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PLASMA CONCENTRATIONS AND CARDIOTOXIC EFFECTS OF DESIPRAMINE AND PROTRIPTYLINE IN THE RAT

G. BIANCHETTI,[1] AURORA BONACCORSI, A. CHIODAROLI, R. FRANCO,[2] S. GARATTINI, R. GOMENI[1] & P.L. MORSELLI[1]

Istituto di Ricerche Farmacologiche 'Mario Negri' Via Eritrea 62, 20157 Milan, Italy

1 Desipramine and protriptyline were administered to anaesthetized rats by two consecutive intravenous infusions in order to obtain a peak level (first infusion) followed by lower steady state concentrations (second infusion) (Wagner, 1974). Theoretical plasma level time courses were confirmed experimentally.

2 Desipramine and protriptyline were measured in atria and ventricles. Increasing infusion rates led to proportional increases in plasma and atrial concentrations. The tissue/medium ratio ranged from 57 to 21 for desipramine and from 43 to 11 for protriptyline according to the time of determination during infusions.

3 Heart rate changes, deviation of the electrical axis of the heart and prolongation of atrioventricular conduction were recorded at fixed times during infusion.

4 Positive chronotropic effects were noted at plasma concentrations ranging from 0.035 to 0.1 μg/ml for desipramine and from 0.04 to 1.2 μg/ml for protriptyline. At higher plasma concentrations the positive chronotropic effect decreased and bradycardia developed. Both drugs induced right rotation of the electrical axis of the heart. Threshold plasma levels giving 40° rotation were 1.35 μg/ml (desipramine) and 1.75 μg/ml (protriptyline). Atrioventricular conduction was prolonged at threshold plasma concentrations of 2.2 μg/ml for desipramine and 3.6 μg/ml for protriptyline.

5 Desipramine is more cardiotoxic than protriptyline. This difference is discussed in relation to the plasma and heart concentration of the two drugs.

Introduction

A variety of side effects may occur during treatment with tricyclic antidepressant drugs, the most serious being the cardiac complications (Muller, Goodman & Bellet, 1961; Alexander & Nino, 1969; Coull, Crooks, Dingwall-Fordyce, Scott & Weir, 1970; Editorial 1971; Williams & Sherter, 1971). Electrocardiographic changes include sinus tachycardia, ventricular extrasystoles, prolongation of the PQ and QRS intervals and ST and T wave abnormalities.

The mechanism of action of these compounds on the heart has been attributed to the combination of their sympathomimetic, anticholinergic and membrane stabilizing effects (Sigg, Osborne & Korol, 1963; Greeff & Wagner, 1969; Schmitt, Cheymol & Gilbert, 1970; Langslet, Grini Johansen, Ryg, Skomedal & Øye, 1971; Barth & Muscholl, 1974; Elonen, Mattila & Saarnivaara, 1974). Several studies have indicated that cardiac effects are qualitatively similar among antidepressants but that from a quantitative point of view they differ widely (Boissier, Simon & Witchitz, 1965; Lechat, Auclair, Fontagné & Prudhommeau, 1969; Barth & Muscholl, 1974; Elonen *et al.*, 1974). The purpose of this study was to make a comparative investigation of the possible relationship between plasma concentrations and cardiac effects of antidepressant compounds in the rat. Since plasma levels reflect the availability of a drug at its site of action, determinations of drug concentrations in plasma may be particularly useful to find whether differences in drug activities might be explained, at least in part, by differences in pharmacokinetic behaviour. Such determinations may also make for more meaningful comparisons of drug effects among different animal species. The experimental approach chosen for this study is the theoretical model proposed by Wagner (1974) to obtain steady state plasma levels in a short period of time.

Desipramine and protriptyline were used for this comparison. These drugs are equally potent as inhibitors of catecholamine uptake in the heart

[1] Present address: E.R.S. Synthelabo, 58 rue de la Glacière, Paris, France.

[2] Present address: Physiologie et Pharmacologie, INSERM U.7, Hôpital Necker, Paris, France.

(Carlsson & Waldeck, 1965; Franco, Bonaccorsi, Castelli, Garattini & Morselli, 1976) while there are a few reports (Boissier *et al.*, 1965) suggesting that desipramine may be a more potent cardiotoxic agent than protriptyline.

Methods

Male Sprague Dawley rats (Charles River, Italy), weighing 200–250 g were anaesthetized with ethyl urethane (1.3 g/kg i.v.). The femoral vein and left carotid artery were cannulated and the animals were allowed to rest for 30 minutes. Desipramine (DMI) and protriptyline (PTP) were administered by two consecutive intravenous infusions. The first infusion lasted 10 min (Q_1) and was followed by a second one (Q_2), by which time steady state plasma levels were reached and maintained. Wagner equations (1974) were used to calculate the infusion rates. The necessary pharmacokinetic parameters were obtained from the disappearance curves of DMI and PTP from plasma of rats given an intravenous injection of 5 mg/kg of the drugs (Table 1). Calculations were made with a Digital PDP 11/45 computer fed the following information: (i) pharmacokinetic parameters; (ii) duration of the first infusion; (iii) the desired steady state plasma level. Table 2 shows the infusion rates in $\mu g\ kg^{-1}\ min^{-1}$ and the theoretical plasma levels. The intravenous infusions of DMI and PTP were delivered by a constant infusion pump (Braun, Germany) at the rate of 0.05 ml/minute. Solutions were warmed to 37°C just before entering the femoral vein. Control animals were infused with 0.9% w/v NaCl solution (saline). During the infusions, the three bipolar standard limb leads of the ECG were recorded on

Table 1 Pharmacokinetic parameters of desipramine (DMI) and protriptyline (PTP) calculated from single bolus intravenous injections (5 mg/kg) in anaesthetized rats according to a two compartment open model

Parameters	*Desipramine*		*Protriptyline*	
*K*el	0.0152	min^{-1}	0.0128	min^{-1}
*K*12	0.0873	min^{-1}	0.0986	min^{-1}
*K*21	0.0503	min^{-1}	0.0349	min^{-1}
α	0.14296	min^{-1}	0.14762	min^{-1}
β	0.00301	min^{-1}	0.00518	min^{-1}
V1	4.956	l/kg	5.31	l/kg
$(T_{\frac{1}{2}})\beta$	230.41	min	133.8	min
TBCl	0.06093	$l\ kg^{-1}\ min^{-1}$	0.08078	$l\ kg^{-1}\ min^{-1}$

Kel = first order elimination rate constant; K12 and K21 = first order distribution rate constants between the two compartments; α and β = disposition rate constant; V1 = apparent volume of the central compartment; $(T_{\frac{1}{2}})\beta$ = apparent plasma half life of the β phase; TBCl = Total body clearance.
The infusion rates in Table 2 were calculated by Wagner's equation (1974) from these data.

Table 2 Desipramine (DMI) and protriptyline (PTP) infusion rates and theoretical steady state plasma levels (μg/ml)

Desipramine			*Protriptyline*		
*Rates of infusion** ($\mu g\ kg^{-1}\ min^{-1}$)		*Theoretical steady state plasma levels (μg/ml)*	*Rates of infusion** ($\mu g\ kg^{-1}\ min^{-1}$)		*Theoretical steady state plasma levels (μg/ml)*
1/10.Q	$Q_1 = 63.6$ $Q_2 = 3.6$	0.035	1/10.Q	$Q_1 = 57.3$ $Q_2 = 5.7$	0.040
1.Q	$Q_1 = 636.6$ $Q_2 = 36.3$	0.35	1.Q	$Q_1 = 573.5$ $Q_2 = 57.5$	0.40
2.Q	$Q_1 = 1273.3$ $Q_2 = 72.6$	0.70	2.Q	$Q_1 = 1147$ $Q_2 = 115$	0.80
3.Q	$Q_1 = 1909.9$ $Q_2 = 108.9$	1.05	3.Q	$Q_1 = 1720$ $Q_2 = 172$	1.20
5.Q	$Q_1 = 3183.2$ $Q_2 = 181.5$	1.75	5.Q	$Q_1 = 2867$ $Q_2 = 287.5$	2.00

* Q_1 = first infusion given for 10 min; Q_2 = infusion maintaining steady state.

OTE Biomedica equipment through subcutaneous needle electrodes. Sensitivity was adjusted so that 1 mV was equal to 1.5 cm. Heart rate and PQ interval were measured graphically. The position of the electrical axis was determined by the procedure of Goldman (1970).

In some experiments, at different times after the start of drug administration, blood was collected (about 5 ml) in heparinized tubes from the carotid artery, and centrifuged for 30 min at 2000 rev/min and 4°C.

The hearts were removed, atria and ventricles were separated, blotted with filter paper and weighed. All specimens were kept frozen until analysis.

Electron capture gas chromatographic determination of desipramine and protriptyline in tissue samples

Atria and ventricles were homogenized with glass homogenizers in 2.5 and 0.1 N HCl respectively.

DMI and PTP concentrations were determined by gas chromatography, following a modified version of the method described by Borgå & Garle (1972). Tissue and plasma samples (0.1–1 ml) were added with phosphate buffer (pH 11, 0.3 M) to a final volume of 2 ml. As an internal marker 4 μg of maproptyline was added to samples containing DMI and 0.8 μg to each sample of PTP. Drugs were extracted with 5 ml of ethyl ether and, after discarding the aqueous phase, re-extracted in 2.5 ml of 0.1 N HCl. The acidic aqueous phase was made alkaline with 0.2 ml of 2 N NaOH and again extracted with 5 ml of ethyl ether. After centrifugation, 4.5 ml of the ether phase were transferred to a test tube and evaporated to dryness at 40°C in a water bath. Heptafluorobutyric anhydride (200 μl of 1 : 10 solution in ethyl acetate) was added to the drug residue. The solution was shaken in glass capped tubes, incubated at 40°C for 30 min and then evaporated to dryness under a stream of N_2 at 40°C for 10 minutes. Samples were dissolved in 0.5 ml ethyl ether, shaken and evaporated again to dryness at 40°C under a stream of N_2 for 15 minutes. The derivative was dissolved in 1 ml (DMI samples) or 300 μl (PTP samples) of ethyl acetate; 1 μl of these solutions was injected into the gas chromatograph. Overall recovery was 75 ± 3% for both drugs. A Carlo Erba Fractovap G-1 gas chromatograph equipped with a ^{63}Ni electron capture detector was used. The chromatographic column was a glass tube, 1 m long, 4 mm i.d., packed with 100–200 mesh Gas Chrom Q, coated with 3% OV 17 (Applied Science Laboratories) treated as previously described (Di Salle, Baker Bareggi, Watkins, Chidsey, Frigerio & Morselli, 1973). The operating conditions were: column temperature 230°C; detector temperature 275°C; carrier gas (N_2) flow rate 60 ml/min, scavenger gas (N_2) flow rate 70 ml/minute. The electron capture detector pulse interval was 30 milliseconds. For both compounds the calibration curves (constructed from the ratio of the peak area for the test compound to that of the internal marker) were linear from 60 to 900 ng/sample. Minimum sensitivity was 15 ng/sample for DMI and 60 ng/sample for PTP.

Drugs and reagents

The following drugs were used: desipramine hydrochloride and maproptyline (34276 Ba) (Ciba Geigy, Basel, Switzerland and Ciba Geigy, Milan, Italy); protritpyline hydrochloride (Merck Sharp & Dohme, Rahway, N.J., USA). All drug concentrations given in the present study are expressed as free bases. Ethyl urethane and the solvents (analytical grade) for determination of desipramine and protriptyline were purchased from Carlo Erba (Milan, Italy). Heptafluorobutyric anhydride was purchased from Fluka (Switzerland).

Results

Desipramine and protriptyline concentrations in rat plasma and heart

The theoretical time courses of DMI and PTP obtained by Wagner's method (1974) follow the continuous lines in Figure 1. Simulated values were confirmed experimentally by measuring plasma levels in the rat during 1.Q infusion (see Table 2) at 10, 40 and 70 minutes. Drug concentrations stabilized at a steady state during the second infusion after reaching peak levels at the end of the loading infusion. Plasma levels increased proportionally as the infusion rate was raised from 1.Q to 5.Q.

In the same experiments DMI and PTP were measured in atria and ventricles, where they accumulated extensively. Both drugs showed similar tissue to plasma ratios after 10 min of infusion, while at 40 and 70 min PTP tissue levels declined faster than those of DMI (Table 3). Higher plasma levels caused a proportional increase in the atria and ventricles (Figure 2).

Effects of desipramine and protriptyline on the ECG tracing of the rat: correlation with plasma-heart levels

As shown in Figure 3 heart rate increased at DMI plasma levels of 0.035 and 0.10 μg/ml; at plasma levels of 0.35, 0.70 and 1.05 μg/ml (steady state values) no changes in heart rate were detected; further increase in the plasma concentration from 1.0 to 4.0 μg/ml (peak levels), produced progressively greater bradycardia.

With PTP the tachycardia was considerably greater than with DMI (plasma concentrations from 0.04 to 1.2 μg/ml). Only following a peak level of 6 μg/ml did

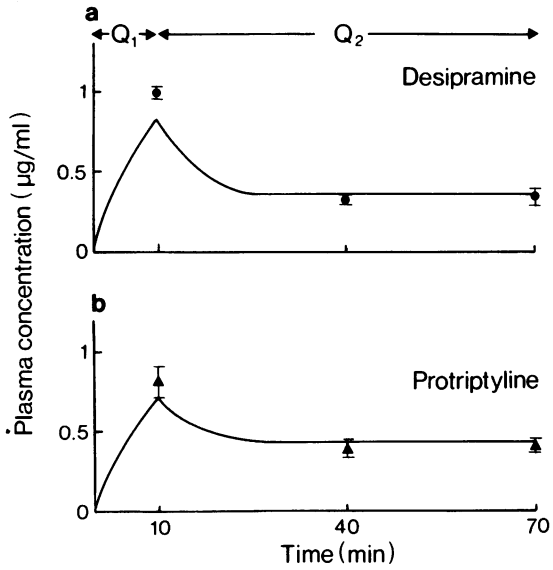

Figure 1 Time course of theoretical and experimental plasma concentrations of (a) desipramine and (b) protriptyline in the rat after two consecutive infusions of the drugs at the rate 1.Q (see Table 2). An initial infusion was given for 10 min then the rate was lowered and maintained for 70 minutes. The continuous line was drawn by a computer while experimental values were measured at 10, 40 and 70 min of infusion. Each point is the average of 6 (at 10 min) or 3 (at 40 and 70 min) determinations. Vertical lines represent s.e. mean.

PTP produce bradycardia. However, a depressant component became superimposed on the stimulation at peak plasma concentrations of 2.0 and 3.5 μg/ml.

Data obtained after 10 min of infusion (plasma concentrations range from 0.79 to 6.0 μg/ml) showed that cardiac alterations were all significantly correlated with plasma and heart levels. Figure 4 shows the relationship between heart rate changes and the concentrations of DMI and PTP in plasma and atria. PTP produces tachycardia at concentrations that are depressant for DMI and this difference persists with both plasma and atrial concentrations. During the steady state period (plasma concentrations range from 0.35 to 2.0 μg/ml) heart rate changes did not correlate with the corresponding plasma levels.

Besides the effect on the heart rate, DMI and PTP induced morphological alterations of the QRS complex, consisting of decreased voltage amplitude of the R wave and greater depth of the S wave, especially in lead 1. These alterations, which are expressed by a right rotation of the electrical axis of the heart, are plasma-level-dependent, and are more marked for DMI than for PTP (Figure 5, above).

Table 3 Desipramine (DMI) and protriptyline (PTP) concentrations in plasma, atria and ventricles during two consecutive infusions

Compound	*Time (min)*	*Plasma levels (μg/ml)*	*Atria levels (μg/g)*	*Ventricle levels (μg/g)*	*Atria/plasma*	*Ventricles/plasma*
Desipramine 1.Q*	10	1.0 ± 0.09	37.4 ± 3	43.77 ± 8	37.4 ± 3	43.7 ± 2
	40	0.32 ± 0.021	15.6 ± 2	10.1 ± 2	48.2 ± 7	30.7 ± 4
	70	0.30 ± 0.025	17.3 ± 1	11.5 ± 1	57.4 ± 5	38.5 ± 4
Protriptyline 1.Q*	10	0.79 ± 0.053	27.9 ± 2	30.9 ± 0.9	32.2 ± 3	37.7 ± 5
	40	0.37 ± 0.014	9.9 ± 0.6	5.8 ± 0.7	27.1 ± 2	18.0 ± 2
	70	0.39 ± 0.047	8.1 ± 1	4.2 ± 0.4	21.0 ± 2	11.5 ± 2

* The infusion rates are shown in Table 2.
All the results are the average of 6 (10 min) or 3 (40 and 70 min) determinations.

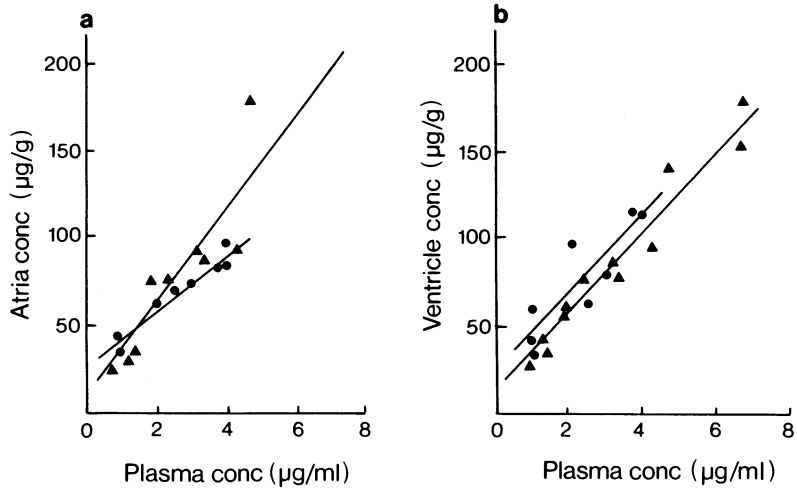

Figure 2 Correlation between plasma concentrations and (a) atrial or (b) ventricular concentrations of desipramine (●) and protriptyline (▲). All determinations were made at the end of the first infusion. The infusion rate ranged from 1.Q to 5.Q (see Table 2). (a) For desipramine $r=0.98$, $P<0.001$; for protriptyline $r=0.96$, $P<0.001$; (b) for desipramine $r=0.87$, $P<0.01$; for protriptyline, $r=0.98$, $P<0.01$.

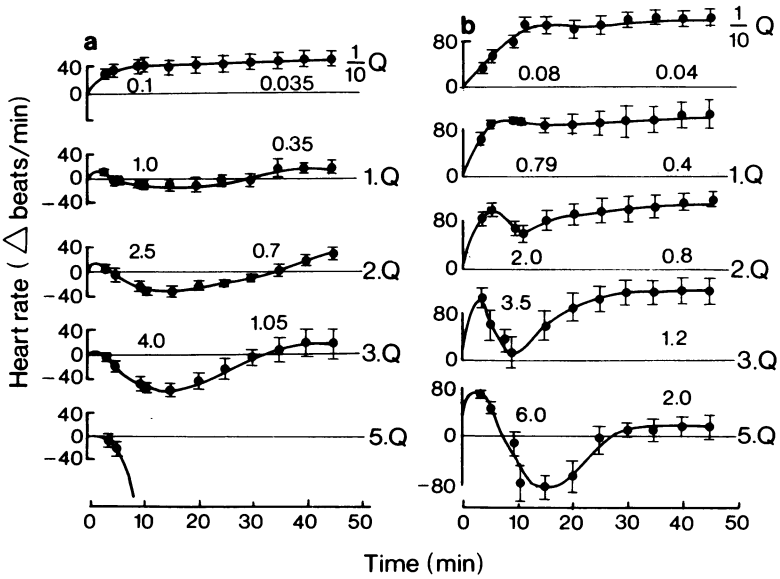

Figure 3 Time course of changes in heart rate produced by (a) desipramine and (b) protriptyline in anaesthetized rats given the two drugs at different infusion rates. 1.Q (and multiples) indicate infusion rates (set out in Table 2). Numbers inside the graph indicate the plasma levels of the drugs in μg/ml at 10 and 40 min during infusions. Groups of 4 or 5 rats were used for each infusion rate. Vertical lines represent s.e. mean.

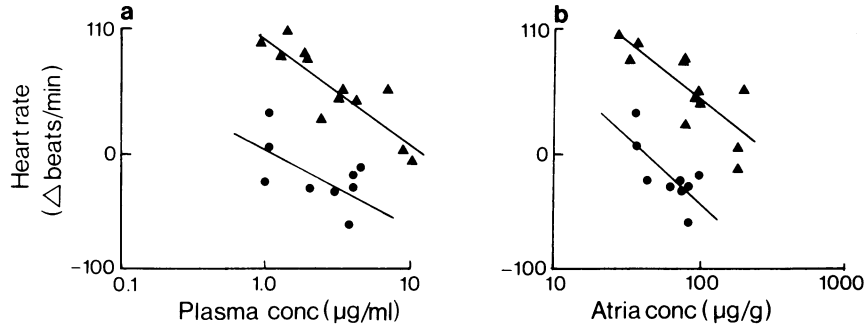

Figure 4 Correlation between (a) plasma or (b) atrial concentrations and changes in heart rate induced by desipramine (●) and protriptyline (▲). Values were obtained after 10 min infusion at rates ranging from 1.Q to 5.Q (set out in Table 2). The statistical significance of these correlations is given in Table 4.

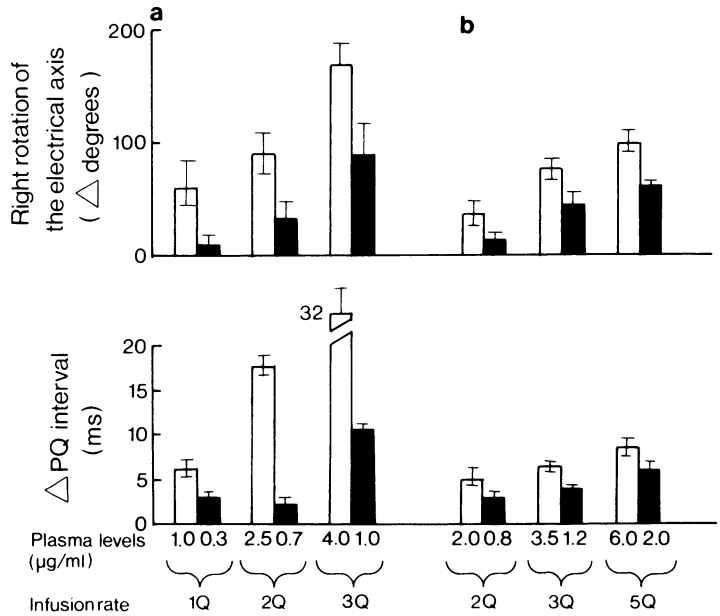

Figure 5 Effect of (a) desipramine and (b) protriptyline on the electrical axis of the heart (above) and the PQ interval (below) in anaesthetized rats given the two drugs at different infusion rates. 1.Q and multiples indicate the infusion rates (set out in Table 2). Plasma concentrations are also shown in μg/ml. Determinations were made at 10 min (open columns) and 40 min (solid columns) during the two consecutive infusions. Desipramine and protriptyline induced a right rotation of the electrical axis of the heart and prolongation of the PQ interval, expressed as the difference from preinfusion values. Groups of 4 or 5 rats were used for each infusion rate. Vertical lines represent s.e. mean.

DMI and, at the highest infusion rates, PTP, slowed atrioventricular conduction. The lengthening of the PQ interval was also plasma-level-dependent (Figure 5, below).

The *r* of correlation and *P* of significance of the relationship between plasma levels and cardiac alterations are shown in Table 4.

From the data obtained during the first 10 min of infusion, at different rates the plasma concentrations capable of inducing given ECG changes were determined. Forty degrees rotation of the electrical axis was caused by 1.35 μg/ml DMI and 1.75 μg/ml

PTP, while 2.2 μg/ml DMI and 3.6 μg/ml PTP lengthened the PQ interval by 20%.

DMI at plasma concentrations of 4 μg/ml caused marked alterations of the ECG tracing, i.e. ectopic beats, bigeminy, partial or complete atrioventricular blockade and repolarization disturbances. This concentration greatly depressed respiration, although this does not appear to be the direct cause of death because animals with or without artificial respiration died within the same time and had similar ECG alterations.

Discussion

The aim of this study was to develop a suitable model for testing the cardiotoxicity of tricyclic antidepressant agents, a severe side effect which limits the use of these compounds in clinical practice. The study was carried out in rats by mimicking, according to the model proposed by Wagner (1974), the situation that arises during repeated therapeutic treatment in man, i.e. an absorption peak after each drug intake followed by a steady state plasma concentration (Alexanderson, 1972; Garattini & Morselli, 1975).

Two widely used tricyclic antidepressant agents, desipramine (DMI) and protriptyline (PTP) were studied. The selected plasma levels, ranging from 0.035 to 6 μg/ml, comprised both therapeutic plasma levels (25 to 700 ng/ml according to Yates, Todrick & Tait, 1963; Åsberg, Crönholm, Sijöqvist & Tuck, 1971; Åsberg, 1974; Garattini & Morselli, 1975) and those found after an accidental overdose (600 to 2190 ng/ml: Spiker, Weiss, Chang, Ruwitch & Biggs, 1975).

In agreement with *in vitro* findings (Babulova, Bareggi, Bonaccorsi, Garattini, Morselli & Pantarotto, 1973; Franco *et al.*, 1976) tricyclic antidepressant agents accumulate in heart tissue at ratios of 21 and 57 for DMI and 11 and 43 for PTP. These ratios are lower than those reported for PTP in the rabbit by Elonen, Linnoila, Lukkari & Mattila (1975) but are comparable to those obtained by Curry (1964) and Rasmussen (1965) in human *post mortem* samples.

The constant ratio between heart and plasma levels indicates that plasma levels are highly predictive of the concentration of these drugs in heart tissue.

The cardiac effects of DMI and PTP analyzed were: (i) changes in the heart rate; (ii) right rotation of the electrical axis (Boissier *et al.*, 1965; Lechat *et al.*, 1969) and (iii) impairment of atrioventricular conduction shown by prolongation of the PQ interval (Fekete & Borsy, 1964; Baum, Shropshire, Rowles & Gluckman, 1971; Elonen *et al.*, 1974).

Both DMI and PTP caused a two-phase effect on heart rate. Relatively low plasma concentrations of both drugs increased the heart rate while higher plasma concentrations reduced it.

Table 4 Statistical analysis of the relationships between plasma concentrations of desipramine (DMI) and protriptyline (PTP) and their cardiac effects

Relationship between plasma levels and changes in:	*Time of infusion (min)*	*Desipramine*			*Protriptyline*		
		No. of rats	r	P	*No. of rats*	r	P
Heart rate	10	8	−0.68	<0.05	10	−0.77	<0.01
Electrical axis position		7	+0.84	<0.02	10	+0.87	<0.01
PQ interval		7	+0.7	<0.05	—	—	—
Heart rate	40	14	−0.1	>0.05	12	−0.15	>0.05
Electrical axis position		14	+0.70	<0.05	12	+0.82	<0.05
PQ interval		—	—	—	—	—	—

The increase in the heart rate attributed to anticholinergic effects and to inhibition of catecholamine uptake (Caincross & Gershon, 1962; Editorial, 1971) does not seem to be related to plasma levels. Tachycardia following tricyclic antidepressants is also frequent in man within the therapeutic range (Ayd, 1968; Editorial, 1971).

The depressant effect on heart rate, probably due to a membrane stabilizing effect (Greff & Wagner, 1969; Schmitt *et al.*, 1970; Marmo, Coscia & Cataldi, 1972; Elonen *et al.*, 1974), was directly related to peak plasma concentrations for both drugs. The lack of correlation during the steady state might be due to low plasma levels producing only tachycardia (PTP) or a combination of positive and negative chronotropic effects resulting in no change of the heart rate (DMI).

Another effect common to both DMI and PTP is the right rotation of the electrical axis of the heart. The threshold plasma concentrations for this effect were found to be 1.35 and 1.75 μg/ml for DMI and PTP respectively, and the intensity was directly related to plasma concentrations.

Finally, impaired atrioventricular conduction (prolongation of the PQ interval) was noted at a level of 2.2 μg/ml for DMI and 3.6 μg/ml for PTP. Impaired atrioventricular conduction was observed in man only following drug overdosage by Vohra (1974), Thorstrand (1974) and by Spiker *et al.* (1975).

Our results indicate that DMI and PTP affect the AV conduction at plasma concentrations above the therapeutic levels. However, the threshold concentrations of DMI and PTP inducing cardiac alterations might be substantially lowered if cardiac function is already impaired or in the presence of other stimuli. Although this suggestion has been made by several authors (Jefferson, 1975) there are other reports with no evidence to support this suggestion (Report from Boston Collaborative Drug Surveillance Program, 1972).

In this investigation and within the limits of the plasma concentrations tested, DMI appeared to be more cardiotoxic than PTP. Although at comparable peak plasma levels, similar concentrations of the two drugs were found in the heart, during the steady state twice as much DMI accumulates as PTP (Table 4). Therefore, as well as its different intrinsic activity, different availability to cardiac tissue may also contribute to making DMI more cardiotoxic than PTP.

The experimental model presented here may be of interest for exploring the cardiotoxicity of other tricyclic antidepressants *in vivo* and for studying factors which may aggravate or inhibit this toxicity. The results obtained could also be of clinical importance since extrapolation is facilitated by the fact that the toxic doses of tricyclic antidepressant drugs are expressed in terms of peak or steady state plasma concentrations.

R.G. was an IBM Italia Fellow.

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