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CARDIOVASCULAR AND GROSS BEHAVIORAL EFFECTS OF AMPHETAMINE, 2-AMINO-1-(2,5-DIMETHOXY-4-METHYLPHENYL) PROPANE (DOM) AND 2-AMINO-1-(2,5-DIMETHOXY-4-METHYLPHENYL) BUTANE (BL-3912A) IN THE CONSCIOUS DOG

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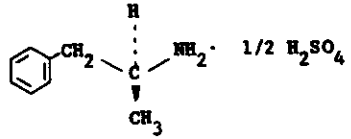
ABSTRACT

Intravenous administration of increasing doses of amphetamine (0.1 - 3 mg/kg), DOM (0.1 - 1 mg/kg) and BL-3912A (0.1 - 5 mg/kg) to conscious beagle dogs resulted in appreciable gross behavioral and cardiovascular changes. Gross behavioral changes ranged from stereotyped activity and disorientation with amphetamine to catatonia with DOM and brief central nervous system stimulation with BL-3912A. In conscious dogs, all three drugs raised mean aortic blood pressure, with amphetamine being the most effective (62 mm Hg) followed by DOM (48 mmHg) and BL-3912A (41 mmHg). Heart rate was consistently reduced only by amphetamine. BL-3912A resulted in depressor responses on blood pressure in anesthetized dogs and this suggests that in the conscious dog BL-3912A may be activating centers in the central nervous system to effect a pressor response. The elevation of blood pressure in the conscious dog induced by amphetamine and DOM is mediated, at least partly, via their peripheral actions.

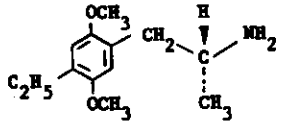
INTRODUCTION

Previous studies dealing with psychotropic drugs related to amphetamine have dealt almost exclusively with the behavioral actions of these agents. There have been few studies with these drugs in which the cardiovascular and behavioral effects were simultaneously observed (Snyder et al., 1970). Most of the studies concerning DOM have dealt with hallucinogenic effects in human subjects and no human studies have as yet been reported with BL-3912A, thus a lack of information exists regarding the cardiovascular actions of these drugs in the conscious dog. This investigation was undertaken to study the behavioral and cardiovascular effects of amphetamine, DOM and BL-3912A in the

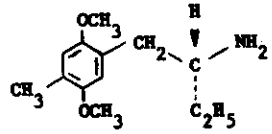
conscious dog as well as the action of BL-3912A in the anesthetized dog. The structure of these compounds is shown in Figure 1.



S-(+)-2-amino-1-phenylpropane sulfate (amphetamine)



R-(-)-2-amino-1-(2,5-dimethoxy-4-methyl-phenyl) propane hydrochloride (DOM)



R-(-)-2-amino-1-(2,5-dimethoxy-4-methyl-phenyl) butane hydrochloride (BL-3912A)

Figure 1 - Structure of amphetamine, DOM and BL-3912A. R- or S- and (-) or (+) refer to the absolute structural configuration and optical rotation, respectively, of the drugs used in this study.

METHODS

Conscious Dogs

Adult beagle dogs, trained to rest quietly in a dog sling, were used in these experiments. Two to three weeks prior to the study, the animals were anesthetized with methoxyflurane and instrumented for the continuous recording of aortic pressure. A small branch of the femoral artery was cannulated such that the polyethylene catheter extended into the lower abdominal aorta. The other end of the catheter was passed under the skin and exteriorized on the dog's back just caudad to the scapular region. This latter end of the catheter was fitted with a cuff to prevent slippage under the skin and closed with a metal plug. The entire catheter system was filled with a dilute

heparinized saline solution. On the day of the experiment, pulsatile and mean aortic pressures were recorded on a Beckman dynograph by means of a Statham P23Dd pressure transducer and a saline filled catheter connected to the implanted catheter. Heart rate was recorded by a Beckman tachometer coupler (type 9847B). Lead II of the surface electrocardiogram was obtained by means of skin electrodes and continuously recorded on a Beckman dynograph. The lead II electrocardiogram was also stored on a Vetter model A analog tape recorder and the electrocardiographic intervals and amplitudes were later analyzed by a Honeywell H-316 computer.

BL-3912A (0.1 - 5 mg/kg), amphetamine (0.1 - 3 mg/kg) and DOM (0.1 - 1 mg/kg) were administered by rapid iv injection (less than 30 sec). The compounds were dissolved in sterile saline and injected via a catheterized saphenous vein. All doses were in terms of the respective salt of the drugs (Figure 1). Cardiovascular and behavioral observations were made with each dose of the drug. Drug responses were compared to control values by means of the t test for unpaired data.

Anesthetized Dogs

Anesthesia was induced in adult dogs with pentothal sodium, 30 mg/kg iv, and maintained with alpha chloralose, 50 - 100 mg/kg iv. The dogs were ventilated by a Harvard 607 respiratory pump connected to a cuffed endotracheal tube. A left thoracotomy was done and a Walton-Brodie strain gauge arch sewn to the left ventricle to record cardiac contractile force. The latter was followed by closure of the thoracotomy. Cannulation of the left femoral vein for drug administration and the left femoral artery for the measurement of aortic pressure was completed. Heart rate was recorded by a Beckman tachometer coupler (9847B). All measurements were made on a Beckman dynograph.

BL-3912A was administered rapidly iv in increasing doses, ranging from 0.3 - 10 mg/kg. Cardiovascular observations were made after each dose.

RESULTS

Conscious Dogs

The acute maximal effects following iv administration of amphetamine on heart rate and mean aortic blood pressure in conscious beagle dogs are shown

in Figures 2 and 3. Amphetamine administration resulted in a dose related pressor effect. Following a dose of 3 mg/kg, aortic blood pressure increased from a control of 109 ± 4 mmHg to 171 ± 11 mmHg in the four dogs studied (mean ± 1 S.E.; $p = <0.01$). Systolic pressure was generally increased to a greater extent than diastolic pressure. Over a dosage range of 0.1 - 1 mg/kg the pressor response was accompanied by a dose related bradycardia (Figure 3). Following a 1 mg/kg dose of amphetamine, cardiac rate decreased from a control of 91 ± 9 beats/min to 62 ± 4 beats/min in the four dogs studied (mean ± 1 S.E.; $p = <0.05$). Administration of 3 mg/kg of amphetamine resulted in no significant change in cardiac rate from predrug controls, although marked elevations in aortic blood pressure were apparent (Figure 2). Accompanying the bradycardia from the 0.1 - 1 mg/kg doses of amphetamine were small increases in the P-R interval of the lead II surface electrocardiogram. Consistent increases in the R and t amplitudes of the lead II surface electrocardiogram were also observed and were most noticeable at 1 and 3 mg/kg. The above changes in the electrocardiogram configuration with 1 and 3 mg/kg of amphetamine were interpreted to be due to the marked pressor responses induced by these doses.

Increasing iv doses of amphetamine (0.1 - 3 mg/kg) resulted in behavioral stimulation that was characterized first by restlessness, then by compulsive licking movements and lastly by rapid, side to side, searching head movements. This latter gross behavioral effect of amphetamine was more intense with increasing dose and became a stereotyped activity (Randrup et al., 1967). Additionally, all dogs became markedly disoriented to their environment after 1 and 3 mg/kg of amphetamine. The higher doses of amphetamine used in the present study were reported to be close to the intravenous LD50 for conscious dogs (Zalis et al., 1965). Thus, after the completion of our observations with amphetamine, all dogs received multiple 1 mg/kg iv doses of chlorpromazine in order to antagonize the long-lasting amphetamine induced cardiovascular and behavioral changes. All dogs recovered uneventfully from this study.

The acute maximal effects following iv injection of DOM on heart rate and mean aortic blood pressure in conscious beagle dogs are shown in Figures 2 and 3. DOM administration resulted in moderate increases in aortic blood pressure and heart rate over the dosage range 0.1 - 1 mg/kg. The largest

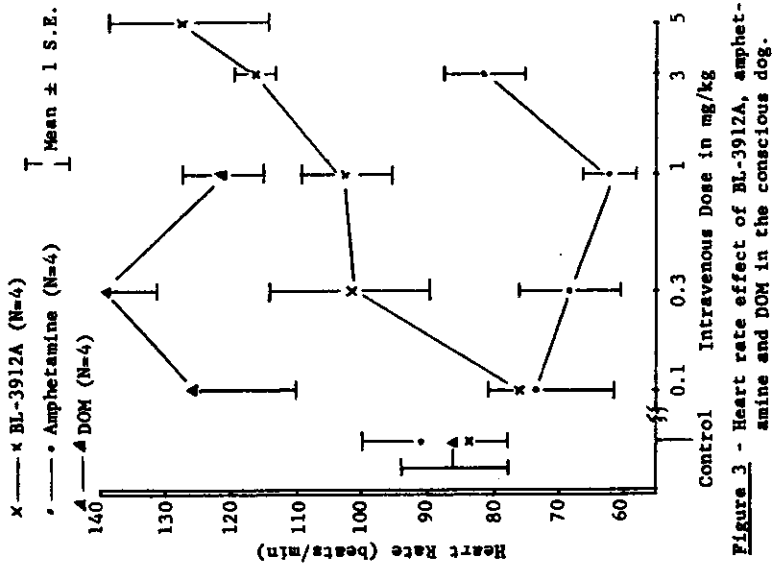


Figure 3 - Heart rate effect of BL-3912A, amphetamine and DOM in the conscious dog.

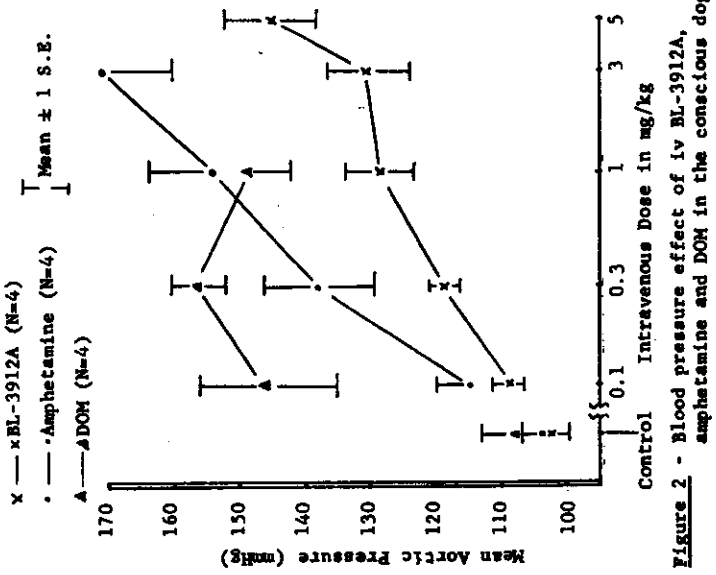


Figure 2 - Blood pressure effect of iv BL-3912A, amphetamine and DOM in the conscious dog.

increase in blood pressure occurred after the second dose of DOM (0.3 mg/kg), in which mean aortic pressure increased from 108 ± 5 mmHg to 156 ± 5 mmHg in the four dogs studied (mean ± 1 S.E.; p = <0.01). Similarly, the largest increase in heart rate occurred after 0.3 mg/kg of DOM, in which rate increased from 86 ± 8 to 139 ± 8 beats/min (mean ± 1 S.E., p = <0.01). Tachyphylaxis to the blood pressure and heart rate effects of DOM was observed after the 0.3 mg/kg dose (Figures 2 and 3). Following the 1 mg/kg dose of DOM, the resultant changes in blood pressure and heart rate returned towards control values after 60 - 90 min. No major changes were observed in the surface lead II electrocardiogram.

The gross behavioral effects induced by 0.1 mg/kg of iv DOM in beagle dogs consisted of mild behavioral stimulation, restlessness, licking movements and searching head movements. The above effects were of brief duration. In contrast, the 0.3 and 1 mg/kg doses of DOM initially produced compulsive gnawing and biting movements. These latter effects were then followed by postural changes which were most evident at 1 mg/kg and consisted of arching of the back, muscle rigidity and catatonia. The head was rotated towards the scapular region of the back and maintained in this position for 60 - 90 min. Three of the four dogs became behaviorally depressed 60 - 90 min after 1 mg/kg of DOM administration. A true stimulatory effect of DOM was seen in one of the four dogs approximately 5 min after 1 mg/kg and this effect consisted of brief episodic convulsions. The stimulatory effect of DOM observed in this one dog resembled the stimulatory effects of DOM previously reported in cats and rabbits by Florio et al (1969). The convulsions observed in this one dog were readily controlled by multiple, small doses (2 - 3 mg/kg) of iv pentobarbital sodium. All dogs recovered uneventfully from DOM administration.

As shown in Figures 2 and 3, iv injection of BL-3912A (0.1 - 3 mg/kg) to conscious beagle dogs resulted in small increases in aortic pressure (104 ± 3 to 130 ± 6 mmHg; mean ± 1 S.E.) and cardiac rate (84 ± 6 to 116 ± 3 beats/min) in the four dogs studied. Administration of 5 mg/kg of iv BL-3912A resulted in a further pressor response to 145 ± 7 mmHg that was significantly different from the predrug control (p = <0.001). Cardiac rate increased further with 5 mg/kg of iv BL-3912A to 127 ± 13 beats/min, which was significantly different from the predrug control (p = <0.05). Blood pressure and heart rate returned to predrug values in approximately 60 min. No major changes were observed in the surface lead II electrocardiograms.

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The gross behavioral effects of iv BL-3912A to conscious beagle dogs was characterized by behavioral excitation (1 and 3 mg/kg) that consisted of increased alertness, restlessness and brief compulsive licking movements (about 3 min). Injection of 5 mg/kg of BL-3912A resulted in further behavioral stimulation, with one of the four dogs having a brief convulsion. The remaining three dogs receiving 5 mg/kg showed brief periods of extension of the hindlimbs and muscle rigidity. The latter effects were interpreted to be preconvulsive behavioral changes induced by BL-3912A. The behavioral stimulatory changes resulting from 5 mg/kg of BL-3912A lasted approximately 60 min. All dogs recovered uneventfully from BL-3912A administration.

Anesthetized Dogs

The effects of iv administration of BL-3912A (0.3 - 10 mg/kg) on the cardiovascular system in anesthetized dogs are summarized in Figure 4. A dose related decrease to BL-3912A administration occurred in heart rate, cardiac contractile force and aortic blood pressure. After a dose of 5 mg/kg the cardiovascular changes were back towards control levels in approximately 5 min, whereas after a 10 mg/kg dose of BL-3912A the cardiovascular parameters were back towards control in approximately 20 min.

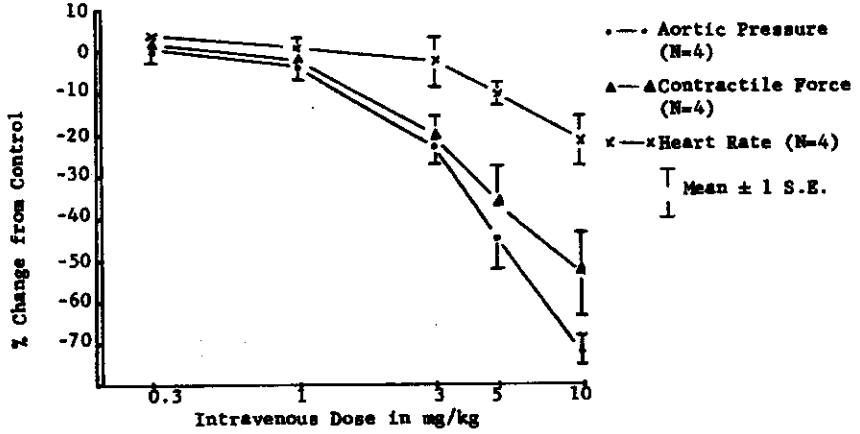

Figure 4 - Cardiovascular effects of BL-3912A in the anesthetized dog.

DISCUSSION

Elevation of blood pressure due to acute amphetamine administration is generally accepted to be due to release of norepinephrine from adrenergic stores (Muschall, 1966). The pressor actions on blood pressure induced by this indirect acting sympathomimetic amine can occur in conscious and anesthetized dogs and indicates that the peripheral catecholamine releasing actions of amphetamine plays a major role in the elevation of blood pressure. Additionally, the marked central nervous system excitation induced by amphetamine and the resultant increases in sympathetic nerve activity may be another mechanism involved in contributing to the amphetamine induced pressor response in conscious dogs. In relation to this, tachyphylaxis to the pressor effect of amphetamine is readily observed in the anesthetized dog (Winder et al., 1948) but not in the present study with conscious dogs. This indicates that with acute administration of high doses of amphetamine (3 mg/kg) central nervous system stimulation probably plays a role in the amphetamine-induced elevation in blood pressure. Our findings that cardiac rate was reduced by amphetamine in conscious dogs (0.1 - 1 mg/kg; Figure 3) could indicate that this was a reflex effect due to the marked rise in systolic pressure.

Recent studies with DOM in anesthetized dogs showed that this drug elevates aortic blood pressure through a direct vasoconstrictor effect on peripheral vascular smooth muscle (Bossier et al., 1972, Cheng et al., 1973). Tachyphylaxis developed rapidly to the pressor effects of iv DOM administration (Cheng et al., 1973).

In the present study in conscious dogs, DOM raised aortic pressure and heart rate at 0.1 mg/kg with little or no further effect at 1 mg/kg. This latter observation tended to indicate that tachyphylaxis to the cardiovascular effects of DOM may also occur in conscious dogs. The gross behavioral effects observed with DOM in the present study, using doses of 0.1 - 1 mg/kg, tended to indicate that marked central nervous system stimulation was not contributing to the cardiovascular effects of DOM in three of the four dogs studied. In the one dog that showed behavioral stimulation after 1 mg/kg of DOM (convulsions), this effect was delayed in onset (5 min) and

occurred after the cardiovascular measurements. Thus, in anesthetized and conscious dogs DOM administration raises blood pressure and this effect is probably mediated in large part through peripheral vasoconstriction.

The present studies with BL-3912A showed that in pentobarbital anesthetized dogs this drug acted as a depressant on the cardiovascular system. Beginning at 1 mg/kg (Figure 4), dose related reductions were apparent in aortic pressure, cardiac contractile force and heart rate. In contrast, administration of iv BL-3912A to conscious dogs resulted in an elevation in blood pressure and heart rate. These changes in the conscious dog were interpreted to be due to the behavioral stimulation resulting from BL-3912A. The depression of various cardiovascular parameters observed in the anesthetized dog with BL-3912A lend further support to the concept that selective central nervous system stimulation and the resultant effects on sympathetic nerve activity may be an important mechanism for elevating blood pressure and cardiac rate in conscious dogs.

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