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ANALYSIS

Evidence and desperation in off-label prescribing: recombinant factor VIIa

Wendy Lipworth and colleagues explore why clinicians prescribe recombinant factor VIIa off-label for major haemorrhage, despite a lack of supporting evidence—and why this matters

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Off label prescribing—that is, prescribing a medicine for an indication not listed in the product information, or for a patient outside the approved age range—is common, but controversial. On the one hand, it can promote clinical innovation and provide options for patients for whom no other alternatives are available. On the other hand, it can be harmful, because safety data are often lacking; it impedes the generation of good quality evidence, and it comes at a considerable cost to patients, governments, and other payers.[1 2]

In this paper, we discuss the off-label use of recombinant factor VIIa (rFVIIa) for major haemorrhage, to provide insights into the forces driving off-label prescribing and to illustrate some of the inevitable limits to evidence based medicine.

Clinical disagreement

rFVIIa is a procoagulant approved for patients with haemophilia and antibody inhibitors against factor VIII or factor IX. Recent studies, however, have shown that up to 97% of rFVIIa prescribing is off-label, with the intent to stop bleeding in conditions such as intracranial haemorrhage, cardiac surgery, trauma, liver transplantation, and prostatectomy.[3] It is estimated that rFVIIa was used in more than 70 000 hospital cases in the United States between 2000 and 2008. During this period its off-label use increased 140-fold, while use for haemophilia in hospitals increased less than fourfold.[3] Although some evidence indicates that rFVIIa might reduce blood loss and transfusion requirements in patients without haemophilia, evidence has also been accumulating that it does not reduce mortality, might be associated with an increased rate of thromboembolic events including stroke and coronary occlusion,[4-9] and costs approximately $10 000 (£6400, €7400) per patient.[10]

According to the principles of evidence based medicine, which allow off-label prescribing only when "adequately data driven,"[10] these findings should lead to a rational reassessment of the place of rFVIIa in clinical practice, and to a restriction of its off-label uses. Indeed, the authors of a recent Cochrane review concluded that use of rFVIIa outside its current licensed indications should be restricted to clinical trials,[8] and it has even been argued that legal action might be taken against those who continue to promote or use rFVIIa inappropriately.[10]

But these conclusions have met with some resistance. For example, in response to a systematic review[11] and editorial[10] published in a recent issue of the *Annals of Internal Medicine*, Karkouti and Levi[12] countered that:

> "When presented with a patient who continues to bleed despite administration of all available therapies, clinicians have 2 choices: keep administering the standard interventions that have failed to work in that patient, or administer a novel therapy like rFVIIa . . . even if the safety data from existing randomized trials… do apply . . . this is probably dwarfed by the risk for allowing blood loss to continue unabated . . . All procoagulant agents have the risk for potential adverse responses, but their individualized risk-benefit profile is largely dependent on the clinical context."

Why use rFVIIa without supportive data?

If we are to resolve this impasse (and others like it) we need to understand why clinicians might continue using rFVIIa for the treatment of haemorrhage, even when faced with accumulating evidence that it does not reduce mortality and could cause harm. A number of intersecting epidemiological, psychological, social, and ethical reasons may explain the dramatic growth in off-label use of rFVIIa despite no substantial evidence of long term benefit.

First, some possible outcomes of using off-label rFVIIa might not be adequately described (or valued) by the existing data. Although rFVIIa does not seem to reduce overall mortality, this does not rule out the possibility that it might be of use—at least

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for some patients, in some situations—by reducing blood loss, transfusion requirements, re-operation, or even mortality. The pursuit of such outcomes might be sufficient to drive practice.

Second, outcome data are not the only kind of evidence that clinicians find compelling; potent ancillary logics might prompt them to use rFVIIa for haemorrhage. The drug has a clearly established mechanism of action and is well known to reduce bleeding in some situations where little else works, so to use it in other patients with bleeding seems theoretically and clinically logical.

Third is the problem of observed association—clinicians may have seen patients stop bleeding after being given rFVIIa, and this may lead to a judgment about its efficacy. Although these clinical observations might be accurate, they may represent simply a temporal relationship rather than a causal one.

Fourth are powerful moral and psychological forces. The "rule of rescue" describes the imperative people feel to rescue identifiable individuals facing avoidable death.[13 14] In such situations, evidence and rational decision making can be overwhelmed by the need to act, irrespective of whether the intervention has a logical basis:

> "There is a fact about the human psyche that will inevitably trump the utilitarian rationality that is implicit in cost-effectiveness analysis: people cannot stand idly by when an identified person's life is visibly threatened if rescue measures are available."[15]

From a moral, cultural, and psychological standpoint, clinicians may feel compelled to prescribe rFVIIa in order to do everything in their power for the patient.

The psychological response to active bleeding is also a powerful force. Blood loss has primal associations[16] and the duty of care arises as much from the primitive response as from moral and legal obligation. Whatever epidemiologists might say, the emotional challenge posed by bleeding is powerful, and the imperative to do something—particularly where not much time is available for reflection—remains strong.

Another likely psychological force is anticipated regret.[17] Because rFVIIa is a relatively safe agent, despite the small risks of stroke or coronary occlusion, clinicians might believe that there is nothing to lose when someone has a life threatening haemorrhage. Those looking after a patient with massive bleeding might anticipate regret at a person in their care dying, and this feeling might dominate both acknowledgment of the risks of thrombosis and the evidence that the intervention is unlikely to reduce mortality.

Clinicians may also prescribe rFVIIa off-label simply because they crave autonomy,[10] or control over their own practice—including determination of what counts as evidence. This is one of the many well known explanations for the sometimes slow clinical uptake of evidence.

Taken together, these factors can dominate our beliefs and commitments in the face of contrary evidence. Action, reason, and even truth, it seems, can be warranted by desperate need. In situations of peer review, a doctor might express doubts about the value of off-label rFVIIa, or admit that the evidence is convincingly against it. In the heat of an emergency, however, the notion that it might be worth trying is likely to break through. The same reasoning could well apply to the patient and his or her family: "If there is any chance that the drug will help, then let us use it." Even sceptical doctors might say the same if asked how they would feel if they themselves were bleeding to death.

Finally, there is the power of commercial opportunism. It is well documented that some drug companies promote the use of their products off-label to encourage patient demand and clinical familiarity, thereby increasing sales.[18] Much of the unjustified support for rFVIIa comes from the medical profession, but the manufacturers have done little to counsel doctors about the poor record of off-label use (and have recently settled a civil lawsuit for improper marketing of rFVIIa for $25m [£16m, €20m]).[19] This is unsurprising given that condoning such use is highly profitable—particularly when the price is so high and the use so common. Indeed, the high price itself—$10 000 per ampoule—might help to convince clinicians that it the drug is effective.

The need for clarity

Clearly, clinicians might both believe it to be true that rVIIa works and desperately need it to be true that the drug contributes to haemostasis in all situations. Anyone wishing to promote adherence to evidence in this context thus needs to contend with both genuine uncertainty and the powerful force of desperation. In desperate situations, anecdote and experience often assume greater salience than statistics. The rules of evidence based medicine might therefore be overridden by urgency and the demands of context.

An apparently irreducible tension exists between appeals to weak evidence, clinical observation, mechanism, and desperate need on the one hand, and appeals to hard (albeit imperfect) evidence on the other. And, in this, rFVIIa is not unique—take, for example, the non-evidence based use of high dose adrenaline during resuscitation efforts.[20] There is no simple solution to this quandary. While it would be easy to dismiss, and insist on stopping, non-evidence based use of rFVIIa on the grounds that it does not reduce overall mortality, we cannot ignore the many compelling reasons for its ongoing use. Nor can we ignore the fact that the existing evidence from systematic reviews does not prove that rFVIIa is completely ineffective in reducing bleeding in all patients. What is needed, therefore, is for clinical leaders and policymakers to further clarify the range of outcomes that might result from the administration of rVIIa (relating to both harms and benefits), what outcomes matter, how much we are prepared to pay for those outcomes, and what we should do until these issues are resolved.

Situations like this take us to the edges of evidence based medicine. The community needs to be reassured that doctors prescribe medicines on the basis of clear evidence about efficacy, safety, and cost effectiveness—particularly in relation to high cost drugs, which are inevitably associated with an opportunity cost. But in cases like that of rFVIIa, such information is lacking or contested. In these situations, there is little to be gained by determining who is right and who is wrong—or threatening legal sanctions against those who choose a particular course of action. It is more important to ensure that clinical decisions can be understood, explained, and justified so that any untoward outcomes can be predicted and managed.

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