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Drotrecogin alfa activated (recombinant human activated protein C) masks ongoing severe sepsis

We wish to draw attention to two cases of severe sepsis where the usual clinical signs of severe sepsis may have been masked by treatment with recombinant human activated protein C (APC).

Case 1: A 49-year-old female was admitted to the intensive care unit (ICU) postoperatively with peritonitis following an ileal perforation from a prior laparoscopy for division of adhesions. She had undergone a laparotomy, surgical repair of the perforation and washing out of the heavily soiled abdominal cavity. On admission to ICU she had 2 out of 4 criteria for the systemic inflammatory response syndrome[1] (heart rate 122 beats per minute, white cell count 1.7 x 10^9/L and temperature 37.4ºC). Her PaO_2/FiO_2 ratio was 136 mmHg and the chest X-ray findings were consistent with an adult respiratory distress syndrome. Clinically she was in hyperdynamic septic shock and, despite adequate intravenous fluids, required a noradrenaline infusion to maintain a mean arterial pressure of 70 mmHg. Her arterial blood base excess was -10 mmol/L and plasma lactate was 2.4 mmol/L. Her plasma coagulation tests revealed an APTR 1.4, INR 1.4 and platelet count 202 x 10^9/L. Her peritonitis was treated with intravenous cefuroxime, gentamicin and metronidazole. Ten hours after ICU admission an infusion of APC was administered at 24 μg/kg/hr for 96 hours. Over the subsequent 4 days her condition improved. The septic shock, metabolic acidosis and fever resolved, her heart rate settled at 90 beats per minute and her white cell count increased to 8.1 x 10^9/L.

Within 24 hours of stopping the APC infusion her temperature and white cell count increased to 39ºC and 12.1 x 10^9/L, respectively. An abdominal CT scan with contrast failed to identify any intra-abdominal collection. However, when a laparotomy was performed, a second small bowel perforation with an associated collection of pus was identified which was dealt with surgically. Following this she improved and was eventually discharged from ICU.

Case 2: A 61-year-old man who had a past history of cluster headaches treated with 10 mg prednisolone daily was admitted to ICU with a community acquired legionella pneumonia. Within 24 hours of admission he developed severe sepsis, respiratory failure requiring mechanical ventilation, cardiovascular failure requiring fluid administration and noradrenaline infusion and renal failure. He was treated with intravenous cefotaxime, erythromycin, co-trimoxazole and hydrocortisone (100mg intravenously 6 hourly). However, he continued to deteriorate requiring high dose vasopressors and continuous renal replacement therapy. An APC infusion began on day 2 at 24 μg/kg/hr for 96 hours. The patient slowly improved. By day five the signs of severe sepsis had improved, the patient was haemodynamically stable (off noradrenaline) and began to wean from the ventilator. However late on day 5, while the patient continued to improve systemically, the abdomen became increasingly tender. An abdominal CT scan revealed free gas and free fluid in the peritoneal cavity.

At laparotomy a perforated sigmoid diverticulum with gross peritoneal soiling and faecal peritonitis was found. A Hartman's procedure was performed and the patient returned to ICU where he continued to improve and was eventually discharged.

APC is a powerful inhibitor of inflammation associated with sepsis.[2-5] The PROWESS study demonstrated reduced mortality in patients with severe sepsis, including patients who had faecal peritonitis.[2] In both our patients the objective and subjective signs of the systemic inflammatory response syndrome improved with APC treatment, despite the presence of perforated bowel and gross peritoneal soiling. We believe that APC may potentially mask the signs of ongoing sepsis and inflammation thereby delaying definitive treatment of ongoing clinical problems.

We wish to highlight the importance of proper 'source control' before and after commencing potent anti-inflammatory agents, and to alert clinicians to the potential of APC to affect clinical signs that have hitherto been used as guides to the resolution of severe sepsis.[1]

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