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The haemodynamic and metabolic effects of tolmesoxide with special reference to impaired myocardial function

John E. Mackenzie, Richard J. Marshall* & James R. Parratt[1]**

Department of Biology, Reckitt & Colman, Hull, HU8 7DS; Department of Pharmacology*, Organon Laboratories, Newhouse, Lanarkshire, ML1 5SH, and Department of Physiology & Pharmacology**, Royal College, University of Strathclyde, Glasgow, G1 1XW

1 The haemodynamic, metabolic and regional blood flow effects of the vasodilator, tolmesoxide (1 mg kg^{-1} min^{-1} for 20 min by intravenous infusion) were examined in two groups of greyhound dogs anaesthetized with α-chloralose and mechanically ventilated. One group of dogs was thoracotomized and subjected to acute coronary artery occlusion. In these dogs tolmesoxide was infused 2.5 h after occlusion when there was evidence of impaired myocardial function.

2 Tolmesoxide administration resulted in marked systemic hypotension which was associated with myocardial stimulation (increase in heart rate and $LVdP/dt_{max}$). These effects were less marked in thoracotomized dogs subjected to coronary artery occlusion. Cardiac stimulation was attenuated by pretreatment with the β-adrenoceptor antagonist, atenolol.

3 Peripheral resistance and left ventricular end-diastolic pressure (LVEDP) were reduced by tolmesoxide. In spite of the systemic hypotension, the marked reduction in LVEDP resulted in an enhanced subendocardial driving pressure and an increased blood flow to ischaemic regions of the left ventricular wall as measured with Xe^{133} clearance. Blood flow to normal regions of the left ventricular wall was also increased by tolmesoxide.

4 A metabolic and respiratory acidosis may have contributed to the haemodynamic effects of tolmesoxide. Plasma renin levels were significantly elevated by the drug.

5 Tolmesoxide administration thus resulted in cardiac stimulation, reduced both pre-load and after-load, yet maintained coronary and pulmonary perfusion. This haemodynamic profile of tolmesoxide would explain the beneficial effects obtained with this drug in the treatment of cardiac failure.

Introduction

Tolmesoxide is a vasodilator which produces non-specific suppression of vascular responsiveness (Doxey, 1978) and is equiactive on arteries and veins (Collier *et al.*, 1978). Clinical studies have shown that tolmesoxide is effective in the treatment of both hypertension (O'Boyle *et al.*, 1982) and heart failure (O'Boyle *et al.*, 1981). To date, there has been no evaluation of the regional and metabolic effects of the drug either in essentially normal animals or in animals with a compromised coronary circulation. The present study considers these aspects and attempts to relate the findings to the clinical benefits of the drug. A preliminary account of some of these results has been presented to a meeting of the British Pharmacological Society (Mackenzie, 1982).

[1]Author for correspondence.

Methods

Two groups of greyhound dogs were used, in the first group (without thoracotomy) regional haemodynamic studies were carried out; in the second (open-chest) group, studies involved mainly an examination of tolmesoxide on blood flow and metabolism in both normal and ischaemic regions of the left ventricular wall.

Regional haemodynamics

Greyhounds (19–32 kg and of either sex) were anaesthetized with thiopentone (20 mg kg^{-1}, i.v.) followed by α-chloralose (80 mg kg^{-1}, i.v.). After endotracheal intubation respiration with 100% oxygen was applied from a positive pressure ventilation pump whose rate

(usually 20 per min) and stroke (usually between 300–400 ml) were adjusted to maintain arterial P_{CO_2} in the range of 35–38 mmHg. Reflex respiratory movements were prevented with an initial dose of pancuronium (0.4 mg kg^{-1}, i.v.) followed by supplemental doses of 0.04 mg kg^{-1} as necessary. This anaesthetic procedure is associated with good haemodynamic and metabolic stability over 6–8 h without the excessive sympathetic activity or acidosis associated with barbiturates or trichlorethylene.

Catheters were positioned in the left femoral artery and, via the right carotid artery, into the left ventricle. The left ventricular pressure signal was differentiated ($LVdP/dt$) to provide an index of myocardial contractility. Blood flow was monitored in the left carotid, mesenteric or renal arteries by use of Biotronix or Statham electromagnetic flow probes. Pulmonary artery pressure (PAP) and pulmonary artery wedge pressure (PAWP) were measured via a Swan-Ganz balloon catheter and recorded on a Hewlett-Packard recorder. This catheter was also used for the injection of saline for the measurement of cardiac output by the thermodilution method with a IL 601 computer. ECG (lead II) was monitored with needle electrodes and blood gases were determined with an IL 613 blood gas analyser. Body temperature was maintained at 37°C by use of a Palmer homeothermic blanket. Blood samples were analysed for plasma electrolytes (Na^+ and K^+ with an EEL 450 flame photometer and Ca^{2+} with a Spin-Chem Kit; Ski Ltd), renin (radioimmunoassay kit, Dow Lepetit) and lactate (Boehringer Mannheim GmbH reagent kit). Tolmesoxide levels in plasma were measured by the h.p.l.c. method described by Lloyd-Jones *et al.* (1981). RX75139 (Reckitt & Colman) was used as an internal standard and the mobile phase (flow 0.7 ml min^{-1}) effluent was monitored with a u.v. detector (wavelength 240 nm).

Coronary artery occlusion studies

In a further group of nine dogs, catheters were inserted under fluoroscopic control into the coronary sinus (via a jugular vein), the left ventricle (via a carotid artery) and the right atrium (via a femoral vein) and were used for blood sampling or pressure measurements with capacitance transducers and an ink-jet writing recorder (Elema-Schönander). Records of left ventricular pressure at high gain allowed accurate assessments to be made of left ventricular end-diastolic pressure (LVEDP). The heart was exposed through a left thoracotomy and the pericardium overlying the antero-lateral aspect of the heart incised. Respiration was continued with O_2 via an endotracheal tube with a 2 cmH_2O positive end-expired pressure (PEEP). Blood flow in the circumflex branch of the left coronary artery was measured by means of a Statham SP 2202 electromagnetic flow-meter. The anterior descending branch of the left coronary artery (LAD) was prepared for occlusion at a point distal to the septal artery branch. A major branch of the vein lying adjacent to the artery (the anterior coronary vein) was catheterized by the Seldinger technique with a 10 cm Longdwel teflon catheter (size 20G). After a 20–25 min stabilization period, the ligature on the LAD was tied in one stage and any ventricular dysrhythmias were treated by bolus intravenous injections of lignocaine (20–60 mg). These doses of lignocaine cause only minimal and transient haemodynamic changes (Marshall & Parratt, 1980). A Portex nylon catheter (o.d. 1.34 mm) was inserted into the peripheral stump of the ligated artery and was used for the measurement of peripheral coronary pressure (PCP) with a capacitance transducer. Small amounts of radioactive ^{133}Xe were injected into this catheter and the clearance of radioactivity (which is an index of nutritive blood flow in the ischaemic region) was measured with a sodium iodide crystal scintillation counter having a collimeter which had a narrow angle of acceptance (Marshall *et al.*, 1974; Parratt *et al.*, 1980).

These models thus allowed a study of the effects of tolmesoxide on haemodynamics and on blood flow distribution to both normal (left circumflex) and ischaemic (Xe clearance) areas of myocardium as well as to peripheral regions of the body. In addition, by comparing coronary sinus and local coronary vein blood gases it was possible to assess the effects of the drug on oxygen handling in both normal and ischaemic regions of the left ventricular wall. At least 2 h were allowed to elapse after coronary artery occlusion to enable the preparation to achieve a degree of stabilization before tolmesoxide was infused.

After control samples had been taken and measurements made, tolmesoxide was infused via the femoral vein at a rate of 1 mg kg^{-1} min^{-1} for 20 min. Samples and readings were taken every 5 min. In 3 additional dogs, set up for peripheral blood flow measurements, tolmesoxide was given as an infusion 5 min after a bolus injection of the β_1-adrenoceptor antagonist atenolol (1 mg kg^{-1}, i.v.).

The drugs used were: pancuronium bromide (Organon), thiopentone sodium (Abbott) and atenolol (ICI). Tolmesoxide (Reckitt & Colman) was dissolved in saline at a concentration to give the equivalent of 1.0 mg kg^{-1} min with an intravenous infusion rate of 1.0 ml min^{-1}).

Statistical analysis

Data were analysed by use of a Wilcoxon's matched pairs signed ranks test and a Friedmans test (which is a non-parametric two way analysis of variance; Winer, 1962; Steel & Torrie, 1980). Differences in treatment were regarded as being statistically significant when

$P < 0.05$.

Details of derived data are given in the paper by Marshall *et al.* (1974). External cardiac work (kg m min^{-1}) was calculated as cardiac output ($l\,min^{-1}$) × mean blood pressure (mmHg) × 13.6×10^{-3} and pulmonary vascular resistance as mean pulmonary artery pressure minus mean pulmonary wedge pressure (mmHg) divided by cardiac output ($l\,min^{-1}$). Regional resistances were calculated from regional blood flows ($ml\,min^{-1}$) and diastolic blood pressure.

Results

Effects of tolmesoxide in closed chest greyhounds

The haemodynamic effects of infusing tolmesoxide intravenously in a total dose of $20\,mg\,kg^{-1}$ over a 20 min period are summarized in Table 1. There was a progressive decrease in systemic arterial pressure (particularly in diastolic pressure) and a marked tachycardia (from 168 ± 18 to 256 ± 11 beats min^{-1} at the end of the infusion). Both cardiac output and $LVdP/dt_{max}$ were increased (Table 1). We did not investigate whether this was a direct effect of tolmesoxide on myocardial contractility or, as seems more likely, a reflex response to systemic hypotension mediated through the cardiac sympathetic nerves although, in those dogs given atenolol ($1\,mg\,kg^{-1}$), tolmesoxide still increased heart rate from 88 ± 15 to 147 ± 10 beats min^{-1}. Both pre-load (as reflected in these studies by changes in pulmonary wedge pressure) and after-load (arterial pressure) were reduced; in themselves these would tend to reduce $LVdP/dt$.

The reduction in peripheral vascular resistance (Table 1) is probably due to generalized arteriolar vasodilatation; resistance to flow was reduced by the drug in all examined vascular beds (renal (by 7–21% from 2.7 ± 1.4 resistance units), femoral (by 9–16% from 6.7 ± 0.8 units), carotid (by 10–25% from 14.4 ± 2.7 units), mesenteric (by 2–16% from 19.2 ± 6.0 units), and coronary (see below)). These changes are similar in degree to those of total peripheral vascular resistance indicating no particular predilection of tolmesoxide for any particular regional vascular bed. Tolmesoxide was without effect on the electrocardiogram apart from a slight reduction in the QT interval. The relevant parameters at the end of the infusion period were PR interval 93 ± 10 to 86 ± 2 ms; QRS interval 55 ± 5 to 67 ± 7 ms; QRS amplitude 1.6 ± 0.2 to 1.8 ± 0.3 mV and QT interval 163 ± 11 to 146 ± 4 ms ($P < 0.05$).

The effects of tolmesoxide on arterial blood gases and on arterial lactate and renin levels are shown in Table 2. The pronounced effects were a highly significant reduction in pH, due both to a metabolic and respiratory acidosis, and a marked increase in circulating renin. There were no significant changes in plasma

Table 1 The haemodynamic effects of an intravenous infusion of tolmesoxide ($1\,mg\,kg^{-1}$, min^{-1} for 20 min, commencing at time 0)

Parameter	Control	5	10	15	20 min
Systolic blood pressure (mmHg)	158 ± 10	149 ± 11	141 ± 12	133 ± 13	128 ± 11 *
Diastolic blood pressure (mmHg)	116 ± 7	104 ± 9	93 ± 11	85 ± 10 *	81 ± 10 *
Mean blood pressure (mmHg)	130 ± 7	121 ± 10	109 ± 11	101 ± 11	97 ± 10 *
Heart rate (beats min^{-1})	168 ± 18	230 ± 8	244 ± 10	253 ± 12	256 ± 11 *
Cardiac output ($l\,min^{-1}$)	2.9 ± 0.2	3.3 ± 0.3	3.1 ± 0.4	3.0 ± 0.4	3.0 ± 0.4
Stroke volume ($ml\,beat^{-1}$)	19 ± 3	14 ± 2	13 ± 2	12 ± 2 *	12 ± 2 *
$LVdP/dt_{max}$ ($mmHg\,s^{-1}$)	3280 ± 360	5810 ± 420	6210 ± 1090	7580 ± 1140 *	7390 ± 590 *
External cardiac work (kg m min^{-1})	5.3 ± 0.5	5.8 ± 0.8	5.1 ± 0.9	4.7 ± 0.9	4.4 ± 0.9
Pulmonary artery pressure (mmHg)	16.6 ± 0.6	15.6 ± 0.6	15 ± 2.2	16.6 ± 0.9	16.9 ± 0.8
Pulmonary wedge pressure (mmHg)	5.7 ± 1.6	5.2 ± 2.1	3.7 ± 1.8	3.3 ± 1.5	4.1 ± 1.7
Systemic vascular resistance ($mmHg\,l^{-1}\,min^{-1}$)	47.3 ± 2.4	39.7 ± 3.2	36.7 ± 2.8	36.6 ± 2.9	35.6 ± 2.8*

Values are means ± s.e.mean from 6–8 observations.
*$P < 0.05$.

Table 2 The biochemical effects of tolmesoxide (1 mg kg^{-1} min^{-1}, i.v. for 20 min); systemic arterial samples in closed-chest anaesthetized greyhounds

Parameter	Control	5	10	15	20 min
Lactate (mM)	0.38 ± 0.06	0.49 ± 0.11	0.41 ± 0.17	0.59 ± 0.04*	0.70 ± 0.16
Renin (ng ml^{-1} h^{-1})	1.9 ± 0.2		2.8 ± 0.6		4.5 ± 0.9*
Arterial P_{O_2} (mmHg)	453 ± 15	454 ± 12	444 ± 18	438 ± 12	431 ± 20
Arterial P_{CO_2} (mmHg)	34.6 ± 2.3	41.2 ± 2.0	42.5 ± 3.9	48.3 ± 3.5*	50.8 ± 5.7*
Arterial pH (units)	7.409 ± 0.018	7.354 ± 0.016	7.322 ± 0.02	7.270 ± 0.029	7.256 ± 0.038*
Base excess (mEq l^{-1})	−1.9 ± 1.0	−2.1 ± 0.8	−4.0 ± 1.0	−4.4 ± 1.4	−6.0 ± 1.6
Tolmesoxide (μg ml^{-1})	–	27 ± 2	42 ± 5	61 ± 4	68 ± 3

Values are means ± s.e.mean of 8 observations except for lactate ($n = 3$) and tolmesoxide ($n = 4$).
*$P < 0.05$.

Na^+ (164 ± 3 mM before infusion and 163 ± 3 mM at the end of 20 min) or K^+ (4.2 ± 0.3 to 4.1 ± 0.3 mM). Ca^{2+} levels were raised at 10 min (1.9 ± 0.06 to 2.11 ± 0.08 mM; $P < 0.05$) but not at 20 min (2.0 ± 0.06 mM l^{-1}).

Coronary occlusion studies in open-chest greyhounds

Although coronary artery occlusion itself did not produce significant changes in heart rate or blood pressure, there were significant reductions, 30 min after occlusion, in cardiac output (2.4 ± 0.3 to 1.8 ± 0.2 l min^{-1}) which were associated with marked increases in total peripheral vascular resistance (49 ± 4 to 62 ± 4 units) and in pulmonary vascular resistance (4.0 ± 0.8 to 7.6 ± 1.0 units). LVEDP was significantly elevated from 6.7 ± 1.1 to 10.1 ± 1.1 mmHg and, in view of unchanged LV$dP/dt_{max}$ and reduced cardiac output this indicates a substantial reduction in myocardial pump function. These haemodynamic consequences of coronary artery occlusion are similar to those previously described in this model (e.g. Marshall *et al.*, 1974). When given 2.5 h after coronary artery occlusion, tolmesoxide produced similar reductions in blood pressure and cardiac output and peripheral vascular resistance as in the closed-chest studies detailed above, although effects on stroke volume and LV$dP/dt$ were much less marked (Table 3). On termination of the infusion all parameters except LVEDP and heart rate, returned to control values within 40 min.

In the dogs in which coronary blood flow was measured by an electromagnetic probe on the left circumflex coronary artery, the tolmesoxide-induced increases in blood flow (from 60 ± 10 to 83 ± 3 ml min^{-1}; $P < 0.05$) were accompanied by slight decreases in coronary sinus oxygen extraction (Table 4); oxygen consumption in the normal region of the myocardium was slightly increased by the drug. Blood flow returned immediately to pre-drug levels on cessation of the infusion.

In contrast to its effects on blood flow in the normal myocardium, tolmesoxide did not produce any marked changes in blood flow in the developing infarct as measured by clearance of radioactive ^{133}Xe. Infarct blood flow was slightly but not significantly increased by tolmesoxide from 19 ± 4 to 25 ± 6 ml 100 g^{-1} min^{-1} ($n = 6$). Subendocardial driving pressure (diastolic peripheral coronary pressure minus LVEDP), which has been shown to be a major determinant of blood flow in ischaemic areas of the left ventricular wall (Marshall & Parratt, 1974) was slightly increased by tolmesoxide (from 6 ± 2 mmHg to 9 ± 1 mmHg; $P < 0.05$); this would, however, be offset by the decreased period of diastole resulting from the tachycardia. The increase in subendocardial driving pressure was due to the fact that although perfusion pressure in diastole (i.e. diastolic PCP) was slightly reduced (from 15 ± 1 to 12 ± 1 mmHg) during tolmesoxide infusion, LVEDP was significantly reduced by the drug (Table 3).

Further evidence that tolmesoxide may have brought about an improvement in the ischaemic area is shown from an analysis of local coronary venous blood gases (Table 4). During tolmesoxide infusion there was a significant increase in coronary venous oxygen tension in spite of a decrease in arterial oxygen (from 393 to 330 mmHg; Table 4). This represents a decrease in oxygen extraction by the ischaemic myocardium which was sustained after cessation of the drug infusion (Table 4). Table 4 also shows that coronary artery occlusion did not affect arterial P_{O_2}, P_{CO_2}, pH or pulmonary shunting; these data also incidentally demonstrate the stability of the animals over the 2.5 h duration of the study.

However, during the infusion of tolmesoxide there were significant decreases in arterial oxygen tension and pH and a significant increase in pulmonary

Table 3 The haemodynamic effects of an infusion of tolmesoxide (1 mg kg^{-1} min^{-1}) administered 2.5 h after coronary artery occlusion in chloralose-anaesthetized greyhounds

	Pre-tolmesoxide	*Maximum response during infusion*
Systolic blood pressure (mmHg)	146 ± 15	117 ± 15**
Diastolic blood pressure (mmHg)	121 ± 14	96 ± 14**
Mean blood pressure (mmHg)	129 ± 13	101 ± 14**
Mean pulmonary artery pressure (mmHg)	12 ± 2	10 ± 2**
Left ventricular dP/dt_{max} (mmHg s^{-1})	1170 ± 135	1670 ± 270*
LVEDP (mmHg)	8.8 ± 0.9	4.4 ± 3**
Heart rate (beats min^{-1})	134 ± 8	174 ± 12*
Cardiac output (l min^{-1})	1.7 ± 0.2	1.9 ± 0.2*
Stroke volume (ml $beat^{-1}$)	11.9 ± 1.1	10.4 ± 1.2
External cardiac work (kg m min^{-1})	3.1 ± 0.8	2.8 ± 0.8
Peripheral vascular resistance (units)	69 ± 5	45 ± 4**
Pulmonary vascular resistance (units)	8.3 ± 1.1	6.5 ± 0.9*

Values are means ± s.e.mean from nine experiments.
Significantly different from pre-tolmesoxide values: $*P < 0.05$; $**P < 0.005$.

shunting calculated according to the method of Hyde (1970) despite the positive pressure ventilation and use of PEEP.

Tolmesoxide administration resulted in a few isolated premature ventricular beats in 5 out of 9 animals. The incidence was 1, 4, 10 and 1, in four animals; in the other dog the only abnormality seen in the electrocardiogram was the occurrence of 6 bigeminal beats 4 min after commencement of the infusion. No ventricular dysrhythmias were seen in the animals in the hour preceding the administration of tolmesoxide.

Discussion

These studies confirm that the predominant effect of infusing tolmesoxide is a reduction in systemic arterial blood pressure (Doxey, 1978). This is rather more marked in diastole and, in some animals, is accompanied by slight increases in cardiac output (especially early in the infusion period). The marked reduction in peripheral vascular resistance (of between 20 and 30%) appears to result from generalized arteriolar dilation; certainly vascular resistance was reduced in all the vascular beds studied although this was less marked in the mesenteric region. Heart rate and LV dP/dt_{max} were both markedly increased and the tachycardia was unaffected by atenolol given in a dose that causes a 20 fold shift in the responses to isoprenaline in this species. It appears likely that tolmesoxide induces cardiac stimulation by both a direct (non-adrenoceptor-mediated) action and via the reflex reduction in arterial pressure. The marked increase in LV$dP/dt$ in the presence of a slightly reduced pre-load (as reflected in changes in pulmonary wedge pressure) and in afterload (changes in arterial pressure) suggests a true increase in myocardial contractility, not all of which is mediated by reflex activation of myocardial β-adrenoceptors. Indeed, the profile of tolmesoxide is similar to that of phosphodiesterase inhibitors in that it causes both profound peripheral vasodilatation and cardiac stimulation. Whilst the plasma calcium concentration was elevated by tolmesoxide it is unlikely to be of significant magnitude to account for the degree of cardiac stimulation observed.

As demonstrated by Robinson's group (Collier *et al.*, 1978) in normal human subjects, tolmesoxide appears to have balanced dilator effects on precapillary and post-capillary resistance vessels. Pulmonary vascular resistance, pulmonary wedge pressure, and LVEDP were all reduced, markedly so in those dogs with compromised left ventricular function induced by myocardial ischaemia (Table 3). The precise mechanism of this relaxation of arteriolar and venous smooth muscle is unknown and is usually described as 'direct' (e.g. Doxey, 1978) meaning simply that it is not mediated by known receptors. Calcium antagonism is not involved (Mikkelsen & Lederballe Pedersen, 1981). One of the most surprising findings was the previously unreported reduction in arterial base excess (Table 2), with marked increases in blood lactate (almost doubled at 20 min). Presumably some form of pulmonary shunting is also occurring, as demonstrated by the reduction in arterial P_{O_2} and the increase in arterial P_{CO_2}, changes which were substan-

Table 4 The effects of acute coronary artery occlusion and the subsequent administration of tolmesoxide (1 mg kg^{-1} min^{-1}) commencing 2.5 h after coronary artery occlusion on blood gases, oxygen content and extraction

	Pre-occlusion	*10 min pre-tolmesoxide*	*During tolmesoxide infusion*
Arterial			
Po_2 (mmHg)	431 ± 45	393 ± 43	330 ± 46
Pco_2 (mmHg)	38 ± 2	37 ± 1	38 ± 1
pH (units)	7.39 ± 0.02	7.38 ± 0.02	7.34 ± 0.02*
% pulmonary shunting	8.0 ± 2.3	8.4 ± 1.6	11.2 ± 2.0**
Coronary sinus (draining predominantly from the normal myocardium)			
Po_2 (mmHg)	28 ± 2	30 ± 2	32 ± 2
Pco_2 (mmHg)	59 ± 3	58 ± 2	57 ± 1
pH	7.30 ± 0.01	7.30 ± 0.01	7.26 ± 0.02*
O_2 content (ml 100 ml^{-1})	10.3 ± 0.7	12.5 ± 1.1	13.3 ± 1.1
O_2 extraction (%)	59 ± 3	55 ± 4	52 ± 4
Coronary vein (draining infarcting zone)			
Po_2 (mmHg)	28 ± 1	25 ± 1†	27 ± 2*
Pco_2 (mmHg)	61 ± 2	61 ± 1†	62 ± 1
pH	7.30 ± 0.01	7.26 ± 0.01†	7.22 ± 0.02*
O_2 content (ml 100 ml^{-1})	9.9 ± 0.7	9.1 ± 0.9	10.2 ± 0.9*
O_2 extraction (%)	62 ± 3	68 ± 4†	62 ± 3**

Values are means ± s.e.mean (9 observations).
Significantly different from pre-ligation control: †$P < 0.05$.
Significant difference from pre-tolmesoxide control: *$P < 0.05$; **$P < 0.005$.

tial by 20 min (Table 2). This combination of metabolic and respiratory acidosis would contribute to the observed vasodilatation of the arteriolar segment of the peripheral circulation and hence to the systemic hypotension.

Considered in isolation from the possible effects of lactic acidosis, the marked fall in blood pressure produced by tolmesoxide would be expected to produce a decrease in myocardial blood flow (as is the case with minoxidil; Radvany *et al.*, 1978). In fact tolmesoxide increased blood flow to the ischaemic region of the left ventricular wall in three of the six experiments and did not cause a coronary steal, which is observed with some other coronary vasodilator drugs in this model (Marshall & Parratt, 1974). This observation may be explained by the significant reduction in left ventricular end-diastolic pressure due either to a venodilator action of the drug or as a consequence of cardiac stimulation. This would result in an elevation of the pressure gradient across the left ventricular wall (sub-endocardial driving pressure; Marshall & Parratt, 1974). Although an increased sub-endocardial driving pressure would be expected to increase blood flow to the deeper regions of the ischaemic left ventricular wall this would be offset by the decrease in the diastolic perfusion time caused by the tolmesoxide-induced tachycardia. The overall haemodynamic effects of tolmesoxide may thus arise from the combined direct vasodilator/cardiac stimulant action and a lactic acid-induced vasodilatation. Whilst the exact mechanisms may be unclear it is evident that tolmesoxide at least causes cardiac stimulation, together with a reduction in both pre-load and after-load, without apparently compromising cardiac function even in situations where blood flow to 30–40% of the free left ventricular wall is compromised. These features have been suggested as the ideal profile of a drug to be used for the treatment of heart failure by Miller *et al.* (1981). Clinical studies on the use of tolmesoxide have confirmed such beneficial effects and there is no evidence for direct drug-induced (or hypotension-induced) ventricular arrhythmias (O'Boyle *et al.*, 1981; Lauwers & Neivel, 1982). Previous clinical studies have indicated that tolmesoxide was unsuitable for use as an antihypertensive agent due to the high incidence of nausea as a side-effect (Silas *et al.*, 1981; Scheen *et al.*, 1981). This side-effect may be due to the so called 'vaso-vagal syndrome' resulting from very low central venous pressures (Epstein *et al.*, 1968). It is possible that these effects are minimized in heart-failure, where there is an abnormally elevated central venous pressure.

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References

COLLIER, J.G., LORGE, R.E. & ROBINSON, B.F. (1978). Comparison of effects of tolmesoxide (RX 71107), diazoxide, hydrallazine, prazosin, glyceryl trinitrate and sodium nitroprusside on forearm arteries and dorsal hand veins of man. *Br. J. clin. Pharmac.*, **5**, 35–44.

DOXEY, J.C. (1978). Tolmesoxide, a drug that lowers blood pressure by a direct relaxant effect on vascular smooth muscle. *Br. J. Pharmac.*, **63**, 111–118.

EPSTEIN, S.E., STAMPFER, M. & BEISER, G.D. (1968). The role of capacitance and resistance vessels in vasovagal syncope. *Circulation*, **37**, 524–533.

HYDE, R.W. (1970). Clinical interpretation of arterial oxygen measurements. *Med. Clin. Nth. Amer.*, **54**, 617–629.

LAUWERS, P. & NEIVEL, J.G. (1982). Haemodynamic changes in heart failure induced by a new vasodilator tolmesoxide. *Eur. J. clin. Pharmac.*, **21**, 473–477.

LLOYD-JONES, J.G., HENSON, R.A., NICHOLS, J.D., GREENSLADE, D. & CLIFFORD, J.M. (1981). Pharmacokinetics of intravenous and oral tolmesoxide. *Eur. J. clin. Pharmac.*, **19**, 119–125.

MACKENZIE, J.E. (1982). The cardiovascular effects of tolmesoxide in the anaesthetised dog. *Br. J. Pharmac.*, **76**, 200P.

MARSHALL, R.J. & PARRATT, J.R. (1974). Drug-induced changes in blood flow in the acutely ischaemic canine myocardium; relationship to subendocardial driving pressure. *Clin. exp. Pharmac. Physiol.*, **1**, 99–112.

MARSHALL, R.J. & PARRATT, J.R. (1980). Prophylactic lignocaine and early post coronary artery occlusion dysrhythmias in anaesthetised greyhounds. *Br. J. Pharmac.*, **71**, 597–600.

MARSHALL, R.J., PARRATT, J.R. & LEDINGHAM, I. McA. (1974). Changes in blood flow and oxygen consumption in normal and ischaemic regions of the myocardium following acute coronary artery ligation. *Cardiovasc. Res.*, **8**, 204–215.

MIKKELSEN, E. & LEDERBALLE PEDERSEN, O. (1981). Comparative studies on the effects of tolmesoxide (RX 711107), a tolmesoxide metabolite (RX 71112) and nifedipine in isolated blood vessels. *Br. J. Pharmac.*, **73**, 799–805.

MILLER, R.R., PALOMO, A.R., BRANTON, B.S., HARTLEY, C.J. & QUINONES, M.A. (1981). Combined vasodilator and inotropic therapy of heart failure: Experimental and clinical concepts. *Am. Heart J.*, **102**, 500–508.

O'BOYLE, C.P., LAHER, M., O'BRIEN, E.T., O'MALLEY, K. & KELLY, J.G. (1982). The clinical pharmacology of tolmesoxide. *Eur. J. clin. Pharmac.*, **23**, 93–97.

O'BOYLE, C.P., McGARRY, K., FITZGERALD, D., KELLY, J.G., HORGAN, J. & O'MALLEY, K. (1981). Clinical pharmacology of tolmesoxide in refractory heart failure. *Eur. J. clin. Pharmac.*, **21**, 169–172.

PARRATT, J.R., MARSHALL, R.J. & LEDINGHAM, I. McA. (1980). Interventions for improving blood flow, oxygen availability and the balance between oxygen supply and demand in the acutely ischaemic myocardium. *J. Physiol. (Paris)*, **76**, 791–803.

RADVANY, P., DAVIS, M.A., MULLER, J.E. & MAROKO, P.R. (1978). Effects of minoxidil on coronary collateral flow and acute myocardial injury following experimental coronary artery occlusion. *Cardiovasc. Res.*, **12**, 120–126.

SCHEEN, A., LUYCKX, A.S. & DE GRAEVE, J. (1981). Cardiovascular effects of intravenous tolmesoxide in hypertensive patients. *Archs Int. Pharmacodyn Thér.*, **251**, 322–334.

SILAS, J.H., PHILLIPS, F.C., FREESTONE, S., TUCKER, G.T. & RAMSAY, L.E. (1981). A clinical and pharmacokinetic evaluation of tolmesoxide in hypertensive patients. *Eur. J. clin. Pharmac.*, **19**, 113–118.

STEEL, R.G. & TORRIE, J.H. (1980). *Principles and Procedures of Statistics*, 2nd edn. New York: McGraw Hill.

WINER, B.J. ed. (1962). *Statistical Principles in Experimental Design*, 2nd edn. New York: McGraw Hill.

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