Studies document widespread, risky use clotting drug on non-hemophilia patients

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In fact, the studies estimate that only 4 percent of the powerful drug's use in U.S. hospitals from 2000 through 2008 was for treating hemophilia patients, while an enormous 96 percent involved cases of heart surgery, trauma, intracranial hemorrhages (bleeding in or near the brain) and a host of other surgical and medical problems. There are few studies examining these broader uses of the drug, known as recombinant factor 7a, and what little evidence does exist reveals a serious problem: The drug can increase the risk of blood clots, which can lead to heart attacks and strokes.

What's more, RF7a is pricey — it costs an estimated $10,000 for an average dose.

"The stakes are high with this one," said Veronica Yank, MD, an instructor in medicine and the first author of one of the studies. "Because it's such a powerful clotting agent, it has the potential when used off-label to damage the lives of patients without providing any real benefit."

Given the safety issues and the expense of RF7a, Yank and her colleagues are urging physicians to exercise greater caution in using the drug until its safety is effectively evaluated for these broader uses.

The studies will be published in the April 19 issue of *Annals of Internal Medicine*, along with an accompanying editorial by Harvard Medical School researchers commending the Stanford team for providing

"compelling data … about the runaway use, uselessness and risk for this expensive treatment."

The editorial goes on to question whether "improper promotion" of RF7a by its maker, Novo Nordisk, led to the rapid expansion of its use. While the company has denied such practices, it is being investigated by the Defense Department for the use of the drug in overseas combat operations, the editorial reports.

The Stanford authors say RF7a provides a good example of what happens when physicians latch onto a "wonder" drug for uses distinctly different from its original purpose. In this case, the medication was developed to treat a small subset of hemophilia patients. In these genetic disorders, the body is deficient in producing specific proteins, or factors, that aid the blood-clotting process. It primarily affects males, and is estimated to occur in one in 5,000 live male births. There are two main forms of the disorder: hemophilia A (a deficiency in factor 8) and hemophilia B (a deficiency in factor 9).

To curtail bleeding in hemophilia patients, physicians usually administer doses of either factor 8 or factor 9, but this treatment doesn't work for the small group of patients whose antibodies see these factors as foreign substances and attack them. RF7a, approved by the U.S. Food and Drug Administration in 1999, was developed for this group.

Despite the limited range of patients for whom the drug was approved, the Stanford authors noted that physicians and surgeons quickly started using RF7a to either prevent or stop heavy bleeding in patients who didn't have hemophilia. It's a practice known as off-label prescribing, meaning that physicians use medications to treat conditions other than those approved by the FDA. While there is nothing illegal about off-label prescribing — and, in fact, it can be invaluable in treating diseases for which few therapies exist — senior author Randall Stafford, MD,

PhD, associate professor of medicine at the Stanford Prevention Research Center, said the danger is that the drug hasn't been rigorously tested for these new uses or with broad ranges of patients.

"Many patients and physicians wrongly assume that the FDA has scrutinized all of the different ways a drug can be used, but they've only examined those uses that have gone through the approval process," Stafford said.

A few previously published studies had raised concerns that RF7a increased the risk of blood clots, and so in 2008 the U.S. Agency for Healthcare Quality and Research, which funded both Stanford studies, asked researchers to probe the issue. The agency specifically wanted to know what kind of clinical evidence existed for five off-label uses of RF7a: heart surgery, intracranial hemorrhage, body and brain trauma, liver transplantation and prostate surgery.

Yank, Stafford and their colleagues searched 10 widely used databases for clinical trials and observational studies of the drug for the five indications. They then rated the available clinical evidence and focused on the randomized clinical trials and observational studies, excluding those that did not directly address clinical outcomes. For the meta-analyses in the first paper, the researchers ended up using data from 16 randomized clinical trials and 10 observational studies.

The researchers found that RF7a didn't reduce mortality rates for any of the five off-label uses, although Yank noted that most of the studies tracked patients for only 30-90 days following the administration of the drug. For the top two uses of the drug, the analyses showed heart-surgery patients who were given RF7a had a 5 percent higher risk of developing blood clots, and intracranial hemorrhage patients had a 3 percent higher risk of developing clots. There was no increased risk of blood clots for body trauma patients, and the evidence was too limited to determine the

clotting risks for brain trauma, liver transplants and prostate surgeries.

For the second study, first author Aaron Logan, MD, PhD, a postdoctoral scholar in hematology and bone marrow transplantation, joined Yank and Stafford in analyzing another database to determine how the drug was being used in U.S. hospitals. The data came from Premier Perspectives and includes information from 615 non-federal hospitals throughout the country.

In reviewing records from 2000 to 2008, the researchers found that the use of RF7a grew 140-fold, from 125 cases in 2000 to 17,813 in 2008, primarily for off-label indications. The researchers also noted that of the five off-label uses the AHRQ wanted the team to investigate, three of them — heart surgery, intracranial hemorrhage and trauma — were among the top uses of the drug. "This type of assessment can be quite eye-opening about the real-world use of these medications on the basis of extremely weak evidence," Logan said.

He also noted that the off-label use of RF7a has spread beyond academic medical centers where new or experimental therapies are often tested. The data showed the proportion of RF7a use in non-academic hospitals grew from 11 percent in 2000 to 67 percent in 2008. "This suggests wide adoption of RF7a as a therapy despite concerns about its efficacy and safety," the authors wrote.

Yank said she and her colleagues hope the two studies will prompt physicians and surgeons to be more cautious about the off-label use of RF7a. "Despite the miraculous ability of this drug to stop bleeding, we have an obligation to 'first do no harm,'" she said.

That sentiment was echoed in the accompanying editorial, by Harvard's Jerry Avorn, MD, professor of medicine, and Aaron Kesselheim, MD, JD, research associate in health policy and management, who wrote that,

"Allowing physician autonomy to choose medications is appealing, but not when it results in such useless, dangerous and costly decisions."

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