Rise in *Clostridium difficile* Infections with Use of Gastric Acid Suppressants

Dial S, Delaney JAC, Barkun AN, Suissa S. Use of gastric acid–suppressive agents and the risk of community-acquired Clostridium difficile–associated disease. JAMA 2005;294:2989–95.

Study Overview

Objective. To determine if use of gastric acid–suppressive agents increases the risk of *Clostridium difficile*–associated disease (CDAD) in a community population.

Design. Retrospective case-controlled study with nested analysis.

Setting and participants. The study population, drawn from the United Kingdom General Practice Research Database (GPRD), included all patients with at least 2 years of follow-up in the GPRD. Cases were defined as patients with a positive *C. difficile* toxin assay and/or clinical diagnosis of CDAD between 1 January 1994 and 31 December 2004; controls were patients who were toxin-negative and/or had no clinical diagnosis of CDAD at the time the case was diagnosed (index date). For the primary analysis, 10 controls per case were randomly selected from the study population and matched on practice. A nested analysis was performed on a subset of CDAD patients who had not been hospitalized in the year prior to the index date (considered community-acquired disease); for this analysis, 10 new controls per community-acquired case were selected and matched on age and practice.

Main outcome measures. Incidence of *C. difficile* and risk associated with gastric acid–suppressive agents.

Main results. 1672 patients were included in the primary analysis, and 1233 patients met criteria for the secondary analysis. The incidence of *C. difficile* increased from less than 1 case per 100,000 in 1994 to 22 per 100,000 in 2004. The adjusted rate ratio of community-acquired CDAD was 2.9 (95% confidence interval [CI], 2.4–3.4) for patients with concurrent use of proton pump inhibitors (PPIs) and was 2.0 (95% CI, 1.6–2.7) for those using H_2-receptor antagonists.

Conclusion. Use of gastric acid–suppressive agents, particularly PPIs, is associated with an increased risk of community-acquired CDAD.

Commentary

Upper gastrointestinal tract symptoms from reflux disease and medication-related gastropathy are common, and acid-suppressive agents such as H_2-receptor antagonists and PPIs are widely used as first-line treatments. It has been well documented that gastric-suppressive therapy leads to increases in intragastric bacterial load, but the clinical significance of this finding has been difficult to demonstrate [1]. Recently, Laheij and colleagues [2] found an increased risk of community-acquired pneumonia with the use of gastric acid–suppressive agents, which suggests a link between increased intragastric bacterial load and acquired infections.

C. difficile is a pathogenic bacillus that has long been associated with use of antibiotics and has been an important cause of nosocomial CDAD, particularly in older or severely ill hospitalized patients and residents of long-term care facilities; however, *C. difficile* has also been an identified cause of diarrhea in patients presenting to a hospital [3]. In recent years, the United States, Canada, and Europe have seen increasing severity and rates of nosocomial CDAD [4,5]. While rates of community-acquired CDAD are typically much lower than infection in hospitalized patients, frequent use of gastric acid–suppressive agents may potentially lead to increases in these rates. Dial and colleagues used a well-defined research database (ie, the United Kingdom GPRD) that contains medical records of more than 3 million people to determine the rate of CDAD in the community to assess if there is an association between gastric acid suppression and community-acquired CDAD. Using a case-control approach, the authors found an exponential rise in the rate of CDAD in the community. A nested case-control analysis controlled for confounding and lessened bias and demonstrated an increased risk associated with use of gastric acid–suppressive agents as well as a dose-response effect (lower risk of CDAD with H_2-receptor antagonists and higher risk with the more potent PPIs). In addition to reconfirming the positive associations between risks for CDAD and age, hospitalization, and antibiotic exposure, they also found associations with less recognized factors, such as renal failure and history of inflammatory bowel disease.

Applications for Clinical Practice

Clinicians should be aware of the increased risk of community-acquired CDAD when prescribing gastric acid–suppressive agents.

–Review by Mark S. Horng, MD

References

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