1 min after administration of increasing doses of a given β-adrenergic blocking agent. The dose-effect curves are shown in Figure 2, where a decrease in the response to isoprenaline in percent of a control response is plotted against ratios of doses of antagonists to those of the agonist. Methoxamine and I.C.I. 50172 were almost ineffective in inhibiting the response to isoprenaline. LB 46 and H 56/28 were the most active, propranolol came next, and DCI and MJ 1999 were the least active. Even if the ratio of doses of DCI and MJ 1999 to those of isoprenaline was increased up to 1000, degree of inhibition never attained that caused by either LB 46 or H 56/28.

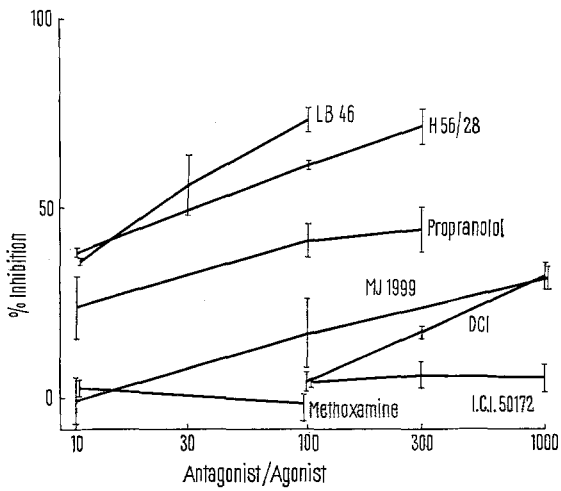

Fig. 2. Dose-effect curves for β-adrenergic blocking agents (antagonists). Ordinates: Percent inhibition of the increased blood flow response to isoprenaline (agonist). Abscissas: Ratios of doses of antagonists to those of the agonist. Means of 5 observations were plotted. Vertical bars refer to ± S.E. of the mean.

The activity of the β-adrenergic blocking agents in inhibiting the increased femoral blood flow response to isoprenaline was as follows: LB 46 ≧ H 56/28 > propranolol > MJ 1999 = DCI. I.C.I. 50172 and methoxamine exerted no inhibitory effect[15].

Zusammenfassung. Die blockierende Wirkung intraarteriell verabreichter, β-adrenergischer Mittel wurde am femoralen Gefässgebiet des Hundes untersucht. DCI, H 56/28 und LB 46 per se regten den arteriellen Blutstrom mit zunehmender Dosierung an, während Methoxamin in umgekehrter Weise wirkte. Eine hemmende Wirkung auf den durch Isoprenalin angeregten Blutstrom fand sich in folgender Reihenfolge: LB 46 ≧ H 56/28 > Propranolol > MJ 1999 = DCI. I.C.I. 50172 und Methoxamin fehlt diese Wirkung.

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Beta-Adrenergic Blocking Effect of Dichloroisoprenaline (DCI), (H 56/28, I.C.I. 50172, LB 46), Methoxamine (MJ 1999) and Propranolol on the Sinus Node Activity of the Dog Heart

In a previous study[1] it was revealed that the β-adrenergic blocking activity of DCI[2,3], propranolol[4], MJ 1999[5–7], H 56/28[8] and LB 46[9] as assessed against the increased femoral blood flow response to isoprenaline in the dog was in the following order: LB 46 ≧ H 56/28 > propranolol > MJ 1999 = DCI. It was also demonstrated that unlike these 5 agents methoxamine and I.C.I. 50172 failed to block activation by isoprenaline of femoral vascular β-adrenergic receptors, although both agents have been reported to be effective in blocking cardiac β-adrenergic receptors[10–13]. Thus, it was of interest to investigate how these 7 β-adrenergic blocking agents block the positive chronotropic response to isoprenaline in the dog heart.

Experiments were performed on 37 adult mongrel dogs weighing 11–18 kg. The animals were anaesthetized with sodium pentobarbital and the vagus nerves on both sides were severed, while sympathetic supply was intact. Thus the sympathetic tone prevailed in this preparation. The sinus node area was perfused in situ with arterial blood via the sinus node artery at a constant pressure of about 100 mm Hg[14,15]. This procedure permitted us to administer drugs selectively to the sinus node area and to observe its response without interference from intra-nodal pressure changes. The mean flow rate of blood measured by means of an electromagnetic flow-meter was 1.8 ± 0.2 (S.E.) ml/min. The heart rate as an index of the

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sinus node activity was measured by triggering an electrocardiotachometer with R waves of ECG by the lead II. Drugs used were as follows: L-isoprenaline hydrochloride, DL-dichloroisoprenaline hydrochloride (DCI), DL-1-(*o*-allylphenoxy)-3-isopropylamino-2-propanol hydrochloride (H 56/28), DL-4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide (I.C.I. 50172), DL-4-(2-hydroxy-3-isopropylaminopropoxy)-indole (LB 46), DL-methoxamine hydrochloride, DL-4-(2-isopropylamino-hydroxyethyl) methanesulfonanilide hydrochloride (MJ 1999) and DL-propranolol hydrochloride. All doses refer to the bases. Intra-arterial injections of drug solutions were made with microsyringes in a volume of 10 µl for 4 sec.

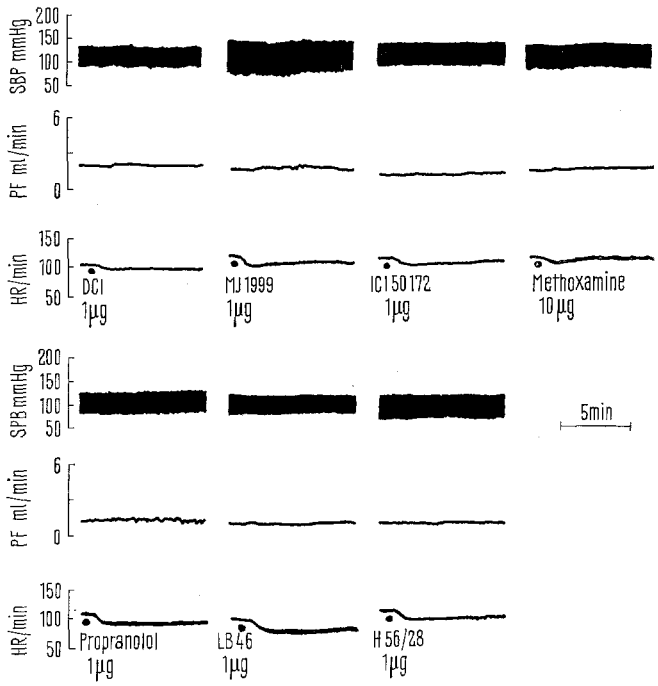

Fig. 1. Effects of administrations of β-adrenergic blocking agents into the sinus node artery on the heart rate (HR). SBP stands for systemic blood pressure and PF for perfusion flow rate.

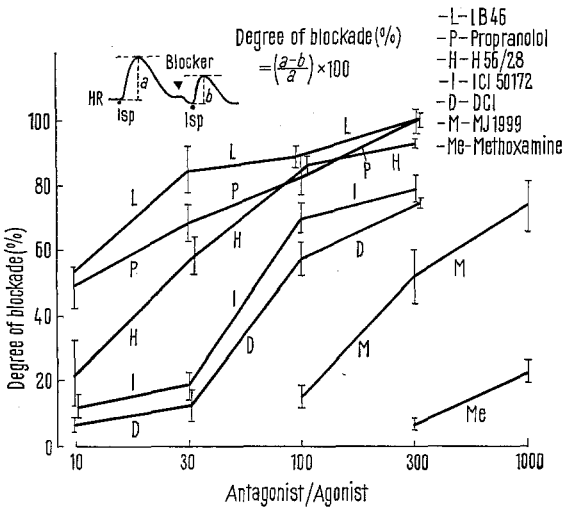

Fig. 2. Dose-effect curves for β-adrenergic blocking agents administered into the sinus node artery. Degree of blockade was calculated in such a way as shown in inset, where Isp refers to administration of isoprenaline. Each curve is the mean of 6–12 observations. Standard errors of the mean are indicated by vertical bars.

Administrations into the sinus node artery of DCI, H 56/28, I.C.I. 50172, LB 46, methoxamine, MJ 1999 and propranolol in doses of 1–10 µg caused definitely a decrease in heart rate (Figure 1). However, in further smaller doses DCI most frequently, and H 56/28, I.C.I. 50172 and LB 46 occasionally produced a sympathomimetic effect, i.e. an increase in heart rate. The activity of methoxamine in producing the negative chronotropic effect was about $^1/_{10}$ that of the remainder. In medium doses some of the agents often caused the sinus arrhythmia in the phases of introduction to and recovery from the phase of maximal deceleration. In higher doses most of the agents produced complete suppression of the sinus node activity which was surmounted by catecholamines.

Dose-effect curves for the 7 β-adrenergic blocking agents (antagonists) were constructed in the following way: a dose of methoxamine was fixed at 10 µg and that of the remainder 1 µg. Antagonists in these doses were challenged by various doses of isoprenaline (agonist) 1 min after administration of the former agents. A percent decrease in the response to a given dose of the agonist administered after a given antagonist from the corresponding control response was designated as a degree of blockade (see an inset in Figure 2). In Figure 2 degrees of blockade of the response to the agonist were plotted against ratios of doses of antagonists to those of the agonist. At an antagonist-agonist ratio of 100, the β-adrenergic blocking activity of the 7 agents was in the order of LB 46, H 56/28, propranolol > I.C.I. 50172, DCI > MJ 1999 > methoxamine. LB 46, H 56/28 and propranolol abolished the positive chronotropic response to isoprenaline at a ratio of 300, while I.C.I. 50172 and DCI caused only an 80% blockade. MJ 1999 produced an 80% blockade at a ratio of 1000. Methoxamine caused only a 20% even at a ratio of 1000[16].

Zusammenfassung. Der Hemmungseffekt sieben β-adrenergischer Blockierungsmittel auf positive chronotrope Wirkung bei zunehmender Dosierung von Isoprenalin wurde durch Verabreichung in die Sinusknotenarterie vergleichend untersucht. Reihenfolge der Wirksamkeit: LB 46, H 56/28, Propranolol > I.C.I. 50172, DCI > MJ 1999 > Methoxamin.

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