses of propranolol produced progressive reductions in the responses to isoprenaline.

The doses of Kö 1313 and propranolol which reduced the three responses by 50% have been determined and are given in Table 2. Kö 1313 was more active in inhibiting the heart rate and diastolic pressure responses than the femoral flow response. Propranolol was 14 times more effective

in inhibiting the fall in diastolic pressure than the increase in heart rate produced by isoprenaline and four times more effective in reducing a femoral vasodilatation than the tachycardia. Kö 1313 was 34 times more active than propranolol in reducing an isoprenaline tachycardia but only two to three times more active in blocking the hypotensive and peripheral vasodilator effects of isoprenaline.

The effects of Kö 1313 and propranolol on heart rate and diastolic arterial pressure. The effects on heart rate and diastolic arterial pressure of the intravenous administration of the series of doses of Kö 1313 and propranolol used in the above experiments are shown in Figures 5 and 6. As the dose of Kö 1313 was increased from 0.001-0.027 mg/kg, a dose dependent decrease in heart rate occurred and with doses of 0.081-0.729 mg/kg a progressive increase in heart rate occurred. The final heart rate after the last dose of Kö 1313 (0.729 mg/kg) was 151.5 ± 9.0 beats/min in comparison to the initial heart rate of 175 ± 9.5 beats/minute. There was a significant difference in these values ($P < 0.05$). The administration of the series of doses of propranolol produced a progressive reduction in heart rate from an initial control value of 159.3 ± 3.7 to 102.0 ± 3.5 beats/min after propranolol (0.729 mg/kg). There is a significant difference in these two values ($P < 0.001$). There was no significant difference between the mean initial resting values in the two groups of dogs.

The effects of increasing doses of Kö 1313 and propranolol on diastolic arterial pressure in the same experiments are shown in Figure 6. There was no significant difference between the initial resting values in the two groups of dogs. No significant change was produced in diastolic arterial pressure by Kö 1313 in doses up to 0.081 mg/kg but significant decreases occurred after 0.243 and 0.729 mg/kg ($P < 0.02$ and

Table 2 Doses of propranolol and Kö 1313 (mg/kg) that produced 50% reduction in the changes in heart rate and diastolic arterial pressure produced by the intravenous injection of isoprenaline and in the increase in femoral flow produced by the intra-arterial injection of isoprenaline. Values are derived from observations in Figure 4.

Drug	Heart rate	Diastolic arterial pressure	Femoral blood flow
Propranolol (mg/kg)	0.105	0.007	0.026
Kö 1313 (mg/kg)	0.003	0.004	0.009

Fig. 5 The changes in heart rate produced by the intravenous administration of a series of doses, 0.001-2.187 mg/kg Kö 1313 and propranolol under different levels of sympathetic activity. R is the resting value before the administration of any drug and IP is the value 10 min after commencement of an infusion of isoprenaline (0.1 $\mu\text{g/kg/min}$). Each point represents the mean ($\pm$ S.E.M.) value obtained from four anaesthetized dogs; (o) during infusion of isoprenaline; (Δ), during ordinary sympathetic activity; and ($\square$), during reduced sympathetic activity.

$P < 0.001$ respectively). The effects of propranolol were similar to those of Kö 1313; decreases in pressure occurred after 0.243 and 0.729 mg/kg but only the latter was significantly different from the initial resting value ($P < 0.01$).

Further observations have been made in eight dogs anaesthetized with morphine and pentobarbitone. After initial recording of heart rate and arterial pressure, a constant intravenous infusion of isoprenaline at (0.1 $\mu\text{g/kg/min}$) was commenced and continued throughout the duration of the experiment. Ten minutes after the intravenous infusion of isoprenaline had commenced, a series of increasing doses of Kö 1313 or propranolol (ranging from 0.001-2.187 $\mu\text{g/kg}$ in a series of trebled increases) was given by intravenous injection at 10 min intervals.

The averaged results for heart rate from the four dogs which received Kö 1313 are shown in Figure 5. The infusion of isoprenaline significantly

($P < 0.01$) increased heart rate but it was progressively reduced by 0.001, 0.003, 0.009 and 0.027 mg/kg of Kö 1313; no change in rate occurred after 0.081 mg/kg but an increase in rate was observed after 0.243 and 0.729 mg/kg. The averaged results from four dogs which received increasing doses of propranolol during the constant intravenous infusion of isoprenaline at (0.1 $\mu\text{g/kg/min}$) are shown in Figure 5. A progressive reduction in heart rate was produced with increasing doses of propranolol.

The effects of the two drugs on diastolic arterial pressure during the infusion of isoprenaline are shown in Figure 6. The infusion of isoprenaline reduced diastolic pressure. The first two doses of both drugs (0.001 and 0.003 mg/kg) increased diastolic pressure. Subsequent doses of Kö 1313 produced a progressive reduction in pressure. Propranolol in doses from 0.009-0.729 mg/kg produced little change in diastolic pressure; a small

Fig. 6 The changes in diastolic arterial pressure produced by the intravenous administration of a series of doses, 0.001-2.187 mg/kg Kö 1313 (closed symbols) or propranolol (open symbols) under different levels of sympathetic activity. R is the resting value before the administration of any drug and IP the value 10 min after commencement of an infusion of isoprenaline ($0.1 \mu\text{g/kg/min}$). Each point represents the mean ($\pm$ S.E.M.) value obtained from four dogs; (●) and (○) during infusion of isoprenaline; (▲) and (△) during normal sympathetic activity.

decrease occurred after the last dose, 2.187 mg/kg.

Observations were made in eight dogs lightly anaesthetized with pentobarbitone and in whom only heart rate was recorded. The heart rate was continuously recorded and when a steady level had been obtained the previously described series of increasing doses of Kö 1313 and propranolol were given at 10 min intervals. Each drug was given to four dogs and the averaged results are given in Figures 5 and 6. The mean resting heart rate in the group of dogs which received Kö 1313 was 82.5 ± 10.8 beats/min. A progressive increase in rate was produced with increasing doses of Kö 1313. The mean resting heart rate in the dogs which received propranolol was 122.8 ± 24.8 beats/min which was higher but not significantly different from the resting value in the group which

received Kö 1313. The first three doses of propranolol, 0.001, 0.003 and 0.009 mg/kg, produced no change in rate; small progressive decreases occurred after each of the succeeding doses. The final rate after the largest dose of propranolol (2.187 mg/kg) was not significantly different from the control value.

Observations in man

Observations were made on five subjects who received a placebo, 20, 40 or 80 mg of Kö 1313 or propranolol by mouth. Heart rate at rest and after head-up tilting, standing and exercise were recorded before and at 1, 2, 3 and 4 h after each treatment. The mean values for heart rate in the five subjects in the four positions 2 h after the administration of the different treatments are given in Table 3. Supine heart rate was the same in all treatment groups. Head-up tilting, standing and exercise increased heart rate in all groups. Heart rate during tilting and the increase produced by tilting were lower after the administration of 40 and 80 mg of Kö 1313 and all doses of propranolol but none of the differences was significant. The heart rate on standing was reduced but not significantly in the Kö 1313 and propranolol-treated groups. The exercise tachycardia and the increase in rate produced by exercise were significantly less after the administration of all doses of Kö 1313 and propranolol. There was no significant difference between the effects of the two drugs or between different doses of the same drug.

Discussion

The fall in diastolic arterial pressure produced by the intravenous injection of isoprenaline has been used as an indication of the effects of this drug on β -adrenoceptors in the peripheral blood vessels (Ahlquist, 1948). As this fall in arterial pressure may elicit reflexes which alter the circulatory effects of isoprenaline (Dunlop & Shanks, 1968), changes in arterial diastolic pressure may not be an accurate measurement of the peripheral vasodilator action of isoprenaline. Thus we have used the increases in blood flow to the hind limb of the anaesthetized dog produced by the injection into the femoral artery of isoprenaline as a more accurate index of the effects of this drug on the β -adrenoceptors in the peripheral blood vessels (Kofi Ekue *et al.*, 1971).

The present observations in anaesthetized dogs confirm reports that Kö 1313 competitively blocks β -adrenoceptors in the heart and peripheral blood vessels (Baum, Rowles, Shropshire & Gluckman, 1971; Cheymol, Honnorat & Schmitt, 1972;

Engelhard & Traunecker, 1969). Although no accurate comparisons were made, these reports indicated that Kö 1313 was probably more active than propranolol in antagonizing the chronotropic action of isoprenaline.

In the present experiments Kö 1313 was 35 times more active than propranolol in blocking the isoprenaline tachycardia and three times more active in blocking the femoral vasodilator response. As it has previously been accepted that propranolol blocks all β -adrenoceptors to the same extent, these results indicate that Kö 1313 has a greater blocking effect on β -adrenoceptors in the heart than on those in peripheral blood vessels. This effect is less than the selectivity exhibited by practolol (Dunlop & Shanks, 1968).

Similar results are described but not discussed in the observations of Cheymol *et al.* (1972). They determined the dose of β -adrenoceptor blocking drug needed to increase by 10 times the dose of isoprenaline required to produce the control effects. The doses of Kö 1313 and propranolol needed when the response was the increase in heart rate were 1.7 and 100 $\mu\text{g}/\text{kg}$ respectively and for the fall in diastolic pressure 150 and 140 $\mu\text{g}/\text{kg}$ respectively. Thus the two drugs are equiactive in inhibiting the peripheral vasodilator action of isoprenaline but Kö 1313 was 35 times more active in inhibiting the isoprenaline tachycardia. These results again indicate that Kö 1313 appears to have a greater effect in blocking cardiac β -adrenoceptors.

The intrinsic sympathomimetic activity of

dichloroisoprenaline was so marked that it increased heart rate in normal anaesthetized dogs (Moran & Perkins, 1958). The intrinsic sympathomimetic activity of the more recently described compounds, practolol, oxprenolol and alprenolol, is much less and may not be apparent in such animals, as a balance occurs between the intrinsic activity and inhibition of normal cardiac sympathetic drive. The sympathomimetic activity of such compounds can be demonstrated by removal or marked reduction of sympathetic activity by the administration of reserpine or syrosingopine (Shanks, 1965; Barrett & Carter, 1970). After such treatment β -adrenoceptor blocking drugs with intrinsic sympathomimetic activity increase heart rate. As propranolol possesses no intrinsic sympathomimetic activity it reduced heart rate in normal anaesthetized dogs and had no effect in those pretreated with syrosingopine (Black, Duncan & Shanks, 1964). Previous observations have indicated that Kö 1313 has some intrinsic sympathomimetic activity (Baum *et al.*, 1971). These authors showed that in conscious dogs Kö 1313 increased heart rate while propranolol did not alter it; in normal anaesthetized dogs propranolol reduced heart rate whereas Kö 1313 produced little change and in anaesthetized dogs pretreated with guanethidine, propranolol had little effect on heart rate while Kö 1313 increased it. Similar conclusions have been obtained in the present study using different methods which did not necessitate the administration of guanethidine or syrosingopine which on their own have effects on

Table 3 Mean ($\pm$ S.E.M.) values for heart rate (beats/min) in five subjects in the supine position and after head-up tilt, standing and exercise, 2 h after the oral administration of a placebo and 20, 40 and 80 mg of Kö 1313 and propranolol. The mean increases ($\pm$ S.E.M.) in heart rate produced by head-up tilt and exercise are included.

Position	Placebo	Kö 1313			Propranolol		
		20	40	80	20	40	80
Supine	57.2 ± 3.7	59.2 ± 6.1	54.6 ± 2.1	57.0 ± 4.7	54.6 ± 4.0	55.0 ± 3.8	53.5 ± 4.4
Tilt							
Absolute	78.2 ± 7.1	78.0 ± 8.4	71.8 ± 2.8	72.0 ± 5.8	70.8 ± 8.3	64.0 ± 5.9	65.0 ± 3.0
Increase	21.0 ± 4.3	18.8 ± 4.4	17.2 ± 1.5	15.0 ± 2.4	16.2 ± 4.5	9.0 ± 3.4	11.5 ± 1.7
Standing	78.4 ± 8.9	71.6 ± 7.7	73.0 ± 5.0	70.8 ± 7.1	67.0 ± 7.2	66.0 ± 5.8	66.0 ± 5.2
Exercise							
Absolute	146.8 ± 7.7	124.0 ± 7.5	115.0 ± 5.7	110.8 ± 5.9	117.8 ± 6.6	115.0 ± 11.6	112.5 ± 6.4
Increase	68.4 ± 3.8	52.4 ± 5.5	42.0 ± 4.2	40.0 ± 3.9	50.8 ± 6.3	49.0 ± 6.0	46.5 ± 2.7

the cardiovascular system. In normal anaesthetized dogs the administration of the smaller of a series of increasing doses of Kö 1313 reduced resting heart rate while the larger doses increased heart rate. Similar effects were produced in dogs in which isoprenaline was infused to simulate an increase in cardiac sympathetic drive. In lightly anaesthetized dogs in which resting heart rate was significantly less than in normally anaesthetized dogs, increasing doses of Kö 1313 produced a progressive and marked increase in rate. This increase in rate was much greater than that produced in either of the other two situations. It was of interest that although the increase in rate in the lightly anaesthetized dogs was much greater, there was no significant difference between the value for heart rate after the largest dose given to all three groups of dogs. Propranolol produced a progressive reduction in heart rate in the normal anaesthetized dogs and in those in which isoprenaline was infused but in the lightly anaesthetized dogs it produced no significant effect on heart rate. These results confirm that propranolol has no intrinsic sympathomimetic activity.

These observations indicate that the effect of a β -adrenoceptor blocking drug on heart rate depends not only on the presence or absence of intrinsic sympathomimetic activity but on the

amount of sympathetic drive to the heart which is present at the particular time.

Intrinsic sympathomimetic activity may have accounted for the fall in diastolic arterial pressure produced by the larger of the series of increasing doses of Kö 1313. This hypotensive effect was greater than that produced by propranolol and occurred both in the normal anaesthetized dogs and in those in which isoprenaline was infused. Previous observations have indicated that Kö 1313 reduced arterial pressure and total peripheral resistance (Cheymol *et al.*, 1972).

The effects of the administration of Kö 1313 to man have not been described previously. The three doses (20, 40 and 80 mg) of Kö 1313 and propranolol had no effect on resting heart rate and reduced, to the same extent, the increases in rate produced by head-up tilt, standing and exercise. It would appear that Kö 1313 under the conditions of the present experiments did not have an intrinsic sympathomimetic effect on heart rate in man. These observations do not mean that the intrinsic sympathomimetic activity of Kö 1313 might not be of value when the drug is used in clinical practice. As Kö 1313 is a potent β -adrenoceptor blocking drug with intrinsic sympathomimetic activity and some degree of cardioselectivity, limited studies in patients are indicated.

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