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12-1-2004

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Joseph A. Woelfel

University of the Pacific, jwoelfel@pacific.edu

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Recommended Citation

Woelfel, J. A. (2004). Community-acquired pneumonia risk with acid-suppressive drugs. *Pharmacist's Letter & Prescriber's Letter*, 20(12), 1–3.

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Community-Acquired Pneumonia Risk with Acid-Suppressive Drugs

Lead author: Joseph A. Woelfel, Ph.D., FASCP, R.Ph., Assistant Editor

Background

Acid suppressive drugs, one of the most frequently prescribed drug classes, continue to grow in sales.¹ Yet their use is not without risk.²

The normal pH of the stomach is a host defense and barrier to ingested pathogens.³ Bacterial overgrowth and colonization with upper gastrointestinal tract bacteria have been identified in studies with acid-inhibitory therapy.^{3,4} Acid-suppressing drugs are associated with bacterial overgrowth in the stomach and influenza viruses in the gastric mucosa.^{3,5} Studies have also shown that bacterial overgrowth depends on the intensity of inhibition of gastric acid secretion and corresponding increase in pH. Both H₂ receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) effectively raise gastric pH. Proton pump inhibitors have greater inhibition of gastric acid secretion compared with H₂ receptor antagonists.^{4,6}

Colonized oral secretions can be aspirated into the lungs and establish pneumonia.⁷

Citation

Laheij RJ, Sturkenboom MC, Hassing R, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955-60.

Methods

Complete medical records for approximately half a million patients were accessed from the Integrated Primary Care Information project, a Dutch general practice research database. The seven-year study included all patients with at least a one-year recorded history. All participants were followed once they had a one-year history until the study ended, or until they had pneumonia, died, or moved out of the practice area. All those with a pre-study pneumonia diagnosis were excluded. All patients exposed to acid-suppressive therapy were compared to those who

did not receive this therapy in the study period relative to their incidence of community-acquired pneumonia. Incidence rates were calculated for exposed and unexposed participants. To prevent confounding by antagonist indication, a nested case-control analysis of patients with pneumonia and using acid-suppressive drugs prior to or at the time of contracting pneumonia was conducted.

Results

A total of 364,683 suppressive therapy exposed and unexposed patients were identified. Person-time of exposure was calculated on the basis of person-years. Overall, 5.3% of these individuals were exposed to suppressive drugs. This represented 7562 person-years. During the study period, 185 cases of radiographic or sputum culture confirmed-pneumonia occurred. The incidence rate of pneumonia in acid-suppressive users was 2.45 and for non-suppressive participants the rate was 0.6 per 100 person-years. The adjusted relative risk for pneumonia for those currently using PPIs compared with those who stopped using PPIs was 1.89 (95% confidence interval, 1.36 to 2.62). H₂RA current users had a 1.63 adjusted relative risk for pneumonia (95% confidence interval, 1.07 to 2.48) compared with those who stopped their use.

A significant dose response was observed in PPI users taking more than one dose per day. They had a 2.3-fold increased risk of pneumonia compared with past acid-suppressive drug users. This dose response was not observed with H₂RAs.

Author Conclusions

Both H₂RA and PPI acid-suppressive drugs are associated with an increase in community-acquired pneumonia risk. This association probably results from their effective suppression of gastric pH which facilitates opportunistic infection by intestinal bacterial and viral organisms.

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Commentary

The availability of acid-suppressive therapy is a major factor in the effective treatment of gastrointestinal ulcerative disease. The rational use of these agents is associated with both efficacy and safety. They represent a major milestone for improvement of the quality of life in patients suffering from these common disorders.

As demonstrated in this study, despite their safety and efficacy, acid-suppressive agents can present risk for certain patients.

In another study of 700 patients by Laheij RJ, et al, those using acid-suppressive drugs were 2.34 times more likely (95% confidence interval, 1.4 to 4.1) than non-suppressive users to have clinical signs of infection. They also visited a physician 3.72 times more often (95% confidence interval, 2.1 to 6.8) for an infection and received an antibiotic 4.19 times more often (95% confidence interval, 2.2 to 8.1) compared with non-suppressive users.⁸

In a recent investigation, both cohort and case-controlled studies were undertaken to assess acid-suppressive therapy as a risk factor for *C. difficile* infection. *C. difficile* diarrhea developed in 6.8% of the 1,187 cohort patients. Of the patients who received antibiotics and a PPI, 9.3% developed *C. difficile* diarrhea, whereas those who received antibiotics but no PPI experienced a 4.4% incidence (RR 2.1, 95% CI 1.4 to 3.4). The relative risk of *C. difficile* was higher in patients receiving PPIs compared with H₂RA recipients (OR 2.1, 95% CI 1.2 to 3.5 vs. OR 1.1, 95% CI 0.4 to 3.4).⁹

In the case-control study, 94 patients developed *C. difficile* diarrhea. The case and control subjects were similar in age, number and type of antibiotic, and comorbidity factors. Of the cases, 64% were receiving PPIs as compared with 36% of the controls (unadjusted OR 3.1, 95% CI 1.7 to 5.6).⁹

These authors concluded that patients receiving PPIs were at greater risk for *C. difficile* diarrhea.⁹

Given these concerns associated with acid-suppressive therapy, at-risk patients should be identified. Community-acquired pneumonia is a danger for those who are generally at risk for infection.¹⁰ At risk groups include those with asthma, chronic obstructive pulmonary disease, children, the elderly, and those who are immunocompromised.¹¹ In these at risk groups,

patients needing acid-suppressive therapy may benefit from sucralfate (*Carafate*) which does not appear to affect gastric acid concentration.¹²

Evidence presented in this study suggests that patients should be treated with acid-suppressing drugs only when necessary and at the lowest effective dose [Evidence level B, epidemiologic study, clinical cohort study].²

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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Cite this Detail-Document as follows: Community-acquired pneumonia risk with acid-suppressive drugs. Pharmacist's Letter/Prescriber's Letter 2004;20(12):201207.



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