Should activated protein C be given to a patient who has an epidural?

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Significant progress has been made recently in the treatment of patients with severe sepsis. A number of evidence-based therapies improve outcome in these patients. The largest study is the PROWESS study, a randomized placebo controlled trial of activated protein C (APC) *vs* placebo (Bernard et al, 2001). This reduced mortality by 19% in a highly selected group of patients with severe sepsis. APC has been licensed for use in patients with multiple organ failure secondary to severe sepsis in the UK since October 2002. Practical dilemmas have arisen surrounding its use in certain situations.

CASE HISTORY

A 72-year-old woman was admitted to hospital with severe abdominal pain. Plain X-ray showed air under the diaphragm. She was given antibiotics and fluid resuscitation was initiated before an emergency laparotomy. A lumbar epidural catheter was placed in the anaesthetic room. Findings at surgery were a perforated sigmoid diverticulum.

During surgery her condition deteriorated, with hypotension no longer responsive to fluid therapy and noradrenaline was commenced. She arrived in the intensive care unit with worsening oxygenation, cardiovascular failure and low urine output. Invasive monitoring was established and fluid therapy optimized. Initial blood tests showed a haemoglobin 10.2 g/dl, white cell count 2.8 x 10^{12}/litre, platelets 75 x 10^9/litre, and an international normalized ratio of 1.6.

Her condition was reassessed 12 hours postoperation. In view of established organ dysfunction and significant risk of death, she was considered for APC. However, the summary of product characteristics (SPC) states that 'patients with an epidural catheter or who are anticipated to receive an epidural catheter during drug infusion' are a contraindication to therapy with APC.

EPIDURALS AND APC

The bleeding complications were comparatively low in the PROWESS study, which may have been a result of its very strict inclusion and exclusion criteria. Although not quoted in the paper, exclusion criteria 15b was 'patients with an epidural catheter or who are anticipated to receive an epidural catheter during APC infusion' (www.fda.gov).

WHAT ARE THE OPTIONS?

1. Do not give APC: This accepts a risk of death of approximately 50% and denies a therapy that in this subgroup has a number needed to treat of about 7. This complies with the SPC, since the presence of an epidural is a contraindication to therapy with APC.

2. Remove the epidural catheter at the earliest opportunity and then commence APC: This has two major problems. First, removal of the epidural catheter at this stage poses the greatest risk of development of spinal haematoma (albeit small) because of the acquired coagulopathy associated with her severe sepsis. Second, a further delay may be introduced before the potentially beneficial therapy can be initiated. This does comply with the SPC, but may not be defensible.

3. Attempt to correct the sepsis-associated coagulopathy with platelets and fresh frozen plasma, then proceed as option 2: Although the small risk of developing a spinal haematoma has probably been reduced there are still drawbacks. First, this type of coagulopathy is often difficult to correct fully. Second, as in option 2 a further delay is introduced before the potentially beneficial therapy can be initiated. This does comply with the SPC.

4. Give APC and accept the small risk of epidural haematoma: This is justified on the grounds that the small risk of a spinal haematoma is outweighed by the reduced mortality with APC treatment. The epidural can be removed after the APC infusion is completed, when the coagulopathy is likely to be more controlled. This does not comply with the SPC, but we would argue is more defensible. This option would be most analogous to the current standard of care where heparins might be started, for say a pulmonary embolus, in a patient who has an epidural in place.

CONCLUSION

APC is a major step forward in treating some patients with severe sepsis. Intensivists, who often make difficult risk–benefit decisions, must learn how to apply trial results to clinical situations. Administration of APC to a patient with an epidural catheter is no different. HM

Bernard GB, Vincent JL, Laterre PF et al (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* **334:** 699–709

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