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THE CARDIOVASCULAR PHARMACOLOGY OF 7-PROPYL-THEOPHYLLINE-DOPAMINE (D4975); COMPARISON WITH DOPAMINE AND DOBUTAMINE

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1 The effects of a newly developed dopamine-xanthine derivative, 7-propyl-theophylline-dopamine (D4975), have been examined in cats anaesthetized with sodium pentobarbitone. When administered intravenously (in doses as low as 0.5 to 1.0 μg/kg) it increased systemic arterial pressure, left ventricular (LV) dP/dt_{max}, dP/dt at fixed ventricular isovolumic pressures and cardiac output. Heart rate effects were minimal.

2 D4975 was about 5 times more active than dopamine or dobutamine in elevating LV dP/dt_{max} or dP/dt at common peak isovolumic pressures (CPIP) and about 10 times more active than dopamine at increasing systemic arterial blood pressure. The effects of D4975 were also more prolonged than those of the other two agents.

3 The effects of D4975 on LV dP/dt_{max} were greatly reduced by the prior administration of propranolol. D4975 has no effect on peripheral β_2-adrenoceptors.

4 It is suggested that the effects of D4975 on the myocardium involve both β_1-adrenoceptor stimulation and inhibition of phosphodiesterase and that the marked and prolonged pressor response is due to resistance to enzymatic breakdown by monoamine oxidase.

5 The results suggest that D4975 might prove valuable in the treatment of the hypotension and reduced myocardial contractility of shock, especially as it is possible to select a dose that increases LV dP/dt_{max} without increasing either heart rate or systemic arterial pressure.

Introduction

One of the most significant clinical developments in the drug treatment of depressed myocardial contractility has been the renewed interest in dopamine and synthetic derivatives. These developments have been discussed in a number of recent reviews on the cardiovascular pharmacology of dopamine which have especially emphasised the use of this amine in the treatment of chronic refractory congestive cardiac failure and in shock resulting from myocardial infarction, bacterial sepsis and trauma (e.g. Goldberg, 1972; 1974; Goldberg, Hsieh & Resnekov, 1977). There is little doubt that dopamine is an extremely useful drug in selected shock states but the complications (gangrene, expecially in patients with pre-existing vascular damage, nausea, vomiting, the increase in afterload due to peripheral vasoconstriction and the precipitation of dysrhythmias) have led to attempts to synthesize other, potentially useful, dopamine derivatives. These have included dobutamine (Tuttle & Mills, 1975) and, more recently, 5-6-dihydroxy-2-methylaminotetralin (Diana, Brenton, Long, Cannon, Laughlin, Dittrich & Montag, 1978).

A rather different approach involves attempts to produce β-phenylethylaminoalkyl-xanthine derivatives (Klinger, 1977). These compounds were originally investigated for potential bronchodilator activity and, indeed, one of them has been developed as such. This is reproterol (7-(3-[2,(3,5-dihydroxyphenyl)-2-hydroxyethylamino]-propyl)theophyllin), a bronchodilator whose effects are mediated through β_2-adrenoceptors (Habersang, Leuschner, Stroman, Domenico & von Schlichtegroll, 1977). This compound was also found to increase cardiac output and to decrease left ventricular end-diastolic pressure (LVEDP) in anaesthetized beagle dogs (Habersang *et al.*, 1977). A related theophylline-dopamine derivative, 7-propyl-theophylline-dopamine (D4975) was found in a preliminary study, by Anttila, Dreyer & Westermann (1977), to be 50 times more potent than dopamine in elevating systemic arterial pressure in anaesthetized rats and 100 times more potent in stimulating the rate of beating of guinea-pig isolated atria. We were interested in this compound from the viewpoint of its possible usefulness as a cardiac stimulant in experi-

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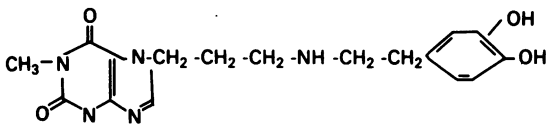
mental endotoxin shock. This paper compares the cardiovascular effects of this compound with those of dopamine and dobutamine in anaesthetized cats.



7-Propyl-theophylline-dopamine (D4975)

Methods

Thirty-two cats of either sex and with a mean weight of 2.2 kg (range 1.0 to 3.9 kg) were deprived of food overnight, anaesthetized with sodium pentobarbitone (36 to 42 mg/kg by intraperitoneal injection) and, usually, allowed to breath spontaneously. Polyethylene cannulae were placed in the right atrium (via the left femoral vein) the aortic arch (via the right common carotid artery in the neck or via the left femoral artery) and in the lumen of the left ventricle (via the left common carotid artery). Pressures were measured from each of these sites with appropriate Elema-Schönander capacitance transducers and were recorded, together with the electrocardiogram and left ventricular (LV) dP/dt, on a Mingograph 81 ink-jet writing recorder. Four of these variables were also displayed continuously on an oscilloscope (Racal Instruments type 9383). Cardiac output was measured by thermodilution (using simple copper-constantan thermocouples; Parratt, 1974) and the heart rate was measured from the electrocardiogram. Body temperature was recorded from the rectum and mid-oesophagus with direct recording thermocouples (Ellab, Copenhagen). Blood gases, pH and arterial lactate were measured by methods previously described in full (Parratt, 1974). Heparin (100 units/kg) was injected intravenously at the start of the experiments.

Dose-response curves were obtained, in the same cats, to dopamine (Sigma), dobutamine (kindly donated through Dr W. E. Brocklehurst, Lilly Research Centre) and D4975 (obtained through the kindness of Dr F. Stroman, Chemiewerk-Homburg, Frankfurt-am-Main). The three drugs were administered intravenously in doses ranging from 0.5 to 40 μg/kg. The effects of D4975 were also examined before, and 10 to 30 min after the intravenous administration of propranolol (0.25 mg/kg).

Results

The initial studies were concerned with the effects of the three compounds on systemic arterial blood pressure, heart rate and left ventricular dP/dt_{max}; the results are illustrated in Figure 1. Both dopamine and D4975 caused dose-dependent increases in arterial blood pressure, the xanthine derivative being five to eight times more active on a molar basis. Even a dose of 0.5 μg/kg of D4975 caused significant increases in left ventricular dP/dt_{max} (1400 ± 300 mmHg/s; $n = 5$) without altering systemic arterial pressure or heart rate (changes less than 10 mmHg or 10 beats/min). Dobutamine did not markedly alter arterial pressure in doses up to 40 μg/kg (Table 1). Left ventricular dP/dt_{max} was significantly increased by all three drugs (Figure 1) and again D4975 was the most active. No further increases in LV$dP/dt_{max}$ were obtained when the dose of D4975 was increased above 2 μg/kg (and up to 40 μg/kg); the increases in dP/dt_{max} being the same (3300 to 3900 mmHg/s) with doses of 5, 10, 20 and 40 μg/kg. With doses above 5 μg/kg there were also significant increases in LVEDP (e.g. + 1.1 ± 0.9 mmHg; $n = 11$ with a dose of 10 μg/kg). It seems therefore that optimum increases in contractility are obtained with a dose of 2 μg/kg (compare also Table 2). In contrast, increasing the dose of D4975 resulted in further elevations in arterial blood pressure. These, together with the changes in heart rate, are summarised in Table 1 where they are compared with the corresponding effects of dobutamine.

Not only was D4975 more active than either dopa-

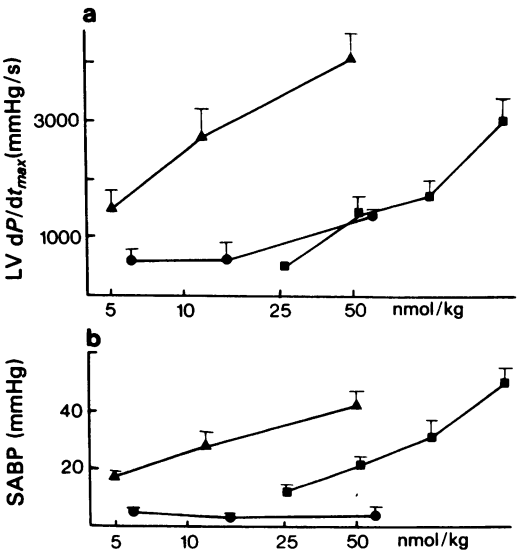


Figure 1 The effects of intravenous injections of dopamine (■), dobutamine (●) and D4975 (▲) on left ventricular dP/dt_{max} (mmHg/s) and arterial blood pressure (mmHg) in cats anaesthetized with sodium pentobarbitone. Values are means of 8 observations; vertical lines show s.e. mean.

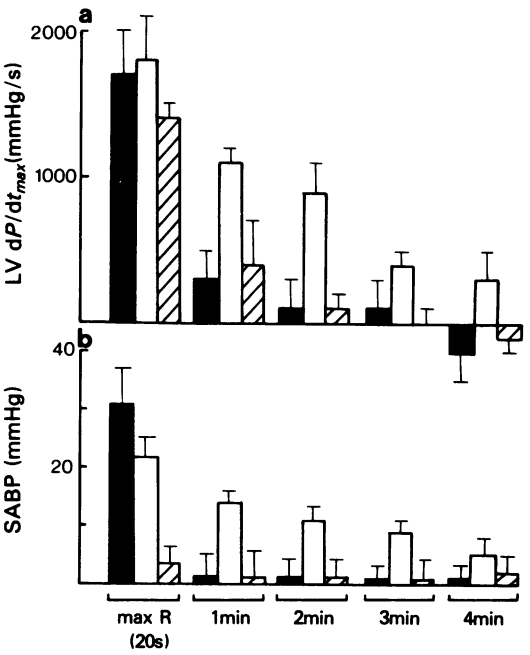


Figure 2 Comparison of the duration of action of dopamine (20 μg/kg, solid columns), D4975 (2 μg/kg, open columns) and dobutamine (20 μg/kg, hatched columns) on (a) LV$dP/dt_{max}$ (mmHg/s) and (b) arterial blood pressure (mmHg). Values are mean of 6 to 8 observations; vertical lines show s.e. mean. The maximum response (max R) was obtained 20 s after the injections.

mine or dobutamine but the effects were more prolonged. This is illustrated in Figure 2. Doses of the three drugs were chosen (20 μg/kg of dopamine and dobutamine; 2 μg/kg D4975) to give approximately similar (30 to 40%; i.e. +1500 mmHg/s) increases in left ventricular dP/dt_{max}. The maximum response to each drug occurred about 20 s after rapid intravenous injection; 2 min after the injection LV dP/dt_{max} had returned to normal in the cats receiving either dopamine or dobutamine. In contrast, significantly increased LV dP/dt and pressor responses were still apparent 4 min after the administration of an equivalent dose of D4975. This is even more pronounced if recovery times (to 50% of the maximal response) are calculated. For both dopamine and dotutamine it was 30 to 45 s; with D4975 it was betweeen 2 and 2.5 min.

One of the problems with using LV dP/dt_{max} as an index of myocardial contractility is its partial dependence upon changes in preload and afterload, although the effect of the latter has been disputed (Schaper, Lewi & Jageneau, 1965). When 'lower doses' of the cardiac stimulants were used (up to 2 μg/kg D4975 and 20 μg/kg of dopamine or dobutamine) preload did not change by more than 0.4 mmHg (from the mean LVEDP of 2.1 ± 0.3 mmHg). However, it is clear, from Figures 1 and 2 that the administration of these doses of dopamine and D4975 (though not dobutamine) resulted in substantial alterations in systemic arterial pressure and hence in afterload. There is no wholly satisfactory way of overcoming this problem but one approach is to calculate dP/dt at fixed pressures during the isovolumic phase of left ventricular contraction (Mason, 1969; Abaitey & Parratt, 1976). This involves recording left ventricular pressure (and dP/dt) using very fast paper speeds (in this case 1000 mm/s) and plotting isovolumic pressure against dP/dt at 10 mmHg intervals. Following the administration of D4975, values for dP/dt were always significantly higher than before drug administration at isovolumic pressures above 30 mmHg. Since, before the drug was administered, the aortic

Table 1 Changes* in systolic (SBP) and diastolic (DBP) arterial blood pressure, and in heart rate, induced by D4975 and dobutamine in anaesthetized cats

	D4975			*Dobutamine*		
Dose (*μg/kg*)	*SBP* (*mmHg*)	*DBP* (*mmHg*)	*Heart rate* (*beats/min*)	*SBP* (*mmHg*)	*DBP* (*mmHg*)	*Heart rate* (*beats/min*)
1	+18 ± 3	+14 ± 3	+5 ± 3	+5 ± 3	+2 ± 1	−1 ± 3
2	+36 ± 9	+23 ± 5	+13 ± 2	+8 ± 2	+3 ± 2	+6 ± 3
5	+46 ± 6	+34 ± 5	+10 ± 3	+4 ± 3	−4 ± 3	+7 ± 2
10	+56 ± 7	+34 ± 4	+13 ± 4	+15 ± 2	+4 ± 2	+13 ± 2
20	+62 ± 11	+45 ± 8	+13 ± 3	+12 ± 4	+3 ± 3	+14 ± 4
40	+70 ± 9	+52 ± 7	+13 ± 11	+12 ± 4	+1 ± 4	+26 ± 5

Values are means ± s.e. of 5 to 13 observations (D4975) and 10 observations (dobutamine).
* The mean pre-drug levels were: 147 ± 3 mmHg (SBP), 98 ± 3 mmHg (DBP) and 209 ± 4 beats/min. All the changes (with the exception of the heart rate responses to 1 μg/kg of both compounds and the DBP response to dobutamine) are significantly different ($P < 0.001$) from the effects of an equivalent volume of 0.9% w/v NaCl solution.

valves opened at a mean pressure of 98 ± 3 mmHg, we chose to compare dP/dt at a common peak isovolumic pressure (CPIP) of 80 mmHg (see Mason, 1969). The *increases* in dP/dt at this CPIP were + 1000 ± 400 mmHg/s (with dopamine, 20 μg/kg), +1300 ± 400 mmHg/s (D4975, 2 μg/kg) and +700 ± 300 mmHg/s (dobutamine, 20 μg/kg); doses of 2 and 5 μg/kg of dopamine and dobutamine did not alter dP/dt at a CPIP of 80 mmHg. These results suggest that the increases in LV dP/dt_{max} obtained with these drugs are predominantly mediated through increases in myocardial contractility rather than indirectly through increases in afterload.

Further evidence that D4975 increases myocardial contractility was obtained from measurements of cardiac output (Table 2). The optimum increase (20%) was obtained with a dose of 2 μg/kg and could be entirely accounted for by the increase in stroke volume. With higher doses (5 and 20 μg/kg) the smaller elevation in output was due to increased heart rate. Smaller, and more variable increases (less than 8%) in cardiac output were obtained with dobutamine (+12 ± 28 ml/min; $n = 8$, with a dose of 5 μg/kg and 27 ± 32 and 22 ± 35 ml/min ($n = 9$) respectively with doses of 10 and 40 μg/kg). These were also due to increases in heart rate; stroke volume was unchanged. Dopamine did not consistently increase cardiac output at any dose level and, in fact, reduced it (by 75 ± 56 ml/min) at a dose level of 5 μg/kg.

It is well documented that dopamine and dobutamine increase myocardial contractility by interacting with β_1-adrenoceptors and it was important to determine whether this is also true for the new dopamine analogue. In two cats therefore the effects of D4975 were examined before and after partial β-adrenoceptor blockade with propranolol (0.25 mg/kg). The results from one of these cats are illustrated in Figure 3. Before propranolol, D4975 increased both systemic arterial pressure and LV$dP/dt_{max}$. After propranolol, the effect of LV$dP/dt_{max}$ was much reduced and was substantial only with the largest dose used (10 μg/kg). Since, when D4975 was administered after propranolol, there was no increase in CPIP (at 80 mmHg)

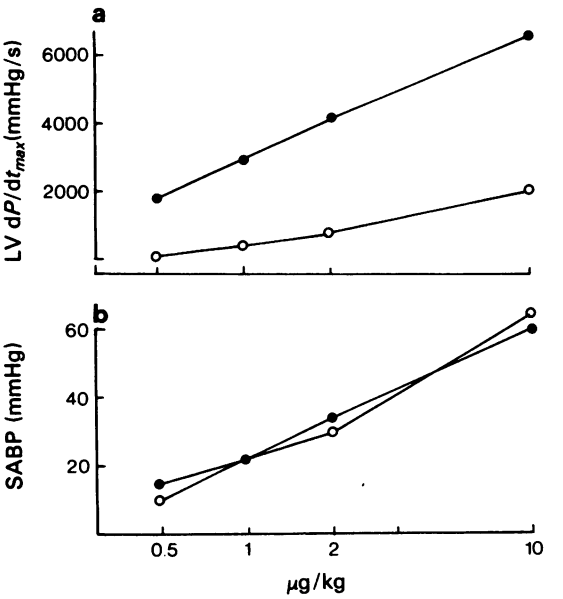


Figure 3 The haemodynamic response to D4975 before (●) and after (○) propranolol (0.25 mg/kg) in an anesthetized cat. (a) Change in LV dP/dt_{max} (mmHg/s) and (b) change in arterial blood pressure (mmHg).

it is likely that the increases in LV$dP/dt_{max}$ obtained when large doses of this compound were given after β-adrenoceptor blockade, were due to the marked increase in afterload (60 mmHg; Figure 3). It was of interest that the pressor response was not modified by propranolol, suggesting that this dopamine derivative has no significant effect on peripheral vascular β-adrenoceptors; this is in marked contrast to adrenaline.

Discussion

The present results comparing dopamine with dobutamine in anaesthetized cats appear to be similar to

Table 2 Changes in cardiac output, heart rate and stroke volume induced by intravenous injections of D4975 in anaesthetized cats

Dose (μg/kg)		*Cardiac output (ml/min)*	*Heart rate (beats/min)*	*Stroke volume (ml)*
	Control	378 ± 46	209 ± 10	1.92 ± 0.21
2		+79 ± 31	+5 ± 4	+0.39 ± 0.15
5		+66 ± 31	+23 ± 11	+0.06 ± 0.15
10		+27 ± 34	+14 ± 5	+0.06 ± 0.13

Values are means ± s.e. of 6 to 12 observations.

those obtained in dogs, whether anaesthetized (Holloway & Frederickson, 1974; Hess, Brückner, Schmidt, Schweichel & Tarnow, 1977; Lumley, Broadley & Levy, 1977) or conscious (Vatner, McRitchie & Braunwald, 1974). The main difference between the two compounds in the present studies was that dopamine markedly increased blood pressure (Figure 1) whereas dobutamine did not (Table 1). Dopamine always decreased heart rate (maximum change -8 ± 7 beats/min with a dose of 40 μg/kg). This is presumably a reflex bradycardia resulting from the elevated systemic arterial pressure. Dobutamine (which did not change arterial pressure) did not increase heart rate except in doses above 10 μg/kg (Table 1). Since even smaller doses (2 and 5 μg/kg) resulted in marked increases in $LVdP/dt_{max}$, the results support the contention of Tuttle & Mills (1975) that dobutamine can selectively increase myocardial contractility. This is also clear from published clinical and animal data (Akhtar, Mikulic, Cohn & Chaudhry, 1975; Hinds & Hawthorne, 1975; Loeb, Khan, Klodnycky, Sinno, Towne & Gunnar, 1975; Rigaud, Boschat, Rocha, Ferreira, Bardet & Bourdarias, 1977). Obviously, when the dose is increased a positive chronotropic response also becomes apparent (Hinds & Hawthorne, 1975, in conscious dogs; Marshall & Parratt, 1976, in anaesthetized greyhounds following acute coronary artery ligation; Sakamoto & Yamada, 1977, in patients following open heart surgery). The present results support the concept that (in an appropriate dose range) this agent possesses positive inotropic activity without markedly influencing heart rate or systemic arterial blood pressure. This need not imply selectively for the β_1-adrenoceptors mediating increases in contractile force (as opposed to those mediating increases in heart rate), a concept originally considered by Tuttle & Mills (1975); the comparative *in vivo* and *in vitro* studies of Lumley *et al.* (1977) show clearly that this is unlikely.

Neither dobutamine nor dopamine consistently increased cardiac output in these cats, in which there was no evidence of left ventricular failure. In fact, dopamine *reduced* cardiac output in a dose (5 μg/kg) that markedly increased $LVdP/dt_{max}$. This finding is similar to that described by Holloway & Frederickson (1974) in anaesthetized dogs and is probably due to a reduced venous return resulting from peripheral vasoconstriction. This effect was never seen with dobutamine.

The dopamine-xanthine derivative (D4975) had a spectrum of activity similar to that of dopamine. Marked increases in systemic arterial pressure occurred, even with a dose as low as 1 μg/kg. This makes the new compound about five times as active as dopamine on a molar basis (Figure 1); this is a much lower figure than that obtained by Anttila *et al.* (1977) in urethane-anaesthetized rats pretreated with atropine and chlorisondamine. In a communication to the March 1977 meeting of the German Pharmacological Society these authors presented data suggesting that D4975 was 50 times as active as dopamine in elevating arterial pressure. Anttila *et al.* (1977) did not apparently examine the positive inotropic effects of D4975 but did find that it was 100 times more active than dopamine at increasing the rate of beating of guinea-pig isolated atria. It is apparent from Figure 1 that D4975 is considerably more than five times as active as dopamine at increasing $LVdP/dt_{max}$, and in fact it is possible to select a dose (0.5 μg/kg) that markedly increased this parameter (by as much as 1400 ± 300 mmHg/s) without greatly altering blood pressure (by more than 10 mmHg) or heart rate (by more than 10 beats/min). It is clear then that some degree of selectivity is possible with this compound. The increases in cardiac output were also much more consistent than with either dopamine or dobutamine and, at least with lower doses, were due to increases in stroke volume rather than in heart rate. There was also a major difference in the duration of activity (Figure 2). 7-Propyl-theophylline-dopamine is thus more active than dopamine and has a longer duration of action. In addition, some selectivity for positive inotropic activity seems possible. It seems that it might have advantages over dopamine as a cardiac stimulant in hypotensive shock states. There is unpublished information (Stroman, 1979 personal communication) indicating that D4975, like dopamine (Goldberg, 1972; 1974; Goldberg *et al.*, 1977) increases renal blood flow. Increased renal blood flow represents one of the major therapeutic advantages of dopamine in the treatment of shock states.

It is not easy to explain the greater efficacy of the dopamine-theophylline derivative over dopamine itself. The original concept of combining xanthines with drugs that stimulate β_2-adrenoceptors was presumably that this combination might result in a more pronounced and prolonged bronchodilator activity. Stimulation of β_2-adrenoceptors in bronchial smooth muscle would result in an elevation of intracellular cyclic adenosine 3',5'-monophosphate (cyclic AMP); if phosphodiesterase (PDE) was inhibited concurrently with the stimulation of adenyl cyclase then the buildup of the intracellular mediator should be more pronounced (increased inactivity) and, further, the levels should be raised for a longer period (increase in duration of activity). There is good evidence that theophylline inhibits PDE, at least in smooth muscle (Pöch, Juan & Kukovetz, 1969). A similar argument can be advanced to explain the greater effect of the dopamine-xanthine derivative on cardiac muscle, although here the effect of xanthines on calcium flux may also be involved. There have been no direct studies to test this hypothesis and myocardial cyclic

AMP levels have not been measured after the administration of D4975 either *in vitro* or *in vivo*. There is evidence however that the positive inotropic effects of dobutamine in the cat myocardium are mediated through the generation of cyclic AMP (Tuttle, Hillman & Toomey, 1976).

Clearly this argument could not account for the more pronounced pressor response of the dopamine-xanthine derivative when compared to dopamine itself (Figure 1). One possible explanation for this is that the dopamine-xanthine compound is more resistant to enzymatic breakdown; this would also account for the increased duration of action (Figure 2). In their anaesthetized rat studies, Anttila *et al.* (1977) found that after blockade of monoamine oxidase (MAO) by pargyline, the pressor effects of intraperitoneally administered dopamine were markedly potentiated, both with respect to intensity and to duration of activity. No such potentiation was seen when D4975 was administered by the same route after pargyline. This suggests that the xanthine-dopamine derivatives are resistant to enzymatic breakdown by MAO and this would partially explain greater activity, and longer duration of action, of D4975 seen in the present experiments.

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