Cardiovascular Effects of Paroxetine, a Newly Developed Antidepressant, in Anesthetized Dogs in Comparison with Those of Imipramine, Amitriptyline and Clomipramine

Syunji YOKOTA, Yoshiyuki ISHIKURA* and Hiroshi ONO
Department of Pharmacology and Toxicology, Hatano Research Institute, Food and Drug Safety Center, 729-5 Ochiai, Hadano, Kanagawa 257, Japan
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Abstract—The cardiovascular effects of various antidepressant drugs including paroxetine, imipramine, amitriptyline and clomipramine, administered intravenously, have been assessed. Paroxetine, imipramine, amitriptyline or clomipramine potentiated the response to norepinephrine (0.1 μg/kg, i.v.) on systemic blood pressure, while paroxetine, imipramine and amitriptyline weakened the response to tyramine (30 μg/kg, i.v.). A marked decrease in systemic blood pressure was observed after large doses of each drug (3 and 10 mg/kg of paroxetine; 1–10 mg/kg of imipramine, amitriptyline or clomipramine); and half of the animals died following administration of 10 mg/kg of imipramine, amitriptyline or clomipramine. Paroxetine did not show a marked effect on heart rate at a dose of up to 3 mg/kg, although 0.1–3 mg/kg of imipramine, amitriptyline or clomipramine dose-dependently caused tachycardia. ECG disturbances were observed in animals administered 10 mg/kg of imipramine, amitriptyline or clomipramine; but in contrast, 10 mg/kg of paroxetine caused only slight changes in the ECG. Prolongation of atrio-ventricular conduction time was observed with all the drugs. It was concluded that the effects of paroxetine on the canine heart are more mild in comparison with other tricyclic antidepressants used, although its pharmacological features are essentially similar to those of other drugs.

Tricyclic antidepressants have been used for therapy of depressive illnesses for a fairly long time with good results, but as a drawback, a number of cases with adverse cardiac effects have been reported (1–5). Most serious of these cardiotoxicities are severe arrhythmias which sometimes can be fatal. In experimental animals, the drugs produced ECG abnormalities including tachycardia and change in myocardial contractile force (6–10). These effects of tricyclic antidepressants have been attributed to their inhibition of norepinephrine re-uptake at the sympathetic nerve ending, anticholinergic action and also to their "quini-dine-like" action (11, 12).

Paroxetine is a newly developed non-tricyclic drug having antidepressant activity which is now under clinical study (13–15). Hitherto performed pharmacological studies have shown that it is a highly selective serotonin re-uptake inhibitor, having weak norepinephrine re-uptake inhibitory properties, and also has a weak anticholinergic action in vitro (16–21).

It is interesting to examine the cardiovascular effects of this compound in comparison with representative antidepressants; and in the present study, we have compared paroxetine with three commonly used antidepressants, imipramine, amitriptyline and clomipramine, in anesthetized dogs.

Materials and Methods
1. Studies in closed-chest anesthetized
dogs with pentobarbital: Mongrel dogs of either sex, weighing 7.8–26.0 kg, were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). A polyethylene cannula was inserted into the right femoral artery to measure systemic blood pressure with a pressure transducer (Statham P23Db, Oxnard, CA, U.S.A.). A rubber tube was inserted into the right femoral vein for administration of drug solutions. A non-cannulating type probe of an electromagnetic flowmeter (Narco RT-500, Houston, TX, U.S.A.) was attached around the left femoral artery to measure femoral blood flow. A polyethylene catheter was inserted into the right atrial appendage and passed into the caval vein to measure central venous pressure (Statham P23BB). Respiration rate was counted with the waves of central venous pressure. ECG electrodes were sutured on the limbs to record the standard limb ECG by means of biophysical amplifiers (San-ei 1205, Tokyo, Japan). A cardiotachometer (Data Graph T-149, Tokyo, Japan) was triggered by R waves from lead II of the ECG. These parameters were recorded on a directly writing oscillograph (San-ei 8S53). After completion of the surgical preparation, 0.1 μg/kg of norepinephrine, 1 μg/kg of acetylcholine and 30 μg/kg of tyramine were administered intravenously in sequence to examine the cardiovascular response of the animal; and then increasing doses (0.1, 0.3, 1, 3 and 10 mg/kg) of paroxetine, imipramine, amitriptyline or clomipramine were administered intravenously at 30–60 min intervals, and their effects were observed.

After administration of 0.1, 0.3 and 1 mg/kg of one of the antidepressants, the previously mentioned doses of norepinephrine, acetylcholine and tyramine were administered to estimate the possible interaction of the antidepressant with these agents. In another series of experiments, atropine was used (0.1 mg/kg, i.v.) to assess the participation of the parasympathetic nerve in the response to paroxetine (0.1, 0.3 and 1 mg/kg) or imipramine (3 and 10 mg/kg).

2. Studies of effects on atrio-ventricular conduction time in open-chest dogs: Mongrel dogs of either sex, weighing 9.2–20.0 kg, were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). Artificial respiration was performed by a Harvard respirator (Harvard Instr. Model 607, Millis, MA, U.S.A.). The thorax was opened by midline sternotomy and the heart was secured in the pericardial cradle. Bipolar electrodes were sutured on to the right atrial appendage and apex of the heart and the electrograms were processed through an atrio-ventricular interval counter (Data Graph HT-11) via biophysical amplifiers (San-ei 1205). Atrio-ventricular conduction time was measured as the interval between these two electrograms. A rubber tube was inserted from the atrial appendage into the right atrium to measure right atrial pressure (Statham P23BB). Systemic blood pressure at the femoral artery and heart rate were measured as described above and these parameters were recorded on a directly writing recorder (San-ei 8S53).

Drug administration was performed via the femoral vein. In another group of dogs, midcervical vagotomy and postganglionic nerve section of the stellate ganglia were performed bilaterally in order to analyze the participation of the autonomic nerve control in the response to the drug.

After the surgical preparation was completed, 0.1, 0.3, 1, 3 and 10 mg/kg of paroxetine, imipramine, amitriptyline or clomipramine were administered intravenously in sequence at 30–60 min intervals, and their effects on atrio-ventricular conduction time were observed.

The drugs used were: paroxetine hydrochloride (Beecham, Surry, U.K.), imipramine hydrochloride (Tofranil®, 1.25% solution for injection, Ciba-Geigy, Takarazuka, Japan), clomipramine hydrochloride (Anafranil®, 1.25% solution, Ciba-Geigy), amitriptyline hydrochloride (Triptanol®, 1% solution, Merck-Banyu, Tokyo, Japan) and pentobarbital sodium (Tokyo Kasei, Tokyo, Japan). The doses of these drugs are expressed as the weight of salt used, while the doses of L-norepinephrine (Fluka, Buchs, Switzerland), acetylcholine chloride (Wako Pure Chemical, Tokyo, Japan), tyramine hydrochloride (Wako Pure Chemical) and atropine sulfate (Tokyo Kasei) are expressed as the weight of base.
Results

1. Effects on the cardiovascular systems in closed-chest anesthetized dogs

Blood pressure and heart rate: Typical recordings obtained by paroxetine administration are shown in Fig. 1, and the peak responses of the blood pressure and the heart rate to each dose obtained at 1–5 min after the injection are summarized in Fig. 2 and Fig. 3, respectively.

Paroxetine at 0.1–1 mg/kg caused a slight but sustained increase in systemic blood pressure dose-dependently, the increase being 15.6±2.9 mmHg with 1 mg/kg. Heart rate was decreased slightly with 1 mg/kg of paroxetine. Three mg/kg of paroxetine caused a transient decrease in systemic blood pressure which was followed by a sustained increase, and it also caused a transient decrease in heart rate. Ten mg/kg of paroxetine caused a marked decrease in systemic blood pressure and bradycardia with or without transient tachycardia, although both parameters recovered after 10–25 min in all animals. Central venous pressure was increased by administration of 3 and 10 mg/kg. Femoral blood flow was decreased at all doses of paroxetine examined.

In atropinized animals, 1 mg/kg of paroxetine increased heart rate slightly, and 3 mg/kg caused bradycardia in half of the animals and caused tachycardia in other animals. Ten mg/kg caused a marked bradycardia, although the change was smaller than that in non-atropinized animals.

Imipramine at doses of 0.1 and 0.3 mg/kg caused a slight decrease in systemic blood pressure which was followed by sustained increase, and it caused a sustained increase in heart rate; at 1 mg/kg, a transient decrease followed by a sustained increase in systemic blood pressure occurred. Three mg/kg of imipramine decreased systemic blood pressure markedly; and 10 mg/kg caused an abrupt and marked decrease in systemic blood pressure and heart rate, and then 2 out of 5 animals died after 2–6 min. Central venous pressure increased with 1, 3 and 10 mg/kg of the drug, and femoral blood flow decreased with 3 and 10 mg/kg of imipramine.

In atropinized animals, imipramine at a

![Fig. 1. A representative experimental record showing the effects of paroxetine on systemic blood pressure (SBP), heart rate (HR), femoral blood flow (FBF) and central venous pressure (CVP) in an anesthetized dog. Dots indicate the points at which paroxetine was injected in the dose indicated.](Image)
A dose of 1 mg/kg caused a marked tachycardia, while a marked bradycardia was induced with 3 mg/kg.

Imipramine showed similar effects to amitriptyline on the systemic blood pressure and heart rate, although central venous pressure was decreased by 0.1–3 mg/kg of amitriptyline, and 3 out of 5 animals died at 10 mg/kg.

Clomipramine, at doses of 0.3 and 1 mg/kg, caused a slight increase in systemic blood pressure, followed by a sustained decrease. Doses of 3 and 10 mg/kg of clomipramine caused marked bradycardia, and 2 out of 5 animals died with 10 mg/kg of the drug.

Respiration rate: Paroxetine, at doses of 3 and 10 mg/kg, increased respiration rate (32% at 3 mg/kg and 58% at 10 mg/kg, respectively), which was less than other drugs.

ECG: Results are summarized in Fig. 4. Paroxetine did not cause any marked changes in the ECG up to 10 mg/kg. Prolongation of PQ and QTc intervals and a spread of QRS width were less than 10% and lasted only 1–2 min after the injection. Three mg/kg of paroxetine prolonged PQ interval by 13 msec, which was not statistically
significant; However, at 10 mg/kg, QRS width was spread by 10 msec (25%) at the maximum, PQ and QTc intervals were prolonged by 13 and 18%, respectively, lasting for 5–10 min, and QRS amplitude was reduced for 2 min. In one experiment, a very high dose of 30 mg/kg of paroxetine was administered which caused a marked QRS spread with deformation and finally a cardiac arrest in the dog after 6 min.

Imipramine at a dose of 1 mg/kg caused a spread of QRS width by 10%, and QTc prolongation by 20%. These changes were more marked at 3 mg/kg, and in addition, PQ interval was prolonged by 11 msec (16%). With 10 mg/kg of imipramine, the configuration of QRS complex was variously changed in 4 of 5 animals, e.g., the QRS spread widely and lost its amplitude with multiple deflection forming a zig-zag wave, and displacement of the ST segment occurred. Moreover, in 2 out of 5 animals receiving 10 mg/kg of imipramine, the P wave was lost, cardiac rhythm was taken over by ventricular rhythm, in consequence, ventricular fibrillation developed.

Amitriptyline at doses of 0.3 and 1 mg/kg caused a slight, transient widening of QRS width and PQ prolongation by 10 msec (13%); but at a dose of 3 mg/kg, it caused more marked prolongations in PQ, QTc intervals and QRS width by 42, 18 and 49%, respectively. At dose of 10 mg/kg, the above mentioned changes were even more marked, and 3 out of 5 animals finally suffered cardiac arrest or ventricular fibrillation.

Clomipramine reduced the amplitude of QRS complex only slightly at a dose of 3 mg/kg. At 10 mg/kg QRS deformation and PQ prolongation occurred, and 2 out of 5 animals suffered cardiac arrest.

2. Interaction of the antidepressants with the effects of norepinephrine, tyramine and acetylcholine on systemic blood pressure

The results are summarized in Fig. 5.

A sequential administration of paroxetine increased the basal systemic blood pressure cumulatively and raised the mean systemic blood pressure from an initial value of 149.4±3.9 mmHg to 156.0±2.6 mmHg during the period before administration of the 3 mg/kg.

Imipramine also potentiated the response to norepinephrine, the increases being 54.8, 105.0 and 91.9% at dose of 0.1, 0.3 and 1 mg/kg, respectively, while amitriptyline did not show a clear-cut interaction. One mg/kg of clomipramine potentiated the response to norepinephrine.

The response of the systemic blood pressure to 30 µg/kg of tyramine was depressed by administration of 1 mg/kg of paroxetine; however, at lower doses (0.1 or 0.3 mg/kg), the response to tyramine was potentiated in 4 out of 5 animals.

Imipramine potentiated the response to tyramine at doses of 0.1 and 0.3 mg/kg in 3 out of 5 animals, but depressed the response to tyramine at a dose of 1 mg/kg in 4 out of 5 animals. Amitriptyline at a dose of 1 mg/kg depressed the response to tyramine significantly, while 0.3–1 mg/kg of clomipramine potentiated the effect.

Paroxetine, 0.1–1 mg/kg, minimized the
decrease in systemic blood pressure evoked by acetylcholine (1 \( \mu g/kg \)) in 3 out of 5 animals, although the inhibition was not statistically significant when the changes in the 5 experiments were compared.

Imipramine, amitriptyline and clomipramine, at doses of 0.1–1 mg/kg, did not show a clear-cut effect on the response to acetylcholine, although 3 out of 5 animals showed a slight potentiation of the response with clomipramine.

3. Effects of the antidepressants on atrioventricular conduction time

Results are summarized in Fig. 6.

Atrioventricular conduction time was prolonged by administration of paroxetine at doses of 1–10 mg/kg. Mean values of prolongation were 6.4 msec (5.7%), 9.8 msec (8.6%) and 27.8 msec (26.5%) at 1, 3 and 10 mg/kg, respectively. These changes became smaller in vagotomized and stellectomized dogs. Maximum prolongation occurred within 1 min of administration, and recovery to the pre-administration value took 6–20 min in both the nerve-intact and vagotomized and stellectomized dogs.

Imipramine at a dose of 1 mg/kg shortened atrioventricular conduction time slightly, but at 3 and 10 mg/kg, it caused prolongation. The prolongation was similar to the change seen with paroxetine in the nerve-intact open-chest dogs, while a more marked prolongation was produced in the vagotomized and stellectomized animals. Amitriptyline caused a slight prolongation of atrioventricular conduction time at 1 mg/kg, while doses of 3 and 10 mg/kg resulted in a marked prolongation. Clomipramine at doses of 1 and 3 mg/kg shortened atrioventricular conduction time, but at 10 mg/kg, a slight prolongation occurred.

Discussion

The pharmacological profiles and cardioxicities of tricyclic antidepressants have been extensively studied. Their well-known pharmacological actions are norepinephrine re-uptake inhibition at the adrenergic nerve ending, anticholinergic activity and a "quinidine-like" effect on cardiac tissue. Inhibition of norepinephrine re-uptake increases heart rate and myocardial contractile force, both of which have been observed with therapeutic doses of tricyclic antidepressants (1, 2). The anticholinergic action may also result in an increase in heart rate besides the more frequently encountered consequence of dry mouth (3, 22).

In the present study, 0.3–1 mg/kg of imipramine, amitriptyline and clomipramine caused tachycardia and an increase in systemic blood pressure whilst paroxetine did not produce marked tachycardia at any dose. Though the mechanism underlying this difference is not entirely clear from the present study, it may have arisen from a difference in the potencies of anticholinergic action and inhibition of norepinephrine re-uptake. It has been reported that paroxetine showed a weaker anticholinergic activity with a potency about 1/1.4–1/9.6 of those of imipramine and amitriptyline by a ligand binding study using \([3H]\)-quinuclidinyl benzilate in guinea-pig brain (15). Therefore, such an anticholinergic action may be playing a role in the induction of tachycardia. However, anticholinergic activities of the antidepressants examined were not clearly

Fig. 6. Effects of antidepressants on the atrioventricular conduction time in open-chest dogs. (A): nerve-intact dogs. (B): vagotomized and stellectomized dogs. Each symbol with vertical bars represents the mean±S.E. in 5 experiments with paroxetine (○—○), imipramine (●—●), amitriptyline (△—△) or clomipramine (▲—▲). *: P<0.05, compared with the control value (paired t-test).
demonstrated in the present study not only for paroxetine but also for the other three by examination of the depressor effect of exogenous acetylcholine. The reason for this discrepancy is not clear, but the dose of acetylcholine selected (1 μg/kg) might have outgone the maximum effective dose.

Recently, the mechanism of the cardio-toxicity, mainly due to conduction disturbances, of tricyclic antidepressants have been considered by several authors to be a result of the combination of anticholinergic action and direct myocardial depressant action or "quinidine-like" action (11, 12, 23–25). The anticholinergic effect may induce sinus tachycardia and shortening of atrio-ventricular conduction, while the myocardial depressant effect may induce intracardiac conduction disturbance resulting in a prolongation of PQ interval and QRS width. In the present study, the antidepressant drugs including paroxetine did not shorten PQ interval as expected from their anticholinergic and sympathomimetic activities, but both PQ interval and QRS width were prolonged at relatively higher doses; and these changes are considered to be due to the disturbance of conduction mainly distal to the AV node (i.e., His bundle and Purkinje systems) by a direct myocardial depressant action of the drug.

Paroxetine did not cause marked prolongation of PQ interval up to 10 mg/kg, and at this dose, it caused only a simple prolongation (slight degree AV block), while similar doses of tricyclic antidepressants caused severe AV block and ventricular arrhythmia. On the other hand, in open-chest dogs, 10 mg/kg of paroxetine clearly prolonged the atrio-ventricular conduction time. In the methods adopted in this experiment, atrio-ventricular conduction time was defined as the interval between the right auricular and ventricular apical electrograms; and therefore, it involved intra-atrial and intra-ventricular conduction time besides the AV nodal conduction time.

Potentiation of the response in systemic blood pressure to norepinephrine by paroxetine was observed in the present study, while the drug diminished the response to tyramine. This diminution of the response to tyramine may reflect a depletion of the stored-norepinephrine at nerve endings, induced by re-uptake inhibition by paroxetine. The slight increase in systemic blood pressure at small or middle doses (0.1–1 mg/kg) of paroxetine and slight increase of heart rate in atropinized animals may also be due to norepinephrine re-uptake inhibition by the drug. Tanigaki et al. reported that paroxetine demonstrated a weaker inhibitory activity on norepinephrine uptake with a potency about 1/1.6–1/4.5 of tricyclic antidepressants in rat hypothalamic synaptosomes (15). Nevertheless, paroxetine did inhibit the norepinephrine uptake, although not so potently in the above mentioned report, and also in the present experiments, paroxetine enhanced blood pressure response to norepinephrine which may have been based on the inhibitory effect of the drug on norepinephrine re-uptake.

In conclusion, paroxetine enhanced blood pressure response to norepinephrine, suggesting that the drug has an inhibitory activity on norepinephrine uptake with not insignificant potency, but demonstrated a lower cardiotoxicity than three commonly used tricyclic antidepressants, imipramine, amitriptyline and clomipramine.

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