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## C1-esterase inhibitor and its effects on endotoxin-induced leukocyte adherence and plasma extravasation in postcapillary venules

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## Keywords

complement, vascular injury, C1-INH, leucocyte-endothelial interaction

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## Comments

This level V trial was well arranged with blinding of observers to the treatment given. However, measurement of individual complement components may have further elucidated complement changes seen in this septic model and clarified the molecular pathway of benefit of C1-INH

## Introduction

The activation of the complement system and the intrinsic cascade of coagulation is thought to have an important role in the pathophysiology of sepsis, in particular the development of septic shock and acute respiratory distress syndrome (ARDS). It is known that endotoxin or lipopolysaccharide (LPS) activates complement and intrinsic cascade via C3a, C5a and bradykinin. These mediators are responsible for vasodilation and increased vascular permeability. Neutrophils are also important in mediating vascular injury during sepsis via adherence to endothelial cells and release of toxic oxygen species and lysosomal proteinases (eg elastase) producing vascular wall injury. In vitro, neutrophil elastase has been shown to inactivate the main inhibitors of complement, coagulation and fibrinolytic systems (C1-esterase inhibitor C1-INH, antithrombin III,  $\alpha$ 2-antiplasmin respectively). Activation of complement and the intrinsic cascade are regulated by C1-INH, which itself is the only known plasma inhibitor of activated C1r and C1s. Previous studies have shown that plasma levels of C3a and C4a are significantly higher in patients with fatal septic shock than in those who survived. C1-INH given in the course of sepsis appears to be beneficial for the prevention of excessive activation of complement and the intrinsic coagulation cascade.

## Aims

This study aimed to investigate the ability of C1-INH to reduce leukocyte-endothelial interaction and vascular injury in sepsis.

## Methods

Thirty two Wistar rats were anesthetized with intra-peritoneal pentobarbitol. Mean arterial pressure (MAP) was measured via the left carotid artery and the right internal jugular vein used for reagent infusions. After laparotomy and 15 min before baseline measurements, rats were given PKH26-GL-labelled erythrocytes and fluorescein isothiocyanate (FITC)-labelled albumin. Rats were randomized to one of four groups and the experimenter blinded to the treatment given. With eight rats in each group, they were randomized to:

- (1) 7.5 U/kg C1-INH bolus 30 min before endotoxin
- (2) 15 U/kg C1-INH bolus 30 min before endotoxin
- (3) Normal saline bolus 30 min before endotoxin
- (4) Normal saline pretreatment 30 min before saline infusion

Endotoxemia was produced by infusion of LPS from *Echerichia coli* diluted in normal saline. Measurements were made at 0, 60 and 120 min. Mesenteric microcirculation was examined with a specially designed microscope. Measurements were made of:

- (1) mean red blood cell velocity and vessel diameter in post capillary venules at stated time points after LPS administration. Wall shear rate was also calculated
- (2) leukocyte-endothelial interactions, expressed as number of adherent cells per 100 mm vessel length
- (3) macromolecular leakage quantified by leakage of FITC-labelled bovine albumin
- (4) cardiovascular parameters (MAP, heart rate (HR)), hematocrit, leukocyte count and platelet count.

The results were analyzed statistically using two way ANOVA followed by Scheffe's test.

## Results

No change was seen in MAP or HR in any of the four groups during the study period. Neither LPS nor C1-INH affected venular diameter. Red blood cell velocity decreased during infusion of LPS in the C1-INH group after 120 min and in the LPS alone group after just 60 min. Leukocyte adherence in all three groups given LPS showed a significant increase after 120 min, and after 60 min in the LPS and C1-INH 7.5 group. There was no increase in adherence in the control group. Macromolecular leakage

was significantly higher in the LPS group after 60 and 120 min compared with the other groups. Values for both C1-INH groups were lower after 60 and 120 min compared to controls but this was not statistically significant.

## Discussion

Previous studies have demonstrated that multi-organ failure develops in septic patients in association with persistent rise in complement activation. LPS infusion leads to increased plasma C3a and C5a. Observations show a relative deficiency of biologically active C1-INH in sepsis. It has, therefore, been postulated that C1-INH may be a therapeutic measure to reduce the severity of sepsis.

In this study C1-INH was shown to attenuate microcirculatory disturbances in a normotensive sepsis model. A dose of 7.5 U/kg attenuated the decrease in red blood cell velocity and venular wall stress. No further benefit was evident with a higher dose of 15 U/kg C1-INH. Leukocyte adherence was prevented by both doses of C1-INH. The increased capillary leak seen in LPS-induced endotoxemia was lowered by both C1-INH treated groups, although the difference was not statistically significant. The authors conclude that there are benefits of 7.5 U/kg C1-INH in attenuation of LPS induced microcirculatory disturbances, with no added benefit of higher dosage. They suggest that low doses of C1-INH given in the early stages of sepsis may have therapeutic potential.

## References

1. Schmidt W, Stenzel K, Med C, Gebhard MM, Martin E, Schmidt H: C1-esterase inhibitor and its effects on endotoxin-induced leukocyte adherence and plasma extravasation in postcapillary venules. *Surgery*. 1999, 125: 280-287.