For Healthcare Professionals

Infectious Smiles

Focus on Anti-infectives

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Clostridium difficile-associated Diarrhea and Proton Pump Inhibitor Therapy: A Meta-Analysis

Introduction

Clostridium difficile is a common spore-forming bacillus that can cause gastrointestinal illness, ranging in severity from mild diarrhea to fulminant colitis and even death. It is the most common infectious cause of health care – associated diarrhea in developed countries.

The recent epidemiological changes in C. difficile-associated diarrhea (CDAD) are notable for an increasing incidence, more virulent strains, and the identification of new “at risk” populations other than traditionally recognized groups such as the elderly and patients with previous illnesses. Although antibiotic use remains the dominant risk factor for CDAD, other documented risk factors include advancing age, severe underlying illness, hospitalization, the use of naso-gastric tubes, anti-neoplastic chemotherapy, and immunosuppressants.

> “Recently, proton pump inhibitors (PPIs) have come under intense scrutiny because of a possible association between these agents and the development of CDAD.”

PPIs are the mainstay of therapy in acid-related disorders, including gastroesophageal reflux disease and peptic ulcer disease. They are among the most commonly prescribed medications in the outpatient and inpatient settings worldwide. PPIs are generally thought to have a safe side-effect profile and this has led to widespread use by clinicians.

Gastric acid is important in eliminating ingested pathogens from the digestive tract. It is thus biologically plausible that suppressing gastric acidity may result in an increased load of pathogenic microbes in the gastrointestinal tract. Both human and animal studies have shown that increased gastric acidity is effective in killing C. difficile and neutralizing its toxin. It has also been shown that there were significant differences in epithelial damage, edema, and neutrophil infiltration in colons when PPIs were used as opposed to when they were not used. Given the millions of individuals on PPIs, even a slight increase in the risk of CDAD conferred by these drugs could have major public health implications.

Several studies have examined the association between PPI use and risk of CDAD, with conflicting results. They showed a stronger association to CDAD with PPIs compared with H2 receptor blocker therapy.

Objectives

Clostridium difficile-associated diarrhea (CDAD) is a major cause of morbidity and increasing health-care costs among hospitalized patients. Although exposure to antibiotics remains the most documented risk factor for CDAD, attention has recently been directed toward a plausible link with proton pump inhibitors (PPIs). However, the results of studies on the association between CDAD and PPIs remain controversial. We have conducted a meta-analysis to summarize the association between PPIs and CDAD among hospitalized patients.

Methods

A systematic search of published literature on studies that investigated the association between PPIs and CDAD from 1990 to 2010 was conducted on Medline and PubMed. The identified articles were reviewed for additional references.

> “The most adjusted risk estimates were extracted by two authors and summarized using random effects meta-analysis. We also conducted a subgroup analysis by study design.”

Publication bias was evaluated using the Begg and Egger tests. A sensitivity analysis using the Duval and Tweedie “trim-and-fill” method has also been performed.

Results

Twenty-three studies including close to 300,000 patients met the inclusion criteria. There was a 65 % (summary risk estimate 1.69 with a 95 % confidence interval (CI) from 1.395 to 1.974; $P < 0.000$) increase in the incidence of CDAD among patients on PPIs. By study design, whether case – control study or cohort study, there was still a significant increase in the incidence of CDAD among PPI users. The risk estimates were 2.31 (95 %CI from 1.72 to 3.10; $P < 0.001$) and 1.48 (95 % CI from 1.25 to 1.75; $P < 0.001$) for cohort and case – control studies, respectively.

Discussion

This study is the first meta-analysis performed to assess the specific association between CDAD and PPIs. Similar analysis in a systematic review has been undertaken previously by Leonard et al. They found that there is an increased risk of C. difficile infection in people taking antisecretary therapy.

Our meta-analysis showed a statistically significant increase in the incidence of CDAD among patients on PPI therapy. Most of the results of the individual studies were consistent with the overall results.

Conclusion

There is sufficient evidence to suggest that PPIs increase the incidence of CDAD. Our meta-analysis shows a 65% increase in the incidence of CDAD among PPI users. We recommend that the routine use of PPIs for gastric ulcer prophylaxis should be more prudent. Establishing a guideline for the use of PPI may help in the future with the judicious use of PPIs. Further studies, preferably high-quality, prospective trials focusing on duration of therapy and dose of therapy are further warranted to show the strength of this association.

Reference

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