COMPARISON OF CARDIOVASCULAR TOXICITIES INDUCED BY DIMETACRINE, IMIPRAMINE AND AMITRIPTYLINE IN ISOLATED GUINEA PIG ATRIA AND ANESTHETIZED DOGS

Hitoshi KATO, Yuji NOGUCHI and Keijiro TAKAGI

Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences,
University of Tokyo, Bunkyo-ku, Tokyo, Japan

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Abstract—Cardiovascular toxicity induced by dimetacrine (DMC), an antidepressant, was investigated in isolated guinea pig atria and anesthetized dogs, and compared with those of imipramine (IMP) and amitriptyline (AMT) which have been widely used as antidepressants. In the electrically driven guinea pig left atria, these three agents depressed the atrial contraction; a statistically significant difference from non-treated control atria was observed in IMP and AMT, 3 x 10^-4 M, and DMC, 10^-3 M. The following order of potency was obtained; AMT>IMP>DMC. In the anesthetized dogs treated with the increasing doses of each agent, hypotensive responses were observed in the doses more than 1 mg/kg i.v.; the order of potency was as follows, AMT>IMP>DMC. A pronounced tachycardia was induced by IMP and AMT, 0.1-3 mg/kg i.v., and DMC, 1-3 mg/kg i.v., and the maximum response was observed in the doses of 1, 1 and 3 mg/kg i.v., respectively. When infused at the rate of 1 mg/kg/min i.v., the agents elicited hyperpnoea, tachycardia (except DMC) and hypotension, followed by respiratory arrest and cardiac arrest. Various changes in the ECG, including extrasystoles and supraventricular or ventricular tachycardia were also observed 10 to 15 min after the onset of infusion of AMT and IMP. However, DMC caused no visible modification in the ECG. The doses of AMT, IMP and DMC required to produce cardiac arrest were 25.4±1.2 (S.E.M.), 27.5±3.8 and 64.0±2.2 mg/kg i.v., respectively. The present study confirmed that fewer cardiovascular complications are caused by clinical use of DMC as compared to other tricyclic antidepressants such as IMP or AMT.

Dimetacrine, 9,9-dimethyl-10-[3-(dimethylamino)propyl] acridan, which has a dimethylaminoacridan moiety instead of a dihydrodibenzazepine moiety in the chemical structure of imipramine, has been confirmed to have the similar activities on the central nervous system to those of imipramine in experimental animals (1, 2). Furthermore, dimetacrine has been reported to be a useful antidepressant for the treatment of various types of depression in foreign countries (3, 4) and also in this country (5, 6). Compared with other antidepressants such as imipramine and amitriptyline, the prominent characteristics of dimetacrine in clinical usefulness have been pointed as follows, 1) a faster onset of action, 2) fewer adverse reactions, and 3) easily injectable into the vein.

Cardiovascular complications such as tachycardia, palpitations, hypotension, arrhythmias, various changes in the ECG and in the most serious cases, death following the administration of tricyclic antidepressants are well documented (7, 8). Accumulated clinical evidence suggests that patients with cardiac diseases are more susceptible to these cardiac adverse reactions (9).
In the present investigation, the comparative study on cardiovascular toxicities induced by dimetacrine and by widely used antidepressants such as imipramine and amitriptyline was conducted using the isolated guinea pig atria and anesthetized dogs.

MATERIALS AND METHODS

Isolated guinea pig atria

Male guinea pigs weighing 250 to 300 g were stunned by a blow on the head and the hearts were quickly removed. The left atrium was isolated and suspended in a 25 ml organ bath containing Krebs-Henseleit II solution (NaCl 6.92, KCl 0.35, CaCl$_2$ 0.28, MgSO$_4$ 0.15, NaHCO$_3$ 2.1, KH$_2$PO$_4$ 0.16 and glucose 2.0 g/liter) gassed with a mixture of 95% O$_2$ and 5% CO$_2$ at 31°C. Supramaximal stimuli, 3 msec in duration and 0.5 Hz in frequency, were continuously applied to the atria using a square-wave stimulator (Nihon Kohden, MSE-3). The force of resulting contractions of the atria was isometrically measured via a force displacement transducer (Nihon Kohden, ST-1) and recorded on a polygraph (Nihon Kohden, RM-150). The atria were maintained at a diastolic tension of 0.5 g and equilibrated for 60 min prior to drug administration. The cumulative doses of each agent, 3 x 10$^{-8}$-10$^{-5}$ M, were administered at 30 min intervals. Changes in the force of contraction induced by the drug solutions were expressed as percent of the force measured at the end of 60 min equilibration period and compared with those of the control atria without application of drug solutions.

Anesthetized dogs

Adult male mongrel dogs weighing 8 to 13 kg were anesthetized with sodium pentobarbital, 35 mg/kg i.v. Respiratory movement was measured by an accordion-type pneumograph placed around the thoraco-abdominal region and a pressure transducer (Nihon Kohden, LPU-0.1). Arterial blood pressure was measured in the right femoral artery by means of a pressure transducer (Nihon Kohden, MPU-0.5) and heart rate by means of a cardiotachometer (Nihon Kohden, RT-2) triggered by the R waves in the ECG taken from lead II. Recordings were made on a polygraph (Nihon Kohden, RM-150).

For the experiments on single i.v. injections, the increasing doses of each agent, 0.1, 0.3, 1, 3, 10 and 30 mg/kg i.v., until cardiac arrest occurred, were given into the cannulated left cephalic vein and were flushed with 1 ml of physiological saline. The changes in arterial blood pressure and heart rate caused by each dose were estimated for each agent.

For the perfusion experiments, dogs were administered with each agent at the rate of 1 mg/kg/min into the left cephalic vein using a syringe pump (Natsume, KM-202) until cardiac arrest occurred. Respiratory movement, arterial blood pressure, heart rate and ECG were recorded as mentioned above, and compared with those in the control animals, which were given physiological saline infusion at the same rate as drug solutions. The doses required to produce respiratory arrest in respiratory movement and cardiac arrest in the ECG were estimated for each agent.

Drugs used

Dimetacrine bitartrate (Nippon Chemiphar Co., DMC), imipramine hydrochloride
(Fujisawa Pharmaceutical Co., IMP) and amitriptyline hydrochloride (Nippon Merck-Banyu Co., AMT) were freshly dissolved in physiological saline. All doses of the agents are expressed in terms of the salt.

RESULTS

Effects on isolated guinea pig left atria

To evaluate the direct cardiac effects of DMC, IMP and AMT, the influence of these agents on the contractile force of electrically driven guinea pig left atria was observed (N=6 for each agent). The effects of the agents in equimolar concentration are shown in Fig. 1. The contractile force of the control atria (N=6) declined to $82\pm5.6$ (S.E.M.)% 2.5 hr after the start of the experiments. On the contrary, DMC, IMP and AMT in the highest concentration, $10^{-5}$ M, decreased the force to $36.5\pm9.1$, $9.7\pm2.7$ and $4.2\pm1.5\%$, respectively. The agents, $3 \times 10^{-7}$ M, caused no statistically significant decline in contractile force from the controls. In concentrations more than $3 \times 10^{-6}$ M, marked negative inotropic effects were observed and the decline in contractile force was significantly greater than that in the controls; IMP and AMT, $3 \times 10^{-6}$ M, and DMC, $10^{-5}$ M, were statistically significant from the controls (p<0.01) and IMP and AMT, $10^{-5}$ M (p<0.001). In a concentration of $10^{-5}$ M, IMP and AMT showed significantly greater negative inotropic effects than DMC (p<0.05). Thus, the agents dose-dependently depressed the contractile force of the isolated atria, and the order of potency was as follows: AMT$\geq$ IMP$>$DMC.

Effects on respiratory movement, arterial blood pressure, heart rate and ECG in anesthetized dogs

The effects of DMC, IMP and AMT administered as single i.v. injections in increasing doses on arterial blood pressure and heart rate in dogs were examined (N=5 for each agent).
The agents in doses more than 1 mg/kg i.v. caused a fall in blood pressure, which was followed by a sustained slight elevation in blood pressure in low doses, i.e. 1–3 mg/kg i.v. The order of their potencies was as follows; AMT > IMP > DMC. Tachycardia was observed after the administrations of IMP, 0.1–3, AMT, 0.1–1 and DMC, 1–3 mg/kg i.v., and their maximum responses were obtained in doses of 1, 1 and 3 mg/kg i.v., respectively. The order of their potencies was as follows; IMP > AMT > DMC. The administrations of IMP and AMT, 10 mg/kg i.v., and DMC, 30 mg/kg i.v., caused an abrupt fall in blood pressure with tachycardia or bradycardia followed by cardiac arrest. Typical recordings obtained from the case with DMC are shown in Fig. 2. Results are summarized in Fig. 3.

The effects of DMC, IMP and AMT infused at the rate of 1 mg/kg/min i.v. on respiratory movement, arterial blood pressure, heart rate and ECG in dogs (N=5 for each agent) were observed, and compared with those of physiological saline as a control group (N=5). Typical recordings obtained from the case with DMC are illustrated in Fig. 4 and the results are summarized in Fig. 5. Respiratory rate increased 10 min after the onset of infusion of IMP and AMT, and 40 min after DMC. Arterial blood pressure fell
5 min after the onset of infusion of IMP and AMT, and 50 min after DMC. In the cases with IMP and AMT, tachycardia was observed immediately after the onset of infusion, whereas DMC caused a gradual decrease in heart rate. In general, the changes in these parameters caused by IMP and AMT were more pronounced and faster in onset than those by DMC. No marked change in the parameters was observed in the control animals treated with physiological saline over 1 hr. Various changes in the ECG such as displacement of the ST segment, flattening or elevation of the T wave, extrasystoles (in a few cases) and sinus, supraventricular or ventricular tachycardia were observed in the cases with
IMP and AMT. DMC caused no visible modification in the ECG. Doses required to produce respiratory arrest and cardiac arrest are shown in Table 1, in which the doses are calculated in terms of the salt. Thus, the order of potencies for their cardiovascular toxicities was as follows: $\text{AMT} \geq \text{IMP} > \text{DMC}$.

### DISCUSSION

Tricyclic antidepressants in adequate doses reportedly cause negative inotropic and chronotropic effects (2,10-13). In the present study, IMP and AMT dose-dependently decreased the contractile force of electrically driven guinea pig atria and in concentrations more than $3 \times 10^{-6} \text{M}$ caused a significant negative inotropic effect. The results appear consistent with those observed by Greeff and Wagner (12) in spontaneously beating guinea pig atria and Marmo et al. (13) in beating guinea pig hearts. DMC was significantly less potent regarding the negative inotropic effect than IMP and AMT. Sasaki (2) reported that in the isolated toad hearts DMC, $10^{-3} \text{g/ml}$, caused a negative inotropic effect and $10^{-4} \text{g/ml}$ cardiac arrest. These effects of tricyclic antidepressants have been regarded as direct ones on heart muscle. From the results of changes in the S-A nodal and atrial action potentials induced by IMP, Matsuo (14) suggested that inhibition of the atrial electrical activity may be due to the quinidine-like or local anesthetic action of the agent.

IMP has been reported to exert a dual action; the small doses elevate blood pressure and increase heart rate and contractility of the heart, and the large doses decrease these parameters in anesthetized cats and dogs (10, 11). In the present study DMC, IMP and AMT, in small doses, i.e. 1–3 mg/kg i.v., caused a fall in blood pressure followed by a sustained slight elevation in blood pressure with tachycardia. Sigg et al. (11) suggested that the hypotensive effect of the tricyclic agents in high doses seemed to be a direct action on the myocardium resulting in a diminution of cardiac output. The same authors also suggested that the effects of IMP in small doses on the hemodynamic parameters mentioned above are thought to be due to a sensitization of adrenergic receptors to norepinephrine resulting from the prevention of the release of norepinephrine from its store sites in the sympathetic nerve endings. A blockade of uptake of administered norepinephrine has been shown for IMP (15). Furthermore, the increase in heart rate is attributed to anti-cholinergic effects of the tricyclic agents (16, 17). These considerations may be adaptable
to the present results. One or more of these factors may also contribute to various changes in the ECG and the genesis of cardiac arrhythmias induced by the tricyclic agents. In the present study, various changes in the ECG, including displacement of the ST segment, flattening or elevation of the T wave, extrasystoles and sinus, supraventricular or ventricular tachycardia were observed following the administrations of IMP and AMT. These changes are similar to the results reported by other investigators (10, 18). Hudak (personal communication) demonstrated tachycardia and nodal rhythm with premature ventricular contractions caused by DMC in unanesthetized dogs. In the present experiments, however, DMC caused no visible modification in the ECG when infused i.v. into anesthetized dogs.

Comparative studies on the LD50 of DMC, IMP and AMT in experimental animals have not been reported. The results from the doses required to produce respiratory arrest and cardiac arrest appear to consist, in the order of potencies, with the values reported by other investigators, especially with the LD50 values in mice i.v.; 57 (1) and 44.6 mg/kg (2) for DMC, 35 mg/kg for IMP (2, 19) and 27 mg/kg for AMT (20).

In controlled clinical studies, no significant difference in the effectiveness of these three agents as antidepressants has been observed (6). Furthermore, the prominent characteristics of DMC in clinical use have been pointed as mentioned above (3–6). The present study confirmed in experimental animals that DMC causes fewer cardiovascular complications than other tricyclic antidepressants such as IMP or AMT.

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