Common drug combination increases risk of recurrent heart attack

TORONTO, JANUARY 28, 2008 – Patients who take the common cardiac drug clopidogrel following a heart attack are at significant risk of a recurrent heart attack if they are also taking certain widely used acid-lowering medications called proton pump inhibitors. The finding, which has significant public health implications, was the result of a study conducted by Dr. David Juurlink and colleagues at the Institute for Clinical Evaluative Sciences (ICES) in Toronto.

The study appears online (ahead of print) today in the *Canadian Medical Association Journal.*

The research, which took place over six years, involved more than 13,000 heart attack patients aged 66 years and older who were started on the blood-thinning drug clopidogrel. Scientists found that patients' risk for readmission to hospital for another heart attack was significantly higher if they were taking one of several proton pump inhibitors (PPIs). The PPIs found to increase this risk were omeprazole, lansoprazole and rabeprazole. The investigators found no such increased risk for patients taking the PPI drug pantoprazole, or among those taking other acid-lowering medications called H2 receptor antagonists.

Clopidogrel, which makes blood platelets less "sticky" and thus less likely to clot, is routinely prescribed to patients after a heart attack to prevent a recurrence. Previous research suggests that, with the exception of pantoprazole, PPIs can inhibit the liver's ability to convert clopidogrel to its active form, a critical step required for clopidogrel to exert its effect. Until now, clinicians have had no "real world" information about the clinical significance of the drug interaction between clopidogrel and PPIs.

The findings have significant public health implications. Most patients treated with clopidogrel also receive acetylsalicylic acid (ASA) to prevent another heart attack, but ASA can cause bleeding from the stomach. Recent guidelines from the American Heart Association, the American College of Gastroenterology, and the American College of Cardiology recommend that all patients aged 60 years or older who are receiving ASA also be treated with a PPI to reduce the risk of bleeding.

"Because clopidogrel and ASA are often prescribed together following a heart attack, it is probable that millions of patients worldwide will be told to take a proton pump inhibitor in addition to clopidogrel," says Dr. Juurlink, the study's lead author, who heads the Division of Clinical Pharmacology and Toxicology at Sunnybrook Health Sciences Centre in Toronto. "Depending on which PPI is prescribed, the effectiveness of clopidogrel in preventing recurrent myocardial infarction may be reduced or eliminated altogether."

PPIs are among the most commonly prescribed drugs in the world, and are used to reduce gastric acid in patients with peptic ulcer disease and gastroesophageal reflux, as well as other conditions. In 2004, there were more than 12.4 million prescriptions for these medications in Canada alone. In 2007, clopidogrel was second on the list of prescription drugs in terms of worldwide sales, with annual total sales of $7.3 billion.

The researchers say their findings highlight a widely unappreciated, extremely common and completely avoidable drug interaction in a population of patients at very high risk for early re-infarction. They suggest that indiscriminate treatment with certain PPIs could result in thousands of additional cases of recurrent heart attack each year.

"Depending on patients' exposure to these drugs following a heart attack, we estimate that between five and 15 per cent of recurrent myocardial infarction among patients taking clopidogrel could be the result of this drug interaction," Dr. Juurlink says.

He adds that doctors could avoid the situation by selectively prescribing the PPI pantoprazole in patients receiving clopidogrel who require treatment with a proton pump inhibitor.

The article, entitled "A Population-Based Study of the Drug Interaction Between Proton Pump Inhibitors and Clopidogrel," will appear in the March 31, 2009 print version of the *Canadian Medical Association Journal.*

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