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A COMPARISON OF THE CARDIOVASCULAR EFFECTS OF DOBUTAMINE AND A NEW DOPAMINE DERIVATIVE (D4975) DURING SHOCK INDUCED BY *E. coli* ENDOTOXIN

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1 The effects of a newly developed dopamine-xanthine derivative, 7-propyl-theophylline-dopamine (D4975) and of dobutamine have been examined in anaesthetized cats before and after the induction of shock with *E. coli* endotoxin.

2 Both D4975 and dobutamine caused dose-related increases in left ventricular (LV) dP/dt_{max} (and $LVdP/dt$ at fixed isovolumic pressures). Significantly smaller increases in $LVdP/dt_{max}$ occurred as early as 0.5 to 1 h after endotoxin, with maximal attenuation at 1 to 2 h and some improvement in sensitivity in cats surviving 2 to 4 h. The maximum response to each drug was markedly reduced in shock.

3 Neither D4975 nor dobutamine had significant effects on heart rate. D4975 caused dose-related increases in systemic arterial blood pressure which were smaller during shock, the changes in responsiveness following those in $LVdP/dt_{max}$.

4 Possible mechanisms responsible for changing myocardial sensitivity to these and other agents are discussed. It is concluded that D4975 may be more useful in the treatment of shock than either dopamine or dobutamine because (a) it is more potent during shock than dobutamine (perhaps as a result of phosphodiesterase inhibition by the theophylline component of D4975); (b) its action is longer-lasting than dobutamine or dopamine and (c) like dobutamine, its effect on heart rate is insignificant.

Introduction

Dopamine and synthetic dopamine derivatives have been used with some success in the treatment of myocardial depression associated with chronic heart failure and shock induced by myocardial infarction, septicaemia and trauma (Goldberg, 1972; 1974; Goldberg, Hsieh & Resnekov, 1977). Recently developed dopamine derivatives include a series of β-phenylaminoalkyl-xanthine compounds (Klinger, 1977). One of these, reproterol (7-(3-[2-(3,5-dehydroxyphenyl)-2-hydroxymethyl-amino]-propyl)theophylline) has been successfully developed as a bronchodilator with an action mediated through β_2-adrenoceptors (Habersang, Leuschner, Stroman, Domenico & von Schlichtergroll, 1977). Another of this group of compounds, D4975 (7-propyl-theophylline-dopamine) has been found to be considerably more potent than dopamine in elevating blood pressure and heart rate in anaesthetized rats (Antilla, Dreyer & Westermann, 1977). We have recently compared the effects of dopamine, dobutamine and D4975 in anaesthetized cats (McCaig & Parratt, 1979) and some of the results obtained indicated that D4975 might be useful as a cardiac stimulant in shock. For example, D4975 was found to be approximately five times more potent than dopamine at increasing left ventricular $(LV)dP/dt_{max}$ and 10 times more potent in elevating systemic blood pressure. In addition, D4975 had a much greater duration of action than either dopamine or dobutamine in doses evoking the same maximal response.

Several workers have observed that during experimental endotoxin shock the positive inotropic effects of noradrenaline and adrenaline are reduced (Bhagat, Cavanah, Merrild, Rana & Rao, 1970; Parratt, 1973; Archer, Black & Hinshaw, 1975). A reduced inotropic effect of dopamine has also recently been observed in patients with septic shock (Samii, Le Gal, Regnier, Gory & Rapin, 1978). There may therefore be changes in the sensitivity of myocardial β_1-adrenoceptors in shock states. The stimulant actions of two other agents, quazodine (Parratt & Winslow, 1974) and glucagon (Bower, Okude, Jolley & Smith, 1970) are also attenuated during shock. These drugs have no

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effects on β_1-adrenoceptors but are both thought to increase cellular cyclic adenosine 3'-5'-monophosphate (cyclic AMP) levels. It is thus possible that the ability of myocardial cells to generate cyclic AMP is reduced during shock. The action of D4975 on β_1-adrenoceptors might be potentiated and protected by the presence within the molecule of the phosphodiesterase inhibitor, theophylline.

This paper describes the cardiovascular effects of D4975 and dobutamine administered before, and at various times after, shock induced by endotoxin in anaesthetized cats.

Methods

Twenty-six cats of either sex were deprived of food overnight and anaesthetized with sodium pentobarbitone (36 to 42 mg/kg by intraperitoneal injection). They were allowed to respire spontaneously wherever possible. When artificial respiration was necessary (e.g. immediately after administering endotoxin) the animals were ventilated with a Palmer positive-pressure pump using room air; the rate was 20 strokes/min and the volume 25 ml/kg body weight. Polyethylene cannulae were placed in both femoral veins and advanced to the level of the right atrium. Pressure in the descending aorta was measured from a catheter inserted via the right femoral artery and the left ventricle (LV) was catheterized via the left carotid artery. Occasionally LV pressure, following a left thoracotomy, was measured by direct ventricular puncture with a steel needle. Appropriate Elema-Schönander capacitance transducers were used to measure pressures which were recorded, along with LV$dP/dt$ and the electrocardiogram, on a Mingograph 81 ink-jet writing recorder. Heart rate was derived from the electrocardiogram and cardiac output was measured by thermodilution using saline at room temperature (Parratt, 1974). Blood gases and pH were monitored with a Radiometer blood gas analyser. Mid-oesophageal and rectal temperatures were measured by direct recording thermocouples (Ellab, Copenhagen). All cats received heparin (100 units/kg) immediately after catheterization of a femoral vein.

Two groups of animals were studied: Group 1: Sixteen cats were given graded intravenous doses of D4975; 12 of these were then given *E. coli* endotoxin (lipopolysaccharide B, Difco) 2 mg/kg intravenously. The responses to increasing doses to D4975 were again examined at four different times (0.5 to 1 h, 1 to 2 h, 2 to 3 h and 3 to 4 h) after endotoxin administration. These times are within the 'delayed shock period' (Parratt, 1973). Group 2: Ten cats were given dobutamine in graded doses by intravenous injection. Eight of these cats were then subjected to endotoxin shock (as in the Group 1 cats) and the responses to selected doses of dobutamine examined at various times during shock.

Drugs

D4975 and dobutamine were gifts from Dr F. Stroman (Chemiewerk-Homburg, Frankfurt-am-Main) and Dr W.E. Brocklehurst (Lilly Research Centre) respectively.

Statistical analysis

All comparisons were made by Student's t test for paired observations and the significance level set at $P < 0.05$.

Results

The pattern of shock development in the two groups of cats (Table1) was essentially the same as previously described (Parratt, 1973; Parratt & Sturgess, 1975; Al-Kaisi, Parratt, Siddiqui & Zeitlin, 1977). There was

Table 1 Haemodynamic changes in Group 1 and Group 2 cats administered *E. coli* endotoxin

Time after endotoxin	*Group 1*				*Group 2*			
	SBP (mmHg)	*DBP (mmHg)*	*HR (beats/min)*	*LV$dP/dt_{max}$ (mmHg/s)*	*SBP (mmHg)*	*DBP (mmHg)*	*HR (beats/min)*	*LV$dP/dt_{max}$ (mmHg/s)*
Pre	132 ± 10	87 ± 9	201 ± 11	4700 ± 400	146 ± 10	105 ± 7	188 ± 13	4800 ± 800
+0.5 h	113 ± 10*	70 ± 11*	202 ± 8	4700 ± 400	114 ± 6*	79 ± 8°	187 ± 11	4800 ± 900
+1 h	97 ± 16°	56 ± 14°	214 ± 7	4100 ± 700	97 ± 7*	66 ± 14	210 ± 16	4300 ± 900
+2 h	156 ± 16	115 ± 10	216 ± 12	7300 ± 600*	153 ± 8	107 ± 4	218 ± 7	6100 ± 1100
+3 h	145 ± 28	107 ± 27	230 ± 13	6700 ± 300	128 ± 23	89 ± 16	213 ± 8	4600 ± 1000
+4 h	162	134	225	8500	131 ± 19	89 ± 14	227 ± 26	5800 ± 1800

Values are means ± s.e. mean of 4–12 observations. Statistical significance of differences from pre-endotoxin values are denoted by $*P < 0.05$; $**P < 0.02$; $°P < 0.01$. SBP and DBP are systolic and diastolic arterial blood pressure respectively.

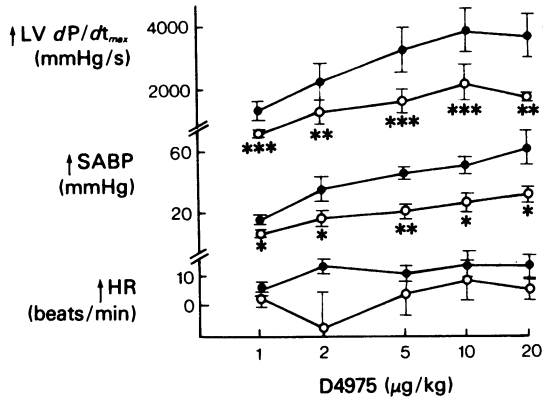

Figure 1 Changes (from the absolute values given in Table 1) in LV$dP/dt_{max}$, arterial blood pressure and heart rate, resulting from the intravenous administration of D4975 in anaesthetized cats, before (●) and 1 to 2 h after (○), *E. coli* endotoxin. Values are means of 4 to 13 observations; vertical lines show s.e. mean. $*P < 0.05$; $**P < 0.02$; $***P < 0.01$

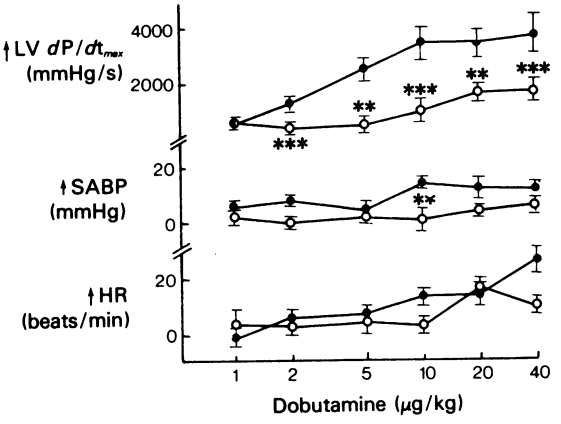

Figure 2 Changes (from the absolute values given in Table 1), in LV$dP/dt_{max}$, arterial blood pressure and heart rate, resulting from the intravenous administration of dobutamine in anaesthetized cats, before (●) and 1 to 2 h after (○), *E. coli* endotoxin. Values are means of 4 to 10 observations; Vertical lines show s.e. mean. $*P < 0.05$; $**P < 0.02$; $***P < 0.01$.

early and significant hypotension (0.5 and 1 h after endotoxin) after which arterial blood pressure returned to near pre-endotoxin levels. Heart rate tended to increase while LV$dP/dt_{max}$ was insignificantly reduced at 1 h and elevated at 2 h into shock (perhaps due to circulating catecholamines). Cardiac output fell progressively in both groups (e.g. from 340 ± 32 ml/min before endotoxin to 265 ± 57 ml/min at 4 h in the Group 2 cats). The repeated administration of either D4975 or dobutamine did not alter the development of shock.

When administered before endotoxin, both drugs evoked dose-related increases in LV$dP/dt_{max}$ without markedly changing heart rate (Figures 1 and 2) or LV end-diastolic pressure. In contrast to dobutamine, D4975 raised systemic blood pressure. In preliminary experiments the cardiovascular effects of both drugs were found to be highly reproducible when given repeatedly to the same animal. However, during endotoxin shock there were marked alterations in the responses to two agents. The increases in LV$dP/dt_{max}$ were considerably reduced, especially early in the shock phase (Figures 1 and 2) and the pressure response evoked by D4975 was markedly attenuated. This diminished responsiveness was evident as early as 0.5 to 1 h after endotoxin, the lowest responses occurred 1 to 2 h into shock, and there was some improvement in responsiveness between 2 and 4 h (e.g. Figure 3). This response pattern was similar for both D4975 and dobutamine.

It is clear from Figures 1 and 2 that the maximum effect of both drugs on LV$dP/dt_{max}$ was also reduced during shock; hence the change in sensitivity could not be overcome simply by increasing the doses. D4975 increased systemic blood pressure up to the largest dose tested (20 μg/kg) both before and during shock, so that no conclusions concerning maximal effects can be drawn. The changes in blood pressure showed the same pattern of attenuation as LV$dP/dt_{max}$.

The effects of dobutamine on LV$dP/dt_{max}$ were reduced more than those of D4975. If one compares for example, the effects of 5 μg/kg dobutamine and 2 μg/kg D4975, it is clear that both evoked similar increases in LV$dP/dt_{max}$ before shock ($+2500 \pm 400$ mmHg/s and $+2300 \pm 600$ mmHg/s respectively). However, 1 to 2 h after endotoxin, the corresponding increases were $+500 \pm 300$ mmHg/s and $+1300 \pm 400$ mmHg/s ($P < 0.01$). This difference held true for other equivalent doses of the two drugs, although the difference in the maximum responses failed to be statistically significant due to the variability of the response to the largest doses of D4975. For example, the maximum increase in LV$dP/dt_{max}$, 1 to 2 h after endotoxin, was $+2200 \pm 700$ mmHg/s D4975, but $+1700 \pm 300$ mmHg/s with dobutamine.

LV$dP/dt_{max}$ response to dobutamine and D4975 was maximal approximately 20 s after the injection and the increase lasted for 2 min (dobutamine) and 4 min (D4975) respectively. The time course of the responses was not altered during shock. Figure 4 shows the duration of the increase in LV$dP/dt_{max}$ for doses of D4975 (5 μg/kg before shock and 10 μg/kg

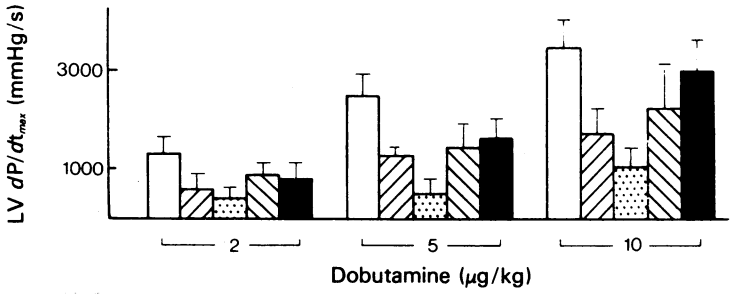

Figure 3 The increases in LV$dP/dt_{max}$ (mmHg/s) induced by dobutamine in anaesthetized cats before and during endotoxin shock. The five histograms for each dose of dobutamine are the control responses (open columns) and the responses 0.5 to 1 h (hatched), 1 to 2 h (stippled), 2 to 3 h (hatched) and 3 to 4 h (solid) after endotoxin administration. Values are means of 4 to 10 observations; vertical lines show s.e. mean.

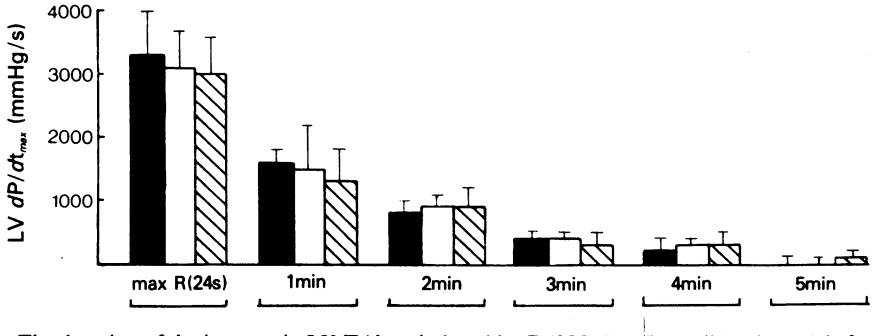

Figure 4 The duration of the increase in LV$dP/dt_{max}$ induced by D4975 (5 μg/kg, solid columns) before endotoxin and (in a dose of 10 μg/kg) 1 h (open columns) and 2 h after endotoxin (hatched columns). The maximal responses (max R) are similar, as is the duration of the response.

during shock) that gave an equivalent intensity of response.

The effects of both drugs were also examined on LV$dP/dt$ at different left ventricular pressures during the isovolumic phase of contraction. LV$dP/dt_{max}$, as an index of myocardial contractility, cannot be assumed to be independent of afterload and this changed quite considerably, especially after D4975. One method of minimizing this problem is to compare LV$dP/dt$ at given pressures during the isovolumic phase (Mason, 1969; Abaitey & Parratt, 1976). Both drugs induced dose-related increases in LV$dP/dt$ at all left ventricular pressures above 30 mmHg. Changes in the increase in this contractility index showed exactly the same pattern as using LV$dP/dt_{max}$. For example the increase in LV$dP/dt$ at a pressure of 60 mmHg with 10 μg/kg dobutamine was +1100 ± 200 mmHg/s in the control state and only +400 ± 200 mmHg/s 1 to 2 h after endotoxin. These results strongly suggest that the true positive inotropic potency of both dobutamine and D4975 is reduced during shock.

Discussion

The results clearly show attenuation of the cardiac stimulatory effects of dobutamine and D4975 during endotoxin shock in the cat. The systemic hypertensive response to D4975 was also diminished. Observations were begun as early as possible in the shock phase, after recovery from the acute pulmonary response (Parratt, 1973; Parratt & Sturgess, 1977). Between 0.5 and 1 h after endotoxin administration smaller increases in LV$dP/dt_{max}$ were observed with both drugs at a time when resting LV$dP/dt_{max}$ was unaltered from pre-endotoxin levels. Maximum depression of the response occurred between 1 and 2 h into shock, corresponding to a time when mean resting LV$dP/dt_{max}$ tended to be somewhat lower than pre-endotoxin values. Some improvement in responsiveness occurred between 2 and 4 h when resting LV$dP/dt_{max}$ was often above control levels. It has previously been shown that cats showing signs of cardiovascular improvement several hours after endotoxin administration exhibited improved sensitivity to noradrenaline and adrenaline (Parratt, 1973).

The question must be raised as to the mechanism responsible for these changes in sensitivity. One possibility is desensitization of the myocardial β_1-adrenoceptors, possibly as a result of the high circulating levels of catecholamines found in experimental shock (Nykiel & Glaviano, 1961; Cavanah, Rao, Sutton, Bhagat & Bachmann, 1970). The fact that minimum sensitivity occurred when resting $LVdP/dt_{max}$ was lowest, might suggest that in some cats endogenous catecholamines were unable adequately to maintain contractility. Since diminished potency is associated with several drugs that are thought to act by increasing cyclic AMP levels (noradrenaline, adrenaline, glucogen, quazodine, see Introduction for references) it is possible that cyclic AMP generation is inhibited during shock. It was considered likely that, if this were so, D4975 should retain greater potency than other β_1-adrenoceptor stimulants since it contains the phosphodiesterase inhibitor, theophylline. Comparison with dobutamine showed that D4975 did indeed retain its higher potency, indirectly supporting the concept of a defect in the cyclic AMP system.

If changes in the myocardium in shock were limited to the β_1-adrenoceptor and/or cyclic AMP systems, an agent that stimulated the heart independently of these (e.g. calcium) should have unaltered potency during shock. We have previously ruled out the possibility that ultrastructural damage could account for changes in sensitivity (McCaig, Kane, Bailey, Millington & Parratt, 1979). It was found in these studies that cardiac muscle isolated from cats 5 h after shock was induced, exhibit only slight mitochondrial damage and oedema, with no damage to the contractile elements. Tension development and electrophysiological properties were essentially normal. However, left ventricular function does deteriorate early in shock since, at 1 h, stroke work can no longer be increased by elevating left ventricular filling pressures by saline infusion (unpublished observations). This supports the concept that changes other than at the cardiac receptor level occur. A similar phenomenon is clear from the results of Cann, Stevenson, Fiallos & Thal, (1972) in a canine septic shock model. Endotoxin has been shown, *in vitro*, to inhibit sarcoplasmic reticular sequestration of Ca^{2+} (Hess & Briggs, 1971) and to inhibit myofibrillar ATPase (Parker & Sardesai, 1973) and these factors might be significant if they could be demonstrated to occur *in vivo*.

Finally, one can ask if D4975 has a possible role in the treatment of circulatory shock. Several factors suggest that it might indeed be useful. Although its potency is reduced in shock this reduction is less marked than with dobutamine or dopamine (unpublished observations). The effects are longer-lasting and like dobutamine, D4975 has minimal effects on heart rate. In addition the smaller increases in systemic blood pressure in response to D4975 during shock decreases the likelihood of unwanted hypertension. D4975 therefore compares favourably with other agents which are commonly used in the treatment of clinical shock and, like dopamine, it has the advantage of being able to increase renal blood flow (Stroman, personal communication).

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