Br. J. Pharmac. (1979), **65**, 331–338

THE RELATIVE TOXICITY OF AMITRIPTYLINE, IMIPRAMINE, MAPROTILINE AND MIANSERIN IN RABBITS *in vivo*

I.E. HUGHES & SALWA RADWAN

The Department of Pharmacology, Medical and Dental Building, The University, Leeds LS2 9JT

1 Conscious or barbiturate-anaesthetized rabbits were slowly infused intravenously with solutions of amitriptyline, imipramine, maprotiline or mianserin, usually until death occurred.

2 Amitriptyline produced death at the lowest dose, imipramine and maprotiline were intermediate while much higher doses of mianserin were required.

3 Convulsions were induced by the antidepressants in all conscious rabbits and the order of potency of the drugs in producing this effect was amitriptyline $\geqslant$ imipramine > maprotiline $\gg$ mianserin.

4 All four drugs produced a reduction in heart rate and blood pressure in the anaesthetized rabbits and the order of potency in this respect was amitriptyline > imipramine > maprotiline > mianserin.

5 All four drugs produced significant changes in the ECG compared with control rabbits. The P-R interval was lengthened (potency order amitriptyline > imipramine $\geqslant$ maprotiline $\gg$ mianserin) and the QRS complex was widened (potency order amitriptyline > imipramine $\geqslant$ maprotiline $\gg$ mianserin).

7 It is concluded that all four drugs show the toxic effects classically associated with tricyclic antidepressants but the relative toxicity amongst these agents varies considerably and is in the order amitriptyline > imipramine > maprotiline $\gg$ mianserin.

Introduction

Poisoning by tricyclic antidepressants is characterized by two major groups of symptoms; those arising from central nervous system toxicity (coma, convulsions) and those arising from cardiovascular toxicity (particularly ECG changes). Although signs of toxicity may be seen both after therapeutic doses and after overdose, the latter situation is of particular importance since suicidal tendencies are often considered to be part of depressive illness and there is evidence for increasing use of antidepressants in self poisoning (OPCS, 1976).

The cardiovascular toxicity of the antidepressants is seen as changes in blood pressure and heart rate and in a variety of cardiac dysrhythmias. These have been reported to include sinus tachycardia, bradycardia, asystole, conduction defects and ventricular and supraventricular dysrhythmias (Rasmussen & Kristiansen, 1963; Thorstrand, 1974; 1976; Jefferson, 1975; Vohra, Burrows & Sloman, 1975). Tricyclic antidepressants are also known to increase the width of the QRS complex (Thorstrand, 1976; Bigger, Giardina, Perel, Kantor & Glassman, 1977) and to lengthen the P-R interval (Burrows, Vohra, Hunt, Sloman, Scoggins & Davies, 1976; Ziegler, Co & Biggs, 1977).

We have previously reported (Harper & Hughes, 1977) an assessment in perfused rabbit hearts of the relative cardiotoxicity of amitriptyline and two newer agents, maprotiline and mianserin (Itil, Polvan & Hsu, 1972; Fell, Quantok & van der Burg, 1973; Mâitre, Waldmeier, Greengrass, Jaekel, Sedlacek & Delini-Stula, 1975; Reiss, Dubey, Fünfgeld, Imhof, Hürzeler, Matussek, Rajagopalan, Raschdorf & Schmid, 1975). However, the perfused heart is performing in a non-physiological environment and is isolated from normal neuronal and hormonal influences and we have therefore re-assessed the relative toxicity of four antidepressants in both conscious and anaesthetized rabbits.

Some of the results described in this paper have previously been communicated to the International Workshop on Mianserin held in Amsterdam in October, 1977.

0007-1188/79/020331-08 $01.00

Methods

Conscious rabbits

New Zealand White rabbits of either sex (1.7 to 3.0 kg) were anaesthetized with sodium pentobarbitone (30 to 50 mg/kg; i.v.). The fur at the front of the neck was shaved, a longitudinal incision was made just below the larynx and a large spinal needle was used to make a subcutaneous tunnel from the operative area to emerge between the scapulae. The right common carotid artery and the right jugular vein were exposed and ligated. An arterial canula (vinyl tube, o.d. 1.17 mm) was passed through the subcutaneous tunnel, inserted into the carotid artery, pushed down until the tip lay close to the aorta and stitched to the sternocephalicus muscle. Similarly, a cardiac electrode (18 cm of 24 s.w.g. tinned copper wire covered with polythene tubing except for the final 1 mm and terminating in a pear shaped blob of polished solder) was inserted into the jugular vein and pushed down until the uninsulated tip was located in or near the right atrium. The skin incision was closed with cotton ligatures, covered with Acriflex Antiseptic Cream and protected with a loose dressing. Small circular areas of skin on the dorsal limb surfaces were shaved and treated with a depilatory cream in preparation for the surface ECG electrodes which were attached later. Ampicillin (100 mg, i.p.) was administered and a 1:50 dilution of Heparin Injection B.P. in 0.9% w/v NaCl solution (saline) was infused slowly through the carotid cannula for 2 h (total dose 2400 u). The skin incision between the scapulae was closed round the exteriorised carotid canula and cardiac electrode which were secured to the back with adhesive tape. The rabbits were kept warm, in a quiet darkened cage and handled very gently until they had completely recovered from the anaesthetic (2 to 4 h). Failure to do this results in high mortality. Some 24 h later rabbits were placed in a restraining box, the surface ECG electrodes were attached (RA, RL, LL) and secured with adhesive tape.

Anaesthetized rabbits

Rabbits as above were anaesthetized with a mixture of a 2% solution of sodium phenobarbitone (200 mg/kg) and a 1% solution of sodium pentobarbitone (Sagital; 5 mg/kg) infused at a rate of 66.1 ml/h through the marginal ear vein, supplemented as necessary with 10 to 35 mg/kg of sodium pentobarbitone given intravenously in divided doses to establish adequate surgical anaesthesia. A tracheal cannula was inserted and respiration maintained artificially (46 strokes/min of 12 ml/kg). A right common carotid arterial cannula and a cardiac electrode were inserted as described above except that exteriorisation was not carried out. Needle electrodes were used to obtain the ECG records.

General procedure

In all animals blood pressure was measured from the carotid cannula with a Bell & Howell pressure transducer (4-327-L221) and recorded on a Devices MX2 recorder. Heart rate was derived from the pulsatile blood pressure record with a Devices Instantaneous Rate-meter and was also displayed on the Devices recorder. The ECG potentials (standard lead II) and the potentials from the cardiac electrode (C, RA, RL) were amplified (Devices 3543 preamplifier), displayed continuously on a Lan-scope (419A) and recorded when necessary on a Mingograph ink writer (Elema-Schönander EM34). The signals were also sent to a storage device (Datalab Transient Recorder DL901) so connected that events seen on the Lan-scope could be captured at will, stored, displayed repeatedly on a slave oscilloscope (Solatron CX1441) and permanent records made on the Mingograph recorder. In this way brief dysrhythmias seen on the Lan-scope could be captured and permanent records obtained on expanded scale without the need to run the recorder constantly at high speed. Animals were allowed to settle down for 30 min, resting values for heart rate and blood pressure were obtained and ECG recordings were made from which the P-R interval and the width of the QRS complex were extracted. In conscious rabbits standard lead II ECG records were severely distorted by movement artifacts and all measurements were therefore made on records from the cardiac electrode. Since the start of the P wave was sometimes poorly defined the P-R interval was measured from the peak of the P wave to the peak of the R wave. The S and T waves were also poorly differentiated and the width of the QRS complex was measured from the first identifiable deflection of the QRS complex to the isoelectric point after the R wave. In anaesthetized animals the P wave was always well defined in lead II and the P-R interval was measured from the start of the P wave to the peak of the R wave and the width of the QRS complex as the time from the first identifiable deflection of the QRS complex to the end of the S wave.

Antidepressants were infused through a cannula in the marginal ear vein from a slow infusor (Braun Melsungen 871100) at a rate of 12 ml/h. Values for the recorded parameters were noted every 15 min, additional ECG records were taken as required and, in the conscious animals, changes in behaviour were noted, particularly the dose of antidepressant required to produce the first convulsive episode and the dose at which convulsions became repeated and severe. In-

fusion was continued until the death of the animal or for 5 h whichever was shorter.

The antidepressants investigated were dissolved in saline containing 3% propylene glycol except for mianserin which was dissolved in hot saline and the infusion apparatus was positioned within a warming coil so that the solution was delivered to the animal at 40°C.

Drugs

Amitriptyline hydrochloride (Roche), ampicillin sodium (Beecham), heparin injection B.P. (5000 u/ml; Evans), imipramine hydrochloride (Geigy), maprotiline methane sulphonate (Ciba), mianserin hydrochloride (Organon), pentobarbitone sodium (Sagital, M & B), phenobarbitone sodium (BDH) and propylene glycol (BDH) were used.

Statistical procedures

Where appropriate, all results are presented as mean ± standard error of the mean (mean ± s.e. mean) and tests for statistical significance were made by Student's *t* test unless otherwise stated.

Results

Choice of doses

Initial experiments were carried out in conscious rabbits to determine the dose rates necessary to produce death of the animals within the period 2 to 4 h. From these initial experiments dose rates were chosen as follows: amitriptyline 10, imipramine 18, maprotiline 25 and mianserin 35 mg kg^{-1} h^{-1}.

In anaesthetized animals the same dose rates were used initially and proved satisfactory except in the case of mianserin. At 35 mg kg^{-1} h^{-1} all 5 animals survived the 5 h infusion period. The dose rate of mianserin was therefore increased to 45 mg kg^{-1} h^{-1} and this proved satisfactory.

Control experiments

Two different vehicles were used for infusion of the antidepressants and three conscious and three anaesthetized animals were infused with each vehicle for 5 h. The minor changes in blood pressure, heart rate, P-R interval, width of the QRS complex and general behaviour which occurred were not significantly different in the groups of animals receiving the different vehicles ($P > 0.3$ in every case) and the data have therefore been combined to give one control group of 6 conscious rabbits and a second control group of 6 anaesthetized rabbits. All tests for statistical significance against control values refer to the appropriate combined control group.

Imipramine was soluble in both vehicles and was infused at 20 mg kg^{-1} h^{-1} in each vehicle into separate conscious rabbits. In hot saline and in saline plus 3% propylene glycol the lethal doses (20 and 25 mg/kg respectively), the doses required to produce the first convulsive episode (17.6 and 15 mg/kg) and the doses at which convulsions became repeated and severe (20 and 22.6 mg/kg) were not markedly different.

Lethal doses

The lethal dose for each of the antidepressants in the conscious and in the anaesthetized animals are shown in Table 1. In both cases mianserin was less toxic than amitriptyline or maprotiline ($P < 0.01$). In conscious animals the lethal doses of imipramine and maprotiline were not significantly different ($P > 0.2$) while amitriptyline was most toxic ($P < 0.02$). However, in the anaesthetized animals imipramine was more toxic than maprotiline ($P < 0.02$) while the lethal doses of amitriptyline and imipramine were not significantly different ($P > 0.2$).

Production of convulsions

Anaesthetized animals did not show convulsive episodes but all conscious rabbits (except controls) developed convulsions at some time during the infusion

Table 1 Lethal doses (mg/kg) of the antidepressants in conscious and in anaesthetized rabbits

	Amitriptyline	*Imipramine*	*Maprotiline*	*Mianserin*
Conscious	36.9 ± 3.8† (5)	72.9 ± 10.8 (6)	57.4 ± 6.0 (6)	92.7 ± 4.0 (6)
Anaesthetized	25.7 ± 3.6† (6)	40.3 ± 10.4 (7)	78.6 ± 6.6 (6)	158.9 ± 25.8‡ (4)

Values are mean ± s.e. mean. The figures in parentheses show the number of observations contributing to each mean value.

† One animal, surviving the infusion period and therefore receiving 50 mg/kg, has been eliminated. ‡ Two animals surviving the infusion period and therefore receiving 225 mg/kg have been eliminated.

Table 2 Dose in conscious rabbits (mg/kg) at which convulsions occurred

	Amitriptyline	*Imipramine*	*Maprotiline*	*Mianserin*
First convulsion	18.0 ± 4.4	22.7 ± 3.2	34.0 ± 2.8	81.2 ± 5.0
Repeated and severe convulsions	34.0 ± 2.4	69.4 ± 11.3	52.0 ± 6.5†	86.2 ± 4.8

Mean values ± s.e. mean are shown; except where indicated 6 observations contributed to each mean value. † $n = 4$; two animals died before developing repeated and severe convulsions.

and the doses required to produce the first convulsive episode (Table 2) were similar for amitriptyline and imipramine ($P > 0.4$) while a significantly higher dose was required of maprotiline ($P < 0.05$) and a higher dose again of mianserin ($P < 0.001$). Most animals developed repeated and severe convulsions (Table 2) and the dose required was usually considerably higher than that producing the first convulsive episode (amitriptyline 1.9 fold, imipramine 3.0 fold and maprotiline 1.5 fold). With mianserin however the ratio between these two doses was 1.06 and animals often progressed straight into repeated and severe convulsions without any preceding minor convulsive episode.

Effect on blood pressure and heart rate

In conscious animals the resting heart rate in the period before the start of the infusion was 253 ± 7 beats/min and resting systolic and diastolic blood pressure were 81.3 ± 2.3 and 61.9 ± 2.5 mmHg respectively (mean ± s.e. mean; $n = 30$). These values were little changed by infusion of vehicle alone but infusion of antidepressants produced convulsions which were associated with massive changes in both blood pressure and heart rate. No attempt has been made to separate the changes produced by the antidepressants themselves from those secondary to the development of convulsions and these parameters are not reported further.

In anaesthetized control rabbits resting heart rate was 228 ± 5 beats/min, systolic and diastolic blood pressure were 73.6 ± 3.8 and 52.8 ± 3.7 mmHg respectively (mean ± s.e. mean; $n = 6$) and showed no major fluctuations during the course of the 5 h infusion. At the end of the infusion period a paired t test showed that both systolic and diastolic pressure had risen (+12.7 and +9.5 mmHg respectively, $P < 0.02$), while the change in heart rate (+5 beats/min) was not statistically significant ($P > 0.2$).

Infusion of the antidepressants produced a fall in systolic and diastolic blood pressure, in heart rate and also in mean arterial pressure which was calculated from the relationship: mean arterial pressure = diastolic pressure + 1/3 pulse pressure (Borkowski & Finch, 1978). In most animals the mean arterial pressure fell by at least 15 mmHg and the average dose of antidepressant required to produce this effect is shown in Table 3. Similarly, heart rate fell by at least 30 beats/min and the doses required are also shown in Table 3. The doses of amitriptyline and imipramine required to lower the heart rate by 30 beats/min were not significantly different ($P > 0.9$) but were both significantly lower than those required of maprotiline ($P < 0.05$) or mianserin ($P < 0.001$). With regard to the effect on blood pressure the order of potency of the antidepressants in lowering mean arterial blood pressure by 15 mm Hg was amitriptyline ⩾ imipramine ⩾ maprotiline ≫ mianserin. The difference in potency between amitriptyline and imipramine and

Table 3 Dose of antidepressants (mg/kg) required to reduce arterial blood pressure and heart rate in anaesthetized rabbits

	Amitriptyline	*Imipramine*	*Maprotiline*	*Mianserin*
Dose for a 15 mmHg fall in mean arterial blood pressure	15.0 ± 4.0 (7)	29.0 ± 10.5 (7)	33.9 ± 6.5 (6)	144.0 ± 30.8† (4)
Dose for a 30 beat/min fall in heart rate	12.2 ± 3.1 (7)	12.8 ± 3.7 (7)	33.9 ± 7.5 (6)	41.9 ± 6.9 (6)

Mean values ± s.e. mean are given. The figures in parentheses show the number of observations contributing to each mean value. † Two animals did not show a fall in blood pressure of this magnitude and have been excluded.

that between imipramine and maprotiline was not significant ($P > 0.2$) though a significantly larger dose of maprotiline was needed than of amitriptyline ($P < 0.05$) and mianserin was required in much larger dose than any of the other drugs ($P < 0.01$).

Effect on P-R interval and width of the QRS complex

In conscious control rabbits, ECG records were obtained for the whole of the 5 h infusion period and the maximum change in the P-R interval and the width of the QRS complex was $+4.4 \pm 0.4\%$ and $+7.7 \pm 3.0\%$ of the initial values respectively (mean ± s.e. mean; $n = 6$). In conscious animals receiving antidepressants the development of convulsions gave rise to considerable movement artifacts but before readings became unobtainable changes in the P-R interval and in the width of the QRS complex were noted (Table 4). All drugs produced a significantly greater increase in the P-R interval and in the width of the QRS complex than was seen in control animals ($P < 0.05$) and although these effects were smallest with mianserin the difference between mianserin and the other drugs was statistically significant only in the case of amitriptyline ($P < 0.05$) and of imipramine (QRS only; $P < 0.05$).

In anaesthetized control animals the initial values for the P-R interval and the width of the QRS complex were 67.2 ± 2.8 and 35.0 ± 1.5 ms respectively (mean ± s.e. mean; $n = 6$) and showed little variation during the 5 h infusion period. At the end of this period the P-R interval and the width of the QRS complex showed mean changes of -1.3 ms and -0.4 ms respectively which were not significantly different from zero ($P > 0.4$; paired t test). Infusion with antidepressants increased the P-R interval and the width of the QRS complex and in each animal the dose of antidepressant which produced an increase of 20% of the initial value of the P-R interval was calculated (Table 4). Amitriptyline, imipramine and maprotiline were not significantly different in potency ($P > 0.05$) while 7 to 13 times more mianserin had to be administered to produce a similar effect ($P < 0.001$) which was only seen in 2 of the 6 animals.

Similarly, doses of the antidepressants producing 20% and 50% widening of the QRS complex were calculated (Table 4) and amitriptyline and imipramine showed no significant differences in potency at either level of effect ($P > 0.05$) while higher doses of maprotiline were needed than of amitriptyline ($P < 0.02$). At least 7 times more mianserin had to be administered than any of the other drugs and these differences were highly significant for both effects ($P < 0.001$).

Production of dysrhythmias

In conscious rabbits movement artifacts made detailed analysis of the ECG records difficult but dysrhythmias involving loss of the QRS complex (sinus arrest or heart block) were easy to identify. As can be seen from Table 5 these were seen in 6 out of 6 (6/6) animals with amitriptyline and maproti-

Table 4 Effect of the antidepressants on the P-R interval and on the width of the QRS complex in conscious and in anaesthetized rabbits

	Amitriptyline	*Imipramine*	*Maprotiline*	*Mianserin*
Conscious rabbits. n =	6	6	6	6
Maximum change (% of initial value) in:				
P-R interval	$+49.7 \pm 5.8\%$ (6)	$+41.8 \pm 4.3\%$ (6)	$+49.9 \pm 8.3\%$ (6)	$+25.6 \pm 8.2\%$ (6)
width of QRS complex	$+75.7 \pm 18.0\%$ (6)	$+57.0 \pm 10.7\%$ (6)	$+40.9 \pm 6.5\%$ (6)	$+24.9 \pm 6.8\%$ (6)
Anaesthetized rabbits. n =	7	7	6	6
Mean dose (mg/kg) required to produce:				
20% increase in the P-R interval	12.2 ± 2.5 (6)	18.7 ± 7.6 (6)	21.4 ± 3.0 (6)	161.4 ± 24.2 (2)
20% increase in the width of the QRS complex	2.6 ± 0.8 (7)	11.2 ± 6.0 (7)	7.1 ± 1.0 (6)	80.0 ± 11.7 (6)
50% increase in the width of the QRS complex	7.4 ± 2.0 (7)	19.9 ± 5.8 (7)	18.0 ± 3.0 (6)	165.1 ± 18.4 (4)

The figures in parentheses show the number of observations contributing to each mean value and the number of animals on which experiments were performed is also shown (n). Note that not all animals showed an effect of the required magnitude.

line, in 2/6 animals with imipramine and were not seen in animals infused with mianserin.

The variety of dysrhythmias seen in the anaesthetized animals is shown in Table 5. Frequently, more than one type of dysrhythmia was seen in an individual animal but, overall, some type of dysrhythmia was seen in 7/7 animals with amitriptyline, 6/6 with maprotiline, 6/7 with imipramine and 4/6 with mianserin. Consideration of Table 5 shows that amitriptyline and imipramine exhibited similar profiles with regard to the production of dysrhythmias although amitriptyline tended to produce ventricular ectopic beats at lower doses. Generally, higher doses of maprotiline were needed and with mianserin even higher doses were needed. Ectopic beats were seen least frequently and were nodal in origin rather than ventricular.

Behavioural changes

In conscious control animals apparently normal activity and interest in the surroundings was maintained to the end of the experiment and no unusual behavioural changes were noted. During infusion of the antidepressants, in every case, the animals became calm and sedated 0.5 to 1.0 h after the start of the infusion and often lay down and became relaxed and flaccid. With mianserin this was often preceded by a period of restlessness with rapid respiration and apparent photophobia. In all cases just before convulsions developed the animals became irritable, restless and showed rapid respiration. With mianserin alone the majority of animals showed increased salivation which was very marked in some cases.

Discussion

Barbiturates were chosen as the anaesthetic agent since halogenated hydrocarbons are known to sensitize the heart to the action of catecholamines (Price, 1975) which may interact with antidepressants in the production of dysrhythmias (Harper & Hughes, 1977). Furthermore, with the anaesthetic combination used, the resting heart rate and blood pressure of the anaesthetized rabbits corresponded reasonably to those found in the conscious animals whereas in initial experiments with chloralose-urethane mixtures, very high values for these parameters were found. Slow intravenous infusion of the antidepressants was adopted as the mode of administration since this mimics the steadily rising plasma level likely to be found in man after oral overdose much more closely than does a single intravenous injection of antidepressant made over a few seconds.

Table 5 Incidence, type of dysrhythmia and dose level (mg/kg) at which the dysrhythmia was first observed during infusion of the antidepressants

	Amitriptyline	*Imipramine*	*Maprotiline*	*Mianserin*
Type of dysrhythmia				
Conscious rabbits: n =	6	6	6	6
Missing QRS complex	22.3 ± 3.1	70.6	23.6 ± 4.0	—
	(6)	(2)	(6)	(0)
Anaesthetized rabbits: n =	7	7	6	6
2nd degree heart block	22.3	18.0	41.8	128.2
	(1)	(1)	(2)	(1)
Nodal or junctional rhythm	—	42.0 ± 24.4	—	160.5
	(0)	(3)	(0)	(2)
Sinus arrest (missed cycle)	—	—	68.7	—
	(0)	(0)	(2)	(0)
Ectopic beats	17.5 ± 3.6 ventricular	35.8 ± 12.2 ventricular	64.3 ± 11.0 ventricular	195.0 nodal
	(7)	(3)	(6)	(2)
ST segment depression	28.7	45.9 ± 23.4	70.0	183.2 ± 24.4
	(2)	(3)	(1)	(4)
Ventricular tachycardia	19.0 ± 7.6	25.5	70.6	—
	(3)	(2)	(2)	(0)
Ventricular fibrillation	16.4	26.1	73.7	118.8
	(2)	(2)	(2)	(2)

Values are mean ± s.e. mean. The number of animals in each group (n) is shown and the figures in parentheses represent the number showing the particular dysrhythmia. Where less than 3 animals showed a particular type of dysrhythmia the standard error of the mean dose has been omitted.

The relative insolubility of the drugs made it necessary to use two vehicles (hot saline and saline plus 3% propylene glycol) for the infusion. In control animals receiving either vehicle alone there were no significant differences in the parameters recorded over the 5 h infusion period and, with imipramine at least, the quantitative toxicity appears to be independent of the vehicle used for administration.

Taking death as the criterion, amitriptyline was the most toxic and mianserin the least in both conscious and anaesthetized animals. This order of toxicity is very different from that found in mice for example where the LD_{50} (oral route) for amitriptyline, imipramine, maprotiline and mianserin is 289, 400, 750 and 200 mg/kg respectively (Van Riezen, 1972; Barnes & Eltherington, 1973) though differences in the detailed methodology used to determine these values makes comparisons difficult. The finding that the dose rate of mianserin which was lethal in conscious animals had to be increased in order to produce death in anaesthetized animals is compatible with a relatively minor cardiovascular toxicity for mianserin. Thus when the more lethal central nervous system effect was eliminated by anaesthesia a much larger dose was needed to produce death from the low level cardiotoxicity.

When maprotiline was administered at $15\,mg\,kg^{-1}\,h^{-1}$ three animals survived the 5 h infusion period (thus receiving 75 mg/kg) while the fourth animal died after 66.75 mg/kg. These doses are all in excess of the mean lethal dose found during administration of maprotiline at $25\,mg\,kg^{-1}\,h^{-1}$ (57.4 mg/kg) though they are all within two standard deviations of the latter value. Nevertheless, a Mann-Whitney rank test (Snedecor & Cochran, 1971) indicates that there is a significant difference between these populations ($P < 0.05$), and this suggests that some pharmacokinetic factor may be influencing the results.

The relative doses of the drugs required to produce similar effects on blood pressure and heart rate might suggest that the cardiovascular toxicity of mianserin is low. However, the complexity of the control mechanisms involved in the maintenance of heart rate and blood pressure make these parameters somewhat unsuited for the assessment of relative cardiotoxicity.

Analysis of the ECG recordings shows that all four antidepressants possess some degree of cardiotoxicity since the P-R interval and the width of the QRS complex showed minimal changes in control animals but were significantly lengthened by all four drugs. Since all four drugs also lowered the heart rate it is possible that this action contributed to the effect on the P-R interval, as these two parameters are said to be related in man (Goldman, 1967). However, changes in the P-R interval in response to heart rate are usually small and in these experiments maprotiline for example produced a 70 to 90% lengthening of the P-R interval. Furthermore, maprotiline and mianserin lowered heart rate by the same amount in approximately equal dose while 7 times more mianserin than maprotiline was required to produce equal effects on the P-R interval. It would seem unlikely therefore that the change in heart rate *per se* can account for the lengthening of the P-R interval.

A marked (up to 100%) widening of the QRS complex was also produced by the antidepressants, amitriptyline being most toxic in this respect and mianserin least toxic. Since the width of the QRS complex is generally thought to be unrelated to heart rate the effects seen on this parameter must be due to a direct action of the antidepressants. Taken together with their effect on the P-R interval, this indicates an ability of all four antidepressants to slow conduction in cardiac tissue, though the doses required to produce this effect are clearly very different.

Dysrhythmias in the form of missing QRS complexes were seen with amitriptyline, imipramine and maprotiline but not with mianserin in conscious rabbits. In the anaesthetized animals the greater clarity of the ECG records permitted a more detailed analysis of the dysrhythmias, and the great variety of dysrhythmias is consistent with the findings in man after antidepressant poisoning (Thorstrand, 1976). Amitriptyline appeared to be dysrhythmogenic at marginally lower doses than imipramine while higher doses of maprotiline were required and higher doses again of mianserin. Taking all these factors into account it would appear that the relative cardiotoxicity of these antidepressants is in the order amitriptyline > imipramine > maprotiline $\gg$ mianserin.

The behavioural changes noted (primarily sedation) were common to all the antidepressants tested but quantitation of this effect was not attempted. It is interesting to note the salivary stimulation produced by mianserin in the conscious animals although again this effect was not quantitated. It is well established that mianserin does not produce the dry mouth classically associated with treatment of depressive illness with tricyclic antidepressants. Indeed, a negative correlation has been reported between the incidence of dry mouth and treatment with mianserin in depressed patients (Coppen, Gupta, Montgomery, Ghose, Bailey, Burns & de Ridder, 1976; Ghose, Karabi Coppen & Turner, 1976).

In view of the fact that the clinically effective doses of amitriptyline, imipramine and maprotiline usually lie in the range 75 to 200 mg per day while that of mianserin is often somewhat lower (60 to 100 per day), the results reported above suggest that the safety margin with mianserin may well be greater than with the other antidepressants.

We would like to express our thanks to Ciba Laboratories

Ltd., to Geigy Pharmaceuticals Ltd. and to Roche Products Ltd. for gifts of antidepressants, to Organon International for financial support and to the Egyptian Government for a scholarship (S.R.).

References

BARNES, C.D. & ELTHERINGTON, L.G. (1973). In *Drug Dosage in Laboratory Animals*. Berkeley, Los Angeles: University of California Press.

BIGGER, J.T., GIARDINA, ELSA G.V., PEREL, J.M., KANTOR, S.J. & GLASSMAN, A.H. (1977). Cardiac anti-arrhythmic effects of imipramine hydrochloride. *New Engl. J. Med.*, **296,** 206–210.

BORKOWSKI, K.R. & FINCH, L. (1978). Cardiovascular responses to intraventricular adrenaline in spontaneous hypertensive rats. *Eur. J. Pharmac.*, **47,** 281–290.

BURROWS, G.D., VOHRA, J., HUNT, D. SLOMAN, J.G., SCOGGINS, B.A. & DAVIES, B. (1976). Cardiac effects of different tricyclic antidepressant drugs. *Br. J. Psychiat.*, **129,** 335–341.

COPPEN, A., GUPTA, R., MONTGOMERY, S., GHOSE, KARABI, BAILEY, J., BURNS, B. & DE RIDDER, J.J. (1976). Mianserin hydrochloride: a novel antidepressant. *Br. J. Psychiat.*, **129,** 342–345.

FELL, P.J., QUANTOK, D.C. & VAN DER BURG, W.J. (1973). The human pharmacology of GB 94—a new psychotropic agent. *Eur. J. clin. Pharmac.*, **5,** 166–173.

GHOSE, KARABI, COPPEN, A. & TURNER, P. (1976). Autonomic actions and interactions of mianserin hydrochloride (Org. GB 94) and amitriptyline in patients with depressive illness. *Psychopharmac.* **49,** 201–204.

GOLDMAN, M.J. (1967). In *Principals of Clinical Electrocardiography*. p. 26. Los Altos, California: Lange Medical Publications.

HARPER, BARBARA & HUGHES, I.E. (1977). A comparison in rabbit isolated hearts of the dysrhythmogenic potential of amitriptyline, maprotiline, and mianserin in relation to their ability to block noradrenaline uptake. *Br. J. Pharmac.*, **59,** 651–660.

ITIL, T.M., POLVAN, N. & HSU W. (1972). Clinical and EEG effects of GB 94, a tetracyclic antidepressant (EEG model in discovery of new psychotropic drug). *Curr. ther. Res.*, **14,** 395–413.

JEFFERSON, J.W. (1975). A review of cardiovascular effects and toxicity of tricyclic antidepressants. *Psychosomatic Med.*, **37,** 160–179.

MÂITRE, L., WALDMEIER, P.C., GREENGRASS, P.M., JAEKEL, J., SEDLACEK, S. & DELINI-STULA, A. (1975). Maprotiline,—its position as an antidepressant in the light of recent neuropharmacological and neurobiochemical findings. *J. int. Med. Res.*, **3,** Suppl. 2, 1–15.

OFFICE OF POPULATION CENSUSES AND SURVEYS. (1976). *Deaths by Poisoning from Solid and Liquid Substances, 1974*. London; OPCS.

PRICE, H.L. (1975). General anaesthetics. In *The Pharmacological Basis of Therapeutics*. ed. Gilman, A. & Koelle, G.B. p. 91. New York: Macmillan Publishing Co.

RASMUSSEN, E.B. & KRISTIANSEN, P. (1963). ECG changes during amitriptyline treatment. *Am. J. Psychiat.*, **119,** 781–782.

REISS, W., DUBEY, L., FÜNFGELD, E.W., IMHOF, P., HÜRZELER, H., MATUSSEK, N., RAJAGOPALAN, T.G., RASCHDORF, F. & SCHMID, K. (1975). The pharmacokinetic properties of maprotiline (Ludiomil) in man. *J. int. Med. Res.*, **3,** suppl. 2. 16–41.

RIEZEN, H. VAN. (1972). Different central effects of the 5-HT antagonists mianserin and cyproheptadine. *Archs int. Pharmacodyn.*, **198,** 256–269.

SNEDECOR, G.W. & COCHRAN, W.G. (1967). Shortcut and non-parametric methods. In *Statistical Methods*, (6th edition). pp. 130–131. Ames, Iowa: University Press.

THORSTRAND, C. (1974). Cardiovascular effects of poisoning with tricyclic antidepressants. *Acta med. scand.*, **195,** 505–511.

THORSTRAND, C. (1976). Clinical features in poisoning by tricyclic antidepressants with special reference to the ECG. *Acta med. scand.*, **199,** 337–344.

VOHRA, J., BURROWS, G.D. & SLOMAN, J.G. (1975). Assessment of cardiovascular side effects of therapeutic doses of tricyclic antidepressants. *Aust. N.Z. med. J.*, **5,** 7–11.

ZIEGLER, V.E., CO, B.T. & BIGGS, J.T. (1977). Plasma nortriptyline levels and ECG findings. *Am. J. Psychiat.*, **134,** 441–443.

(Received July 27, 1978. Revised August 24, 1978.)