Drotrecogin alpha (activated) in two patients with the hantavirus cardiopulmonary syndrome

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RC McDermid, RTN Gibney, RJ Brisebois, NM Skjodt. Drotrecogin alpha (activated) in two patients with the hantavirus cardiopulmonary syndrome. *Can Respir J* 2006;13(5):272-274.

Hantavirus cardiopulmonary syndrome (HCPS) is associated with rapid cardiopulmonary collapse from endothelial injury, resulting in massive capillary leak, shock and severe hypoxemic respiratory failure. To date, treatment remains supportive and includes mechanical ventilation, vasopressors and extracorporeal membrane oxygenation, with mortality approaching 50%. Two HCPS survivors initially given drotrecogin alpha (activated) (DAA) for presumed bacterial septic shock are described. Vasoactive medications were required for a maximum of 52 h, whereas creatinine levels and platelet counts normalized within seven to nine days. Given the similar presentations of HCPS and bacterial septic shock, empirical DAA therapy will likely be initiated before a definitive diagnosis of HCPS is made. Further observations of DAA in HCPS seem warranted.

Key Words: Drotrecogin; Hantavirus; Respiratory failure; Septic shock

The hantavirus cardiopulmonary syndrome (HCPS) is a mouse-borne illness that was first described in 1993 (1), but it is now recognized retrospectively back to 1959 (2). HCPS is highly prevalent in northern Alberta, with a reported intensive care unit mortality of 46% (3), and is characterized by acute hypoxemic respiratory failure, hypotension, thrombocytopenia, renal dysfunction, hemoconcentration and coagulopathy. Initially, HCPS may be indistinguishable from bacterial septic shock with adult respiratory distress syndrome (ARDS). Drotrecogin alpha (activated) (DAA) reduces mortality in patients with severe septic shock (4). We report two HCPS survivors given DAA before their HCPS diagnoses were confirmed as part of an open-label preapproval drug access study with proxy consent.

CASE PRESENTATIONS

Patient 1: Acute physiology and chronic health evaluation (APACHE) II score 29 (67.2% predicted mortality)

In November 2001, a 46-year-old previously healthy woman presented with a seven-day history of malaise, headache and myalgia. She developed rapidly progressive hypoxemic respiratory failure associated with a nonproductive cough. She had noticed mice in her home, but not any droppings.

On admission, the patient's pulse was 105 beats/min, her blood pressure was 165/80 mmHg, her temperature was 36.4°C and she had a respiration rate of 30 breaths/min. A cardiac

Le drotrecogin alpha activé chez deux patients atteints du syndrome pulmonaire à hantavirus

Le syndrome pulmonaire à hantavirus (SPH) s'associe à un collapsus cardiopulmonaire rapide découlant d'une lésion endothéliale et entraînant une fuite capillaire importante, un choc et une grave insuffisance respiratoire hypoxémique. Jusqu'à présent, on administre un traitement de soutien, qui inclut la ventilation mécanique, les vasopresseurs et l'oxygénation extracorporelle. La mortalité avoisine les 50 %. Est décrit le cas de deux survivants du SPH qui ont d'abord reçu du drotrecogin alpha activé (DAA) pour soigner un choc septique bactérien présumé. Des médicaments vasoactifs ont dû être administrés pendant une période maximale de 52 heures, tandis que les taux de créatinine et la numération plaquettaire se sont normalisés en sept à neuf jours. Étant donné la présentation similaire du SPH et du choc septique bactérien, un traitement empirique au DAA sera probablement entrepris avant qu'on pose un diagnostic définitif de SPH. D'autres observations du DAA dans le SPH semblent justifiées.

examination was normal, without an elevated jugular venous pulse. Coarse crackles were heard throughout all lung zones. The rest of the examination was unremarkable. Admission laboratory investigations showed a partial pressure of oxygen (PO_2) of 82 mmHg, a partial pressure of carbon dioxide (PCO_2) of 27 mmHg, pH of 7.39 on a nonbreather mask, a hemoglobin level of 179 g/L, a leukocyte count of $26.4 \times 10^9/L$ (including 22% immature forms without toxic changes), a platelet count of $53 \times 10^9/L$, a serum sodium level of 125 mmol/L, a creatinine level of 128 $\mu\text{mol/L}$, an international normalized ratio of 1.2 and a prolonged partial thromboplastin time of 56 s. A chest radiograph revealed dense bilateral opacification.

After blood cultures were drawn, she received cefotaxime and azithromycin, and was transferred to the intensive care unit, where she underwent immediate intubation. Hantavirus serology was collected because of the heightened clinical suspicion of HCPS. Despite a low tidal volume ventilation strategy, a positive end-expiratory pressure of 15 cmH₂O and a fraction of inspired O₂ of 1.0, her PO_2 (69 mmHg) did not improve. A pulmonary artery catheter was inserted and revealed a cardiac index (CI) of 2.4 L/min/m², a pulmonary capillary wedge pressure (PCWP) of 16 mmHg and a systemic vascular resistance index of 2470 dynes·s/cm⁵. Pulmonary artery pressures were elevated (44/27 mmHg). Her serum lactate level was 2.2 mmol/L. Twelve hours after admission, she was started on a 24 $\mu\text{g/kg/h}$ DAA infusion that was maintained for 96 h. Continuous renal

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replacement therapy with citrate anticoagulation was started 36 h after admission for renal failure. Dobutamine and high-dose noradrenaline infusions were continued for 52 h to maintain adequate perfusion. Dialysis was discontinued on day 6, with continuing improvements in creatinine levels. Her platelet count recovered on day 9. She was extubated on day 10 and was transferred back to her local hospital on day 13. She was immunoglobulin (Ig) M-positive and IgG-negative for the Sin Nombre hantavirus.

Patient 2: APACHE II score 26 (56.9% predicted mortality)

In December 2002, a 50-year-old male oil field engineer with a remote traumatic splenectomy presented with a seven-day history of myalgia, nausea, vomiting and nonbloody diarrhea. Three days after presentation, he developed acute respiratory failure with bibasilar interstitial chest opacification. He was treated with oral antibiotics, but his hypoxemia worsened over the ensuing 24 h. He had recently been cleaning out old farm buildings, but had not noticed any mouse droppings. He had no ill contacts. He had been vaccinated against pneumococcus 10 years prior, but not against influenza or meningococcus.

On transfer, the patient was alert and oriented. His temperature was 38.4°C, his pulse was 109 beats/min, his blood pressure was 130/80 mmHg and he had a respiration rate of 28 breaths/min. His jugular venous pulse was not elevated. Bibasilar crackles were heard. He had no peripheral edema. The rest of the examination was unremarkable.

Admission laboratory values showed a PO_2 of 46 mmHg, a PCO_2 of 32 mmHg, pH of 7.45 on a nonrebreather mask, a hemoglobin level of 164 g/L, a leukocyte count of $19.3 \times 10^9/L$ (including 18% immature forms without toxic changes), a platelet count of $86 \times 10^9/L$ and a creatinine level of 67 $\mu\text{mol/L}$.

After cultures were performed, the patient received intravenous cefotaxime, azithromycin, vancomycin and a single dose of tobramycin. Hantavirus serology and nasal swabs for respiratory viruses were collected. He was intubated and ventilated with low tidal volumes. Within hours, he developed hypotension and oliguric renal failure (creatinine level of 176 $\mu\text{mol/L}$), requiring a 20 $\mu\text{g/min}$ noradrenaline infusion. His oxygenation did not improve (PO_2 of 55 mmHg) on a fraction of inspired O_2 of 1.0 and positive end-expiratory pressure of 20 cmH_2O . He was heavily sedated, given neuromuscular blockade, and ventilated in a prone position. A pulmonary artery catheter was inserted and showed a CI of 3.9 L/min/m^2 and a PCWP of 12 mmHg. His pulmonary artery pressure was 28/13 mmHg. A 250 μg adrenocorticotrophic hormone stimulation test demonstrated a baseline cortisol of 528 nmol/L with a 1 h rise of only 147 nmol/L. The patient's serum lactate level was 3.5 mmol/L and he was started on intravenous hydrocortisone, a low-dose vasopressin and enteral fludrocortisone. After an intravenous fluid challenge, his noradrenaline infusion was reduced to 10 $\mu\text{g/min}$ and his creatinine level fell to 147 $\mu\text{mol/L}$. He was maintained on a 24 $\mu\text{g/kg/h}$ DAA infusion for 96 h starting 27 h after transfer.

Noradrenaline and vasopressin were stopped after 24 h and 31 h, respectively. By 48 h, the patient's creatinine level and platelet count had recovered. With an appropriate post-DAA delay, pleural drains were inserted to relieve large exudative effusions and he was extubated the next day. He was discharged with no significant sequelae after 11 days. He was IgM-positive and IgG-positive for the Sin Nombre hantavirus, and otherwise had negative culture results.

DISCUSSION

Microvascular thrombosis is central to the pathophysiology of multiorgan failure, the main cause of mortality in patients with severe sepsis (5). DAA has potent antithrombotic, fibrinolytic and anti-inflammatory effects. DAA reduces intravascular fibrin generation, preventing disseminated intravascular coagulation. DAA inhibits factors Va and VIIIa, neutralizes the platelet activator inhibitor-1, potentiates the activity of the tissue plasminogen activator and reduces the production of inflammatory cytokines, particularly tumour necrosis factor- α , interleukin (IL)-1 β and IL-6. The inhibition of inflammatory cytokines may decrease the diffuse endothelial injury associated with septic shock.

Profound systemic inflammation is characteristic of HCPS. High levels of IL-2, IL-6, interferon- γ and soluble receptors for tumour necrosis factor- α are found in the serum of patients with HCPS. Large numbers of cytokine-producing mononuclear cells are present in the lungs of patients dying from HCPS, in contrast to those dying from other causes of ARDS or from non-ARDS diseases (6). Surprisingly, there is little overt pulmonary capillary endothelial damage seen on electron microscopy, alternatively suggesting inflammation-induced intercellular gap formation (7). A capillary leak syndrome similar to HCPS can be induced with high-dose IL-2 chemotherapy (8). In contrast to the hemorrhagic fever syndromes, complement activation and circulating immune complexes are not seen in HCPS (8). Mild coagulopathies, particularly partial thromboplastin time prolongation, are common, but disseminated intravascular coagulation is unusual in HCPS.

HCPS starts with prodromal fever, myalgia and gastrointestinal symptoms followed by severe and rapidly progressive noncardiogenic pulmonary edema and shock. A low CI with normal PCWP and a normal to high systemic vascular resistance index are typical (9). Predictors of poor outcome include a CI of less than 2.5 L/min/m^2 , a serum lactate level of more than 4 mmol/L and refractory shock (10). Most deaths occur the first day, but in survivors, hypotension usually persists for two to four days, resolving as rapidly as the initial deterioration.

DAA did not seem to harm and may have even benefited both patients who were initially very unstable and required high doses of vasopressors to maintain acceptable perfusion. The first patient had a low CI and pulmonary hypertension, suggesting a mortality rate approaching 100% without salvage cardiopulmonary bypass. Following DAA infusion, patients 1 and 2 required vasoactive medication for only 52 h and 31 h, respectively. Both patients returned home within two weeks.

CONCLUSION

HCPS may initially be indistinguishable from bacterial septic shock, so some HCPS patients will receive DAA before the definitive diagnosis of HCPS. Two such HCPS patients recovered with no apparent complications after receiving DAA. Further case collection and investigation of DAA in HCPS seems warranted.

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