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Study confirms cardiac surgery drug increases death rate

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The largest study to date of a controversial cardiac surgery drug shows it increases death rates and damages kidney function, according Duke University Medical Center researchers.

Aprotinin, a drug used to limit bleeding, was temporarily suspended from marketing in the U.S. in November 2007 after a small Canadian study was stopped because similar findings were discovered. The drug, Trasylol, is manufactured by Baylor AG.

"We're not surprised by the results," says Dr. Andrew Shaw, an associate professor in Duke Medicine's department of anesthesiology and the lead author of the paper which appears in the February 21 edition of the New England Journal of Medicine. "It's what we expected to find."

The Duke study is significant because "it is more than twice the size of the next largest study of aprotinin," says Shaw. The prospective data was collected between 1996 and 2005. "Unlike the highly selected nature of randomized trial populations, our data represent the every day cardiac bypass surgery patient population. The data were collected at a time when aprotinin was thought to be safe."

The Duke team started analyzing its database of patients after a 2006 NEJM study reported aprotinin use may increase the risk of heart attack, stroke and serious kidney injury.

"We were looking for an association between exposure to the drug and

subsequent adverse outcomes," Shaw says. "We found an increased incidence of death in patients who received aprotinin. That higher death rate seemed to persist even when we were able to control for the differences seen between the patient groups."

Shaw and his Duke colleagues also linked aprotinin to impaired kidney function. "Kidney function is measured by serum creatinine levels which indicate how well the blood is filtering waste products," he says. The study found aprotinin use increased serum creatinine levels, but they did not report an increase in patients needing dialysis. Shaw believes "that's because we probably didn't have enough patients who needed dialysis in our study to detect a significant statistical difference, although the incidence was numerically higher."

Of the 10,275 patients studied, 1343 patients (13.2%) received aprotinin, 6776 patients (66.8%) received aminocaproic acid (another drug used to limit bleeding) and 2029 patients (20.0%) received no therapy. All patients underwent coronary-artery bypass surgery (CABG), and 1181 of them also underwent valve surgery. Patients who received either aminocaproic acid or no therapy did not have high rates of death or poor kidney function seen in the aprotinin group.

After gaining FDA approval in 1993, aprotinin was used routinely during cardiac surgery, particularly on high-risk patients, to reduce bleeding and the need for blood transfusion. According to previously published research, patients undergoing cardiac surgery receive approximately one fifth of all the red cell transfusions in the U.S., and each unit transfused is known to increase the risk of infection.

Shaw says this study does not rule out the possibility that the increased death rate was due to high-risk, sicker patients receiving the drug. "You would expect sicker patients would be more likely to die," he said.

“The unanswered question is, ‘are there differences between the patient groups that we were unable to detect that led to the increased death rate, or is the death rate due to exposure to the drug?’

“Our study doesn’t answer that question nor was it designed to,” he says. “But it does further raise the question of the safety of aprotinin. And, on a broader scale, it highlights the importance of post-marketing observational studies of drugs that are widely used.”

Source: Duke University