Association between proton pump inhibitors and spontaneous bacterial peritonitis in cirrhotic patients: a systematic review and meta-analysis

Trikudanathan G, Israel J, Cappa J, O'Sullivan DM

CRD summary
This review found a statistically significant association between acid suppressive therapy using proton pump inhibitors and the development of spontaneous bacterial peritonitis in patients with cirrhosis. Lack of information about the studies and their quality mean that the authors’ conclusions should be interpreted with substantial caution and may not be reliable.

Authors' objectives
To determine the nature of the association between proton pump inhibitors and spontaneous bacterial peritonitis in patients with cirrhosis.

Searching
MEDLINE (from 1966) and EMBASE (from 1990) were searched up to June 2010; search terms were reported. Reference lists from retrieved studies, reviews and major gastroenterology meetings were searched to May 2010 to identify additional studies. The "related articles" feature on PubMed was used to locate further studies. There were no language restrictions.

Study selection
Observational studies (with a comparator arm) in adult patients (8 years or older) with spontaneous bacterial peritonitis who were receiving proton pump inhibitor therapy of any dose frequency and duration were eligible for inclusion.

All the patients in the included studies had cirrhosis with proven spontaneous bacterial peritonitis (defined as a paracentesis yielding ≥ 250 polymorphonuclear leucocytes in the ascitic fluid). The comparator arms of the studies included patients not on gastric acid suppression (proton pump inhibitor) therapy. The outcome evaluated was the association between the use of proton pump inhibitors and the development of spontaneous bacterial peritonitis.

Two reviewers independently selected the studies for inclusion; the authors stated there were no disagreements between the reviewers.

Assessment of study quality
Methodological quality was assessed based on the similarity of the groups at baseline, selection methods, measurement of exposure variables, description of valid primary outcomes and analytical methods for control group matching and control confounding.

The authors did not state how many reviewers assessed study quality.

Data extraction
Data were extracted to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted data.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using a random-effects model. $I^2$ was used to evaluate heterogeneity across the studies. The reviewers assessed publication bias by visual appraisal of funnel plots.

Results of the review
Four studies (n=772 patients) were included in the review. Sample sizes ranged from 113 to 403 patients. The authors did not report the results of the quality assessment. All the studies were retrospective case-control studies that examined the risk of spontaneous bacterial peritonitis among patients in hospital with cirrhosis. Follow-up ranged from 34 to 60 months.

A statistically significant association was found between the use of proton pump inhibitors and the development of spontaneous bacterial peritonitis (OR 2.77, 95% CI 1.82 to 4.23, $I^2$=22%).

The funnel plot showed no evidence of publication bias.

**Authors’ conclusions**

There was a potential association between the use of acid suppressive therapy using proton pump inhibitors and the development of spontaneous bacterial peritonitis in patients with cirrhosis.

**CRD commentary**

The review addressed a clear question and some criteria for inclusion were defined. Appropriate databases were searched with no language restrictions. Attempts were made to identify studies from conference proceedings. Although the authors examined the results for publication bias using recognised methods, the small number of studies with small sample sizes means that the results of this analysis may not be valid. Steps were taken by the reviewers to minimise errors and bias for the selection of studies in the review, but were not reported for the quality assessment or the extraction of data.

Although the methodological quality of the studies were evaluated, the results of this assessment were not summarised in the review, so the reliability of the results was unknown and the statistical combination of the results in a meta-analysis may not have been appropriate. The results of observational studies were associated with a number of potential biases, so the results should be interpreted with substantial caution.

Some flaws in the review process and the lack of information about the quality of the observational studies included in the review mean the authors’ conclusions should be interpreted with a substantial degree of caution and may not be reliable.

**Implications of the review for practice and research**

**Practice**: The authors stated proton pump inhibitors should be used judiciously and only when indicated in patients with cirrhosis.

**Research**: The authors stated that additional prospective studies with larger sample sizes were required to further evaluate the relationship between proton pump inhibitors and spontaneous bacterial peritonitis, and to determine whether the avoidance of proton pump inhibitors could reduce the incidence of spontaneous bacterial peritonitis.

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