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Sepsis-related acute kidney injury: a protective effect of drotrecogin alfa (activated) treatment?

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Background: Drotrecogin alfa activated (DrotAA) is licensed for treatment of patients with severe sepsis and organ failure. Among the latter, acute kidney injury (AKI), defined as the persistence of oligo-anuria following adequate resuscitation, is one of the most apprehended. We conducted a prospective, observational, and controlled study to test the hypothesis that DrotAA beneficially affected the evolution and outcome of AKI, complicating acute sepsis-induced cardiopulmonary failure.
Methods: Forty-six patients were studied. Thirty subjects received standard treatment for sepsis without DrotAA. In the remaining 16 patients, DrotAA was added as a continuous infusion of 24 μg/kg/h for 96 h.
Results: Mean age, causes of sepsis, and severity/organ failure scores were comparable between patients treated with or without DrotAA. Mortality at 28 days was high and comparable between both treatment groups (56% vs. 69%, DrotAA vs. no DrotAA; $P = 0.5$). When oligo-anuria was present at the start of the study, it persisted during treatment in all patients, with no significant difference between groups. Both treatment groups presented with baseline mean daily fractional excretion of sodium values >2% that remained high during the observation period, regardless of whether DrotAA was given or not. Kidney histology showed a preserved renal architecture with tubular necrosis in all specimens. Similar glomerular, tubulo-interstitial, and vascular alterations were present in both treatment groups.
Conclusion: In this small cohort of patients with severe sepsis who received adjuvant DrotAA treatment, no effect on urine output, tubular function, or mortality could be demonstrated.

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SEVERE sepsis and its related complications, including shock and multi-organ failure, are among the most common causes of morbidity and mortality in intensive care units (ICU).[1] Acute kidney injury (AKI) is a common complication of sepsis and considerably aggravates the prognosis.[2] The pathogenesis of sepsis-related AKI is still poorly understood. Data from experimental animal models indicate that intrarenal vasoconstriction is predominant in early sepsis while tubular function remains intact.[3] The early vasoconstrictor phase is joined by a pro-inflammatory phase involving a cytokine, chemokine, and adhesion molecule 'storm', which propagates tubular injury. Increased production of nitric oxide enhances the loss of vascular renal autoregulation.[4] In human sepsis, much of the sepsis-induced deleterious effects on renal function may be related to persistent alterations in microcirculatory blood flow. As in other organs, this may result in a significant loss of capillary perfusion and may lead to a kidney oxygenation deficit.[5,6]

Recent advances in the treatment of severe sepsis with beneficial effects on morbidity and mortality include early goal-directed resuscitation,[7] tight glycaemic control,[8,9] administration of stress doses of corticosteroids,[10] and adjuvant therapy with recombinant human activated protein C (APC).[11] Patients in the ICU who received early goal-directed and corticoid treatment had a lower incidence of sepsis-associated AKI than those who did not (40% vs. 55%; $P = 0.015$).[12] Glycaemic control using a protocol-driven intensive insulin infusion reduced kidney injury by 41% ($P = 0.007$) in a population mainly composed of post-surgical critical care patients[8] and to a lesser extent ($P = 0.04$) in medical ICU patients.[9] However, this type of treatment is intrinsically preventive and none of these studies assessed the evolution and outcome of established sepsis-induced AKI.

The PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial established drotrecogin alfa activated (DrotAA) (Xigris®, Eli Lilly Co., Indianapolis, IN) as a treatment that reduced the overall mortality rate in patients with severe sepsis.[11] The observed survival benefit was most striking in the more severely ill patients at a high risk of death[11] and appeared to be largely driven by a significantly faster resolution of cardiovascular and respiratory failure and a lower likelihood of haematological organ dysfunction (i.e. less pronounced or no platelet decrease).[13] However, the trial failed to show any beneficial effect on AKI.[11,13]

The time course of deteriorating kidney function in septic patients is difficult to establish. Current methods to detect kidney dysfunction are not able to reflect abrupt changes or lack specificity and/or sensitivity. Also, sepsis-induced loss of kidney function is a late symptom of a process of kidney injury that started outside the hospital. Consequently, patients with sepsis-associated AKI may already present some degree of tubular necrosis at ICU admission. Therefore, it is doubtful whether urine output, serum creatinine concentration, and creatinine clearance are useful variables for dynamic evaluation of kidney function in this particular population. The development of a marker with robust early diagnostic and prognostic potential in sepsis-associated AKI remains challenging. Onset of tubular dysfunction leads to an increase in urinary sodium concentration and fractional excretion of sodium (FeNa),[14] which can be easily calculated and followed over time in septic AKI. Other urinary biomarkers of tubular dysfunction have been studied in the critical care setting. Among the most promising are kidney injury molecule-1,[15] Na^+/H^+ exchange isoform 3 protein,[16] neutrophil gelatinase-associated lipocalin,[17] and interleukin-18.[18] Unlike FeNa, however, these biomarkers are not available for routine use in the ICU and only a few studies using these molecules have included septic patients. Therefore, we chose FeNa as a marker of tubular dysfunction in a cohort of patients with severe sepsis to assess whether DrotAA could influence kidney function.

Materials and methods

Patients

The protocol was approved by the Committee for Ethics in Human Research of our hospital. Informed consent was obtained from the next-of-kin of each patient. Severe sepsis and septic shock were defined according to consensus guidelines.[19] AKI was defined as the persistence of oligo-anuria (diuresis <400 ml/24 h) following adequate fluid resuscitation (i.e. associated with maximal cardiac output evaluated by repeated echocardiography) and, if needed, the administration of norepinephrine aiming at a mean arterial pressure >65 mmHg. Patients with severe sepsis-induced cardiorespiratory failure and no pre-existing renal failure were consecutively enrolled in the study. All patients had radial and central venous catheters inserted and were mechanically ventilated under continuous analgesic sedation with midazolam and fentanyl. Empiric broad-spectrum antibiotic therapy was immediately provided and adapted within 24 h according to culture results. Diuretics were not administered. Standard resuscitation treatment comprised fluids, vasopressor, and/or inotropic support (when needed), stress doses of hydrocortisone (if shock was present), red blood cell transfusion aiming at a haemoglobin level around 10 g/dl, insulin to maintain blood glucose <150 mg/dl, stress ulcer and deep venous thrombosis prophylaxis, and adequate nutrition. Patients were not randomized whether or not to receive DrotAA. Rather, the decision to start DrotAA was left at the discretion of the attending ICU physician. Prescription of DrotAA followed national guidelines allowing administration of the drug in septic patients with at least two organ failures unless an absolute or a relative contraindication for the drug was present (i.e. considered to be at increased risk for bleeding; recent trauma; recent intracranial surgery, bleeding or stroke; recent gastrointestinal blood loss; and treatment with medication that impaired haemostasis). The latter group of patients formed the 'control' population. DrotAA was given as a continuous infusion of 24 μg/kg/h for 96 h.

If needed, renal replacement therapy (RRT) was provided as continuous pump-driven veno-venous haemofiltration (Baxter, BM25, Unterschleissheim, Germany) that was started after initial haemodynamic stabilization. A high-flux haemofilter was used, maintaining extracorporeal blood flow at 110 ml/min. Ultrafiltrate was replaced at a rate of 35 ml/kg/h by a bicarbonate-buffered substitution solution. Indications for starting RRT were fluid overload, severe metabolic acidosis, uncontrollable hyperkalaemia, and a BUN >100 mg/dl, occurring either alone or in combination.

Measurements

The following parameters were recorded: age, APACHE (Acute Physiology And Chronic Health Evaluation) II, and APACHE III[20] score at study inclusion, daily SOFA (Sequential Organ Failure Assessment)[21] scores during the 4-day treatment with or without DrotAA, and mortality at 28 days. Urine output with urinary sodium and creatinine was measured once and serum creatinine levels twice daily. Daily urine sampling started on the first day of study (from d0 to d1) at 08:00 hours and was repeated for 3 consecutive days (from d1 to d4). The FeNa was calculated as [(urine sodium/plasma sodium)/(urine creatinine/plasma creatinine)] $\times$ 100.

For both logistic and permission reasons, autopsy with kidney prelevation could be performed within 2 h after death in only 13 patients (six DrotAA-treated and seven DrotAA-untreated). Transversal slices of the kidneys were fixed in 4% buffered formaldehyde at room temperature for 24 h and embedded in paraffin for histological examination. Paraffin sections of 4 μm were cut and stained with haematoxylin–eosin–saffran, periodic acid Schiff, Masson trichrome, and Perls. The slices were examined by light microscopy by a pathologist (C. G.) blinded to the patients' treatment group. Lesions were reported in a descriptive way. Global architecture, tubulo-interstitial, and vascular lesions were evaluated. Additional description of tubular injury looked at the presence of cytoplasmic hyaline droplets associated with protein reabsorption, hydropic vacuolization due to administration of exogenous solutes, cytoplasmic haemosiderin deposition related to intravascular haemolysis, and intra-luminal hyaline casts due to protein precipitation.

Statistical analysis

SPSS package 13.0 for Windows (Chicago, IL) was used for statistical analysis. The *T* test was used to evaluate differences in age, urine output, SOFA and APACHE scores, and mortality between DrotAA-treated and -untreated patients. Values were expressed as means $\pm$ SD. A two-tailed *P* value <0.05 was considered to be statistically significant. FeNa levels in survivors were compared using a one-way analysis of variance with the Bonferroni test for multiple comparisons, assuming significance at $P<0.05$.

Results

Forty-six patients, recruited from the emergency and hospital wards, were consecutively enrolled. Thirty patients received a protocolized standard treatment for severe sepsis, and 16 patients were treated with DrotAA.

Mean age, causes of sepsis, and severity/organ failure scores were comparable between patients treated with or without DrotAA (Table 1). Haemodynamic variables (cardiac output, mean arterial, and cardiac filling pressures) and parameters of oxygenation and ventilation (including pH), adjusted for catecholamine need and mortality, were not statistically different between groups during the 4-day treatment period (data not shown). Twenty-eight-day overall mortality was 65%. Fifty-six per cent (9/16) of the patients in the DrotAA group and 69% (21/30) of the patients in the control group died ($P = 0.5$). In the population as a whole, 18 (39%) patients (five DrotAA-treated and 13 DrotAA-untreated) were oligo-anuric at a certain time point during the study. In four of them, all untreated, daily urine output exceeded 400 ml on d4. However, patients who were oligo-anuric at onset (d0; three DrotAA-treated and eight DrotAA-untreated) remained so throughout the whole study period with no significant difference in urine output between groups.

Table 1

Patient characteristics.

	DrotAA treatment	No DrotAA treatment	*P*
Age (years)	66 $\pm$ 15	67 $\pm$ 15	0.8
Gender (male/female)	10/6	18/12	
Cause of sepsis [*n* (%)]			
Pulmonary	7 (44)	16 (53)	
Abdominal	3 (19)	2 (7)	
Urinary	2 (12)	4 (13)	
Catheter	1 (6)	3 (10)	
Unknown	3 (19)	5 (17)	
APACHE II	30 $\pm$ 11	31 $\pm$ 9	0.6
APACHE III	87 $\pm$ 27	85 $\pm$ 31	0.9
SOFA score (*n*)			
Day 0 (46)	8.9 $\pm$ 2.1 (16)	9.1 $\pm$ 3.4 (30)	0.8
Day 1 (46)	8.7 $\pm$ 2.7 (16)	8.7 $\pm$ 3.4 (30)	1.0
Day 2 (42)	8.5 $\pm$ 2.5 (16)	8.2 $\pm$ 3.7 (26)	0.8
Day 3 (39)	8.0 $\pm$ 2.3 (15)	8.3 $\pm$ 3.3 (24)	0.8
Day 4 (36)	7.6 $\pm$ 2.6 (14)	6.9 $\pm$ 1.9 (22)	0.3

Demographic characteristics, cause of sepsis, and severity/organ failure scores for all patients. Results are expressed as means $\pm$ SD.

DrotAA, drotrecogin alfa (activated); APACHE, Acute Physiology And Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; *n*, number of patients evaluated.

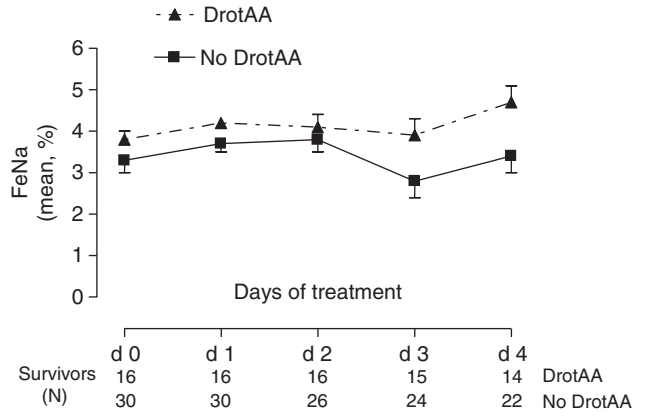


Fig. 1. Fractional urinary excretion of sodium (FeNa) in survivors with severe sepsis-induced acute kidney injury, with and without addition of drotrecogin alfa activated (DrotAA) to standard care. Values are presented as means ± SD. No significant differences were found between groups at any time point.

FeNa could be calculated in all the patients studied. FeNa values exceeding 2% were observed during the whole treatment period. FeNa did not differ significantly between groups at any time point and was not influenced by DrotAA (Fig. 1).

RRT was required in 22 patients, of whom six were treated with DrotAA. DrotAA-treated or -untreated patients who received RRT did not differ with respect to age, number of organ failures, and severity scores (data not shown). Twenty-eight-day overall mortality in patients requiring RRT was 77%. Seventy-five per cent (12/16) of the patients who did not receive DrotAA and 83% (5/6) of the patients treated with DrotAA died. Fifteen (88%) of these non-survivors, both treatment groups taken together, remained oligo-anuric during the first 2 days of observation.

Microscopy showed a preserved global renal architecture in all patients. Glomerular, interstitial, and blood vessel alterations were all grossly similar between groups. Evidence of acute tubular necrosis was present in all specimens. Tubuli in DrotAA-treated and -untreated patients did not differ in hyaline droplet or haemosiderin content, degree of hydropic vacuolization, or presence of intraluminal hyaline casts (Table 2).

Table 2

Tubular microscopy in patients treated with or without DrotAA.

	Hyaline droplet changes	Haemosiderin deposition	Intra-luminal hyaline casts	Hydropic vacuolization
No DrotAA				
1	–	+	+	–
2	+	–	–	–
3	+	–	–	–
4	++	+	–	–
5	+++	+	–	+
6	+	+	–	+
7	+	+	–	–
DrotAA				
1	–	+	+	–
2	+++	+	–	–
3	+	+	+	–
4	+	–	+	+
5	+++	+	–	–
6	–	+	–	–

Histological findings in tubuli from kidneys prelevated within 2 h after death in patients treated with or without DrotAA, assessed by light microscopy. Specimens were stained with haematoxylin–eosin–saffran, periodic acid Schiff, Masson trichrome, and Perls and studied descriptively by a pathologist blinded to the patients' treatment.
DrotAA, drotrecogin alfa (activated).

Discussion

The clinical, biochemical, and histological approach that was used in our study failed to demonstrate a beneficial effect of DrotAA on sepsis-induced kidney injury. Persistent oligo-anuria was associated with worse outcome in our study population, regardless of whether DrotAA was given or not. All patients also exhibited FeNa levels that largely and consistently exceeded 2%, suggesting upfront and persisting presence of acute tubular necrosis.[14] Standard resuscitation including DrotAA did not affect FeNa. Finally, microscopic examination revealed only aspecific structural alterations that were comparable between patients treated or not treated with DrotAA.

DrotAA, the recombinant form of human APC, has primarily anticoagulant actions *in vivo* but *in vitro* experiments indicate that its effect may be essentially driven by a modulating role on endothelial function through EPCR/PAR-1 receptor stimulation.[22] DrotAA has indeed been shown to improve microcirculatory blood flow in primate[23] and rodent[24] models of sepsis through removal of microthrombi and inhibition of the noxious interactions between activated neutrophils and endothelial cells. Animal experimental data suggest a possible beneficial effect of APC on the septic kidney. APC increased renal blood flow, lowered vascular permeability, tempered local inflammatory and oxidative reactions, and reduced histological changes in a rodent ischaemia/reperfusion model.[25] Suppression of endogenous protein C in polymicrobial sepsis in rats was strongly associated with increased renal dysfunction and injury due to biopsy-proven acute tubular necrosis.[26] When

given 3 h after induction of endotoxic shock in rats, APC significantly improved renal and peritubular capillary blood flow. This was associated with a downregulation of inducible nitric oxide synthase and a reduction of local angiotensin 2 production.[27]

Despite these promising experimental data, a protective effect of APC on the kidney during clinical sepsis has not been proven. Indirect evidence obtained from studying the sublingual microcirculation in patients with severe sepsis suggested that DrotAA could improve microvascular blood flow, independent of changes in arterial pressure and cardiac output[28] but whether this also applies to the renal circulation is unknown. *Post hoc* analysis of the PROWESS trial did not reveal a difference in the renal SOFA score between DrotAA- and placebo-treated patients. Subsequent clinical trials and post-commercial studies evaluating the use of DrotAA in septic conditions have neither looked at nor noticed a specific effect of the drug on the kidney. Using FeNa as a marker of tubular dysfunction, our study is the first to indicate that standard resuscitation including DrotAA probably does not affect severe sepsis-associated AKI in a normal clinical setting. Moreover, FeNa values tended to be consistently higher in the DrotAA-treated patients. It remains speculative as to whether this reflects an intrinsic unwarranted tubular effect of the drug or merely selection bias.

Several authors, using the SOFA score to evaluate risk factors and outcome of AKI in septic patients, identified oliguria[29,30] and acute tubular necrosis[30] as independent risk factors for mortality. We could not demonstrate any difference in the 'total SOFA' score between groups throughout the study period. Moreover, approximately half of the studied patients required RRT, which excluded measurement of creatinine clearance and renal SOFA score as valid parameters to assess renal function.

Some major flaws and limitations of our study must be stressed. Unlike in the animal setting, comparative evaluation of kidney function and morphology in patients with severe sepsis is hazardous due to the heterogeneity of the study population (difference in patient age, degree and duration of hypotension, type and dose of adrenergic support, underlying kidney disease, baseline renal function, ...) or may be 'contaminated' by confounding factors proper to an ICU environment (e.g. concomitant use of nephrotoxic drugs, diuretics, and contrast agents). We tried to minimize excessive bias by using equivalent goal-directed resuscitation measures in all patients, by excluding subjects with a prolonged ICU stay and known underlying or chronic kidney disease, and by avoiding diuretics and nephrotoxic agents during the acute treatment phase. The inherent and hardly quantifiable difference between time of development of septic AKI and time of enrolment in the study is somewhat smoothened by the similar 'baseline' FeNa values in both DrotAA-treated and control patients.

The use of FeNa as a marker of tubular injury may be questioned. Renal vasoconstriction at the onset of sepsis results in an increased tubular sodium reabsorption, thereby decreasing urinary sodium concentration and FeNa. When tubular damage occurs, FeNa will increase. Thus, FeNa values vary with respect to timing of measurement from onset of sepsis-induced tubular necrosis. This may explain why FeNa measurements range from very low to high in the more 'controlled' animal setting[31] while in human sepsis, when AKI is of unknown duration, FeNa values as high as 9% to 10% have been recorded.[32, 33]

In summary, mortality in this small cohort of severe septic patients with acute cardiopulmonary and renal failure remained very high in spite of rigorous resuscitation and evidence-based treatment, including RRT and DrotAA. Impaired tubular function, as expressed by persistently elevated FeNa, was observed in all patients with sepsis-induced AKI regardless of DrotAA infusion. We advocate that the use of FeNa as a marker of sepsis-related AKI should be evaluated in a larger prospective study.

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