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Cardioprotective actions of pentoxifylline in an animal model of acute myocardial ischaemia

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1 The action of pentoxifylline on some of the consequences of acute myocardial ischaemia was studied in cats *in vivo*.

2 Occlusion of the left anterior descending coronary artery (LAD) for 5 h resulted in a significant elevation in the ST-segment of the ECG, a reduction in free platelet count in right atrial blood and a loss of creatine phosphokinase (CK) and cathepsin D activities in homogenates of the severely ischaemic myocardium as compared to non-ischaemic myocardium.

3 Intravenous infusions of pentoxifylline (0.30 mg kg^{-1} min^{-1} for 1 h and 0.15 mg kg^{-1} min^{-1} for the remainder of the 5 h observation period, starting 0.5 h after LAD occlusion) significantly reduced the loss of enzymes from the ischaemic myocardium, prevented any further increase in the ST-segment and restored the platelet count to its control level.

4 There were no significant changes in plasma immunoreactive 6-oxo-prostaglandin $F_{1\alpha}$ (6-oxo-$PGF_{1\alpha}$) and thromboxane B_2 (TXB_2), although a tendency for a reduction in TXB_2 levels was observed.

5 Pentoxifylline seems to affect, beneficially, the myocardium in this animal model of acute myocardial ischaemia. The reason for this cardioprotective action remains to be elucidated. It is, however, noteworthy that the overall profile of action of pentoxifylline resembles that of PGI_2 administration in this model.

Introduction

Pentoxifylline (3,7-dimethyl - 1 - (5-oxo-hexyl)-xanthine) is an agent that relaxes vascular smooth muscle and is used clinically for treatment of peripheral vascular disease. It also increases red cell flexibility and improves the flow properties of blood (Leonhardt & Grigoleit, 1977; Müller & Lehrach, 1980; Nishio *et al.*, 1982). The mechanism of action of pentoxifylline is not completely understood. Previous experimental work suggests that pentoxifylline, like other methylxanthines, inhibits phosphodiesterase in several tissues, including the heart (Argel *et al.*, 1980) vascular tissue (Stefanovich, 1973) and platelets (Stefanovich *et al.*, 1977). This may result in enhanced tissue cyclic adenosine-3′5′-monophosphate (cyclic AMP) levels. However, it is not known whether this increase in cyclic AMP accounts for the effect of the compound on vascular tone and blood-born cells or is an accompanying phenomenon which is particularly evident at high drug concentrations.

In an earlier investigation it was shown that pentoxifylline increases the local oxygen tension and blood supply to the cerebral cortex of anaesthetized cats. This effect was also detectable after occlusion of one carotid artery (Popendiker *et al.*, 1971). Recently, preliminary evidence was obtained in clinical studies that pentoxifylline produced a significant improvement in the rheological properties of blood in patients suffering from ischaemic cerebrovascular accidents (Schneider & Kiesewetter, 1982). These, and other data (see Müller & Lehrach, 1980), suggest that pentoxifylline, by improving regional perfusion, may exert salutary actions on organ preservation under conditions of restricted blood supply.

As far as we are aware, the substance has not yet been investigated under conditions of acute myocardial ischaemia. Hence the present study was designed to evaluate the actions of pentoxifylline in acute myocardial ischaemia produced by coronary artery ligation *in vivo*. This investigation was stimulated by the recent observation that pentoxifylline enhances vascular prostaglandin I_2 (PGI_2) production both *in vitro* and *in vivo* (Weithmann, 1981; Matzky *et al.*, 1982). PGI_2 has been demonstrated to protect the myocardium from acute ischaemic damage (Ogletree *et al.*, 1979; Ohlendorf *et al.*, 1980). It has also been

shown that the structurally related theophylline ethylenediamine (aminophylline), increased transmural blood flow in severely ischaemic zones of the dog myocardium and improved myocardial function (Rutherford *et al.*, 1981).

A preliminary account of some of these results was presented to the International Prostaglandin Conference (Bad Ischl, Austria) in September 1982.

Methods

Myocardial ischaemia

Adult cats of either sex (body weight 2.7–3.4 kg) were anaesthetized with pentobarbital sodium (30 mg kg^{-1}, intravenously.) The thorax was opened under positive pressure ventilation, the heart exposed and the left descending coronary artery permanently occluded about 10–12 mm distally to its origin. Details of the operative procedures have been described previously (Ogletree *et al.*, 1979; Schrör *et al.*, 1980).

Functional measurements

A catheter for blood sampling was placed into the right atrium via the left external jugular vein. Another was placed in the abdominal aorta via the right femoral artery for measurement of mean arterial blood pressure (MABP). Standard lead III of the ECG was recorded with needle electrodes and used for calculation of the ST-segment changes and heart rate. A pressure-rate index was computed as the product of MABP × heart rate. This index was taken as an indicator of myocardial oxygen demand (Baller *et al.*, 1981).

Sampling and analysis of blood

Samples of right atrial blood (3 ml) were taken immediately before coronary artery occlusion (time 0) and at 0.3, 1, 3 and 5 h thereafter. Blood samples of sham-operated control cats were drawn at equivalent times. Blood was collected into polyethylene tubes, prefilled with disodium-edetate (EDTA) (0.1 M) and indomethacin (30 μM) in order to avoid *ex vivo* prostaglandin formation. The cells were separated by centrifugation at 10,000 *g* for 15 min at 4°C. The supernatant was subjected to radioimmunoassay of thromboxane B_2 (TXB_2) and 6-oxo-$PGF_{1\alpha}$ (see below).

Another 0.3 ml sample of right atrial blood was taken with a plastic syringe immediately after introducing the anaesthetic, just before myocardial ischaemia (MI), and at 20, 40 and 60 min after MI and then hourly up to the end of the observation period. A 100 μl of the blood sample was immediately transferred into a plastic tube which was prefilled with 40 μl (200 i.u.) of heparin. The mixture was gently shaken and a 20 μl aliquot was transferred into test tubes (Thromboplus, Sarstedt, Nürnberg, W. Germany) for platelet counting in a Thoma-chamber using an interference-phase contrast microscope.

Radioimmunoassay

Radioimmunological determinations of TXB_2 and 6-oxo-$PGF_{1\alpha}$ were performed directly in unextracted plasma. Free and bound fractions of eicosanoids were separated by a double antibody method using goat anti-rabbit γ-globulin (Calbiochem-Behring Corp., Gießen, West Germany) following the procedure described by Peskar *et al.*, (1978). The specific antibodies were generated in rabbits. Preparation of the antigens and the immunization schedule were also according to the methods used by Peskar *et al.* (1978). Cross-reactivity data can be obtained from the authors. Fifty % displacement of [^{3}H]-TXB_2 and [^{3}H]-6-oxo-$PGF_{1\alpha}$ was obtained at 45 pg TXB_2 per tube and 55–60 pg 6-oxo-$PGF_{1\alpha}$ per tube, respectively. The detection limits for a volume of 0.2 ml were 40 pg TXB_2 ml^{-1} plasma and 50 pg 6-oxo-$PGF_{1\alpha}$ ml^{-1} plasma.

Sampling and analysis of cardiac tissue

After 5 h the hearts were excised, rinsed in ice-cold 0.9% w/v NaCl solution (saline) and placed into cold saline. The free left ventricular wall of the heart was divided into normal and ischaemic regions (about 600 mg each) by simple inspection of the myocardial surface. Transmural samples of the severely ischaemic anterior myocardium and of the normal posterior left ventricular myocardium were excised, blotted and weighed. Anatomically equivalent areas were excised from sham-operated animals. The tissue samples were homogenized in 0.125 M sucrose (1:20 v/v) containing 25 mM EDTA and 0.1 mM mercaptoethanol for determination of myocardial creatinine phosphokinase (CK) activity (assay kit Boehringer, Mannheim, W. Germany). Cathepsin D and free amino nitrogen were determined by standard methods as described in detail previously (Ogletree *et al.*, 1979; Schrör *et al.*, 1980). The protein content was assayed according to the method of Lowry *et al.*, (1951).

Evaluation

The cats were allowed to recover for 30 min after the end of the surgical procedures. Then, the left anterior descending coronary artery was occluded at time 0 for a total time of 5 h. Infusion of pentoxifylline or

vehicle was started at time 30 min with 0.3 mg kg^{-1} min^{-1} for 1 h and then maintained at 0.15 mg kg^{-1} min^{-1} until the end of the observation period. This dose schedule was chosen because it did not result in consistent changes in general haemodynamics, whereas higher doses tended to increase the heart rate and to decrease mean arterial blood pressure.

Drugs

Pentoxifylline (Hoechst, Werk Albert, Wiesbaden, W. Germany) was dissolved in distilled water at 10 mg ml^{-1}. Further dilutions were made with physiological saline. Indomethacin (Merck, Sharp & Dohme, München, W. Germany) was dissolved in 1 M Tris buffer (pH 8.4) at 1 mg ml^{-1} and further diluted with distilled water. Propranolol hydrochloride (ICI, London) was dissolved in distilled water.

Statistics

All values in the text are expressed as the mean ± s.e.mean of n observations. Statistical analysis was performed using Student's t test; P levels of less than 0.05 were considered significant.

Results

Haemodynamics and ECG

Initially, the mean arterial blood pressures (MABP) in the experimental groups were not different from each other. MABP decreased within 20 min after coronary artery ligation and then remained unchanged throughout the 5 h observation period. Pentoxifylline tended to decrease the MABP at time 1 h, that is 30 min after starting the infusion. However, this was a transient response and no significant differences from vehicle-treated controls could be detected at any time of the experiment ($P > 0.05$) (Figure 1).

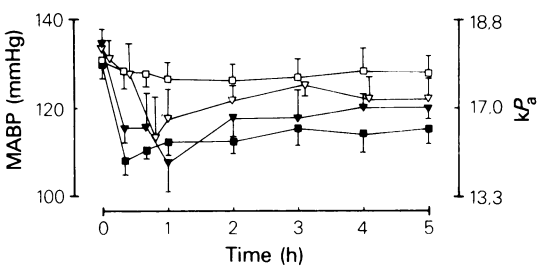

Figure 1 Mean arterial blood pressure (MABP) in cats subjected to coronary artery occlusion (closed symbols) or to a sham operation (open symbols) and treated with either pentoxifylline (triangles) or vehicle (squares). Each point represents the mean ± s.e.mean of 6–11 observations.

The heart rate (HR) ranged between 170–190 beats min^{-1} in the experimental groups and was not significantly altered by pentoxifylline infusion in comparison to the respective vehicle-treated groups ($P > 0.05$). Similarly, the computed product of HR × MABP, an indirect index for myocardial oxygen consumption was not significantly changed by pentoxifylline at any time of the experiment.

Coronary artery ligation was followed by an immediate and sustained elevation of the ST-segment. Treatment with pentoxifylline prevented any further increase in the ST-segment in the groups of animals subjected to coronary artery occlusion and actually maintained the ST-segment at the 30 min level, i.e. immediately before starting infusion. This was significantly less at 2 to 5 h than in the vehicle-treated MI group ($P < 0.05$) but also significantly more than seen with both the vehicle- and pentoxifylline-treated sham-MI groups ($P < 0.05$) (Figure 2).

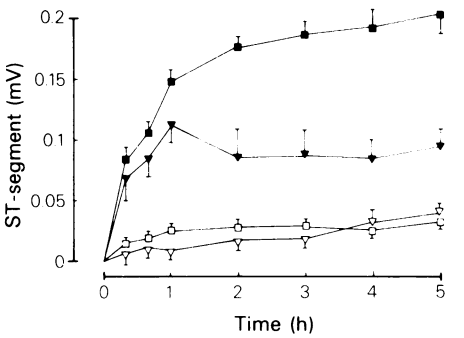

Figure 2 Changes in the ST-segment (in standard lead III) in cats subjected to coronary artery occlusion (closed symbols) or to sham operation (open symbols) and treated with either pentoxifylline (triangles) or vehicle (squares). Each point represents the mean ± s.e.mean of 6–11 observations.

Biochemical determinations

The ischaemic area of left ventricular myocardium exhibited a significant loss of CK activity when compared to corresponding areas of sham-operated animals. There was also a loss of bound cathepsin D and of free amino nitrogen, indicating a significant proteolysis and release of lysosomal enzymes. All these changes were no more apparent when the animals were treated with pentoxifylline (Figure 3).

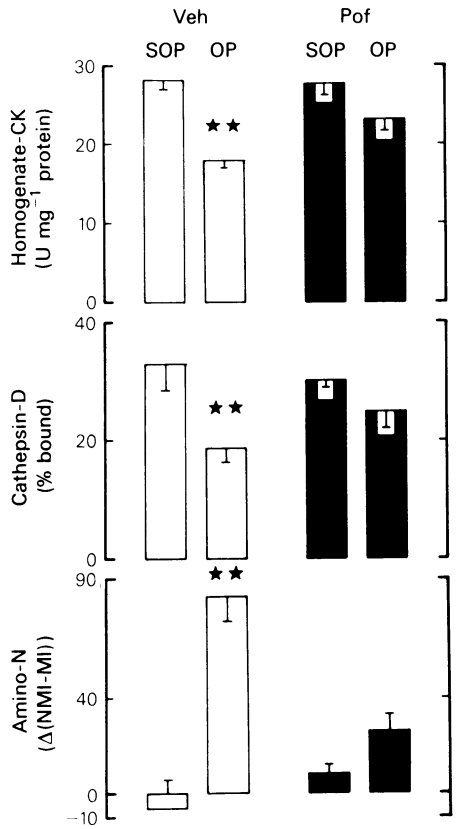

Figure 3 Myocardial creatine-phosphokinase (CK) and cathepsin D activities and free amino nitrogen (difference between non-ischaemic (NMI) and ischaemic (MI) areas of the same heart) in cats subjected to coronary artery occlusion (OP) or sham operation (SOP) and treated with either vehicle (veh) or pentoxifylline (pof). Each bar represents the mean ± s.e.mean of 5–11 observations. ** $P < 0.01$ (OP vs. SOP).

Platelet count

The platelet count in peripheral venous blood of the cats ranged between 500,000 to 600,000 platelets μl^{-1}. This initial platelet count was reduced by about 20% in all groups of animals studied during the operative procedures. Coronary artery ligation in MI cats treated with vehicle was followed by another significant drop in free platelet count in right atrial blood within 20 min and then remained unchanged during the further observation period. Administration of pentoxifylline elevated this MI-induced depression in free platelet count to the number seen in sham-operated, vehicle-treated animals ($P > 0.05$ at 1–5 h). A similar increase was also found with sham-operated cats treated with pentoxifylline in comparison to vehicle-treated animals ($P < 0.05$ at 1–5 h)

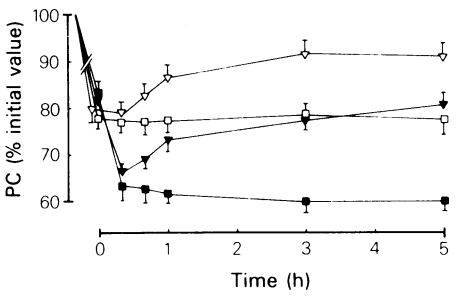

Figure 4 Platelet counts (PC) in right atrial blood in cats subjected to coronary artery occlusion (closed symbols) or to sham operation (open symbols) and treated with either pentoxifylline (triangles) or vehicle (squares). Each point represents the mean ± s.e.mean of 6–11 observations.

(Figure 4). This action of pentoxifylline did not occur immediately but required approximately 40 min before it was complete.

Plasma thromboxane and 6-oxo-PGF$_{1\alpha}$ levels

No specific change in the levels of 6-oxo-PGF$_{1\alpha}$ were observed following either coronary artery occlusion or pentoxifylline administration. The initial plasma levels were of the order of 480 ± 88 and 502 ± 150 pg ml^{-1} and then did not alter significantly throughout the 5 h observation period.

The results with immunoreactive thromboxane B_2 are summarized in Figure 5. Despite some tendency for pentoxifylline to reduce the enhanced TXB_2 level in the MI vehicle group, this effect was not significant ($0.05 < P < 0.10$ at time 5 h).

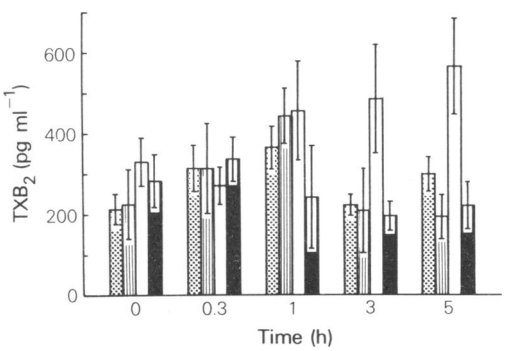

Figure 5 Plasma thromboxane B_2 (TXB_2) level in cats subjected to coronary artery occlusion and treatment with vehicle (open columns) or pentoxifylline (solid columns) as compared to sham-operated cats treated with vehicle (stippled columns) or pentoxifylline (hatched columns). Each column represents the mean, and the vertical lines s.e.mean, of 5–6 observations at times 0–5 h.

Discussion

The present data indicate that in anaethetized cats, pentoxifylline exerts significant protective effects in acute myocardial ischaemia. This was demonstrated by attenuation of the ST-segment elevation, inhibition of the loss of myocardial CK activity from the ischaemic area, and maintenance of cellular integrity by inhibition of lysosomal enzyme release and proteolysis.

There are several possible explanations for these apparently beneficial effects. First, pentoxifylline could have improved the local metabolic situation of the ischaemic myocardium by an action on blood cells, in particular red cells and platelets. According to Born (1977), red cells sticking together in occluded vessels may release significant amounts of nucleotides, e.g. ADP, which in turn facilitate platelet activation and secretion. The local hyperosmolarity in the ischaemic area, due to release of lactate, pyruvate (Rösen *et al.*, 1981) and potassium ions (Zylka *et al.*, 1980) will reduce red cell deformability and the flow properties of blood (Meiselman *et al.*, 1967; Giombi & Burnard, 1970). It has been demonstrated that pentoxifylline can increase the flow properties of blood and improve the red cell flexibility when this is reduced under hyperosmolar conditions (Leonhardt *et al.*, 1977; Nishio *et al.*, 1982). Similar data have been shown for cerebral ischaemia in man (Schneider *et al.*, 1982). This could result in an increased oxygen supply even if coronary vascular tone remained unaltered. In addition, recent studies by Folts (1982) have provided direct evidence that red blood cells become concentrated proximally to a partially occluded coronary artery and that they appear to be partially damaged and lysed. Thus, the formation of platelet aggregates in stenosed coronary arteries (Folts *et al.*, 1976) may be mediated by indirect actions on erythrocytes rather than on the platelets themselves. *In vitro*, pentoxifylline does not modify the effects on platelets of a variety of stimulating agents, at least in concentrations below 0.1 mM (Weithmann, 1981; Matzky *et al.*, 1982).

Pentoxifylline could also have improved perfusion to ischaemic areas. Recent studies by Rutherford *et al.* (1981) have indicated that aminophylline, another methylxanthine, can increase blood flow to ischaemic areas of the dog myocardium. Direct measurements of regional myocardial blood flow have not been performed in the present investigation. However, we have shown in a previous study using this model that the regional myocardial blood flow in severely ischaemic myocardium is not modified by treatment with a prostacyclin analogue that also exerted significant cardioprotective and antiplatelet actions similar to those found here with pentoxifylline (Beckmann *et al.*, 1983). Thus, active coronary vasodilatation is not necessary for the improvement of function in the ischaemic myocardium.

Methylxanthines are also known to inhibit phosphodiesterases at high concentrations and this was also found with pentoxifylline (Stefanovich, 1973; Stefanovich *et al.*, 1977; Argel *et al.*, 1978). Inhibition of this enzyme would result in enhanced cyclic AMP, for example after stimulation by catecholamines. However, in the present study there was no evidence for increased sympathomimetic activity (such as increases in heart rate, myocardial oxygen consumption or blood pressure). In other studies in this species however, pentoxifylline administration did result in modest increases in heart rate (Popendiker *et al.*, 1971).

Pentoxifylline has been shown to stimulate vascular PGI_2 formation in both human and animal vascular tissue (Weithmann, 1980; Matzky *et al.*, 1982) but not to influence thromboxane formation after stimulation by arachidonic acid. In the present investigation, pentoxifylline did not alter the plasma levels of either TXB_2 or 6-oxo-$PGF_{1\alpha}$. This is perhaps not surprising, since operative procedures (such as thoracotomy), profoundly stimulate eicosanoid formation. Similar high 6-oxo-$PGF_{1\alpha}$ and TXB_2 levels have also been found in dogs, subjected to thoracotomy before coronary artery occlusion (Coker *et al.*, 1981). In comparison, the plasma level of immunoreactive 6-oxo-$PGF_{1\alpha}$ in pentobarbital-anaesthetized, artificially respirated cats without thoracotomy was found to be 43 pg ml^{-1} (Förstermann *et al.*, 1982) and 50 pg ml^{-1} (Schrör, Thomsen & Peskar, unpublished observations). It is also possible that cats metabolize both PGI_2 and 6-oxo-$PGF_{1\alpha}$ to 6,15-dioxo-13, 14-di-hydro-$PGF_{1\alpha}$ (Förstermann *et al.*, 1982). Since our 6-oxo-$PGF_{1\alpha}$ antibody possesses a 3% cross-reactivity against this compound, it could be that some of the immunoreactive 6-oxo-$PGF_{1\alpha}$ measured was in fact the 6,15-dioxo-13, 14-dihydro-metabolite. Thus, one should not overestimate the findings of an apparently unchanged 6-oxo-$PGF_{1\alpha}$ in this model.

Methylxanthines may enhance the antiplatelet action of PGI_2 *in vivo*. For example, theophylline (0.2–0.4 mg kg^{-1} min^{-1} i.v.) potentiates the inhibitory effects of exogenous PGI_2 on bleeding time and thrombus formation in rabbits (Ubatuba *et al.*, 1979). Pentoxifylline was found to enhance the PGI_2-induced inhibition of ADP-induced platelet aggregation *in vitro* at concentrations (5–50 μM) which were devoid of any direct antiplatelet activities (Weithmann, 1981). Therefore, enhancement of PGI_2-mediated effects may also be involved in some of the actions of pentoxifylline described here (cardiac preservation, antiplatelet effects).

In conclusion, the present data indicate that pentoxifylline exerts significant cardioprotective effects

in an animal model of acute myocardial ischaemia. Possible explanations for this beneficial effect are antiplatelet actions (as evidenced by the resolution of preformed platelet aggregates and a tendency for reduced circulating plasma thromboxane levels) and an enhanced perfusion of the ischaemic myocardium by improvement of the flow properties of blood. Since the overall profile of activity of pentoxifylline in this model of acute myocardial ischaemia closely resembles that of exogenous PGI_2, it is possible that endogenous PGI_2 is involved in this cardioprotection, for example by the local enhancement of its biological activity by pentoxifylline. This would also explain the antiplatelet actions of the compound *in vivo*.

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