Should we treat severe sepsis with activated protein C?

Andrew Mackillop

Sepsis is an infection-induced syndrome defined as the presence of two or more of the following features of systemic inflammation:

- Fever or hypothermia
- Leukocytosis or leukopenia
- Tachycardia
- Tachypnoea (Bone et al, 1992).

When an organ system begins to fail the sepsis is considered severe and has a mortality rate of 30–50%. It is a result of an uncontrolled inflammatory and procoagulant response to infection. This, in turn, can have catastrophic effects on the microvascular circulation (Ware and Matthay, 2002) and can severely compromise end organ perfusion.

The use of recombinant human activated protein C (drotrecogin alfa) is currently a hot topic in the critical care arena. It has anticoagulant and anti-inflammatory properties which have been shown to reduce the 28-day mortality which is caused by severe sepsis in a multicentred randomized controlled trial (PROWESS trial; recombinant human activated Protein C Worldwide Evaluation in Severe Sepsis) (Bernard et al, 2001). Recombinant human activated protein C has now been released on the British market. Should clinicians embrace this new treatment or be more cautious and adopt a 'wait and see' approach?

WHY WE SHOULD START USING ACTIVATED PROTEIN C NOW

Previously, there have been many drug treatments tested in sepsis trials with unimpressive results. Activated protein C represents a breakthrough in the treatment of severe sepsis. This is supported by the robust nature of the PROWESS trial, into which 1700 patients were recruited. The mortality in the placebo group was 30.8%, whereas it was 24.7% in the treatment group. This gives an absolute risk reduction of 6.1% and a number needed to treat of 16.

This means that activated protein C is more effective at reducing mortality than other well-established medical treatments such as thrombolysis for myocardial infarction. The PROWESS trial has been scrutinized by both the American Food and Drug Administration and the European Commission. Following these analyses both of these organizations have acknowledged that clinicians should have access to the drug.

When treating a critically ill patient with severe sepsis how is the clinician to respond to an inquiry from a relative as to why the patient is not receiving activated protein C? It is a proven therapy which can help to treat a dangerous disease.

WHY WE SHOULD WAIT AND SEE

The PROWESS trial is a very impressive paper that is difficult to criticize. However, during the review by the Food and Drug Administration Center for Drug Evaluation and Research a few uncomfortable revelations were made (www.fda.gov/ohrms/dockets/ac/01/transcripts/3797t1.doc). First, the inclusion criteria were changed half way through the trial. Second, the formulation of the drug was changed at the same point in the trial.

It is only left for doctors to wonder why these events were not clearly described in the published paper and what effect they may have had on the eventual outcome of the trial. The Food and Drug Administration review process also unearthed a further discrepancy in that the number of 'do not resuscitate' orders in the placebo group far exceeded those in the treatment group.

It is also important to note that activated protein C is a powerful anticoagulant which was trialled against placebo in a thrombotic condition. It would seem to be logical to repeat the trial comparing it against another perhaps cheaper anticoagulant such as heparin?

Although PROWESS is a substantial trial it is only a single trial. Bearing in mind that the cost of activated protein C is £4904 per patient it would be prudent to await a full evaluation of it by the National Institute of Clinical Excellence. HM

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