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First, do no harm: Hospital patients given anti-heartburn drugs have higher risk of dying

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Right now, in any American hospital, about half of the patients have a prescription for an acid-reducing drug to reduce heartburn or prevent bleeding in their stomach and gut.

But that well-intentioned drug may actually boost their risk of dying during their hospital stay, a new study finds - by opening them up to infections that pose more risk than bleeding would.

In fact, according to a computer simulation based on real-world risk and benefit data, around 90 percent of hospital inpatients who were first prescribed these drugs in the hospital have a higher risk of dying when they're taking them, compared with their risk if they hadn't gotten the prescription.

And for around 80 percent of patients who were already on these common drugs, called proton-pump inhibitors or PPIs, when they arrived at the hospital, staying on them also may lead to a small increase in the risk of dying.

The extra risk of death comes from the fact that reducing acid in the stomach can increase the risk of infections - especially pneumonia and *Clostridium difficile*, both of which pose a serious risk to hospitalized patients who develop them.

The study, which uses a computer model to achieve a result that otherwise would require an impractically large clinical trial, is published in the *Journal of General Internal Medicine* by a team from the University of Michigan Medical School and VA Ann Arbor Healthcare System.

"Many patients who come into the hospital are on these medications, and we sometimes start them in the hospital to try to prevent gastrointestinal, or GI, bleeds," says lead author Matthew Pappas, M.D., MPH.

"But other researchers have shown that these drugs seem to increase the risk of pneumonia and *C. diff*, two serious and potentially life-threatening infections that hospitalized patients are also at risk for," he continues. "Our new model allows us to compare that increased risk with the risk of upper GI bleeding. In general, it shows us that we're exposing many inpatients to higher risk of death than they would otherwise have - and though it's not a big effect, it is a consistent effect."

As a result of the new findings, he says, very few hospital patients should start taking or continue on PPIs as a preventive measure against gastrointestinal bleeding.

Pappas, a hospitalist physician at U-M with an engineering background and a VA Health Services Fellow, worked with Sandeep Vijan, M.D., MPH, who treats patients at the VAAHS and is a member of the VA Center for Clinical Management Research and U-M's Institute for Healthcare Policy and Innovation. Pappas is a clinical lecturer, and Vijan a professor, in the U-M Medical School's Division of General Medicine. The project's only funding was Pappas's fellowship support.

Cutting PPI use to cut infection risk

Pappas notes that nationally, some efforts have already shown ways to

reduce the rate of new PPI prescriptions to hospitalized patients - about 20 percent of whom receive such orders right now.

But truly reducing PPI use in hospitals to the most appropriate patients - those with existing GI bleeding - will take more effort, Pappas predicts.

That's because PPIs are built into many heuristics, or rules of thumb, that guide much hospital care. For instance, when a patient receives high-dose steroids in the hospital, the physician may automatically also prescribe a PPI to prevent the GI bleeding that steroids can cause.

"In fact, in running our simulation, we thought we would find some populations such as those on steroids or other medications often prescribed together with PPIs, who would not experience the increased mortality risk," Pappas says. "But that turned out not to be the case." GI bleeds are risky, it's true. But hospital-acquired pneumonia and *C. diff* are much more common.

Although research is still needed on why PPI use increases a patient's vulnerability to hospital-acquired pneumonia and *C. diff* infection, the effect of the acid-reducing drugs on gut bacteria likely has a direct impact. In the case of pneumonia, suppressing acid production may increase the amount of bacteria in the stomach and throat, which can then get into the lungs and cause pneumonia.

Model can be used for other risk-benefit balancing

Pappas notes that the model he developed with Vijan and recent U-M Ford School of Public Policy graduate Sanjay Jolly could be applied to many other situations where a common preventive or treatment measure in medicine also carries with it an increased risk of an unwanted effect.

Using such models, based on data from observational studies, could

answer important questions in medicine without needing to carry out massive prospective clinical trials. To answer the question of whether the predicted increase in mortality risk caused by PPIs in inpatients is real, he says, would take a clinical trial of more than 64,000 patients randomly assigned to receive PPIs or not. Since PPIs are available as generic medications, the likelihood of such a study being funded and performed is nearly zero.

"Any time there are complex risk/benefit tradeoffs, without the possibility of a high-quality trial, this kind of simulation can help us come up with answers to inform clinical care," he says.

For instance, he's now studying the issue of "bridging" medication in patients who have been prescribed blood-thinning medications to prevent a stroke. Such patients often receive a prescription for an injected drug that will reduce stroke risk during the week or two before their regular oral drugs take effect. But that injection carries its own risk.

"Humans aren't very good at recognizing very rare events, and reacting appropriately to things that are unlikely to happen," says Pappas. "Physicians have an instinct to want to prevent very bad, though rare events - but everything we do carries risks. We need to be mindful of the things we are doing to prevent rare outcomes, and keep the risks in perspective. Computers can help."

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