Cardiovascular Effects of Preparation CIBA 34,276-Ba and Imipramine

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Abstract

The cardiovascular effects of compound CIBA 34,276-Ba and imipramine were compared.

In the conscious dog, intravenous infusion or oral administration of compound CIBA 34,276-Ba had only a slight effect on blood pressure and heart rate, whereas the intravenous administration of imipramine gave rise to clear-cut tachycardia and did not influence blood pressure.

In dogs anaesthetized with chloralose, compound CIBA 34,276-Ba reduced blood pressure and heart rate slightly, diminished cardiac output when given in high doses and increased total peripheral resistance. Imipramine administered in the same doses had no effect on blood pressure, increased heart rate and led to qualitatively similar but quantitatively more pronounced changes in cardiac output and peripheral resistance than compound CIBA 34,276-Ba.

In cats anaesthetized with allobarbitone, compound CIBA 34,276-Ba and imipramine in doses up to 3 mg/kg i.v. had only a slight effect on blood pressure, contractile force and heart rate. A negative inotropic effect was evident after intravenous administration of 3 mg/kg imipramine.

In the isolated guinea-pig atrium imipramine increased cardiac contractile force in a concentration of 1 mcg/ml, while both compounds displayed a cardiodepressant effect with 10 mcg/ml.

In conscious renal hypertensive rats, both compounds had no effect on blood pressure, but reduced blood pressure in the same animals anaesthetized with ether.

Compound CIBA 34,276-Ba (Fig. 1) belongs to a new class of chemical compounds which, in clinical trials, produced antidepressive effects similar to those of the tricyclic antidepressive compounds [1]. Like imipramine and related compounds, CIBA 34,276-Ba markedly inhibited noradrenaline uptake through the nerve cell membrane in the brain and in several sympathetically innervated organs [2].

Since this influence on catecholamine metabolism might be involved in several of the cardiovascular effects of tricyclic antidepressants [3, 4], it seemed of interest to compare the cardiovascular effects of CIBA 34,276-Ba with those of imipramine in animal experiments.

Figure 1
CIBA 34,276-Ba.

CH₂CH₂CH₃NHCH₃

Methods

(a) Non-anaesthetized dogs: blood pressure and heart rate
(1) Intravenous infusion
Conscious trained mongrel dogs were given intravenous infusions of CIBA 34,276-Ba or imipramine at a rate of 0.2 or 0.5 mg/kg per minute for 10 minutes. Controls received physiological saline under the same conditions. Blood pressure in a percutaneously punctured femoral artery was measured continuously, and every 5 minutes an ECG tracing (lead II) was recorded to determine heart rate. The experiments lasted 60 minutes from the beginning of the infusion. Each dose of each compound was given to 4 dogs.

(2) Oral administration
Compound CIBA 34,276-Ba and imipramine were administered in gelatine capsules to 3 dogs in daily doses of 20 mg/kg p.o. over a period of 4 days. A control group (n = 4) received capsules containing lactose. Blood pressure and heart rate were recorded for periods of about 10 minutes before each daily dose and thereafter at hourly intervals for 7 hours. In these dogs, blood pressure and heart rate were measured by means of an indwelling
catheter [5] passed into the aorta from the femoral artery. In a further series of experiments, blood pressure in the femoral artery was measured for about 10 minutes after percutaneous puncture, and heart rate was determined from the pulse wave. These dogs were treated for 4 days with 10 mg/kg of compound CIBA 34,276-Ba or imipramine daily, and the measurements were repeated 2 hours after administration of the fourth dose and 4 days after administration of the fourth dose. The controls were given lactose. At each dose-level 4 dogs were treated.

(b) Anaesthetized dogs: blood pressure and heart rate

Dogs were anaesthetized with 60 mg/kg chloralose administered intravenously, blood pressure in the aorta was measured by means of a catheter passed from the femoral artery and heart rate was determined from the pulse wave.

Compound CIBA 34,276-Ba and imipramine were each given to 4 dogs by intravenous infusion at a rate of 0.5 mg/kg for 40 minutes. The experiments lasted 240 minutes from the beginning of the infusion.

In further experiments, imipramine-induced tachycardia was investigated more closely. To determine whether this effect was dose-dependent, imipramine was given by intravenous infusion over a period of 20 minutes to one group of 3 dogs at a rate of 0.2 mg/kg per minute and to another group of 6 dogs at a rate of 0.5 mg/kg per minute. After an interval of one week, 3 of the dogs in the latter group received a second infusion with the same amount of imipramine 10 minutes after the intravenous administration of 1.0 mg/kg of oxprenolol, an adrenergic beta-receptor blocking agent. In these experiments heart rate was recorded for 80 minutes from the beginning of the infusion.

(c) Open-chest dogs: cardiac output, stroke volume, total peripheral resistance

In dogs anaesthetized with chloralose (60 mg/kg i.v., additional injections during the experiment if necessary) and receiving artificial respiration, the thorax was opened and blood flow in the ascending aorta was measured with an electromagnetic flow-meter (Nycotron). Blood pressure in the femoral artery was measured and heart rate was determined from the pulse wave. Total peripheral resistance was calculated from mean arterial blood pressure and cardiac output, and stroke volume from heart rate and cardiac output. Compound CIBA 34,276-Ba and imipramine were infused over a period of 20 minutes at 2 different rates: 0.5 mg/kg per minute or 0.2 mg/kg per minute. Each dose of each compound was given to 3 dogs. A control group of 4 dogs received 0.9% saline under the same conditions. The experiments lasted 240 minutes from the beginning of the infusion.

(d) Anaesthetized cats: blood pressure

Cats were anaesthetized with 35 mg/kg s.c. and 35 mg/kg i.p. allobarbitone-urethane (Dial® CIBA). Blood pressure in the carotid artery was measured with a mercury manometer. In one series of experiments the two compounds were administered in progressive doses from 0.1 (n = 2) or 1.0 mg/kg i.v. (n = 3) up to the lethal dose. In a second series of experiments, single injections of 1.0 mg/kg i.v. (n = 3) or 3.0 mg/kg i.v. (n = 4) were given.

(e) Open-chest cats: cardiac contractile force, heart rate, blood pressure

In cats anaesthetized with allobarbitone-urethane (35 mg/kg s.c. and 35 mg/kg i.p.) or pentobarbitone (30 mg/kg i.p.) and receiving artificial respiration, the thorax was opened and a strain gauge arch was sutured to the left ventricle. Contractile force of the ventricle, blood pressure in the carotid artery, and heart rate were measured. The injections were given into the jugular vein.

Compound CIBA 34,276-Ba and imipramine were each given intravenously to 5 cats in cumulative doses of 0.1, 0.3, 1 and 3 mg/kg at intervals of 20 minutes.

(f) Renal hypertensive rats: blood pressure measurement with and without anaesthesia

Stable arterial hypertension of more than 200 mm Hg was produced in rats by clamping the left renal artery according to Goldblatt’s method.

In conscious animals the caudal blood pressure was determined from the pulse wave using the piezo crystal apparatus described by GEROLD et al. [6], the rats having been kept at a temperature of 30 °C for 30 minutes before the measurement was made and being restrained in Plexiglas cages during the measurement.

In rats anaesthetized with ether, caudal blood pressure was measured plethysmographically according to the method of BYROM and WILSON [7].

The blood pressure measurements were first made under light ether anaesthesia and then 2 hours later in the same conscious animals. Immediately thereafter, oral doses of 100 mg/kg CIBA 34,276-Ba or 30 mg/kg imipramine were administered.

6 hours after administration blood pressure was measured in the conscious animal and immediately afterwards under ether anaesthesia.

In anaesthetized animals the duration of the reduction in blood pressure following a single dose was also recorded, blood pressure being measured 2, 6 and 22 hours after administration. In these experiments, compound CIBA 34,276-Ba was given orally in doses of 30 and 100 mg/kg and imipramine in doses of 10 and 30 mg/kg p.o. Each dose of each compound was tested in 6 animals.

(g) Isolated guinea-pig atria: cardiac contractile force and heart rate

These experiments were carried out in isolated, spontaneously beating right atria and in left atria stimulated at a rate of 156 per minute. The resting tension amounted to 0.5 g. The bath fluid used was Krebs-Henseleit solution heated to 32 °C and gassed with 95% O2/5% CO2. Compound CIBA 34,276-Ba and imipramine were each tested on 8 atria in successive concentrations of 1, 10 and 100 mcg/ml. Each concentration was allowed to act for 10 minutes. Heart rate was measured in the right atria, and contractile force was determined isometrically in the left atria.