REVERSIBLE ADRENERGIC α -RECEPTOR BLOCKING ACTION OF 2,4'-DIMETHYL-3-PIPERIDINO-PROPIOPHENONE (TOLPERISONE)

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Abstract—The vascular action of 2,4'-dimethyl-3-piperidino-propiofenone hydrochloride (tolperisone hydrochloride), a centrally acting muscle relaxant, was investigated in pentobarbital anesthetized dogs. Tolperisone given intravenously produced a transient hypotension, tachycardia, and hyperventilation. The drug increased the femoral arterial flow, and decreased the superior mesenteric arterial flow following an initial transient increase. When injected directly into femoral and mesenteric arteries, tolperisone caused a rapid increase in both arterial flows (vasodilatation). However, femoral vessels were about 90 times as sensitive as mesenteric vessels to tolperisone. These results indicate that tolperisone shifts the blood volume from mesenteric (visceral) vessels to femoral (skeletal) ones. The femoral vasodilatation produced by i.a. tolperisone was not depressed by the pretreatment with i.a. propranolol, atropine or chlorphenylamine. Tolperisone decreased the contractile force in an isolated and cross-circulated papillary muscle. Tolperisone produced adrenaline reversal and antagonized the pressor response to noradrenaline. Moreover, femoral vasoconstriction caused by i.a. adrenaline was converted to vasodilatation and that caused by i.a. noradrenaline was depressed during an i.a. infusion of tolperisone. These results indicate that tolperisone blocks adrenergic α -receptors. The blocking action was rapid in onset, short-lived, and in addition, competitive.

2,4'-Dimethyl-3-piperidino-propiofenone hydrochloride (tolperisone hydrochloride), synthesized by Nádor and Pórszász (1) causes strong relaxation of skeletal muscle through the central nervous system in animals (2) and has been used in patients with spastic paralysis. On the one hand, Molnár (3) indicated that the drug was also effective in the therapy of peripheral arterial disease. Furthermore, Görög et al. (4) showed that tolperisone directly dilated the femoral artery in anesthetized cats and rats and inhibited the response to adrenaline or noradrenaline in the isolated hind quarter of rats. In the present study, to elucidate the vascular action of tolperisone, we investigated the effect of tolperisone on systemic blood pressure, peripheral blood flow, and cardiac contractile force using adrenergic drugs and various blockers of the autonomic nervous system.

MATERIALS AND METHODS

Adult mongrel dogs of either sex (8-18 kg) were anesthetized with 30 mg/kg of sodium pentobarbital i.v. and a constant level of anesthesia was maintained by i.v. infusion at the rate of 5 mg/kg per hour.

Arrangement for studies of systemic effects: A tracheal tube was inserted and the rate

of respiration was measured through a pressure transducer (Nihon Kohden, LPU-0.1). Systemic blood pressure was measured in the carotid artery with a polyethylene cannula and a pressure transducer (Nihon Kohden, MPU-0.5). Mean arterial blood pressure was recorded by electric integration with a 2.0 second time constant. Heart rate was obtained from the systemic blood pressure recording. Non-cannulating probes of electromagnetic flowmeters (Nihon Kohden, MF-26) were fitted to the femoral and superior mesenteric arteries. Drug solutions in volumes of 0.1 to 1.0 ml were injected into the femoral vein and flushed in with 2 ml of saline for 8 sec.

Arrangement for femoral and superior mesenteric circulation: A tracheal tube was inserted and the animals were ventilated artificially with a respirator (Harvard, Model 607). Cannulae were inserted into the proximal and distal ends of the cut femoral artery or superior mesenteric artery, respectively. The two cannulae were connected by a rubber tubing. The blood flow through the artery was measured by cannulating probes of electromagnetic flowmeters (Nihon Kohden, MF-26) set between the two cannulae. Drug solutions in a volume of 10 or 30 μ l were close-arterially injected for 4 sec into the femoral and mesenteric arteries through rubber tubings.

Isolated and cross-circulated papillary muscle preparation: The isolated papillary muscle of the dog heart was prepared according to the method described by Endoh and Hashimoto (5). The papillary muscle arteries were perfused through the anterior septal artery with the arterial blood conducted from a donor dog by means of a peristaltic pump (Harvard, Model 1210). Sodium heparin, 500 units/kg was given at the beginning of the perfusion and 100 units/kg was added at one-hour intervals. Isometric contraction was measured through a force-displacement transducer (Nihon Kohden, SB-1T). The muscle was loaded with a weight of 1 g and electrically driven at a frequency of 120 per min with rectangular pulses of 0.6–1 V and 5 msec duration using an electronic stimulator (Nihon Kohden, MSE-3R) and an isolation unit (Nihon Kohden, MSE-3M). Drug solutions in a volume of 10 or 30 μ l were injected into a rubber tubing connected to the arterial cannula.

All recordings were made on an ink-writing rectigraph (Nihon Kohden, WI-386-A).

Drugs: Tolperisone hydrochloride and d-chlorphenylamine maleate were prepared in the Research Laboratories of Nippon Kayaku Co. Other drugs used were: acetylcholine chloride (Daiichi Seiyaku), 1-adrenaline hydrochloride (Daiichi Seiyaku), atropine sulfate (Iwaki Seiyaku), 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) (Aldrich), histamine dihydrochloride (Tokyo Kasei Kogyo), 1-isoprenaline hydrochloride (Nikken Kagaku), dl-noradrenaline hydrochloride (Sankyo), phenoxybenzamine hydrochloride (Tokyo Kasei Kogyo), and propranolol hydrochloride (Sumitomo Kagaku Kogyo). Doses refer to salts. All drugs were dissolved in physiological solution immediately before use.

RESULTS

Cardiovascular actions

Intravenous injections of 1, 3 and 10 mg/kg of tolperisone caused a dose-related hypotension which developed immediately and returned to the control level in about 1 min

FIG. 1. Cardiovascular effects of tolperisone in the anesthetized dog. (A) Effects of i.v. injections of tolperisone (1–3 mg/kg) on phasic and mean blood pressure, heart rate, respiration, and mesenteric and femoral arterial flows. (B) Effects of i.a. injections of tolperisone (0.01–3 mg), isoprenaline (0.03–0.3 μ g) and acetylcholine (0.001–3 μ g) on femoral and mesenteric arterial flows. (C) Effects of i.a. injections of tolperisone (0.3–10 mg) on developed tension and blood flow of isolated and cross-circulated papillary muscle.

(Fig. 1A). At a dose of 10 mg/kg, tolperisone showed a secondary and prolonged hypotension after the initial rapid effect. Tolperisone caused a tachycardia independently of the dose; the maximum increase in heart rate caused by 10 mg/kg being smaller than that caused by 1 or 3 mg/kg. Tolperisone transiently stimulated the rate of respiration, and at 10 mg/kg it increased not only the rate but also the amplitude of breathing followed by a decrease. Tolperisone caused a dose-dependent increase in femoral arterial flow, while in mesenteric arterial flow it caused a dose-dependent decrease immediately following an initial momentary increase.

When injected intra-arterially into femoral and mesenteric arteries, tolperisone caused a rapid increase in the rate of both arterial flows in a dose-dependent manner (Fig. 1B). Acetylcholine, and isoprenaline also increased both arterial flows. When compared in the increase by 100% of the blood flow, the ratios of a dose in the mesenteric artery to a dose in femoral artery were about 2, 90, and 200 for isoprenaline, tolperisone, and acetylcholine, respectively.

In the isolated papillary muscle preparation, tolperisone (0.3–10 mg) i.a. produced initially a rapid decrease and secondarily a long-lasting one in the contractile force (Fig. 1C). The increase in the perfused blood flow caused by tolperisone, however, was short-lived.

Modification by propranolol, atropine or chlorphenylamine

An increase in femoral arterial flow caused by tolperisone (30–300 μ g) i.a. was not affected by a single i.a. injection of 30 μ g of propranolol, a single i.a. injection of 0.1 μ g of atropine or an i.a. infusion of 0.1 mg of chlorphenylamine per min. At the doses used, propranolol, atropine and chlorphenylamine sufficiently depressed the effect of 0.01 μ g of isoprenaline, 0.03 μ g of acetylcholine and 0.3 μ g of histamine, respectively. Fig. 2 shows dose-response curves for the increase in femoral arterial flow to tolperisone before and after the treatment with each blockade.

FIG. 2. Lack of the blocking effect of an i.a. injection of propranolol (30 μ g), an i.a. injection of atropine (100 μ g) or an i.a. infusion of chlorphenylamine (0.1 mg/min) on the increase in femoral arterial flow of the anesthetized dog to i.a. injections of tolperisone (30–100 μ g). Each point represents the mean of 5 observations on 5 animals. Vertical bars show the standard error.

Effects on responses to catecholamines, DMPP and bilateral carotid occlusion

As shown in Fig. 3, pressor responses to 1 $\mu\text{g}/\text{kg}$ of adrenaline and 1 $\mu\text{g}/\text{kg}$ of noradrenaline were apparently reversed and attenuated, respectively, during the i.v. infusion of 300 $\mu\text{g}/\text{kg}$ per min of tolperisone. DMPP (10 $\mu\text{g}/\text{kg}$) or bilateral carotid occlusion for 30 sec induced pressor response was also depressed by tolperisone. Tolperisone completely abolished an increase in systolic blood pressure caused by isoprenaline, but had no effect on the positive chronotropic action of the amine.

When injected intra-arterially into femoral artery, adrenaline (0.1–1 μg) and noradrenaline (0.1–1 μg) decreased the blood flow (vasoconstriction) in a dose-dependent manner (Fig. 4). An intra-arterial infusion of 100 μg of tolperisone per min into femoral artery caused a rapid increase in the blood flow. The vasoconstrictor response to adrenaline was converted to a vasodilator one during the infusion of tolperisone. Tolperisone also depressed the vasoconstrictor response to noradrenaline and brought out the β -adrenergic

FIG. 3. Effects of an i.v. infusion of tolperisone (300 $\mu\text{g}/\text{kg}$ per min) on pressor responses to noradrenaline (1 $\mu\text{g}/\text{kg}$), adrenaline (1 $\mu\text{g}/\text{kg}$), DMPP (10 $\mu\text{g}/\text{kg}$) and bilateral carotid occlusion (BCO) (30 sec) and on depressor response to isoprenaline (0.3 $\mu\text{g}/\text{kg}$) in the anesthetized dog.

FIG. 4. Effects of an i.a. infusion of tolperisone (0.1 mg/min) on vasoconstrictor responses of femoral artery to i.a. noradrenaline (0.1–1 μg) and adrenaline (0.1–1 μg) in the anesthetized dog.

component of the amine. A single i.a. injection of phenoxybenzamine (10 mg) attenuated the vasoconstrictor effect of noradrenaline. Although an adequate blockade produced by phenoxybenzamine was established in 30 min or so and lasted for the 3 hours observation period, the depressive effect of tolperisone appeared within 5 min and disappeared immediately following a withdrawal of the infusion. At the doses used, tolperisone did not affect blood pressure and heart rate, while phenoxybenzamine caused an irreversible hypotension and bradycardia.

Fig. 5 shows dose-response curves for the decrease in femoral arterial flow to noradrenaline i.a. before and after treatment with tolperisone i.a. or phenoxybenzamine i.a. Both tolperisone (0.5–1 mg/min) and phenoxybenzamine (3–10 mg) markedly shifted the dose-response curve to noradrenaline to the right. An i.a. infusion of 1 mg of tolperisone per min was as potent as a single i.a. injection of 10 mg of phenoxybenzamine in blocking the vasoconstrictor effect of noradrenaline on femoral vessels.

FIG. 5. Dose-response curves for decrease in femoral arterial flow of the anesthetized dog to i.a. noradrenaline (0.1–1 µg) before and after single i.a. injections of phenoxybenzamine (3–10 mg) or i.a. infusions of tolperisone (0.5–1 mg/min). Each point represents the mean of 5 observations on 5 animals. Vertical bars show the standard error.

DISCUSSION

The intravenous administration of tolperisone produced a transient hypotension and tachycardia in the anesthetized dog. Since the increase in heart rate was not dose-dependent, it is likely to be a compensatory reflex elicited by a rapid fall in arterial blood pressure. Effect on respiration that preceded the fall in blood pressure is probably due to a direct stimulation of respiratory center. Femoral arterial flow was increased (vasodilatation), but mesenteric arterial flow was decreased (vasoconstriction) following an initial slight increase. This result suggests that tolperisone first causes a decrease in peripheral vasomotor tone which may be a primary effect for hypotension and tachycardia and the hypotension accounts for the compensatory vasoconstriction of the mesenteric artery. Tolperisone decreased the force of contraction in an isolated preparation of papillary muscle which lasted for a long time. This negative inotropic effect may contribute to the long-lasting hypotension caused by the largest dose of the drug.

The close-arterial administration of tolperisone caused a rapid and short-lived increase in both femoral and mesenteric arterial flows. Femoral vessels (skeletal vessels), however, are sensitive to much lower doses of tolperisone than are mesenteric vessels (visceral vessels). Therefore, it is likely that tolperisone injected i.v. produces a greater reduction of the femoral vascular tone than the mesenteric tone, i.e. the drug causes a selective femoral vasodilatation.

The increase in femoral arterial flow caused by tolperisone was not depressed by the pretreatment with propranolol, atropine, or chlorphenylamine indicating that the vasodilator action of tolperisone cannot be attributed to stimulation of adrenergic β -receptors, muscarinic or histamine receptors.

The intravenous infusion of tolperisone produced adrenaline reversal and antagonized the pressor response to noradrenaline. Moreover, the vasoconstrictor responses of femoral vessels to i.a. adrenaline and i.a. noradrenaline were reversed and blocked, respectively, during an i.a. infusion of tolperisone. Pressor response to DMPP or reflex pressor response to bilateral carotid occlusion was also attenuated by tolperisone. An increase in heart rate caused by isoprenaline was not affected by the drug. These results indicate that tolperisone is an adrenergic α -receptor blocking agent and the site of action is within the vasculature. The blockade caused by tolperisone is competitive with noradrenaline at the α -receptor, because large doses of the amine partially restored the vasoconstrictor responses. The α -receptor blocking action of tolperisone developed immediately and disappeared with termination of the infusion. The duration of the action was far shorter than that of other α -adrenergic blocking agents reported (6) and tolperisone elicited the blockade with few cardiovascular effects. The immediate onset and transient action suggest that tolperisone makes a direct contact with receptive sites and is rapidly eliminated from these sites.

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