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PATIENT SAFETY NETWORK

Novel Drug Misuse

July 1, 2004
Angus DC, Milbrandt EB. Novel Drug Misuse. PSNet [internet]. 2004.
https://psnet.ahrq.gov/web-mm/novel-drug-misuse

Case Objectives

- Define the inclusion and exclusion criteria for patients in PROWESS.
- Understand why the FDA included APACHE score as an indication criterion for drotrecogin alfa (activated) use.
- Outline the roles that the FDA, hospitals, professional medical societies, and the pharmaceutical industry play in ensuring appropriate use of novel therapeutics.
- Understand the importance of errors of commission and omission.

Case & Commentary: Part 1

A 48-year-old man was admitted to the intensive care unit after a motor vehicle collision. The patient experienced severe crush injuries after spending 7 hours pinned under a large vehicle at the bottom of a ravine while awaiting rescue. He underwent bilateral fasciotomies of the lower extremities for compartment syndrome. Post-operatively the patient developed renal failure; an Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 26. Recalling an article in the New England Journal of Medicine reporting a decrease in mortality associated with early administration of drotrecogin alfa (activated) to patients with elevated APACHE scores and sepsis, the team decided to start the patient on the drug.

Severe sepsis is defined as sepsis associated with acute organ dysfunction.(1) Each year in the United States, approximately 750,000 cases of severe sepsis occur, more than one quarter of which are fatal despite advances in medical care.(2) Drotrecogin alfa (activated) is a recombinant form of human activated protein C, an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation. It appears to be an important modulator of the coagulation and inflammation associated with severe sepsis.(3) Drotrecogin alfa (activated) is approved by the Food and Drug Administration (FDA) for mortality reduction in adult patients with severe sepsis who have a high risk of death as determined, for example, by an APACHE II score greater than 25.(4) This approval is based on a large multicenter, randomized, placebo-controlled trial (PROWESS) that showed that treatment with drotrecogin alfa (activated) was associated with a 6.1% absolute reduction in 28-day mortality in patients with severe sepsis compared to placebo

(24.7% vs. 30.8%, p=0.005).(3)

Patients included in PROWESS had a known or suspected infection, 3 or more signs of systemic inflammation (temperature ?38° C [100.4° F] or ?36° C [96.8° F]; heart rate ?90 beats/min; respiratory rate ?20 breaths/min, PaCO2 10% immature neutrophils), and sepsis-induced dysfunction of at least one organ system for less than 24 hours. Patients had to receive the drug within 48 hours of the onset of sepsis. Patients were primarily excluded if they had any condition that increased the risk for bleeding, including active internal bleeding, recent hemorrhagic stroke, intracranial or intraspinal surgery, severe head trauma, intracranial mass lesion, platelet count

The mortality benefit of drotrecogin alfa (activated) was largest in the sickest patients, such as those with an APACHE II score >25. Since the original PROWESS study, a follow-up study has confirmed a large, sustained benefit in sicker patients with an improvement in survival that remains highly significant over a follow-up period of more than 2.5 years.(5) At the same time, the follow-up study found little benefit in less sick patients, and another randomized trial of patients with sepsis but low risk of death (ADDRESS) was recently stopped by the Data Safety and Monitoring Board on the basis of clear lack of effect. Drotrecogin alfa (activated) does have anti-coagulant properties, and there was a trend to an increased incidence of serious bleeding in the therapy arm in PROWESS (3.5% vs. 2.0%, p=0.06). However, serious bleeding occurred primarily in patients with an identifiable predisposition to bleeding, and blood-transfusion requirements were similar between groups after adjustment for duration of survival. Several large uncontrolled series since PROWESS have reported similar bleeding rates.

The reasons for the observed benefit in sicker patients coupled with an apparent lack of benefit in less sick patients have been the subject of great controversy and debate.(6-10) Answers at the current time are largely speculative, but two partially interrelated possibilities seem most likely. First, the *relative* risk reduction in mortality is constant across the spectrum of severe sepsis, yielding an *absolute* risk reduction in less sick patients that is too small to be detected statistically given sample size constraints of the current studies. Second, as in the first case, the relative risk reduction in *sepsis*-related mortality is constant, and therefore associated with smaller absolute reductions in less sick patients. However, the *absolute* risk of death due to bleeding is constant, and nullifies any potential benefits from reduced sepsis-associated mortality in patients at lower risk of death from sepsis.

Even though the reason for the absence of clear benefit in less sick patients is unknown, strong evidence supports the FDA recommendation that drotrecogin alfa (activated) be considered in the treatment of patients who present with severe sepsis, with the key caveats that the therapy be reserved for patients who are at high risk of death and who are not at undue risk for bleeding.

Case & Commentary: Part 2

Eighteen hours after infusion, the patient developed severe bleeding and hemodynamic instability requiring multiple transfusions and aggressive fluid resuscitation to maintain hemodynamic stability. Review of the case by the clinical pharmacist noted that the patient did not have signs or symptoms consistent with sepsis. The patient's organ dysfunction was due to severe rhabdomyolysis.

Ensuring appropriate use of novel and potentially toxic therapeutics is a challenging endeavor. FDA-approved labeling indications help to guide clinicians in the use of a new therapeutic agent. Off-label use, however, is permitted, as occurred here. Hospital pharmacy and therapeutics (P&T) committees use methods such as mandatory consults, checklists, and pharmacy review to control the use of potentially toxic medications. This approach can be very effective, but it may miss opportunities to improve care through provider education. Evidence-based guidelines developed by professional medical societies help to bridge the gap in terms of provider education. Unfortunately, guidelines are expensive to develop and disseminate, and they are often ignored. The pharmaceutical industry, with its massive detailing and advertising efforts, is particularly effective at reaching providers but has an obvious conflict of interest when it comes to guiding physicians in the choice and use of its own medications. The coordinated efforts of each of these groups may be required to ensure appropriate use of new medications. Such a multi-pronged approach could match FDA indications with P&T oversight and disseminate professional medical society guidelines using unrestricted pharmaceutical industry sponsorship.

Some efforts to improve the care of critically ill patients have used portions of this approach. For instance, the Surviving Sepsis Campaign (11) is an international effort to increase awareness and improve outcome in severe sepsis. Using unrestricted industry educational grants, a group of international critical care and infectious disease experts came together to develop guidelines that the bedside clinician could use to improve outcome in severe sepsis and septic shock. No industry members were on the committee, and no industry input influenced guidelines development. The next phase of this program will be dedicated to the use of the management guidelines to evaluate the impact on clinical outcomes.

While these concepts apply to any novel therapeutic, specific issues surround the use of high-cost biopharmaceutical agents. Cost alone may limit the use of these new agents, even in the face of strong evidence in favor of their use. On the other hand, the profit potential of these high priced products may lead to marketing efforts that result in increased and sometimes inappropriate use. This is a dynamic tension that our health care system will have to increasingly grapple with in the coming years.

Case & Commentary: Part 3

The patient later died due to complications from his multiple injuries.

The decision to administer drotrecogin alfa (activated) to this patient whose organ system failure was not due to sepsis was an error, one that could have been avoided in a number of ways. Perhaps the most relevant are provider education and P&T-based controls. If the team caring for this patient were aware of the indications and contraindications for drotrecogin alfa (activated), its use and the attendant bleeding complications could have been avoided. A checklist-based pharmacy review prior to dispensing this medication would have revealed the contraindication as well. Wong-Beringer and colleagues used such an approach in an order form, which included explicit inclusion and exclusion criteria and which required infectious disease and critical care specialist approval prior to dispensing the drug (Figure).(12) Their approach was applauded as a way not only to prevent inappropriate use, but also to increase awareness of patients who might benefit from treatment.(13)

While this case is tragic in that it represents a potentially avoidable error of commission, perhaps the greatest threat to patient safety associated with drotrecogin alfa (activated) is the error of omission.(14) As with other proven life-saving interventions, such as aspirin and beta-blockers in coronary artery disease and angiotensin-converting enzyme inhibitors in congestive heart failure (15), failure to treat must be viewed as a medication error that leads to unnecessary morbidity and mortality.(14) Anecdotal reports suggest that drotrecogin alfa (activated) is frequently underutilized, even in patients with clear indications for its use. The drug's high cost, concerns about safety, and failure to recognize eligible patients are thought to underlie some of this underutilization.(13) However, as reviewed above, when given to appropriate patients, the risks of bleeding are clearly outweighed by the overall gains in survival. This gain in survival has now been demonstrated to be sustained over a prolonged follow-up, information that was considered by the Centers for Medicare and Medicaid Services when they ruled that the Medicare program would reimburse hospitals for use of drotrecogin alfa (activated). Furthermore, several studies have demonstrated that, despite the initial drug acquisition cost, drotrecogin alfa (activated) has a very acceptable cost-effectiveness profile, similar to, or better than, many well-adopted health care interventions.(16-18)

Unfortunately, P&T restrictions and FDA labeling are unlikely to prevent errors of omission. Educating providers about the indications, contraindications, and cost-effectiveness (16) of this intervention will be essential to increasing use of this life-saving medication. Other approaches that may prove useful and which are reviewed elsewhere include academic detailing using local opinion leaders, paper or computer-based reminders, and case audit and feedback.(19) Even with all of these approaches, influencing providers to take a particular course of action is challenging. Recognizing this, some hospitals are establishing teams of emergency department and intensive care unit specialists to facilitate rapid sepsis identification, assessment, and treatment.(20) This sort of systems-based approach has been effective in other disease states, such as acute ischemic stroke or myocardial infarction, where rapid diagnosis and treatment is central to improving outcomes.

Take-Home Points

- Drotrecogin alfa (activated) is FDA-approved for mortality reduction in adult patients with severe sepsis who have a high risk of death as determined, for example, by an Acute Physiology and Chronic Health Evaluation II (APACHE II) score >25.
- The most serious adverse event associated with the use of drotrecogin alfa (activated) is bleeding. Those who are at increased risk of severe bleeding should not be treated with the drug.
- Ensuring appropriate use of novel and potentially toxic therapeutics is a challenging endeavor that requires a multi-pronged approach.
- Errors of commission and omission can both lead to unnecessary morbidity and mortality.

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Faculty Disclosure: *Dr. Angus has disclosed that he has the following financial arrangements or relationships with the manufacturers of commercial products discussed in this educational activity: Grants/Research Support: Eli Lilly and Company. Consultant: Eli Lilly and Company. Speakers' Bureau/Honorarium: Eli Lilly and Company. In addition, Dr. Angus has indicated that the commentary does not include information about or discuss investigational or off-label use of pharmaceutical products or medical devices.*

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Figure

Figure. Sample Order Form with Selection Criteria for Use of Drotrecogin Alfa.

Click on thumbnail for full view of Figure.

Example of a two-page order form explicitly stating patient selection criteria for the use of drotrecogin alfa. Includes criteria for SIRS, organ dysfunction, APACHE II scoring, as well as absolute and relative contraindications. Originally published in Wong-Beringer A, Liao C, Nguyen M, Pallares J. Applying patient selection criteria for drotrecogin alfa therapy in practice. Am J Health Syst Pharm. 2003;60:1345-52.

This project was funded under contract number 75Q80119C00004 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The authors are solely responsible for this report's contents, findings, and conclusions, which do not necessarily represent the views of AHRQ. Readers should not interpret any statement in this report as an official position of AHRQ or of the U.S. Department of Health and Human Services. None of the authors has any affiliation or financial involvement that conflicts with the material presented in this report. View AHRQ Disclaimers