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PLASMA NORTRIPTYLINE AND CARDIAC RESPONSES IN YOUNG AND OLD RATS

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1 The relationship between plasma concentrations and cardiac effects of nortriptyline was studied in anaesthetized young and old rats.

2 Nortriptyline was administered by two consecutive intravenous infusions which resulted in a peak plasma concentration followed by steady state values. Increasing infusion rates were followed by proportional increases in the drug plasma concentrations ranging from 0.15 to 6.0 μg/ml.

3 In young rats, nortriptyline induced an increase in the heart rate, a right rotation of the electrical axis and a prolongation of the PQ interval. Heart rate changes were not correlated with nortriptyline plasma concentrations, while significant correlations were found for the other two parameters. Plasma concentrations inducing 20% increase of the PQ interval and 40 degrees rotation of the electrical axis were 1.65 and 1.69 μg/ml respectively. Arrhythmias occurred at concentrations higher than 5.2 μg/ml.

4 Nortriptyline caused more severe cardiac effects in old than in young animals. However, plasma concentrations of nortriptyline in old rats were two to five times higher than those found in young rats at similar infusion rates. A higher concentration of the drug at its sites of action seems to be responsible for the more severe cardiac toxicity of nortriptyline observed in old rats.

Introduction

The cardiac effects of tricyclic antidepressant agents have been well documented both in cases of accidental overdosage (Vohra, 1974; Thorstrand, 1974) as well as during chronic therapy (Coull, Crooks, Dingwall-Fordyce, Scott & Weir, 1970; Editorial 1971). ECG changes include tachycardia, arrhythmias, widening of the PQ and QRS complex, ST and T wave abnormalities. It has also been shown that antidepressant drugs aggravate cardiac disease especially in elderly people suffering from hypertension and atherosclerosis (Muller, Goodman & Bellet, 1961; Kristiansen, 1961; Skou, 1962; Thompson, 1973).

According to some authors (Alexanderson & Sjöqvist, 1971; Spiker, Weiss, Chang, Ruwitch & Biggs, 1975) there is a positive correlation between cardiac side effects and plasma concentrations of the drugs in humans. ECG alterations were also observed in laboratory animals treated with antidepressant drugs. In the rat, desipramine and protriptyline prolong the PQ interval, depress the heart rate and cause rotation to the right of the heart electrical axis. All these effects are dependent on the plasma concentrations of the drugs (Bianchetti, Bonaccorsi, Chiodaroli, Franco, Garattini, Gomeni & Morselli, 1977).

The present paper examines the possibility that nortriptyline may be a more cardiotoxic agent in the old than in the young rat. Well defined cardiac effects were related to plasma concentrations in both groups of animals in order to check whether a more marked cardiotoxicity in old animals could be attributed to altered sensitivity to the drug, or to greater availability of the drug at its sites of action.

Methods

Experimental procedure

Young (7 weeks old, 200–250 g body wt.) and old (2 years old, 700–900 g body wt.) rats supplied by Charles River (Italy) were anaesthetized with ethyl urethane at doses of 1.3 and 1.0 g/kg respectively. The femoral vein and left carotid artery were cannulated and the animals were allowed to rest for 30 minutes. Nortriptyline was administered by two consecutive intravenous infusions. The first infusion lasted 10 min (Q_1) and was followed by a second one (Q_2) at a

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Table 1 Pharmacokinetic parameters of nortriptyline calculated from the disappearance curve of the drug after intravenous injection of 5 mg/kg in anaesthetized young rats. The disappearance curve fitted a two compartment open model

Kel	0.03306 min^{-1}
K_{12}	0.1805 min^{-1}
K_{21}	0.1119 min^{-1}
α	0.31366 min^{-1}
β	0.01179 min^{-1}
V_1	4.2918 1/kg
$(T_{\frac{1}{2}})_\beta$	58.78 min
TBCl	0.13769 1/kg min

Kel: first order elmination rate constant; K_{12} and K_{21}: first order distribution rate constants between the two compartments; α and β: disposition rate constants; V_1: apparent volume of the central compartment. $(T_{\frac{1}{2}})_\beta$: apparent half life of the β-phase; TBCl: total body clearance.
The infusion rate 1.Q calculated from Wagner's equation (1974) was as follows: 369 µg/kg for the first 10 min (Q_1); 35 µg/kg for the rest of the infusion (Q_2). The other rates were multiples of 1.Q.

slower rate, by which steady state plasma levels were reached and maintained. The pharmacokinetic parameters obtained after a bolus injection of nortriptyline (see Table 1) were used to calculate the infusion rates according to Wagner's equations (1974). The infusion rates ranges from 1/3 ($Q_1 = 121$ µg kg^{-1} min^{-1} and $Q_2 = 11.6$ µg kg^{-1} min^{-1}) to 8 times Q ($Q_1 = 2952$ µg kg^{-1} min^{-1} and $Q_2 = 280$ µg kg^{-1} min^{-1}). A Digital PDP 11/40 computer was used for calculations. The intravenous infusions of nortriptyline were delivered by a constant infusion pump (Braun, Germany) at the rate of 0.05 ml/minute. Because of the poor solubility of the drug in water the rate was increased to 0.1 or 0.2 ml/min for the highest concentrations of nortriptyline. Solutions were heated to 37°C just before entering the femoral vein. During infusions, the three bipolar standard limb leads of the electrocardiogram were recorded on 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 at fixed intervals. QRS and QT intervals could not be quantified since the lack of isoelectric tract and the difficulty in determining the end of the T wave in the rat ECG complex do not permit accurate measurements of these parameters. The position of the electrical axis of the heart was determined following the procedure described by Goldman (1970).

Blood was collected from the cannulated carotid artery in heparinized tubes and centrifuged for 30 min at 2000 rev/min at 4°C. Three samples of 0.5 ml were withdrawn from old animals, at 10, 30 and 60 min

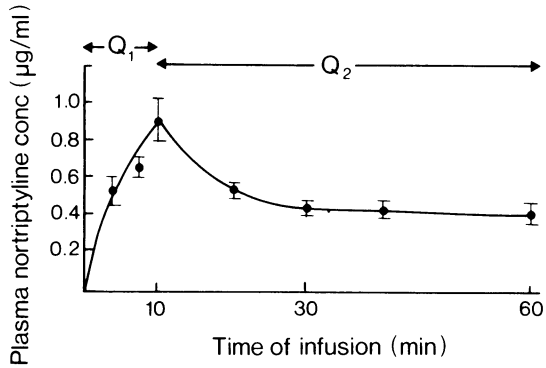

Figure 1 Time course plasma levels of nortriptyline in young rats given two consecutive infusions (Q_1 and Q_2) of the drug at the rate 1.Q (see Table 1 for corresponding values). Each point is the average of 3–5 determinations. Vertical lines show s.e.

after starting infusion. From young rats, blood was collected only once at the end of the experiment. When rats were killed their hearts were removed, blotted with filter paper and weighed. All specimens were kept frozen until analysis.

Gas-chromatographic determination of nortriptyline in tissue samples

Atria and ventricles were homogenized with glass homogenizers in 2.5 and 8 ml 0.1 N HCl respectively. Nortriptyline in biological samples was quantitatively determined by electroncapture gas-chromatography following the procedure described for desipramine and protriptyline (Bianchetti *et al.*, 1977). The overall recovery was 75%. The calibration curve, constructed from the ratios of the peak areas of the test compound to those of the internal marker maproptyline, was linear from 50 to 400 ng/sample. Minimal sensitivity was 50 ng/sample.

Drugs and reagents

Nortriptyline hydrochloride was supplied by Recordati, Milan, Italy; maprotyline (34276 Ba) was supplied by Ciba Geigy, Basel, Switzerland. All drug concentrations are expressed as free bases. Ethyl urethane and the solvents (analytical grade) used for nortriptyline determinations were purchased from Carlo Erba, Milan, Italy.

Results

Nortriptyline plasma and heart concentrations in young and old rats

The time course of the plasma levels of nortriptyline given to young rats by two consecutive infusions at

the rate 1.Q is shown in Figure 1. Plasma levels progressively increased during the first infusion (Q_1), then rapidly declined and stabilized at a steady state during the second infusion (Q_2).

When infusion rates were decreased to 1/3.Q or increased up to 8.Q, plasma levels at 10 and 60 min increased proportionally (Table 2). Heart concentrations measured at the same times showed that nortriptyline was taken up in the heart by a factor of 12–23 times compared to the plasma concentrations.

Old rats were given nortriptyline at the infusion rate 2.Q and 3.Q. Their plasma concentrations were determined at 10, 30 and 60 min from the beginning of infusion. Table 3 shows the plasma and heart levels found in each animal. At both infusion rates the concentrations of the drug in plasma and heart were three to five times higher than in young rats. Four rats out out of seven survived after the first 10 min of infusion. In these animals, after a very high peak, plasma concentrations rapidly declined within 30 min of infusion, then slightly increased with time till 60 minutes. Nortriptyline uptake by the heart of old rats was not different from that in the heart of young rats, as indicated by similar heart/plasma ratios in both groups of rats.

Cardiac effects of nortriptyline in young rats

In young rats nortriptyline infusions induced marked changes in the ECG tracing. Some of these alterations, i.e. heart rate changes, rotation of the electrical axis to the right and prolongation of the PQ interval, were plotted with the corresponding plasma concentrations and tested for correlation at 10 and 60 min of infusion. Except for a mild increase in heart rate (+23 beats/min after 60 min), no alterations to the ECG tracing were induced by saline infusion.

In most of the animals nortriptyline increased the heart rate at plasma concentrations ranging from 0.1 to 6.0 μg/ml. This increase was greater after 60 min than after 10 min of infusion, and was not plasma concentration-dependent (Figure 2).

The right rotation of the electrical axis and the prolongation of the PQ interval induced by nortriptyline were significantly correlated with plasma concentrations. Figures 3 and 4 show that the slopes of the regression lines after 60 min of infusion are significantly less steep than those obtained after 10 minutes. The threshold plasma concentrations of nortriptyline causing 40 degrees rotation of the electrical axis and a 20% increase of the PQ interval,

Table 2 Plasma and heart concentrations of nortriptyline in young rats at 10 and 60 min during nortriptyline infusions

Infusion rates	*Plasma (μg/ml)*		*Heart (μg/ml)*		*Heart/plasma ratio*	
	10 min	*60 min*	*10 min*	*60 min*	*10 min*	*60 min*
1/3.Q	0.32 ± 0.06	0.15 ± 0.01	5.73 ± 0.27	1.91 ± 0.33	19.0 ± 4.0	12.6 ± 2.5
1.Q	0.90 ± 0.12	0.40 ± 0.02	12.92 ± 0.65	5.02 ± 0.63	15.5 ± 2.4	12.8 ± 2.0
2.Q	1.71 ± 0.16	0.86 ± 0.07	24.81 ± 1.00	13.39 ± 1.62	14.7 ± 1.5	17.0 ± 3.2
3.Q	2.26 ± 0.16	1.35 ± 0.40	38.69 ± 3.26	21.28 ± 1.80	17.2 ± 1.7	16.0 ± 1.0
4.Q	3.02 ± 0.18	1.70 ± 0.18	63.84 ± 8.44	26.52 ± 2.77	21.2 ± 3.9	16.5 ± 2.0
5.Q	3.35 ± 0.31	2.57 ± 0.20	74.88 ± 5.92	32.34 ± 2.24	23.2 ± 2.5	12.0 ± 1.7
7.Q	5.20 ± 0.50	3.30 ± 0.28	not measured		–	–
8.Q	6.0 ± 0.55	3.70 ± 0.31	not measured		–	–

Table 3 Individual plasma and heart concentrations of nortriptyline in old rats at 10, 30 and 60 min during nortriptyline infusion

Infusion rates	*Rat No.*	*Plasma (μg/ml)*			*Heart (μg/g)*		*Heart/plasma*	
		10 min	*30 min*	*60 min*	*10 min*	*60 min*	*10 min*	*60 min*
2.Q	1	5.30	1.20	n.d.				
	2	4.50	1.05	1.70		26.7		15.7
	3	5.85	1.65	2.25		53.7		22
	4	6.75	2.05	2.65		45.6		17
3.Q	5	11.10	died at 10 min		121.8		11	
	6	8.40	died at 10 min		222.1		26	
	7	9.45	died at 10 min		177.0		18.7	

Rat no. 3 showed AV dissociation and arrhythmias before nortriptyline infusion.
n.d. = not measured.

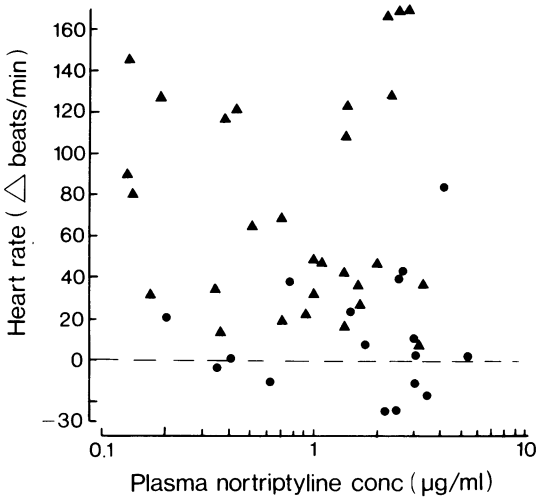

Figure 2 Relationship between plasma concentrations of nortriptyline (abscissa scale) and changes in heart rate (ordinate scale) in young rats at 10 (●) and 60 (▲) min of nortriptyline infusions given at the rates 1/3.Q–8.Q. Regression coefficient for (●)=0.108 and for (▲)=0.103; $P>0.05$ for both.

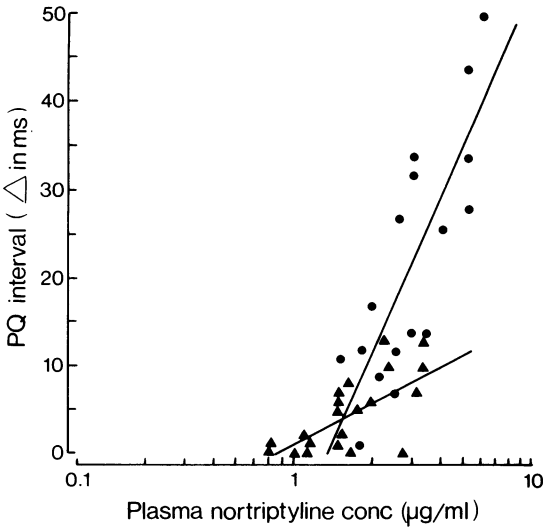

Figure 3 Relationship between plasma concentrations of nortriptyline (abscissa scale) and the shift to the right of the electrical axis of the heart (ordinate scale) in young rats at 10 (●) and 60 (▲) min of nortriptyline infusions given at the rates 2.Q–8.Q. Preinfusion electrical axis values were 60°. The correlation lines are significantly different: for (●) $r=0.73$, $P<0.01$, a=−979 (490–1469), b=311 (167–455); for (▲) $r=0.61$, $P<0.01$, a=−275 (100–451), b=44 (39–149).

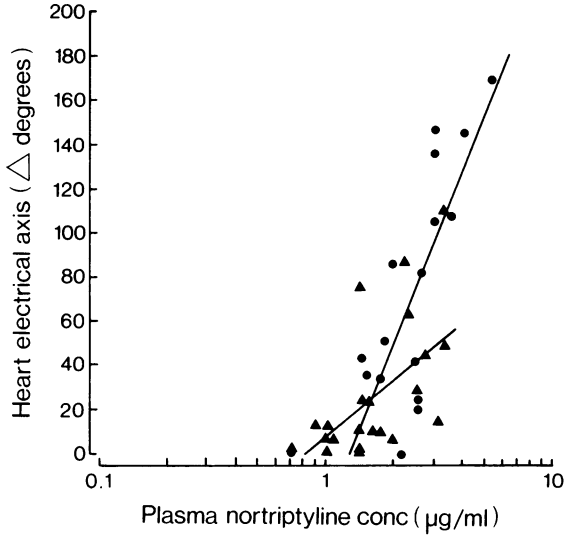

Figure 4 Relationship between plasma concentrations of nortriptyline (abscissa scale) and the prolongation of the PQ interval (ordinate scale) in young rats at 10 (●) and 60 (▲) min of nortriptyline infusion given at the rates 2.Q–8.Q. Preinfusion PQ interval values were 54.7 ± 4 ms. The two correlation lines are significantly different: for (●) $r=0.84$, $P<0.001$, a=−204 (132–276), b=64 (22–43); for (▲) $r=0.70$, $P<0.01$, a=−44 (21–67), b=15 (4–11).

calculated from the equation of the regression lines (10 min), were 1.65 and 1.69 μg/ml respectively. A significant correlation between these two last ECG alterations and heart nortriptyline levels was also found as might have been expected from the constant ratio of nortriptyline concentrations in tissue and plasma.

Arrhythmias (extrasystoles, bigeminism, AV dissociation and ventricular tachycardia) occurred in young rats at peak plasma levels higher than 5.2 μg/ml at the infusion rate 7.Q and 8.Q.

Cardiac effects of nortriptyline in old rats

The basal ECG tracing of old rats showed some characteristics worthy of mention. The heart of these animals (246 beats/min) was slower than in young animals (314 beats/minute). Hypertrophy of the left ventricle in old animals was indicated by the position of the electrical axis (between 0° and 30°) and then confirmed by postmortem anatomical examination. Atrioventricular conduction was not significantly different in young (54.75 ± 4 ms) and old rats (61.6 ± 6 ms) while the QRS complex in three out of seven old rats was widened. Atrioventricular dissociated and extrasystoles were noted in the ECG tracing of one old rat out of seven.

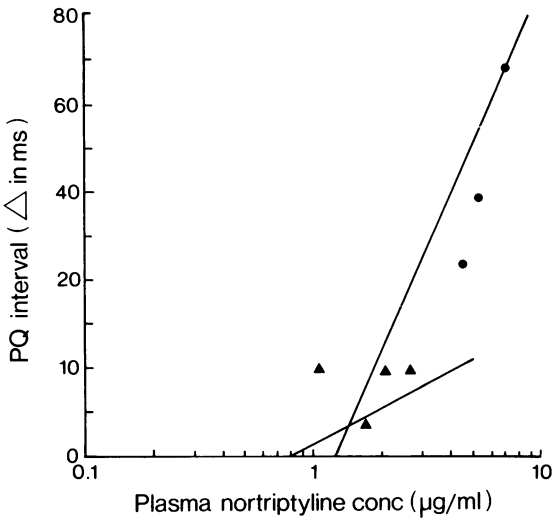

Figure 5 Relationship between plasma concentrations of nortriptyline (abscissa scale) and the prolongation of the PQ interval (ordinate scale) in old rats at 10 (●) and 60 (▲) min of nortriptyline infusion given at the rate 2.Q and 3.Q. Preinfusion PQ values were 61.6 ± 6 ms. The small number of animals prevented statistical analysis of these data. For comparison the two correlation lines obtained in young rats are shown.

Nortriptyline infusions (2.Q and 3.Q) induced marked alterations in the ECG tracing of old rats. The heart rate slowly increased in rats given the drug at infusion rate 2.Q while arrhythmias (extrasystoles, bigeminism, AV dissociation and ventricular tachycardia) were observed in rats treated at infusion rate 3.Q. An exception was rat No. 3 (Table 3) which was arrhythmic before the start of the experiment and did not show any worsening of the ECG tracing during nortriptyline infusion. In rat No. 4 arrhythmias appeared after about 10 min of infusion, at a plasma level of 6.75 μg/ml, and disappeared when plasma concentrations decreased during the second infusion. In rat Nos 5, 6 and 7, peak plasma levels ranged from 8.40 to 11.0 μg/ml; arrhythmias appeared between the 3rd and 5th min of infusion and the animals died from heart blockade within 10 minutes.

The electrical axis position was not altered at infusion rate 2.Q. At rate 3.Q the early appearance of arrhythmias masked any alteration of this parameter. The PQ interval increased in all the animals. When possible, this increase was related with corresponding plasma concentrations as shown in Figure 5, where the correlation lines calculated for young rats are provided for comparison. Although statistical analysis could not be carried out because of the limited number of observations, it seems likely that similar plasma concentrations of nortriptyline increase the PQ interval in young and old rats to much the same extent.

Discussion

The cardiac effects of nortriptyline were studied in the rat by analyzing the relationship of drug plasma concentrations with three main effects: (1) changes in the heart rate; (2) deviation of the electrical axis and (3) prolongation of the PQ interval.

Plasma concentrations of nortriptyline used in the present experiments ranged from 0.15 μg/ml up to 11.0 μg/ml, thus covering both the therapeutic and the overdose limits found in humans (Asberg, Crönholm, Sjöqvist & Tuck, 1971; Asberg, 1974; Garattini & Morselli, 1975; Spiker *et al.*, 1975).

These concentrations were measured during nortriptyline infusion at 10 min (peak levels) and at 60 min (steady state levels). Heart determinations of nortriptyline, made at the same times, indicate that nortriptyline accumulation in cardiac tissue was greater by a factor of 12–23, thus showing behaviour rather similar to other tricyclic antidepressant drugs such as protriptyline and desipramine (Bianchetti *et al.*, 1976). Since this ratio was constant at any infusion rate, at any time and in both young and old animals, we assumed that plasma concentrations were an adequate parameter to relate with the cardiac effects induced by the drug. Nortriptyline, at plasma concentrations ranging from 0.15 to 6.0 μg/ml, mainly provoked an increase in heart rate, which was not plasma concentration-dependent, similar to the tachycardia induced in man by plasma levels ranging from 0.02 to 0.295 μg/ml (Freyschuss, Sjökvist, Tuck & Asberg, 1970). Only in a few rats, at the highest plasma concentrations, nortriptyline caused a feeble, inconsistent depressant effect on the heart rate.

Heart rate changes induced by tricyclic antidepressant drugs are supposed to result from the combination of cholinolytic, sympathomimetic and membrane stabilizing effects, (Cairncross & Gershon, 1962; Editorial, 1971; Elonen, Mattila & Saarnivaara, 1974; Barth & Muscholl, 1974). The prevalence of one effect over the others may be characteristic of each drug: nortriptyline, while sharing with desipramine and protriptyline the tachycardia effect, seems not to have the plasma concentration-related depressant effect on heart rate shown by the other compounds (Bianchetti *et al.*, 1977).

The two other cardiac parameters, rotation of the electrical axis and prolongation of the PQ interval, were correlated with plasma concentrations of nortriptyline ranging from 1.5 μg/ml to 6.0 μg/ml. Nortriptyline seems similar to desipramine but is more potent than protriptyline if we compare the threshold plasma concentrations producing 40° rotation of the electrical axis and 20% increase of the PQ interval.

These are 1.65 and 1.69 μg/ml for nortriptyline, 1.35 and 1.75 μg/ml for desipramine and 2.2 and 3.6 μg/ml for protriptyline (Bianchetti *et al.*, 1977). Apart from the threshold values, the correlations need further attention. The steeper relationship during the loading infusion (10 min) in comparison with that during the steady state (60 min) indicates that the cardiac alterations decrease with time of exposure to the drug, when the animal had been primed with relatively higher concentrations of nortriptyline. The mechanism of this decreasing sensitivity is not known but it recalls the tolerance that humans develop to some of the side effects of these drugs during chronic treatment (Alexanderson & Sjöqvist, 1971; Asberg, 1974; Burrows, Scoggins, Turececk & Davies, 1974).

Despite the very small number available, old rats gave useful information on the sensitivity of their heart to nortriptyline. The drug was much more cardiotoxic in old than in young rats, given equal doses. However, this difference disappeared when well defined pharmacological end points were related to similar plasma concentrations of nortriptyline in the two groups: arrhythmias occurred in old rats at plasma concentrations higher than 5.2 μg/ml, which was the threshold value for the onset of similar arrhythmias in young rats. Furthermore, the relationship between plasma levels and prolongation of the PQ interval was strikingly similar in both groups of animals. Although old rats showed signs of altered conduction (as indicated by the widened QRS interval) and increased vascular resistance (as suggested by the hypertrophy of the left ventricle), there was no evidence of their heart being supersensitive to nortriptyline. Slower drug metabolism and excretion, described in old animals for other classes of drugs (Kato & Takanaka, 1968; Klinger, 1969), is probably responsible for the higher plasma concentrations and therefore for the apparently higher toxicity of nortriptyline in old rats.

As already pointed out in the introduction, some authors have suggested that old people are more sensitive than young people to the cardiotoxic effects of antidepressant drugs. Since there is no information on the plasma levels of tricyclic antidepressant drugs in old patients, the more severe cardiotoxicity, might in part result from age-related alterations in drug metabolism and excretion.

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