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Effects of α-methyldopa on blood pressure in the anaesthetized dog

P. R. BLOWER, R. H. POYSER† AND M. I. ROBERTSON*

Beecham Pharmaceuticals, Research Division, Medicinal Research Centre, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD, U.K.

Intravenous infusion over 1 h of 20 mg kg^{-1} of α-methyldopa produced hypotension in the anaesthetized dog. The magnitude of this effect was, however, inversely correlated with bodyweight. Either rapid intravenous injection of α-methyldopa or slow infusion of α-methyldopate was less effective in lowering blood pressure than infusion of free α-methyldopa, in dogs of equivalent bodyweight. Infusion of α-methyldopa into a vertebral or internal carotid artery produced hypotensive responses but these were no greater and generally less than those obtained to intravenous infusion. α-Methyldopa was therefore capable of producing hypotension in the dog but no evidence was obtained for this being the result of an action within the brain.

Although α-methyldopa is an effective antihypertensive agent in man, there is conflicting evidence about its blood-pressure lowering activity in the dog. Goldberg, DaCosta & Ozaki (1960), for example, reported that α-methyldopa produced hypotension in the conscious normotensive dog but other workers were unable to demonstrate appreciable blood-pressure reductions in the anaesthetized normotensive dog (Stone, Porter & others, 1961; Kroneberg, 1963; Day & Rand, 1964). In the conscious hypertensive dog, Stone & others (1961) and Sweet, Wenger & O'Malley (1974) reported α-methyldopa to be ineffective whereas Kroneberg (1963) observed a significant antihypertensive response to the drug.

Even in other species such as the rat and the cat, where the effectiveness of α-methyldopa is less in doubt, the site of the blood-pressure lowering action is a subject of controversy. Some evidence supports a central site of action (Henning & Van Zwieten, 1968; Day, Roach & Whiting, 1973; Finch & Haeusler, 1973) but other data indicate a direct action on blood vessels (Zaimis, 1965; Ayitey-Smith & Varma, 1970).

In this paper we report our investigations on the effects of α-methyldopa on blood pressure in the anaesthetized normotensive dog. We have administered the compound intravenously and examined some possibilities to account for the discrepancies in the literature on the response of this species to the drug. In addition, we have compared the effects following intravenous administration with those which followed intra-arterial injection into vessels supplying different regions of the brain.

*Present address: Department of Pharmacology, Union International Research Centre, Old London Road, St. Albans, Herts AL1 1PX, U.K.
†Correspondence

METHODS

Thirty-four beagle dogs of either sex, 4·6–18·4 kg, were anaesthetized by an intravenous injection of 35 mg kg^{-1} of pentobarbitone sodium. A cannula was inserted into the right femoral artery and connected to a pressure transducer (Bell and Howell Ltd., type 4-327-L221) for the measurement of arterial blood pressure. Heart rate was obtained from the amplified blood pressure signal using a Devices instantaneous ratemeter (type 2751). A cannula was inserted into the trachea and attached to a Fleisch pneumotachograph head type I connected to an Ether differential gas pressure transducer (type UP1 ± 10 in water) for measurement of respiratory peak air flow and rate. Blood pressure, heart rate and the respiratory responses were monitored on a Devices M8 or M19 pen recorder. The blood pressure was expressed as mean blood pressure which was calculated as diastolic pressure plus one-third pulse pressure.

Each dog was prepared for either intravenous dosing with drug or vehicle alone or for administration of drug or vehicle alone via a vertebral or internal carotid artery.

Cannulation of the vertebral artery was performed essentially as described by Constantine & McShane (1968). The right vertebral artery was exposed in the neck region and the shaft of a 20 gauge needle, attached to nylon tubing, was inserted cephalad and held in position by a loose tie. A similar technique

was used to cannulate the right internal carotid artery. Intravenous dosing was via the right femoral vein.

Throughout all experiments the animals were breathing spontaneously and their body temperatures were maintained as close as possible to 38°. For most experiments, and unless otherwise specified, α-methyldopa was used as the free compound (methyldopa B.P.) and administered at a dose level of 20 mg kg^{-1} bodyweight in slightly-acidified (pH 4·5) normal saline. Control experiments showed that, by each route of administration, acidified saline alone had no significant effects on blood pressure, heart rate and respiration. In four dogs, using the intravenous route, the dose of 20 mg kg^{-1} of α-methyldopa was administered as a dilution of commercial Aldomet Injection, this being a preparation of α-methyldopate hydrochloride.

All injections had a volume of 13·2 ml and were infused over a period of 1 h, using a Palmer slow-injection apparatus, except in some additional experiments employing the intravenous route when the injection of free α-methyldopa was given within 1 min.

RESULTS

Generally, blood pressure in the anaesthetized dog changed little during intravenous infusion of α-methyldopa but immediately afterwards there was a fall which was at a maximum 2–3 h after dosing started. The blood pressure subsequently returned towards the pre-dose value (Fig. 1).

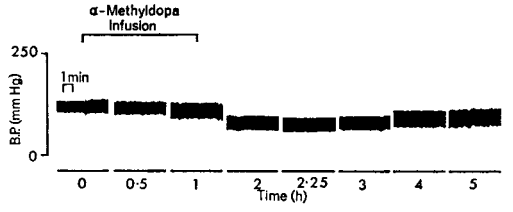

FIG. 1. Hypotensive response to intravenous infusion of 20 mg kg^{-1} of α-methyldopa in an anaesthetized beagle dog, bodyweight 8·5 kg. The blood pressure before and at various times after the commencement of the α-methyldopa infusion is shown.

Quantitatively, the hypotensive response to intravenous infusion of α-methyldopa varied between dogs, being minimal in large animals. Statistical analysis indicated a significant inverse correlation ($P < 0·01$) between the magnitude of the blood pressure fall and animal weight (Fig. 2A). There was no correlation ($P > 0·1$) between the hypotensive response and the initial mean blood pressure value

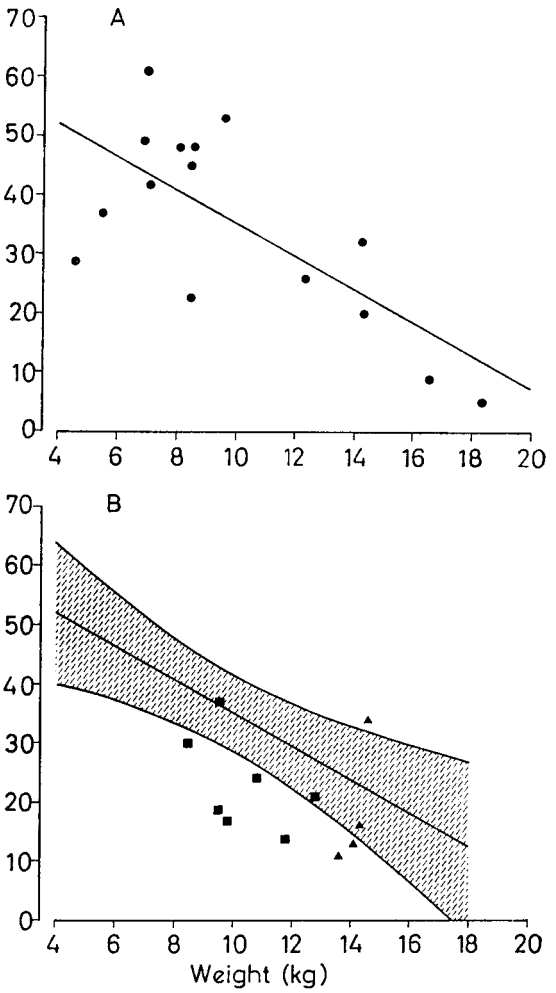

FIG. 2. Hypotensive responses following infusions of 20 mg kg^{-1} of α-methyldopa into a femoral vein, vertebral artery and internal carotid artery of anaesthetized beagle dogs. For each route of administration the α-methyldopa was dissolved in 13·2 ml of acidified (pH 4·5) normal saline and infused at a constant rate over a period of 1 h. Responses are plotted against weight and each point shown represents a single dog. A. Hypotensive response to intravenous infusion, the line being the calculated regression line, $r = -0·72$, $P<0·01$. B. Hypotensive responses to infusions into a vertebral (■) or internal carotid artery (▲) shown together with the regression line plus 95% confidence limits for intravenous administration. Ordinate: Fall in mean b.p. (mm Hg).

which averaged 123 (± s.e.m. of 5·8) mm Hg for the 15 dogs in the intravenous infusion group. In addition the hypotensive response did not depend on the sex of the animal.

In four dogs of 7–9 kg, the dose of α-methyldopa was injected within 1 min. This, too, produced hypotension, but the blood pressure fall (mean

± s.e.m.) for the group (17 ± 3·4 mm Hg) was significantly less ($P < 0·01$, Student's t-test) than that (45 ± 3·4 mm Hg) for the six dogs in the same weight range receiving the dose as an infusion over 1 h.

The hypotensive response to infusion of α-methyldopa was reduced when α-methyldopate was used instead of the free compound. In four dogs of 6–9 kg, infusion over 1 h of 20 mg kg^{-1} of α-methyldopa as α-methyldopate produced a fall in mean blood pressure (during a 5 h post-infusion period) of 13 (± s.e.m. of 1·9) mm Hg. This was significantly less ($P < 0·001$, Student's t-test) than the response (45 ± 4·3 mm Hg) for the seven dogs within the same weight range receiving the infusion of the free compound.

Preparation of dogs for injection into an internal carotid or vertebral artery did not significantly alter ($P > 0·5$) resting mean blood pressure, compared with dogs set up for intravenous injection. Resting mean blood pressure averaged 131 (± s.e.m. of 14·5) mm Hg for the internal carotid group (n = 4) and 119 (± 7·2) mm Hg for the vertebral artery group (n = 7). On completion of the infusion of α-methyldopa into either of these two arteries, a hypotensive response developed which followed a similar time course to that seen after intravenous infusion. To compare the magnitude of responses between routes, the maximum hypotensive effect in each dog receiving α-methyldopa by the internal carotid or vertebral arteries was plotted against bodyweight and superimposed on the regression line, with 95% confidence limits, for the intravenous route. The resulting figure (Fig. 2B) indicated that the hypotension following internal carotid or vertebral artery infusion was no greater and generally less than that to intravenous infusion of α-methyldopa.

Although α-methyldopa produced hypotension by each route of administration upon cessation of the infusion, qualitative differences in responses between routes were observed during the infusion. In all four dogs receiving α-methyldopa via the internal carotid artery, pressor responses ranging from 11 to 93 mm Hg (mean ± s.e.m. of 45 ± 17 mm Hg) were observed as the drug was administered. These ceased abruptly when the infusion was completed. Pressor responses were observed in two of the seven dogs for which the vertebral artery route was used, and were never seen during intravenous infusion.

Heart rate and the respiratory parameters were not appreciably altered by α-methyldopa treatment in any experiment.

DISCUSSION

The data showed that α-methyldopa lowered blood pressure when infused intravenously into the anaesthetized dog. However, the response was more pronounced in smaller animals and proved to be inversely correlated with bodyweight. This influence of weight may explain the differences in results obtained by previous authors (see Introduction). Other factors which could explain such differences are the speed of injection and the type of α-methyldopa preparation used. Administration of α-methyldopa within 1 min was less effective in lowering blood pressure than infusion of the same dose over 1 h, in dogs within the same weight range. Similarly, an hour-long infusion of α-methyldopate, which is the ethyl ester of α-methyldopa, was less effective than infusion of the free compound. Why α-methyldopa was less effective on rapid administration is not clear but could be involved with kinetics of tissue uptake, distribution, elimination and/or enzymatic conversion. α-Methyldopate may be less effective because of slow hydrolysis *in vivo* to liberate free α-methyldopa (see Dollery, 1975).

In the rat and the cat, α-methyldopa is metabolized to α-methylnoradrenaline which is believed to be responsible for the hypotensive effect (Day & Rand, 1964; Henning & Rubenson, 1971; Heise & Kroneberg, 1972; Day & others, 1973). Porter & Titus (unpublished observations cited by Torchiana, Wenger & others, 1966) found that the dog converted little α-methyldopa to α-methyldopamine and α-methylnoradrenaline. It may be, however, that in the dog such metabolism of α-methyldopa diminishes with age which could explain the negative correlation we obtained between reduction of blood pressure and weight. The weight of dogs, up to a certain limit, usually reflects age and the dogs of low weight we used were all young animals.

Our results with vertebral artery infusion of α-methyldopa in the anaesthetized dog contrast with those of Henning & Van Zwieten (1968) in the anaesthetized cat where a greater fall in blood pressure occurred after the arterial administration than after intravenous infusion. The dose of α-methyldopa (20 mg kg^{-1}) we administered to dogs was the same as that used by Henning & Van Zwieten (1968) as was the method of administration (i.e. infusion over 1 h). Differences between the two species in the relative effectiveness of these two routes of administration may stem from differences in the anatomical distribution of tributaries of the vertebral artery in the cat and the dog. In the latter species a much more diffuse area is perfused than in the cat where the

perfusion remains limited to the pontomedullary area. However, the antihypertensive agent clondine is more effective in the dog via vertebral artery than intravenous administration (Constantine & McShane, 1968), suggesting that in this species the vertebral artery route is certainly of value for detecting a central action to lower blood pressure. Thus our results with α-methyldopa provide no evidence for a central action of this compound to cause hypotension in the dog.

The increases in blood pressure seen during arterial infusions of α-methyldopa were most evident when the internal carotid artery was used and it thus seems likely that the drug produced the pressor effect by an action in the mid or fore brain. This action would appear to depend on an adequate concentration of α-methyldopa being maintained in the brain as the effect ceased immediately the infusion was completed. It may be that during infusions of α-methyldopa by the two arterial routes, and also possibly the intravenous route, a centrally-mediated pressor effect opposed the postulated peripheral hypotensive action. This could account for the hypotensive effects not usually developing until the infusions were completed.

In conclusion the present findings demonstrated that intravenous infusion of α-methyldopa produced hypotension in the anaesthetized dog and that this effect was inversely correlated with weight. Experiments to administer α-methyldopa into two main arteries supplying the brain provided no evidence for a central site of action of the drug to lower blood pressure. This is in contrast to some conclusions reached by others using different species.

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