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ACUTE KIDNEY INJURY

Alkaline phosphatase in sepsis-induced AKI

Alkaline phosphatase may be useful for the treatment of critically ill patients who have severe sepsis or septic shock and evidence of acute kidney injury (AKI), according to a randomized, double-blinded study published in *Critical Care*.

"Alkaline phosphatase is able to remove phosphate from different molecules and thereby acts as a detoxifying enzyme. It is depleted in the kidney during an ischemic or inflammatory insult and shortage of such a detoxifying enzyme might be related to further renal damage during sepsis," explains Peter Pickkers, an author on the recent trial. "We wanted to investigate whether administration of exogenous alkaline phosphatase would prevent further damage to the kidneys during sepsis, the most prevalent cause of renal damage and one for which no specific therapies are available to treat or prevent. Beneficial effects of alkaline phosphatase have been shown in animal models of sepsis, and our group has also previously reported that treatment with alkaline phosphatase is associated with decreased expression of nitric oxide in the kidneys of patients with sepsis and that this reduction is associated with an attenuation of the urinary excretion of markers of tubular injury. In our most recent study, we investigated whether administration of alkaline phosphatase resulted in a beneficial effect on clinically relevant end points of renal damage."

The study included 36 adults who had severe sepsis or septic shock and AKI and were admitted to one of seven participating intensive care units in The Netherlands or Belgium between June 2008 and November 2009. The researchers randomly assigned patients to either an intravenous bolus injection of alkaline phosphatase (67.5 units per kg body weight) over 10 min followed by a continuous infusion (132.5 units per kg per 24 h) over 48 h, or to matching placebo. The primary efficacy outcome measure was a prospectively defined composite end point of progress in renal function variables (recovery of endogenous creatinine clearance, need for renal replacement therapy [RRT] and duration of RRT) over 28 days. Secondary end points included changes in urinary excretion of biomarkers of renal injury (kidney injury molecule 1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], interleukin 18 [IL-18] and glutathione S-transferase [GST] A1-1 and P1-1), serum concentrations of circulating inflammatory mediators (lipopolysaccharide-binding protein [LBP], IL-6, C-reactive protein [CRP] and procalcitonin), changes in sequential organ failure assessment (SOFA) score, length of stay in the intensive care unit, length of stay in hospital, and all-cause mortality.

Baseline parameters were similar in the two treatment groups at study entry. The researchers found that the primary efficacy variable (the combined end point of renal parameters) was better in the alkaline phosphatase group than in the placebo group over the 28-day study period ($P = 0.02$). When the researchers looked at components of the combined end point individually, they found that recovery of endogenous creatinine clearance during the first 7 days was better in the group of patients treated with alkaline phosphatase than in those who received placebo, and that this effect was sustained over 28 days. Need for RRT did not differ between groups, and although RRT duration tended to be shorter in patients on alkaline phosphatase, this result was not statistically significant.

Pickkers *et al.* also found that urinary excretion of some markers of tubular injury (KIM-1 and IL-18) declined significantly more in patients on alkaline phosphatase than in those on placebo. Declines in levels of NGAL and GST enzymes did not differ between the groups, but the authors state that the result may not have reached significance owing to large variance between patients and inadequate power. Declines in serum concentrations of the inflammatory markers CRP, LBP and IL-6 were more pronounced in the alkaline phosphatase group than in the placebo group, although changes in procalcitonin did not differ between groups. SOFA scores, length of hospital stay and rates of all-cause mortality did not differ between groups, but length of stay in the intensive care unit was significantly shorter in patients on alkaline phosphatase than in those on placebo. The incidence of treatment-emergent adverse events was similar in the two treatment groups.

"Previous research concerning the prevention or treatment of renal damage in patients with sepsis has been disappointing," says Pickkers. "The results of our study suggest that alkaline phosphatase treatment may be efficacious for these patients and a larger trial, preferably one using recombinant human alkaline phosphatase, is needed to further investigate these findings. In addition, preclinical research needs to be carried out in order to further unravel the mechanism of action of alkaline phosphatase."

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Original article Pickkers, P. *et al.* Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial. *Crit. Care* doi:10.1186/cc11159