CRITICAL CARE II — METABOLISM; OXYGEN TRANSPORT

A232

TITLE: *CARDIORESPIRATORY EFFECTS OF PENTOXIFYLLINE IN SEPTIC AND NON-SEPTIC STATES*

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Cellular and subcellular mechanisms have been identified as the possible cause of beneficial effects of pentoxifylline (PTX) on the hemodynamic and respiratory responses to septic shock in animals.[1,2] We examined whether PTX is also effective in human septic states.

METHODS: PTX (5mg/kg) was administered in 12 patients who fulfilled established sepsis criteria (S) before and after surviving sepsis (NS) over a period of 3 hr. Heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), stroke volume index (SVI), oxgen consumption and transport indices (VO_2I and DO_2I) and the arterio-venous oxygen difference ($AvDO_2$) were measured during a control period, 1, 2 and 3 hr after the start of the PTX infusion and 1 hr after its termination. As there were no significant differences during PTX administration the respective data were pooled. Statistical differences were calculated with ANOVA for multiple comparisons and Tukey's test. A $p<0.05$ was accepted as significant.

RESULTS: There were no differences between S and NS in the control period. Following PTX, HR increased and SVI remained unchanged in S, while, reciprocally, in NS SVI increased while HR was unchanged. VO_2I and $AvDO_2$ increased in S significantly more than in NS, while DO_2I was stable in both groups.

DISCUSSION: A mild cardiac stimulation with no effect on the peripheral vasculature characterizes the hemodynamic profile of PTX in septic and non-septic states. Increases of oxygen consumption and $AvDO_2$ during septicemia which point towards an improvement of oxygen utilization in the peripheral tissue, might reflect the reported beneficial effects of PTX in animal models of septic shock.[1,2]

TABLE

		control	PTX	1h later
HR	S	103±5	108±2++	107±3
bpm	NS	95±5	96±2	97±3
MAP	S	81±4	86±1	84±3
mmHg	NS	83±5	84±2	83±2
CI	S	4.8±0.5	5.4±0.2	5.3±0.4
$l/min/m^2$	NS	5.0±0.4	5.7±0.2	5.6±0.2
SVI	S	47±5	50±2++	50±4++
ml/m^2	NS	53±4	59±2*	58±3
VO_2I	S	158±6	181±6++*	172±6
$ml/min/m^2$	NS	148±22	151±8	155±18
DO_2I	S	710±71	770±32	767±75
$ml/min/m^2$	NS	705±67	770±45	771±96
$AvDO_2$	S	3.3±0.3	3.3±0.2+	3.2±0.2
ml/dl	NS	2.9±0.4	2.7±0.1	2.7±0.2

means ± SEM, significant differences:
S from NS: + p<0.05, ++ p<0.01
*PTX from control: * p<0.05, ** p<0.01*

References:
1) Tighe D et.al: Crit Care Med 18:184, 1990
2) Welsh CH et.al: Am Rev Resp Dis 137:144, 1988

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TITLE: IN VIVO MODULATION OF HUMAN NEUTROPHIL FUNCTION BY PENTOXIFYLLIN IN SEPTIC PATIENTS.

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Pentoxifyllin (PTX) a methylxanthine derivative is generally used for treatment of symptoms of peripheral vascular diseases. Furthermore PTX is able to modulate neutrophil function in vitro and especially to inhibit respiratory burst activity (RBA) in human polymorphnuclear granulocytes (PMN). These effects indicate that PTX may be useful in the treatment of granulocyte mediated diseases and symptoms. We therefore investigated the in vivo effect of PTX on human PMN of septic patients.

METHODS: PTX (5mg/kg) was administered in 12 patients who fulfilled established sepsis criteria. Controls were determined in septic patients without PTX treatment. Cells were isolated before treatment (control samples) and two hours after by a two-step dextran sedimentation and sodium metrizoate Ficoll gradient centrifugation. Remaining erythrocytes were removed by hypotonic lysis. RBA was measured in a chemiluminescence assay after stimulation with FMLP (formyl-methionyl-leucyl-phenylalanin), PMA (phorbol-myristate-acetate) and opsonised zymosan.

RESULTS: After PTX treatment RBA stimulated with FMLP and PMA was significantly decreased compared to control samples (table). No significant difference was observed when RBA was stimulated with opsonised zymosan. Patients without PTX therapy were found to have unchanged high PMN activity.

Influence of PTX on PMN function (RBA) of septic patients.

	control	PTX
FMLP (1mg/ml)	107.6+21.7mV	47.4+12.3mV*
PMA (100ng/ml)	526.4+53.9mV	347+46.3mV*
ZYMOSAN (500ng/ml)	122.3+16.5mV	115.7+16.7mV

n=12, mean+SEM, * p<0.05

DISCUSSION:
Pentoxifyllin displays definite modulatory effects on granulocyte function of septic patients. PTX may prove to be a valuable drug not only for the treatment of plasma and red-cell rheological pathology, but also in granulocyte-mediated diseases as septic syndrome.