J. Pharm. Pharmacol. 1979, 31: 583–587 Received December 27, 1978

Haemodynamic effects of the carboxylic ionophore monensin when administered before and during shock induced by *E. coli* endotoxin

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The haemodynamic effects of the carboxylic ionophore monensin have been examined in cats anaesthetized with sodium pentobarbitone. Marked increases in left ventricular dP/dt_{max} (and dP/dt at fixed isovolumic pressures) and slight increases in cardiac output and stroke volume occurred, indicating increased myocardial contractility. Heart rate was unchanged but systemic arterial pressure was substantially increased. Satisfactory increases in contractility and arterial pressure were obtained when monensin was infused intravenously in a total dose of 0·25 mg kg^{-1} over 10 min. Larger doses, especially if rapidly injected, resulted in very marked increases in myocardial contractility leading eventually to cardiac failure. The haemodynamic effects of monensin were markedly reduced during shock induced by *E. coli* endotoxin and there was unfortunately no evidence to suggest that this extremely potent compound might be potentially beneficial in this form of profound cardiovascular shock.

Ionophores (meaning 'ion bearers') are compounds of moderate molecular weight (e.g. 500–1500), originally isolated from microorganisms, which form lipid soluble complexes and carry a variety of cations across cell membranes (see review by Pressman & de Guzman 1975). Because of the ability of some ionophores to transport Ca^{2+} and catecholamines, Pressman suggested that they be examined for possible effects on the heart and circulation. The cardiac effects of some of these compounds are dramatic, with very long-lasting increases in myocardial contractility and coronary blood flow. The carboxylic antibiotic ionophore X-537A (RO 2-2985, isolated from a species of streptomyces and containing a single carboxyl group which is usually deprotonated when complexed with cations) has been the most extensively investigated (de Guzman & Pressman 1974; Pressman & de Guzman 1975; Schwartz et al 1974; Hanley et al 1975; Watson 1978). It increases external cardiac work without markedly altering myocardial oxygen consumption and hence increases myocardial efficiency; this is in contrast to the effects of catecholamines (Pressman & de Guzman 1975).

It was originally considered that the transport of Ca^{2+} and catecholamines (especially noradrenaline) could explain the haemodynamic effects of antibiotic ionophores but this concept clearly does not explain why other ionophores (e.g. A 23187), with similar Ca^{2+} and amine binding properties, do not have a positive inotropic action (Schwartz et al 1974). In addition, another carboxylic ionophore, monensin, despite low Ca^{2+} and amine binding properties, has marked haemodynamic effects in anaesthetized dogs, increasing myocardial contractility and, independently, coronary blood flow (Pressman & de Guzman 1975; Somani et al 1975). Because this was the most active of the carboxylic ionophores investigated by Pressman & de Guzman (1975), and because they have suggested that 'carboxylic ionophores might be expected to find application in reversing shock of various etiologies', we have examined the haemodynamic effects of this compound in cats before and during shock induced by *Escherichia coli* endotoxin.

MATERIALS AND METHODS

Cats, 13 of either sex, were anaesthetized with sodium pentobarbitone (40 mg kg^{-1} i.p.) and allowed to breathe spontaneously. Cannulae were placed in the right atrium (via a femoral vein), the aortic arch (via a femoral artery) and the lumen of the left ventricle (via the left common carotid artery). Pressures were measured from each of these sites using appropriate Elema-Schönander capacitance transducers and were recorded, together with the electrocardiogram (standard limb leads) and left ventricular dP/dt, on a Mingograph 81 ink-jet

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writing recorder. Four of these parameters were also displayed continuously on an oscilloscope (Racal Instruments). Cardiac output was measured by thermodilution using simple copper-constantan thermocouples in the aortic arch and rectum and room temperature saline as the injectate (Parratt 1974). The heart rate was measured from the electrocardiogram. Body temperature was recorded from the mid-oesophageal region using direct recording thermocouples (Ellab, Copenhagen). Heparin was injected intravenously (100 units kg^{-1}) at the commencement of the experiment.

Monensin sodium (donated through the kindness of Dr R. Tuttle, Eli Lilly Research Laboratories, Indianapolis) was freshly dissolved in a mixture of equal quantities of ethanol and distilled water and was administered intravenously either by single injection (in doses ranging from 0·25 to 2·0 mg kg^{-1}) or by continuous infusion (0·25 mg kg^{-1} total dose over 10 min). Shock was induced in five of the animals by the intravenous administration of *E. coli* endotoxin (Difco Laboratories) in a dose of 2 mg kg^{-1} given over one minute. This dose is an LD80 in this species and produces a delayed shock characterized by systemic hypotension, a reduced cardiac output and elevated arterial lactate concentrations (see, for example, Parratt 1973; Parratt & Sturgess 1975; Al-Kaisi et al 1977).

RESULTS

In three cats the effects of single intravenous injections of monensin (0·25 to 2·0 mg kg^{-1}) were examined. There were marked increases in both left ventricular (LV) dP/dt_{max} and systemic arterial pressure but in two of the cats, especially with the higher doses, massive increases in left ventricular filling pressure (LVEDP) also occurred which were still apparent up to 1 h after the injection. One of the cats subsequently died in left ventricular failure. Clearly monensin is a potent cardiovascular drug which, in large doses (1–2 mg kg^{-1}), and especially if rapidly administered, can result in haemodynamic deterioration.

In subsequent studies it was decided to administer the drug by slow intravenous infusion (over 10 min) in a relatively low dose of 0·25 mg kg^{-1}. Eleven cats were used. Six responded to the infusion with substantial and progressive (Fig. 1) elevations in LV dP/dt_{max} (maximum increase + 3740 ± 750 mm Hg s^{-1}). One of the problems with the use of LV dP/dt_{max} as an index of myocardial contractility is its partial dependence upon afterload. Since, in these studies, monensin markedly elevated systemic arterial pressure (by +34 ± 9 mm Hg systolic and by +19 ± 6 mm Hg diastolic, from the pre-drug levels of 159 ± 9 and 118 ± 8 mm Hg respectively), left ventricular dP/dt was measured at fixed isovolumic pressures (Mason 1969; Abaitey & Parratt 1976). Because monensin increased LVdP/dt at a common peak isovolumic pressure (CPIP) of 80 mm Hg (by a mean of +1800 ± 400 mm Hg s^{-1}) it can reasonably be concluded that the increase in $LVdP/dt_{max}$ observed after the administration of the drug is predominantly due to an increase in myocardial contractility. This is supported by the findings that there was a sub-

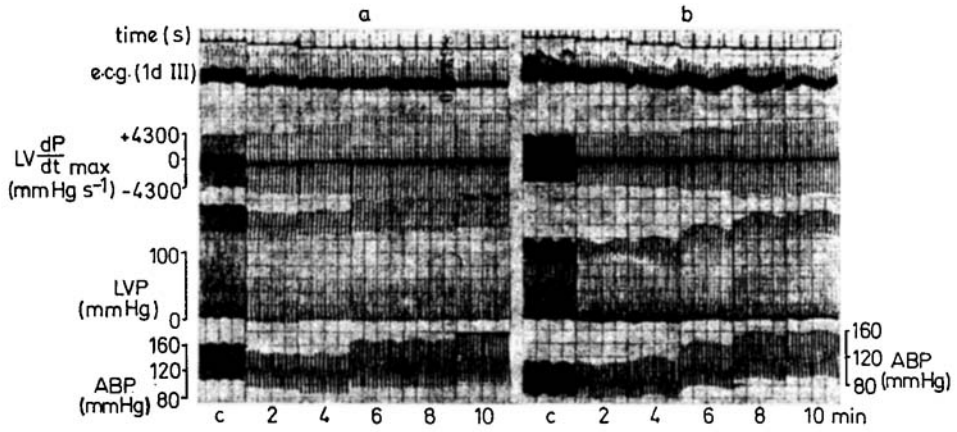

FIG. 1. The haemodynamic effects (electrocardiogram, LV dP/dt, left ventricular pressure and aortic blood pressure) of monensin (total dose of 0·25 mg kg^{-1} infused intravenously over 10 min) in an anaesthetized cat before (on the left) and 1–2 h after (on the right) *E. coli* endotoxin. C represents the pre-drug situation and representative records (4–5 s in duration) are shown at different times after the commencement of the infusion. Notice that the increase in LV dP/dt is much less marked during endotoxin shock.

stantial reduction in left ventricular filling pressure in most of the cats (mean reduction $-0{\cdot}9 \pm 1{\cdot}0$ mm Hg) and, in four out of six experiments, increases in cardiac output (of $+62 \pm 35$ ml min^{-1} from a mean control level of 329 ± 29 ml min^{-1}) and stroke volume (of $+0{\cdot}3 \pm 0{\cdot}1$ ml/beat). Heart rate was unchanged ($+3 \pm 12$ beats min^{-1} from the control pre-drug rate of 221 ± 15 beats min^{-1}). This should not be taken as implying that monensin increases myocardial contractility (increases in LV dP/dt and cardiac output; reduction in LVEDP) with little direct effect on heart rate; a direct positive chronotropic effect could have been masked by reflex vagal stimulation resulting from the substantial elevations in systemic arterial pressure. Infusion of the carrier solution (1:1 ethanol and distilled water) had no significant haemodynamic effects when administered, in appropriate quantities, over a 10 min infusion.

The haemodynamic effects of monensin varied with the dose administered and this is also clear from Fig. 1. Two and 4 min after the commencement of the infusion (i.e. after a total dose of up to 0·1 mg kg^{-1}) there was a slight (less than 20 mm Hg) reduction in systemic arterial pressure. LVEDP was also decreased at these times although LV dP/dt_{max} was elevated. This further supports the conclusion that increased LV dP/dt_{max} is mainly not secondary to increased afterload. As the infusion was continued, pressure tended to rise and there were further increases in both +ve and −ve LV dP/dt. Monensin thus increases the intensity of both the contraction and relaxation processes in cardiac muscle. After the infusion was terminated LV dP/dt_{max} and arterial pressure declined, at a similar rate, towards pre-drug levels but remained elevated above control for between 30 and 40 min (Fig. 2).

One surprising and unexplained finding was the complete failure of four of the 11 cats to respond to this dose of monensin; one other cat also failed to respond to the initial dose but then gave consistent haemodynamic responses to subsequent infusions.

Shock was induced with *E. coli* endotoxin in five of the cats in which monensin gave a positive response. Monensin was then infused at two different times (1–2 h and 2–3 h) after the commencement of shock. The haemodynamic effects of this dose of endotoxin are shown in Table 1 and are similar to those described elsewhere (Parratt 1973; Parratt & Sturgess 1975; Al-Kaisi et al 1977) i.e. slight, but significant, systemic hypotension, tachycardia and a reduced cardiac output. The effects of monensin were profoundly modified during this delayed shock phase. The increases in LV dP/dt_{max} were significantly less than those observed before endotoxin was administered (Table 2; Fig. 1), especially after 2–3 h, when monensin had no effect on either LV dP/dt or systemic arterial pressure (Table 2). During shock monensin tended to *increase* LVEDP (e.g. by $+1{\cdot}0 \pm 1{\cdot}4$ mm Hg at 1–2 h and by $+1{\cdot}5 \pm 1{\cdot}9$ mm Hg at 2–3 h), in contrast to the reduction before shock (by $-0{\cdot}9 \pm 1{\cdot}0$ mm Hg), and *reduced* cardiac output (e.g. by -45 ± 21 ml min^{-1} at 2–3 h). Changes in LV dP/dt at a common

Table. 1. The delayed haemodynamic response to endotoxin in cats receiving monensin. Values quoted are means ±s.e.m. with the number of observations in parenthesis.

	Control 1 (pre-monensin)	Control 2 (pre-endotoxin)	Time after endotoxin (h) 0·5	1	2	3
Systolic blood pressure (mm Hg)	152 ± 7 (5)	161 ± 11 (5)	119 ± 13** (5)	110 ± 12† (5)	117 ± 20 (5)	108 (2)
Diastolic blood pressure (mm Hg)	112 ± 7 (5)	122 ± 9 (5)	89 ± 10* (5)	72 ± 8‡ (5)	77 ± 12 (5)	61 (2)
Heart rate (beats min^{-1})	220 ± 13 (5)	232 ± 11 (5)	256 ± 11* (5)	256 ± 12 (5)	242 ± 21 (5)	225 (2)
LV $\frac{dP}{dt}$ max (mm Hg s^{-1})	5500 ± 900 (5)	6700 ± 1000 (5)	5400 ± 600 (5)	4800 ± 1000* (5)	4000 ± 700 (5)	3000 (2)
LVEDP (mm Hg)	1·7 ± 0·6 (5)	5·7 ± 4·6 (5)	1·9 ± 0·9 (5)	0·5 ± 1·5 (5)	4·7 ± 2·7 (5)	510 (2)
Cardiac output (ml min^{-1})	407 ± 72 (5)	353 ± 37 (5)	254 ± 24 (5)	303 (2)	274 ± 49 (4)	211 (2)
Stroke volume (ml beat^{-1})	1·89 ± 0·42 (5)	1·55 ± 0·23 (5)	1·02 ± 0·10 (5)	1·19 (2)	1·04 ± 0·12 (4)	0·80 (2)

Statistical significance of differences from control 2 is indicated by *$P<0{\cdot}05$; **$P<0{\cdot}02$; †$P<0{\cdot}01$; ‡$P<0{\cdot}001$.

Table 2. The effects of monensin (0·25 mg kg^{-1} infused intravenously over 10 min) before and during shock induced by endotoxin. Values quoted are means ± s.e.m. with the number of observations in parenthesis.

	Control	Time after endotoxin (h) 1–2	2–3
LVdP/dt$_{max}$ (mm Hg s^{-1})	+3700±700 (7)	+1000±300** (6)	0±400† (5)
Heart rate (beats min^{-1})	+3±12 (7)	−2±7 (6)	−4±7 (5)
Systolic blood pressure (mmHg)	+34±9 (7)	+23±6 (6)	−2±6* (5)
Diastolic blood pressure (mmHg)	+19±6 (7)	+13±5 (6)	−4±4* (5)

* $P<0·05$; ** $P<0·02$;† $P<0·01$.

peak isovolumic pressure (80 mm Hg) were also much less at 1–2 h (500 ± 300 mm Hg s^{-1} cf. with +1800 ± 400 mm Hg s^{-1} before shock) and a *reduction* in LV dP/dt occurred at 2–3 h (by 400 ± 20 mm Hg s^{-1}). The haemodynamic effects of monensin (e.g. at 1–2 h) were also more short-lived; LV dP/dt and systemic arterial pressure were back to pre-drug levels within 10 min (contrast Fig. 2).

DISCUSSION

These studies confirm previously published brief reports (Pressman & de Guzman 1975; Somani et al 1975) that monensin is a drug with marked haemodynamic effects. In most of the cats there were substantial increases in myocardial contractility (as assessed by changes in cardiac output, LV dP/dt$_{max}$ and LV dP/dt at fixed isovolumic pressures) although there appeared to be little difference between doses that (in some animals) had no haemodynamic effects and those that (in other cats) precipitated cardiac failure following massive increases in myocardial contractility and systemic arterial pressure. The dose finally selected (0·25 mg kg^{-1}), when given by slow intravenous infusion, gave rise to substantial and long lasting increases in myocardial contractility and in systemic arterial pressure (e.g. Fig. 1). Clearly monensin, as originally suggested by Pressman (for historical introduction see Pressman & de Guzman 1975; Pressman 1976), and on the basis of the present experiments, might be expected to find application in 'reversing shock of various etiologies'.

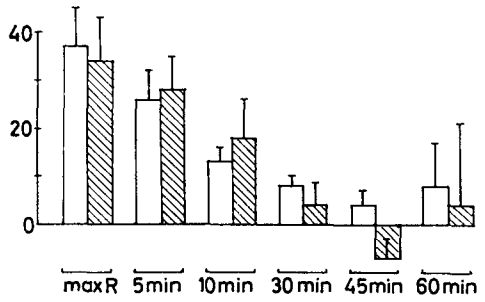

FIG. 2. The duration of the effects of monensin (0·25 mg kg^{-1} total dose administered intravenously over 10 min) in anaesthetized cats. Open columns left ventricular dP/dt$_{max}$ (× 10^2 mm Hg s^{-1}: ordinate); hatched columns arterial blood pressure; mm Hg: ordinate). Values are changes from pre-drug levels (Mean ± s.e.m. of 7 observations) at the end of the infusion period (maximal response) and at various times after the infusion was terminated.

There is certainly a need for such drugs in reversing the depression of myocardial contractility observed in many patients with shock induced by Gram -ve bacteraemia, where 'the use of a positive inotropic agent is (still) a categorical imperative' (Siegel & Fabian 1967). Ideally such a drug should have a prolonged duration of action and be suitable for intravenous administration. From these standpoints the results with monensin, administered during shock, were disappointing since the positive increases in myocardial contractility observed before shock was induced were not observed (or were drastically reduced) when the drug was administered during the delayed endotoxin-induced shock phase (Fig. 1, Table 2). In fact, rather than having beneficial effects, monensin administered during shock (especially 2–3 h post-endotoxin) was detrimental; there were reductions in cardiac output and LV dP/dt and increases in left ventricular filling pressure.

This modification of the effects of a cardiac stimulant by endotoxin is not restricted to monensin. It occurs with other cardiac stimulants, such as the catecholamines (Parratt 1973), glucagon (Bower et al 1970) and the phosphodiesterase inhibitor quazodine (Parratt & Winslow 1974). All these drugs probably act by increasing intracellular levels of cAMP, either by activating adenylate cyclase (catecholamines, glucagon) or by inhibiting cAMP breakdown (quazodine). There is some uncertainty regarding how monensin increases myocardial contractility and systemic arterial blood pressure. Indeed, these may not be related phenomena (Fig. 1). It appears that any involvement of catecholamines is indirect since monensin is virtually devoid of any capacity to transport catecholamines

Pressman & de Guzman 1975). The available evidence, such as it is, does however suggest that the effect of monensin on myocardial contractility (although not on coronary blood flow) is mediated through a catecholamine mechanism since such increases are 'almost completely abolished' by pretreatment with the cardioselective β-adrenoceptor blocking agent H 87/07 (Somani et al 1975). An ability to release noradrenaline from noradrenergic stores is a possibility although there is no convincing evidence for this. Whatever the mechanism, the present studies suggest that there is no experimental evidence to support the hypothesis that monensin has any therapeutic potential as a cardiac stimulant in the treatment of shock induced by endotoxin.

Acknowledgements

We are grateful to the Medical Research Council for continued financial support, to Eli Lilly for the gift of monensin and Drs Berton Pressman and Peter Somani for so enthusiastically introducing one of us (J. R. P.) to the world of ionophores.

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