Comparison of β-Adrenergic Blocking Activity of Dichloroisoprenaline (H 56/28, I.C.I. 50172, LB 46), Methoxamine (MJ 1999) and Propranolol in the Canine Femoral Vascular Bed

In 1948 AHLQUIST[1] classified adrenergic receptors into alpha and beta according to differences in their responsiveness to sympathomimetic amines closely related structurally to adrenaline. This proposal was supported by discovery of a β-adrenergic blocking activity in dichloroisoprenaline (DCI)[2,3] and methoxamine[4]. Since then, more selective β-adrenergic blocking agents have been synthetized. Recently new β-adrenergic blocking agents capable of producing a selective blockade of some, but not all, β-adrenergic receptors have been discovered[5–7]. In this connection, it would be worthwhile qualifying the blocking property of various β-adrenergic blocking agents according to their effect on β-adrenergic receptors in the vasculature. The present paper reports the intrinsic activity of DCI, H 56/28[8], I.C.I. 50172[5–7], LB 46[9], methoxamine, MJ 1999[10–12] and propranolol[13], and their blocking activity on the increased femoral blood flow response to isoprenaline.

Twenty-one adult mongrel dogs of both sexes, weighing 11–13 kg, were anaesthetized with sodium pentobarbital. Arterial blood led from the proximal ends of the cut femoral arteries on both sides was made flow into the distal cut end of the same artery on either side through plastic tubing at the systemic blood pressure. Femoral blood flow was measured by means of an electromagnetic flow-meter interposed in the midway of the tubing. Coagulation of blood was prevented with sodium ω-heparin[14] (Taiyo Fishery). The mean systemic blood pressure monitored at the carotid artery was maintained at the same level throughout the experiment by transfusion of fresh blood. The heart rate was also monitored by triggering an electrocardiotachograph with pressure pulses of the systemic blood pressure. L-isoprenaline hydrochloride was used as an agonist, and 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-1-hydroxyethyl) methanesulphonanilide hydrochloride (MJ 1999), and DL-propranolol hydrochloride as antagonists. All of the agents were injected intra-arterially in a volume of 0.1 ml for 10 sec. All doses refer to the bases. In most experiments 0.1 μg of isoprenaline was administered to activate β-adrenergic receptors when this dose exerted no systemic effect. When the systemic effect appeared, the dose of isoprenaline was reduced to 0.05 μg.

DCI (1–100 μg), H 56/28 (1–30 μg) and LB 46 (1–30 μg) caused a dose-dependent increase in femoral blood flow in that order of decreasing degree of activity, while methoxamine (1–10 μg) caused a dose-dependent decrease. I.C.I. 50172 (10–100 μg), MJ 1999 (1–100 μg) and propranolol (1–30 μg) per se elicited no significant change in this parameter.

Time course of the β-adrenergic blocking effect was investigated in the following way: the vascular responses to 0.1 μg of isoprenaline (agonist) injected 1, 5 and 10 min after administration of 10 μg of a given β-adrenergic blocking agent (antagonist) were compared with a control response and a decrease in the response in percent of a control was expressed as percent inhibition. Time-effect curves for the 7 β-adrenergic blocking agents obtained as above are illustrated in Figure 1, where each curve is a mean of 5 observations. As depicted clearly in this figure, LB 46, H 56/28, propranolol and MJ 1999 exhibit a maximal inhibitory effect on the response to isoprenaline at 1 min in that order of decreasing degree of inhibition. Duration of the inhibition by the 4 agents was roughly proportional to the degree of the maximal inhibitory effect; the effect of LB 46 was the longest, H 56/28 came next, propranolol third, and MJ 1999 fourth. DCI, I.C.I. 50172 and methoxamine at an antagonist-agonist ratio of 100 were almost ineffective.

Since the maximal inhibition appeared at 1 min after administration of β-adrenergic blocking agents, dose-effect curves for the 7 β-adrenergic blocking agents were determined by injecting 0.1 (or 0.05) μg of isoprenaline

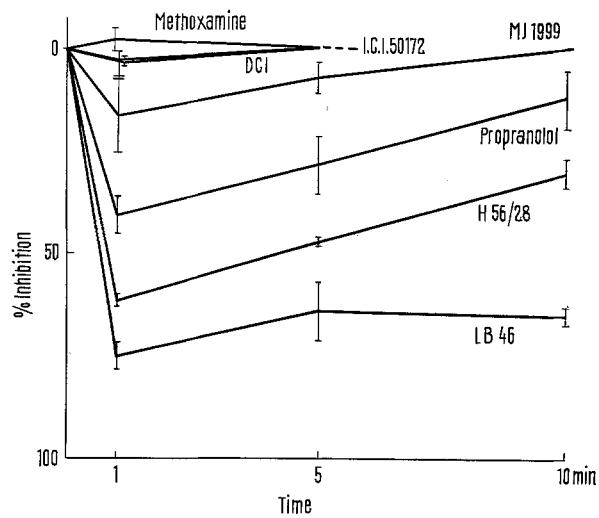

Fig. 1. Time-effect curves for β-adrenergic blocking agents (10 μg). Ordinates: Percent inhibition of the increased femoral blood flow response to isoprenaline (1 μg). Abscissas: Time between injection of β-adrenergic blocking agents and those of isoprenaline. Means of 5 observations were plotted. Vertical bars refer to ± S.E. of the mean.

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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.

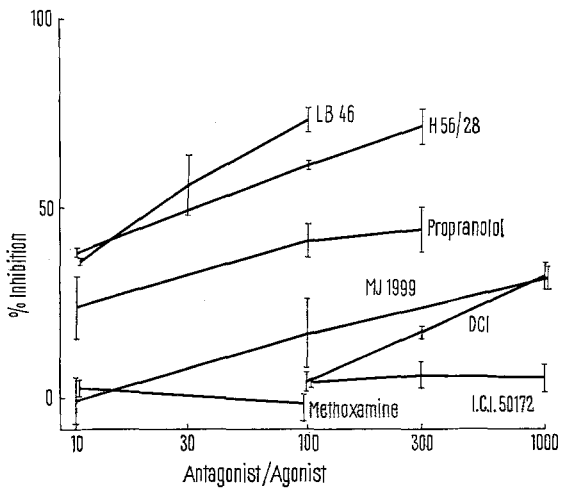

Fig. 2. Dose-effect curves for β-adrenergic blocking agents (antagonists). Ordinates: Percent inhibition of the increased blood flow response to isoprenaline (agonist). Abscissas: Ratios of doses of antagonists to those of the agonist. Means of 5 observations were plotted. Vertical bars refer to ± S.E. 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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[15] The authors wish to express their thanks to Dr. K. K. CHEN for the supply of DCI, to Dr. B. ÅBLAD of AB Hässle for H 56/28, to Dr. A. M. BARRETT of Imperial Chemical Industries for I.C.I. 50172, to Dr. K. SAAMELI of Swiss Sandoz for LB 46, and to Dr. P. M. LISH of Mead Johnson Research Center for MJ 1999.

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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