Circulatory effects of the PDE-inhibitors piroximone and enoximone

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- 1 The isolated circulatory response to intravenous application of the phosphodiesterase (PDE) inhibitors piroximone and enoximone was studied.
- 2 In a randomized sequence of 30 male patients undergoing elective aortocoronary bypass grafting either piroximone (0.5 mg kg⁻¹; *n* = 10) or enoximone (0.5 mg kg⁻¹; *n* = 10) were given during steady state of cardiopulmonary bypass (CPB). A group in which NaCl was given as a placebo served as a control (*n* = 10).
- 3 MAP was reduced by piroximone (maximum -23 mm Hg) and enoximone (maximum -18 mm Hg), whereas it increased in the control (+20 mm Hg). Volume of the extracorporeal circuit indicating venous pooling decreased more pronouncedly in the enoximone patients (-440 ml) than in the piroximone group (-300 ml).
- 4 Laser Doppler flows (LDFs) increased in both PDE-III inhibitor groups with the higher and longer increase in the enoximone-treated patients (LDF-forehead maximum +44%, LDF-forearm maximum +33%). Piroximone-induced increase in both LDFs was less pronounced with respect to both time and degree (LDF-forehead maximum +30%, LDF-forearm +12%).
- 5 Oxygen consumption (VO₂) was significantly higher in the PDE-III inhibitor-treated than in the control patients.
- 6 Piroximone and enoximone showed significant vasodilatory properties at the arterial and venous side (= 'venous pooling'), from which patients with heart failure would profit.
- 7 Vasodilation could be observed for a longer period and was more pronounced in the enoximone-treated than in the piroximone patients. Alterations in capillary skin blood flow measured by laser Doppler technique gave evidence for an improvement in nutritive microcirculation, which was slightly more pronounced in the enoximone patients.

Keywords cardiac surgery phosphodiesterase inhibitor piroximone enoximone haemodynamics microcirculation

Introduction

In recent years interest has been focused on identifying new therapeutic approaches to the management of patients with heart failure. Phosphodiesterase (PDE)-III inhibitors seem to be an attractive class of substances for treatment of low output syndrome [1, 2]. As PDE-III inhibitors 'bypass' the β -adrenoceptor, they can be successfully used even in patients suffering from β -receptor down-regulation phenomenon [3]. Besides

their positive inotropic properties, the beneficial effects of PDE-III inhibitors appear also due to their vasodilatory actions (= 'inodilators'). Imidazolone-derivative amrinone and imidazolone-derivative enoximone are substances which are at the moment available for the treatment of acute heart failure in several countries. Piroximone is a new PDE-III inhibitor which is believed to be better controllable because of its shorter half-life

[4, 5] than enoximone or amrinone. Positive inotropic effects appear to be similar to enoximone. Only little is known about the (micro-) circulatory effects of PDE-III inhibitors in man, particularly when using piroximone. Thus the aim of this study was to investigate the isolated circulatory response and the influence on microperfusion of the new PDE-III inhibitor piroximone in comparison with enoximone.

Methods

Patients and grouping

Thirty male patients undergoing elective aorto-coronary bypass grafting were investigated. All patients gave informed consent according to the protocol of the Ethic Study Board of the hospital. All patients were on anginal medication with nitroglycerine. Excluding criteria were pre-treatment with β -adrenoceptor blockers, calcium channel antagonists, angiotensin-converting-enzyme inhibitors (ACEI), and concomitant valve disease or renal insufficiency.

Approximately 20 min after start of cardiopulmonary bypass (CPB), three groups were randomly selected during haemodynamic steady-state:

Group 1 ($n = 10$): PDE-III inhibitor piroximone (0.5 mg kg^{-1}) was given as an intravenous bolus (within 1 min)

Group 2 ($n = 10$): 0.5 mg kg^{-1} of the PDE-III inhibitor enoximone was given as an intravenous bolus (within 1 min)

Group 3 ($n = 10$): a similar amount of saline solution as PDE-III inhibitor was given as a placebo (= control group).

Anaesthesia and cardiopulmonary bypass (CPB)

All patients were premedicated 1 h before the start of anaesthesia with flunitrazepam (0.025 mg kg^{-1}) and morphine sulphate (0.15 mg kg^{-1}). Anaesthesia was induced with midazolam (0.15 mg kg^{-1}), fentanyl (0.004 mg kg^{-1}), and pancuronium bromide (0.1 mg kg^{-1}). Maintenance of anaesthesia was performed with weight-related doses of fentanyl (total dose: 0.035 mg kg^{-1}), midazolam (total dose: 0.60 mg kg^{-1}), and pancuronium bromide (total dose: 0.25 mg kg^{-1}). No volatile anaesthetics were used. Before the start of CPB, 0.3 mg fentanyl and 5 mg midazolam were given to the patients. The groups did not differ with regard to anaesthesia procedure.

CPB was carried out with a membrane oxygenator (Monolyth, Sorin, Torino, Italy). The circuit was primed with $1,000 \text{ ml}$ of Ringer's solution, $1,000 \text{ ml}$ of dextrose 5%, and 250 ml of albumin 5%. A flow of $2.4 \text{ l min}^{-1} \text{ m}^{-2}$ was maintained within the entire CPB. A mono-atrial cannulation technique was used for drainage of the venous blood. Almost normothermia (nasopharyngeal temperature $34.3 \pm 0.3^\circ \text{C}$, rectal temperature $33.4 \pm 0.4^\circ \text{C}$) was used. A haemofiltration device (HF-80, Fresenius, Bad Homburg, FRG) was used to adjust haemoglobin (Hb) between 8.0 to 9.0 g dl^{-1} . PaCO_2 was kept between 35 and 40 mm Hg and PaO_2

between 150 and 250 mm Hg during the entire period of CPB by varying fresh gas flow to the membrane oxygenator.

Measured parameters

Mean arterial perfusion pressure (MAP) and systemic vascular resistance [SVR: $\text{mean arterial pressure (MAP)} - \text{central venous pressure (CVP)} \times 80 / \text{cardiac output (CO)}$] were monitored to assess changes in arterial vessels. Volume of the extracorporeal circuit was continuously measured to evaluate changes in venous capacitance vessels. Blood gas analyses, haemoglobin (Hb), osmolarity, plasma viscosity and colloid oncotic pressure (COP, Sartorius membrane $20,000$ dalton) were also measured from arterial blood samples. Blood gas analyses were also taken from venous blood, which was returned to the extracorporeal circuit. Oxygen consumption [VO_2 : $\text{cardiac output (CO)} \times \text{arterial-venous oxygen content difference (AVDO}_2) \times 10$] and oxygen delivery [DO_2 : $\text{cardiac output (CO)} \times \text{oxygen content (CaO}_2) \times 10$] were also documented.

In addition to monitoring macrocirculatory alterations, changes in microvascular blood flow were measured by means of a two-channel laser Doppler skin blood flux monitor (MBF-3D, Moor Instruments, Devon, Great Britain), which uses a solid laser diode as a laser light source at about 810 nm . It uses optical fibres to transmit light to the tissue and photo-diode detection of the collected light. The device yields electrical signals proportional to the number of moving blood cells. The reflected light is registered by a photo-detector and processed in real time to yield an output in millivolts of arbitrary flow units (= laser Doppler flow [LDF]). The laser Doppler measures blood flow in approximately 2 mm^3 of tissue. Response time of the system is approximately 0.2 s [6]. The coefficient of variation was reported to be approximately 6% [7]. Detailed technique and theoretical background have recently been described elsewhere [8, 9]. With the help of double-sided adhesive tapes, one laser probe was placed on the patient's forehead (probe 1), the other one on the inner part of the patient's right forearm (probe 2). Next to the laser Doppler probes, temperature probes were placed to measure skin temperatures simultaneously with rectal, nasopharyngeal and blood temperatures.

Measurements were documented before injection of PDE-III inhibitors or placebo until 30 min thereafter. During this period no anaesthetics or volume was added to the circuit, and blood temperatures were kept strictly constant.

Statistics

Mean values $\pm$ standard deviation (s.d.) were calculated for all parameters. The data were analysed by using two-way analysis of variance including multivariate analysis of variance (followed by Scheffe's testing). Because the laser Doppler flux monitors output flow in arbitrary flow units, percentage changes of LDF from baseline values were also calculated. These percentage changes were additionally tested by H-test

(Kruskal and Wallis). P values < 0.05 were considered statistically significant.

Results

Demographic data and data from cardiopulmonary bypass were without differences among the groups (Table 1). Hb, osmolality, plasma viscosity, COP and all measured temperatures were also similar for the three groups (Table 1).

Mean arterial (perfusion) pressure was lowered significantly by piroximone (maximum -17 mm Hg) and enoximone (maximum -25 mm Hg), whereas it increased in the control (maximum $+20$ mm Hg) (Figure 1). In the piroximone patients, perfusion pressure returned to baseline value approximately 15 min after injection, in the enoximone group a slight decrease (-8 mm Hg) was even seen at the end of the investigation period. SVR was also significantly reduced by the PDE-III inhibitors with the most pronounced decrease in the enoximone patients (Figure 1). Volume of the cardiopulmonary bypass (CPB) system was more reduced in the enoximone (maximum -440 ml, 30 min after injection) than in the piroximone patients (maximum -300 ml) (Figure 2). LDF measured at the forehead (Figure 3) increased significantly after injection of piroximone (maximum $+30\%$ in the 4th min). Enoximone resulted in a higher increase in LDF (LDF-forehead maximum $+44\%$) which also lasted longer than in the piroximone patients ($P < 0.03$). LDF-forearm (Figure 3) showed a similar course, however, enoximone patients (maximum $+33\%$ between 4th and 10th min) had a significantly higher flux than the piroximone-treated group (maximum $+10\%$ between the 2nd and 3rd min).

Oxygen consumption (VO_2) was significantly higher in the PDE-III inhibitor-treated than in the control patients with an overall higher increase in VO_2 in the enoximone patients (maximum $+45$ ml min^{-1}) than the piroximone group (maximum $+22$ ml min^{-1}) ($P = 0.04$) (Figure 4). Oxygen delivery (DO_2) was without differences among the three groups (Figure 4).

None of the patients suffered from sequelae attributable to the study.

Table 1 Patients' characteristics and data from cardiopulmonary bypass (CPB) (mean $\pm$ s.d.)

	Piroximone	Enoximone	Control
Age (years)	65.2 $\pm$ 5.5	60.2 $\pm$ 3.5	63.2 $\pm$ 5.0
Weight (kg)	74.2 $\pm$ 4.4	77.2 $\pm$ 3.9	75.2 $\pm$ 5.3
LVEF (%)	59.3 $\pm$ 8.0	64.3 $\pm$ 4.0	62.5 $\pm$ 5.5
LVEDP (mm Hg)	12.9 $\pm$ 8.9	15.9 $\pm$ 5.3	16.9 $\pm$ 4.9
Ischaemia (min)	56.9 $\pm$ 7.7	64.9 $\pm$ 7.7	66.9 $\pm$ 7.7
CPB (min)	92.4 $\pm$ 9.5	90.4 $\pm$ 8.8	89.4 $\pm$ 7.5
Temperature ($^{\circ}\text{C}$)			
rectal	33.8 $\pm$ 0.3	33.4 $\pm$ 0.2	33.7 $\pm$ 0.3
nasopharyngeal	34.3 $\pm$ 0.1	34.8 $\pm$ 0.2	34.7 $\pm$ 0.4
skin-forehead	31.8 $\pm$ 0.5	31.4 $\pm$ 0.6	31.7 $\pm$ 0.7
skin-forearm	30.1 $\pm$ 0.8	31.0 $\pm$ 0.9	30.1 $\pm$ 0.9

LVEF: left ventricular ejection fraction; LVEDP: left ventricular end diastolic pressure; Ischaemia: duration of aortic cross-clamping.

Figure 1 Changes (mean $\pm$ s.d.) in perfusion pressure and systemic vascular resistance (SVR) from baseline values. ■ enoximone $n = 10$; Δ piroximone $n = 10$; $\circ$ control $n = 10$; * $P < 0.05$ different from piroximone and enoximone group; ** $P < 0.05$ different from enoximone group.

Figure 2 Changes (mean $\pm$ s.d.) in the volume of the cardiopulmonary bypass (CPB) system from baseline values. ■ enoximone $n = 10$; Δ piroximone $n = 10$; $\circ$ control $n = 10$; * $P < 0.05$ different from piroximone and enoximone group; ** $P < 0.05$ different from enoximone group.

Discussion

PDE-inhibitors are a heterogeneous group of compounds, which have one common activity: the inhibition of phosphodiesterase. The increase in cAMP leads to an increase in slow Ca^{++} inward current, by which myocardial contractility is enhanced [10]. Increasing the sensitivity of the myofilaments to Ca^{++} and other nuclear mechanisms may also be involved in the inotropic properties of these agents. Enoximone has been reported to possibly produce inhibition of the

Figure 3 Changes (mean $\pm$ s.d.) in laser Doppler flow (LDF) from baseline values. ■ enoximone $n = 10$; Δ piroximone $n = 10$; $\circ$ control $n = 10$; * $P < 0.05$ different from piroximone and enoximone group; ** $P < 0.05$ different from enoximone group.

Figure 4 Changes (mean $\pm$ s.d.) in oxygen consumption (VO₂) and oxygen delivery (DO₂) in the three groups. ■ enoximone $n = 10$; Δ piroximone $n = 10$; $\circ$ control $n = 10$; * $P < 0.05$ different from control group; ** $P < 0.05$ different from piroximone and control group.

Na⁺-K⁺-adenosine triphosphate, as well. All PDE-III inhibitors act by direct positive inotropy and peripheral vasodilation. There are, however, several PDE-III inhibitors available and the question arises, which is the most beneficial to manage patients with low output syndrome (LOS).

In the pathophysiology and pharmacology of LOS, regional blood flow profile and the distribution of cardiac output are an important aspect. An increase in cardiac output is not always identical with an improvement in nutritive organ perfusion. Catecholamines, for example, may improve cardiac output dramatically, but effective nutritive regional perfusion may be even deteriorated. However, many of the haemodynamic problems in this situation are secondary to a reduced blood flow to various organs, which promotes further deterioration of microcirculatory blood flow [11].

The microcirculatory profile of cardiovascular active agents have not been well studied. In the clinical setting it is difficult to evaluate blood flow at the microcirculatory level correctly. Vasodilation produces conceivable increase in sympathetic tone thus influencing myocardial function and directly or indirectly (macro- and micro) circulation. Since blood flow is kept constant and the influence of ventricular actions are excluded, CPB represents a unique opportunity to evaluate the isolated effects of vasoactive drugs on circulation [12, 13]. Other aspects of flow regulation (i.e. rheological resistance offered by the flowing blood and its constituents) were kept stable within the present study (Hb, osmolarity, viscosity). One major advantage of laser Doppler technique for assessing microcirculatory perfusion is that it gives a continuous signal which responds rapidly to vascular perturbation. A linear relationship with *in vitro* measurements of red-cell flux and *in vivo* measurements of blood flow assessed by other methods was documented [14–17]. Changes of LDF at the forehead are believed to be of higher importance (= region of high perfusion) than changes at the forearm (= region of low perfusion) because the facial region is the skin area which is much better perfused and much more susceptible to flow alterations than the majority of the rest of the body [19]. One objection may be that only skin blood flow is monitored by this technique. However, it has been suggested that monitoring of skin capillary blood flow may provide useful information related to total and organ body perfusion [20] and thus may be helpful when monitoring the critically ill [21, 22].

Both PDE-III inhibitors used in the present study are imidazole derivatives. However, they vary significantly with regard to pharmacokinetics. In healthy volunteers, terminal plasma half-life of piroximone ranged from 150 to 331 min [23]. Keely *et al.* [24] reported a half-life of about 1.3 h. The plasma half-life of 1 mg kg⁻¹ piroximone given intravenously was shown to be approximately 1 h [25]. Their inotropic potency appears to be similar, however, only little is known concerning their circulatory effects. Leier *et al.* [26] found that enoximone given orally (1 mg kg⁻¹) significantly increased cardiac output (by approximately 18%) and hepatic-splanchnic blood flow (by approximately 15%), while renal blood flow was reduced (by approximately 13%). Increasing the dose (2 mg kg⁻¹ orally) caused a

similar increase in cardiac output, whereas hepatic blood flow decreased (by approximately 9%) and renal blood flow even slightly increased (by 1%). In dogs with induced congestive heart failure, Petein *et al.* [27] showed that piroximone (1.0 mg kg^{-1} as a bolus followed by $50 \mu\text{g kg}^{-1} \text{ min}^{-1}$) significantly increased cardiac index (by +49%) and muscular blood flow (by +36%) without changing renal blood flow (-1%). These results imply that changes in organ perfusion widely depend on the dose and way of administration. Moreover, the underlying disease is also of importance when looking at circulatory changes (e.g. congestive heart failure vs post-CPB low output syndrome).

In the present study, piroximone as well as enoximone produced significant arterial and venous vasodilation. The benefits of unloading not only the left heart (by arterial vasodilation) but also the right side of the heart (by venodilation) result in a reduced left ventricular chamber size and an improved distensibility via ventricular interdependence. Enoximone was shown to be a more potent vasodilator and acting longer than piroximone. The same applied to the increase in skin capillary perfusion. Whether a recruitment of capillaries or direct changes in microvascular tone were responsible for these changes cannot definitely be con-

cluded from the present results.

LDFs were increased significantly in spite of a decrease in MAP. This supports evidence that we should no longer be too much pressure-oriented, but look at flow. VO_2 in the present study was increased after injection of piroximone and enoximone. This indicates an improved O_2 consumption at the cellular level most likely due to the increase in microcirculatory blood flow. In animal experimental studies in endotoxic shock, oxygen supply was significantly increased by the administration of PDE-III inhibitor amrinone [28].

It is concluded that the new PDE-III inhibitor piroximone exerts circulatory effects which are comparable with those of enoximone. Both produced significant vasodilation at the arterial and venous side, which definitely can be distinguished when measurements were carried out during CPB. Although blood pressure was reduced, microcirculatory skin perfusion was improved and VO_2 was increased. Apart from the effects on myocardial contractility, this influence can be beneficial for patients with acute heart failure. However, modification in regional perfusion profile remains to be further elucidated when using PDE-III inhibitors in the critically ill.

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