CARDIAC EFFECTS OF ANTIDEPRESSANTS

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The present study was undertaken to investigate the cardiac effects of 5 antidepressive tricyclic derivatives namely imipramine, desipramine, amitriptyline, trimeprimine and noxiptiline (Fig. 1). The following parameters were studied:

- 1) In vivo: Effects on ECG, their anti-arrhythmic and anticoronarospastic activity.
- 2) In vitro: Effects on the inotropism, chronotropism and coronary flow.

FIG. 1. Structure formulas of the tricyclic derivatives studied: imipramine (1), desipramine (2), trimeprimine (3), amitriptyline (4) and noxiptiline (5).

MATERIAL AND METHODS

1. *Animals and drugs*

Adult rats of either sex weighing 130–290 g and of Morini strain were used. Guinea-pigs (400–500 g) were supplied locally. No pregnant animals of either species were used.

Drugs used were procainamide sulfate (Sigma); aconitine sulfate (Simes); reserpine (Ciba); BaCl₂ and CaCl₂ (C. Erba); K-strophanthoside (Maggioni); pitressin (Parke Davis); imipramine hydrochloride and desipramine hydrochloride (Geigy); amitriptyline hydrochloride, trimeprimine malcate and noxiptiline hydrochloride (Bayer). The substances were dissolved in distilled H₂O.

2. *ECG studies*

Rats anaesthetized with ethylurethane (1 gm/Kg; i.p.) were immobilized on a lying bed and prepared for ECG recording on lead II. The electrocardiograph used was a Cardioline mod. Epsilon 2 (paper sliding speed 50 mm/sec; setting 1 mV/cm). All the drugs were administered intravenously i.e., external jugular vein.

3. *In vitro studies on heart*

Guinea pigs were sacrificed by a blow on the neck. The beating heart was taken out immediately, mounted on Langendorff-Spadolini apparatus. It was perfused with oxygenated Ringer-Locke solution at 38°C with a 60 cm H₂O pressure at the level of the coronary ostioles. The frequency and the amplitude of the cardiac contractions as well as the coronary flow was measured as described by Marmo et al. (1). The perfusion with Ringer-Locke medicated with tricyclic derivatives was carried out for a period of 20 min. It was preceded and followed by perfusions with normal Ringer-Locke solution for a period of 10 min each.

4. *Studies on the anti-arrhythmic and anti-coronary spastic activity*

The lethal and the ECG effects were recorded on anaesthetized rats and guinea-pigs after intravenous administration of the following drugs:

- I: Rats a) BaCl₂ (50 mg/kg/min, i.v. up to death; 0.5 ml liquid/animal/min)
b) CaCl₂ (100 mg/kg/min, i.v. up to death; 0.5 ml liquid/animal/min)
c) Aconitine (15 µg/kg/min i.v. up to death; 0.5 ml liquid/animal/min)
- II: Guinea-pigs a) K-strophanthoside 50 µg/kg/min i.v. up to death; 0.5 ml liquid/animal/min)
b) Pitressin (1.5 I.U./kg i.v. in 10 sec)

The animals were pretreated intravenously. One minute before administration of the toxic drugs, either with NaCl 0.9% (5 ml/kg in 4 min) or with the tricyclic derivatives (5 mg/kg in 4 min; 5 ml liquid/kg). The ECG were recorded in lead II.

RESULTS

1. *ECG studies*

Intravenous perfusion of tricyclic derivatives (Imipramine, desipramine, trimeprimine, amitriptyline and noxiptiline) at a dose of 5 mg/kg/min up to death, produced the following effects in anaesthetized rats:

- a) *Excitability disturbances*: i.e. sinus bradycardia, sometimes preceded by a slight

and transitory tachycardia; occasionally either an ectopic rhythm supraventricular or a nodal rhythm accompanied with supraventricular extrasystoles.

b) *Conduction disturbances:* Alterations in atrioventricular conduction, i.e. lengthening of PR interval atrioventricular blocks of 1st, 2nd and 3rd grade; blocks of the branch.

c) *Depolarization disturbances:* aspects of ventricular overload especially on the right type; the ventricular repolarization was usually very precociously disturbed, with sliding of ST and flattening or inversion of T-wave, which do not seem to be determined by ischemic lesion.

The onset of cardiotoxic and lethal effects due to i.v. perfusions of the tricyclic derivatives (except amitriptyline) was retarded in animals pre-treated for 24 hr with reserpine at the dose of 5 mg/kg, i.p. (Figs. 2-6 and Table 1).

2. Perfusion studies (in vitro)

Perfusion for a period of 20 min with the tricyclic derivatives on guinea-pig hearts beating in vitro, did not significantly modify the coronary flow, the chronotropism and the inotropism in concentrations of 10^{-9} – 10^{-7} (g/ml) of noxiptiline, imipramine, desipramine, trimeprimine and amitriptyline. In the case of noxiptiline at concentrations of 10^{-6} (g/ml), a slight increase of the frequency and the amplitude of cardiac contractions was often recorded (the increase in amplitude was a consequence of an intensification of the

FIG. 2. Effects of an i.v. perfusion with imipramine on ECG of a normal rat (a) and a rat pre-treated for 24 hr with reserpine (b). 0=basal ECG. Side numbers indicate time at which ECG was carried out. Rats *a* and *b* died after 7 min (a) and 10 min 30 sec (b) from the beginning of perfusion with imipramine.

FIG. 3. Effects of an i.v. perfusion with desipramine on ECG of a normal rat (a) and a rat pre-treated for 24 hr with reserpine (b). 0=basal ECG. Side numbers indicate time at which ECG was carried out. Rats *a* and *b* died after 7 min 30 sec (a) and 8 min 50 sec (b) from beginning of perfusion with desipramine.

FIG. 4. Effects of an i.v. perfusion with trimeprimine on ECG of a normal rat (a) and a rat pre-treated for 24 hr with reserpine (b). 0=basal ECG. Side numbers indicate time at which ECG was carried out. Rats *a* and *b* died after 7 min 40 sec (a) and 11 min 50 sec (b) from beginning of perfusion with trimeprimine.

FIG. 5. Effects of an i.v. perfusion with amitriptyline on ECG of a normal rat (a) and a rat pre-treated for 24 hr with reserpine (b). 0 = basal ECG. Side numbers indicate time at which ECG was carried out. Rats *a* and *b* died after 7 min 35 sec (a) and 7 min 30 sec (b) from beginning of perfusion with amitriptyline.

FIG. 6. Effects of an i.v. perfusion with noxiptiline on ECG of a normal rat (a) and a rat pre-treated for 24 hr with reserpine (b). 0 = basal ECG. Side numbers indicate time at which ECG was carried out. Rats *a* and *b* died after 8 min (a) and 10 min 15 sec (b) from beginning of perfusion with noxiptiline.

TABLE 1. Lethality caused by i.v. perfusions of different drugs (5 mg/kg/min up to death) on normal rats (a) or on rats pre-treated (b) for 24 hr with reserpine (5 mg/kg i.p.).

Number of animals	Experimental group	Treatment	Survival min $\pm$ S.E.
4	<i>a</i>	Imipramine	6'20'' $\pm$ 49''
4	<i>b</i>	Imipramine	10'15'' $\pm$ 56'' (*)
4	<i>a</i>	Desipramine	7'45'' $\pm$ 35''
4	<i>b</i>	Desipramine	9'06'' $\pm$ 38''
4	<i>a</i>	Trimeprimine	7'25'' $\pm$ 54''
4	<i>b</i>	Trimeprimine	11'30'' $\pm$ 46'' (*)
4	<i>a</i>	Amitriptyline	7'40'' $\pm$ 42''
4	<i>b</i>	Amitriptyline	7'30'' $\pm$ 28''
4	<i>a</i>	Noxiptiline	8'10'' $\pm$ 52''
4	<i>b</i>	Noxiptiline	10'24'' $\pm$ 43'' (*)

(*) Statistically significant values ($P < 0.05$) to groups *a*. S.E. = standard error.

FIG. 7. Isolated hearts of 8 guinea-pigs. Between the 2 signs a perfusion (duration 20 min) of Ringer-Locke medicated with amitriptyline (A), with imipramine (B), with desipramine (C) or with trimeprimine (D), in concentrations of 10^{-6} or of 10^{-5} (g/ml).

diastolic relaxation), not combined to significant variations of the coronary flow. At concentrations of 10^{-6} (g/ml) imipramine, desipramine, trimeprimine and amitriptyline and of 10^{-5} (g/ml) noxiptiline, all drugs significantly reduce the coronary flow, and the frequency and the amplitude of cardiac contractions (both as to systolic phase and diastolic phase) (Figs. 7, 8 and Table 2).

3. Anti-arrhythmic and anti-coronaryspastic studies

The tricyclic derivatives (imipramine, desipramine, trimeprimine, amitriptyline and

FIG. 8. Isolated hearts of 3 guinea-pigs. Between the 2 signs a perfusion (duration - 20 min) of Ringer-Locke medicated with noxiptiline in concentrations of 10^{-7} , 10^{-6} or of 10^{-5} (g ml).

TABLE 2. Effects in vitro of the tricyclic derivatives on coronary flow, chronotropism and the inotropism of guinea-pig heart.

Drug		Percentage variations of coronary flow (A), of chronotropism (B) and of inotropism (C) compared to the values of controls after 20 min perfusions with the following concentrations (g ml) of the drugs				
		1×10^{-8}	1×10^{-7}	1×10^{-6}	1×10^{-5}	1×10^{-4}
Imipramine	A	0	2.4	0	44	100
	B	0	0.9	1.5	15	100
	C	1.1	0	0.7	28	100
Desipramine	A	0	0	0.5	30	100
	B	0	-1.2	0	18	100
	C	0.8	0.9	1.1	44	100
Trimipramine	A	0	-2.3	0	48	100
	B	1.4	0	0.9	16	100
	C	0.7	0	3.5	36	100
Amitriptyline	A	0	3.4	0	57	100
	B	0	2.1	0	14	100
	C	0.2	0	1.9	29	100
Noxiptiline	A	2.7	0	1.9	0.9	68
	B	1.8	1.2	-0.7	-14.2	29
	C	0.6	1.5	2.1	-9.7	98

Each value represents the average of 3 experiments.

noxiptiline) (Table 3) (1 min before the toxic drug, 5 mg/kg, i.v.): a) moderately antagonized the cardiotoxicity in the rat caused by CaCl_2 (retarding only the onset of ventricular extrasystoles and fibrillation*), cardiotoxicity and lethality in the rat caused by aconitine (retarding the onset of ventricular fibrillation and death time) and in the guinea-pig caused

* Amitriptyline anticipates the onset of ventricular extrasystoles caused by CaCl_2 .

TABLE 3 Effects of i.v. perfusions with CaCl_2 , BaCl_2 and aconitine in the rat and with k-strophantoxide in the guinea-pig. The animals were pre-treated or not for 1 min with different drugs.

Pre-treatment 5 mg/kg i.v. in 4 min	Time of onset of arrhythmias (ventricular extrasystoles) sec $\pm$ S.E.	Time of onset of ventricular tachycardia sec $\pm$ S.E.	Time of onset of ventricular fibrillation sec $\pm$ S.E.	Time of death sec $\pm$ S.E.
<i>CaCl₂ (100 mg/kg min up to death, i.v.)</i>				
Controls	70 $\pm$ 11		80 $\pm$ 4	290 $\pm$ 38
Imipramine	120 $\pm$ 20 (*)		200 $\pm$ 22(*)	230 $\pm$ 24
Desipramine	165 $\pm$ 16 (*)		260 $\pm$ 19(*)	349 $\pm$ 48
Amitriptyline	29 $\pm$ 8		120 $\pm$ 11(*)	180 $\pm$ 20
Trimepramine	130 $\pm$ 12 (*)		150 $\pm$ 14(*)	184 $\pm$ 16
Noxiptiline	152 $\pm$ 14 (*)		190 $\pm$ 18(*)	223 $\pm$ 25
Procainamide	242 $\pm$ 18 (*)		278 $\pm$ 23(*)	430 $\pm$ 23(*)
<i>BaCl₂ (50 mg/kg min up to death, i.v.)</i>				
Controls			48 $\pm$ 6	175 $\pm$ 14
Imipramine			90 $\pm$ 5(*)	240 $\pm$ 20(*)
Desipramine			45 $\pm$ 3	178 $\pm$ 16
Amitriptyline			30 $\pm$ 4	180 $\pm$ 12
Trimepramine			60 $\pm$ 8	195 $\pm$ 18
Noxiptiline			30 $\pm$ 2	143 $\pm$ 12
Procainamide			98 $\pm$ 5(*)	268 $\pm$ 16(*)
<i>Aconitine (15 μg/kg min up to death, i.v.)</i>				
Controls	181 $\pm$ 14	230 $\pm$ 29	302 $\pm$ 18	456 $\pm$ 47
Imipramine	260 $\pm$ 30 (*)	410 $\pm$ 32 (*)	490 $\pm$ 50(*)	910 $\pm$ 72(*)
Desipramine	300 $\pm$ 28 (*)	420 $\pm$ 35 (*)	510 $\pm$ 48(*)	1140 $\pm$ 84(*)
Amitriptyline	380 $\pm$ 26 (*)	540 $\pm$ 40 (*)	720 $\pm$ 56(*)	1155 $\pm$ 95(*)
Trimepramine	210 $\pm$ 17	340 $\pm$ 20 (*)	380 $\pm$ 28(*)	780 $\pm$ 64(*)
Noxiptiline	196 $\pm$ 11	271 $\pm$ 21	419 $\pm$ 32(*)	603 $\pm$ 58(*)
Procainamide	514 $\pm$ 40 (*)	726 $\pm$ 48 (*)	763 $\pm$ 72(*)	1271 $\pm$ 83(*)
<i>k-Strophantoxide (50 μg/kg min up to death, i.v.)</i>				
Controls	365 $\pm$ 52		499 $\pm$ 28	620 $\pm$ 98
Imipramine	520 $\pm$ 58 (*)		670 $\pm$ 56 (*)	1110 $\pm$ 102(*)
Desipramine	485 $\pm$ 38 (*)		598 $\pm$ 48 (*)	890 $\pm$ 92(*)
Amitriptyline	540 $\pm$ 46 (*)		710 $\pm$ 62(*)	1030 $\pm$ 96(*)
Trimepramine	645 $\pm$ 42 (*)		1350 $\pm$ 104(*)	1440 $\pm$ 110(*)
Noxiptiline	471 $\pm$ 43 (*)		590 $\pm$ 37(*)	867 $\pm$ 87(*)
Procainamide	536 $\pm$ 32 (*)		760 $\pm$ 48(*)	1119 $\pm$ 79(*)

Each value represents the average of 6 experiments.

(*) Statistically significant values calculated as compared to controls ($P < 0.05$).

S.E. = standard error.

by k-strophantoxide (retarding the onset of ventricular extrasystoles and fibrillation and deathtime). Imipramine, desipramine, amitriptyline and trimepramine showed an anti-arrhythmic activity, very slightly stronger than that of noxiptiline in the case of aconitine and k-strophantoxide; b) did not modified the cardiotoxicity and lethal effects in the rat, caused by BaCl_2 (only imipramine moderately retarded the onset of cardiotoxic and lethal

FIG. 9. Effects of pitressin on ECG of guinea-pigs treated for 1 min with NaCl 0.9% (a) or with noxiptiline (b). 0—basal ECG; 0'—ECG carried out 1 min from NaCl (a) or noxiptiline (b). Side numbers indicate times from pitressin.

FIG. 10. Effects of pitressin on ECG of guinea-pigs treated for 1 min with amitriptyline (a), with imipramine (b), with desipramine (c) or with trimeprimine (d). 0—basal ECG; 0'—ECG carried out 1 min from the tricyclic derivatives. Side numbers indicate time from pitressin.

effects); c) do not remarkably modify the ecgraphic signs of coronary spasm (alterations of ST segment; increase in height or inversion of T wave, lengthening of PQ and QT segments) and of rhythm disturbances (sinus bradycardia, ventricular extrasystoles, partial and total

atrio-ventricular blocks and branch blocks) caused by pitressin in the guinea-pig (Figs. 9, 10). Procainamide (Table 3) showed evident anti-arrhythmic effects, stronger than those of the tricyclic derivatives with regard to CaCl_2 , BaCl_2 and aconitine; with regard to k-strophantocide, the anti-arrhythmic activity of procainamide was weaker than that of trimeprimine and equivalent to or slightly stronger than that of imipramine, amitriptyline and that of desipramine respectively.

DISCUSSION

The tricyclic antidepressives (imipramine, desipramine, amitriptyline, trimeprimine and noxiptiline) in vitro caused (in adequate concentrations) a negative inotropic and chronotropic effects (with reduction of the coronary flow). In vivo (in adequate doses) caused disturbances of excitability, conduction and of depolarization, qualitatively similar to those observed by other authors in experimental and clinical studies (2-18).

In adequate doses, the 5 tricyclic antidepressives showed a slight anti-arrhythmic activity with regard to k-strophantocide in the guinea-pigs, and to aconitine and CaCl_2 in the rats. They did not modify the cardiotoxicity caused by BaCl_2 in the rat and by pitressin in the guinea-pigs. The anti-arrhythmic activity which we have recorded for imipramine, desipramine, amitriptyline and trimeprimine with regard to k-strophantocide, CaCl_2 and aconitine agrees with the observations made by several authors; i.e. Kosmider and Smolarz (17) for imipramine with regard to digoxine; Fekete and Borsy (7) for imipramine, desipramine, trimeprimine, amitriptyline, with regard to CaCl_2 , aconitine and intra-cardiac electrical stimulation, and by Schmitt (13) for imipramine with regard to ouabaine, aconitine and adrenaline.

The effects observed on the heart (in vitro and in vivo) and the anti-arrhythmic effects can be ascribed (also considering their local anesthetic activity and other investigations of ours) to a direct action of the drugs on the cell membrane with a reduction of the transmembrane potential and of the active ionic transport at the level of the myocardic cells.

SUMMARY

The present investigation was carried out for a toxicological experimental study with imipramine, desipramine, amitriptyline, trimeprimine and noxiptiline on ECG and on the isolated heart. The 5 tricyclic antidepressives showed at high doses: a) a decrease in the cardiac inotropism, chronotropism, excitability, conduction and depolarization and a decrease in coronary flow; b) a slight anti-arrhythmic activity.

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