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POTENTIATION OF ADENOSINE BY PENTOXIFYLLINE IN THE INHIBITION OF SUPEROXIDE ANION PRODUCTION OF HUMAN POLYMORPHONUCLEAR LEUKOCYTES

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Introduction: Pentoxifylline (PTX) can effectively prevent septic organ failure. PTX inhibits the production of oxygen radicals and enhances the chemotaxis of PMNL. Because these effects are shared by adenosine (ADO) acting via specific receptors (A1/A2) this study characterizes the mode of action of PTX and ADO on human PMNL. **Material and Methods:** Superoxide anion formation of FMLP (10^{-7}M) activated PMNL was measured by chemiluminescence activity (CA). **Results:** 1.) The inhibition mediated by ADO is potentiated by PTX (Figure 1). 2.) The analysis of the dose-response curves revealed a **sequential synergism** as the underlying mechanism of potentiation. 3.) The receptor antagonist 8-phenyltheo-phylline (8-PT) reduced only the ADO-mediated inhibition of the CA (Figure 2).

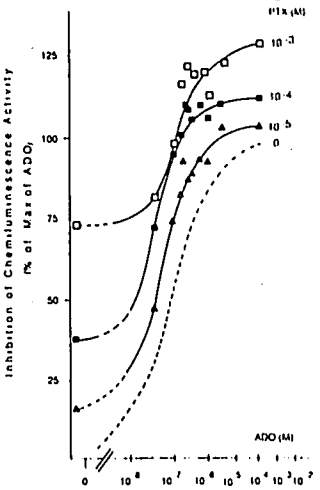

Figure 1: Potentiation of ADO-mediated inhibition by PTX. (Mean±S.E., n=6).

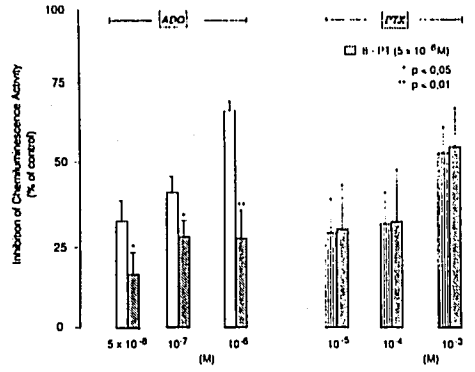

Figure 2: Effect of 8-PT on ADO- and PTX-mediated inhibition of CA. (Mean±S.E., n=6).

Table 1: Plasma levels of ADO in healthy volunteers (HV) and septic patients (SP).

	HV	SP
ADO (nmol/l)	120	510*

(Mean±S.E., n=12, *:p<0.05)

Conclusions: Because sequential synergism is the mechanism of potentiation of ADO by PTX, it is unlikely that PTX acts via A1/A2-receptors. This even more as 8-PT failed to reduce the action of PTX. The sequential synergism suggests: 1.) ADO inhibits PMNL by increasing intracellular cAMP. 2.) PTX potentiates this effect by inhibiting the degradation of cAMP due to the reduction of the phosphodiesterase activity. Because plasma ADO is almost 5 times higher in SP than in HV, the beneficial therapeutic influence of PTX during sepsis might be due to the potentiation of the effects of ADO on human PMNL.

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TITLE: IMPROVEMENT OF OXYGEN UTILIZATION BY PENTOXIFYLLINE IN PATIENTS WITH SEPTIC SHOCK

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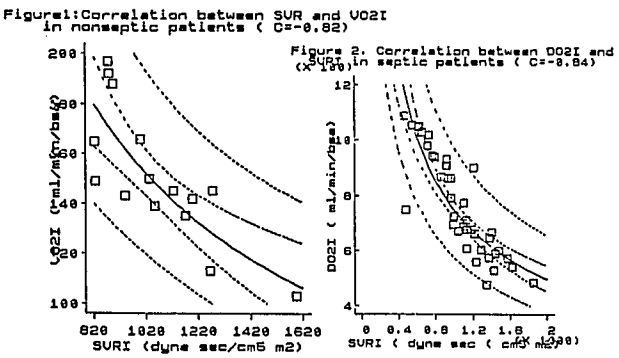
Peripheral vascular failure, even if complicated by inability to maintain an adequate cardiac output and oxygen consumption may be a major determinant of outcome in septic shock (1). The beneficial effects of pentoxifylline (PTX) on vascular disorders as a result of increasing erythrocyte flexibility and reduced blood viscosity (2) implicates investigations of these substance in human septic shock syndrome. These effects could result in improvement of oxygen transport and utilization in tissues with microcirculatory flow disturbances. The goal of the present study was to investigate the effect of PTX on oxygen delivery (DO2) and consumption (VO2) in accordance to changes in peripheral vascular resistance.

METHODS: After approval of the Institutional Human Ethics Committee, PTX (5 mg/kg) was administered in 12 patients who fulfilled esthablished sepsis criteria and after surviving sepsis (nonseptic-control) over a period of 3 hr. Cardiac output (thermodilution) , heart rate, systemic and pulmonary pressures together with indices of stroke volume, systemic vascular resistance (SVRI) oxygen consumption (VO2I) and delivery (DO2I) were derived at five timepoints of measurement: control, 1, 2 and 3 hr during PTX-infusion and 1 hr after its termination. Statistical analysis was made using ANOVA with repeated measurements and a simple linear regression model.

RESULTS: By focusing on oxygen consumption and delivery , there were no significant differences between both groups during the control period. After infusion of PTX, VO2I rose significantly from 158±6 to 181±6 ml/min/bsa in septic patients compared to nonseptic controls (148±22 to 151±8 ml/min/bsa). DO2 was not statistically significant between the two groups. However, by looking on the relationship between SVRI and DO2, the only significant correlation occured in septic patients (r^2= 70%, figure 2) , whereas the VO2 correlates higly significant with SVRI in nonseptic controls (r^2= 67% , figure 1) .

DISCUSSION: In contrast to the nonseptic state, during septicemia oxygen consumption is reported to be dependent on oxygen delivery, which in turn is flow dependent (3), and normally, increases in oxygen delivery increase VO2. In our investigation, oxygen uptake rose without any significant changes in DO2 in septic patients. These findings and the absolute poor correlation to peripheral vascular resistance implicates a relative independency of oxygen utilization from cardiac output in these patients. However, this points towards an beneficial effect of PTX on increased metabolic demand in peripheral tissues.



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