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EDITORIAL

Interaction or relationship between *Helicobacter pylori* and non-steroidal anti-inflammatory drugs in upper gastrointestinal diseases

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Abstract

According to a meta-analysis, *H pylori* and non-steroidal anti-inflammatory drugs (NSAID) independently and significantly increase the risk of gastroduodenal ulcer and ulcer bleeding. Their coincidence is frequent, demonstration of a possible relationship and consequent attitude is of important implications. But unfortunately, no consensus has been approved in the past years and their interactions are still controversial. *H pylori* and NSAID are known to share a number of pathogenic mechanisms, but there is no evidence for the significant synergic action between these two risk factors. Their relationship is independent, additive, synergistic or antagonistic without considering the influence of other factors because studies on this subject are different in almost all aspects of their methodology, including the definition of a NSAID user as well as the types, doses, duration and their indications for NSAID use, as well as their end-points, definition of dyspepsia and regimes used for eradication of *H pylori*. These might contribute to the conflicting results and opinions. *H pylori* infection in humans does not act synergistically with NSAID on ulcer healing, and there is no need to eradicate it. This notion is supported by the finding that the eradication of *H pylori* does not affect NSAID-induced gastropathy treated with omeprazole and that *H pylori* infection induces a strong cyclooxygenase-2 (COX-2) expression resulting in excessive biosynthesis of gastroprotective prostaglandin which in turn counteracts NSAID-induced gastropathy and heals the existing ulcer. Other investigators claimed that *H pylori* infection acts synergistically with NSAID on ulcer development, and *H pylori* should be eradicated, particularly at the start of long-term NSAID therapy. Eradication of *H pylori* prior to NSAID treatment does not appear to accelerate ulcer healing or to prevent recurrent ulcers in NSAID users. However, some recommendations can be drawn from the results of clinical trails.

H PYLORI AND ASPIRIN

Aspirin has a role in the prevention of cardiovascular and cerebrovascular disease, Alzheimer's dementia and several cancers. The widespread use of aspirin, however, is limited as many older subjects are currently unable to take aspirin because of gastrointestinal (GI) side-effects, such as gastroduodenal mucosal damage and increased risk of upper gastrointestinal bleeding. Cardiovascular patients on long-term low-dose aspirin have a stable risk of major upper GI bleeding, which is higher than that in controlled clinical trials[1]. Many aspirin users should receive prophylactic treatment since they often have several risk factors for upper GI complications. The best therapeutic approach for reducing GI toxicity in low-dose aspirin users is still ill-defined, because the causal relationship between intake of aspirin and *H pylori* appears to be more complex, but there is now wide agreement that *H pylori* infection increases mucosal damage and the risk of upper GI bleeding in low-dose aspirin users. In high-risk patients with a history of ulcer bleeding, curing *H pylori* infection alone without acid suppression has substantially reduced the risk of rebleeding caused by low-dose aspirin. Omeprazole appears to be very effective in reducing both acute gastroduodenal mucosal damage and upper GI bleeding in the high-risk patients taking low-dose aspirin, Thus, it appears that eradication of *H pylori* in patients who presented with GI bleeding and are scheduled to resume low-dose aspirin has the same efficacy as a daily dose of 20 mg of omeprazole for a 6-mo period. It was reported that it is not necessary to shift aspirin to clopidogrel in patients with GI bleeding[2], suggesting eradication of *H pylori* prevents recurrent peptic ulcer or ulcer bleeding in *H pylori*-positive patients, who continue to take low-dose-

aspirin. Maintenance therapy with proton pump inhibitor (PPI) is not generally required. However, it is reasonable to eradicate *H pylori* infection in those with increased risk of gastrointestinal complications (previous history of peptic ulcer, age over 65 years, concomitant use of corticosteroids, anticoagulants or individual non-steroidal anti-inflammatory drugs (NSAID) with higher risk for gastrointestinal complications, serious cardiovascular disease), but it does not guarantee complete protection and therefore a proton pump inhibitor should also be given. Switching from low-dose-aspirin to clopidogrel is not necessary. There are no valid data supporting *H pylori* eradication in low-risk patients on long-term therapy with low-dose-aspirin[3].

H PYLORI AND NSAIDS IN UNCOMPLICATED PUD PATIENTS

Whether *H pylori* eradiation plays a part in the healing and recurrence of ulcers in long term NSAID users remains unknown. It was reported that *H pylori* eradication does not confer any significant advantage on the healing of gastric and duodenal ulcers associated with long term NSAID use in arthritis patients[4], which is supported by a basic study[5] showing that *H pylori* infection is associated with increased cyclooxygenase-2 (COX-2) expression in gastric antral mucosa of both NSAID users and nonusers, but not in gastric ulcer, where the effect of NSAID inhibition plays a major role.

Further more, *H pylori* eradication is associated with significantly slower healing of gastric ulcers than in those not undergoing *H pylori* eradication treatment[6]. However, the effect of *H pylori* eradication on healing of NSAID induced duodenal ulcers does not appear to be so dramatic. There is evidence that it may be possible to prevent *H pylori*-associated duodenal ulcer by eradicating the infection. An evidence-based approach to treatment suggests that NSAID users should undergo *H pylori* eradication therapy if they have a duodenal ulcer, whether they continue NSAID. *H pylori* eradication should not be recommended universally or in high-risk gastric ulcer patients (female, older age and higher NSAID dose) who require management with acid suppression. Because there is evidence that *H pylori* infection does not potentate the risk of ulcer formation or ulcer complications in NSAID users. If such an effect occurs, it is likely to be relatively mild. Some data even indicate that[7] *H pylori* can protect against NSAID-induced gastric ulcers, suggesting that gastric ulcer healing is significantly enhanced in the presence of *H pylori* infection. Routine testing for and eradication of *H pylori* infection are not recommended for current takers of NSAID with no or low risk of peptic ulcers and its complications[8]. But more gastroenterologists believe that use of NSAID increases the risk of peptic ulcer in *H pylori* positive and negative patients and that *H pylori* eradication therapy should be given to all *H pylori*-infected patients with peptic ulcers irrespective of their use of NSAID[10].

Randomized trials comparing *H pylori* eradication to non-eradication in patients receiving NSAID showed that *H pylori* eradication reduces the incidence of peptic ulcer in the overall population receiving NSAID[4]. It appears to be especially effective in non-steroidal anti-inflammatory drug-naive patients. Nonetheless, *H pylori* eradication seems less effective than treatment with a maintenance proton pump inhibitor for preventing NSAID-associated ulcers.

The effect of *H pylori* eradication therapy on the healing of gastric ulcers remains controversial, but more gastroenterologists advise eradication of *H pylori* in this subgroup[9]. We recommend testing for and cure of *H pylori* infection in patients prior to the initiation of NSAID therapy and in those who are currently on NSAID and have a history of dyspepsia, peptic ulcer or ulcer complications. After eradication therapy, acid-suppressant therapy is advised to heal the ulcer. The success of *H pylori* eradication should always be confirmed because of the recurrent risk of peptic ulcer disease and bleeding in *H pylori*-infected patients[10].

The critical review of these studies indicates that the discrepancy arises mainly from heterogeneity in risk factors, patients and outcome measurements[11]. The main confounding factors are the type of treatment, nonaspirin NSAID or low-dose aspirin, different strains of *H pylori*, variable host response and type of ulcer. Therefore, both risks of *H pylori* and NSAID should be removed if possible, because it is not certain which factor is responsible for the ulcer[12].

H PYLORI AND NSAIDS USE IN COMPLICATED PEPTIC ULCERS

It was reported that the frequency of *H pylori* infection is significantly lower in patients with bleeding ulcers than in controls[13]. Interaction term, male multiple ulcers and NSAID use are independent risk factors for bleeding ulcers. There was a negative interaction between *H pylori* and NSAID use. Negative interaction between the two variables suggests that the presence of *H pylori* is associated with a lower risk of bleeding in ulcer patients taking NSAID. *H pylori* and NSAID use are independent risk factors for duodenal ulcer bleeding, whereas NSAID use is the main risk factor for bleeding gastric ulcers[14]. Interaction between these two factors is associated with reduced risk of bleeding gastric ulcers, but not of bleeding duodenal ulcers.

Established risk factors for NSAID-associated ulcer complications include advanced age, female gender, peptic ulcer history , use of non-selective NSAID and anticoagulant drugs or corticosteroids. Probable risk factors comprise *H pylori* infection and heavy consumption of alcohol, use of selective serotonin re-uptake inhibitors and smoking, *etc.* other factors. Knowledge of absolute risk estimates is important for clinical decision making[15].

Relapse of lesions in patients taking NSAID is highly site and type specific, and is not adversely affected by *H pylori* status, indicating that local mucosal factors predispose to ulceration in patients taking NSAID[16]. Identification of the responsible mucosal changes aids understanding and improves treatment. This finding

encourages analyzing the mechanism of relapse of peptic ulcer. After reviewing most of these articles we conclude that it *H pylori* eradication alone is insufficient in preventing recurrent peptic ulcer or ulcer bleeding in *H pylori*-positive patients on NSAID. Maintenance therapy with proton pump inhibitors (PPIs) or switching from nonselective NSAID to COX-2 inhibitors is required after eradication of *H pylori* in primary *H pylori*-negative patients with increased risk for gastrointestinal complications.

Clinically, maintenance treatment should be given after *H pylori* eradication if aspirin and or NSAID therapy is needed in patients with peptic ulcer bleeding. PPI significantly reduces the cumulative relapse of symptomatic and complicated ulcers in patients requiring NSAID after eradication of *H pylori*.

TREATMENT OF NSAIDS - RELATED DYSPEPSIA

NSAID-induced dyspepsia occurs in 10%-30% of patients treated with NSAID, leading to discontinuation of treatment in 5%-15%. Gastrointestinal tolerability of COX-2 selective inhibitors is better than THAT OF non-selective NSAID. *H pylori* infection does not influence gastrointestinal tolerability of NSAID. Therefore, patients should not be tested and treated for *H pylori* infection unless they have a history of peptic ulcer. Symptoms of NSAID-induced dyspepsia are poorly correlated with gastroduodenal mucosal damage. Therefore, upper gastrointestinal endoscopy should be performed only if symptom relief is not achieved with the first line empirical treatment and/or if symptoms suggestive of complications, such as bleeding. Proton pump inhibitors appear to be the treatment of choice for NSAID-induced dyspepsia[17].

H PYLORI AND COX-2

COX-2 inhibitors appear not to be ulcerogenic. The use of COX-2 inhibitors reduces significantly the gastrointestinal side effects of anti-inflammatory treatment. Management of *H pylori* in patients taking these drugs can be based upon the same risk assessment as in patients not taking NSAID. Treatment with celecoxib is as effective in patients with a recent history of ulcer bleeding as treatment with diclofenac plus omeprazole, with respect to the prevention of recurrent bleeding[18]. Selective COX-2 inhibitors (coxibs) can effectively treat pain and inflammation while reducing risk of gastropathy[19]. In case of patients with risk of NSAID-induced gastrointestinal toxicity, treatment with nonspecific NSAID should be selected[20].

SUGGESTIONS

Because the prevalence of *H pylori* infection and its associated diseases such as peptic ulcer and gastric cancer is different in different countries, it is not surprise to see different approvals for treatment. The clinical and cost-effectiveness advantage of *H pylori* screening have improved the patients' ulcer risk or the protective effect of *H pylori* eradication.

Many important issues should be considered when assessing the interaction between *H pylori* and NSAID. A better understanding of the interaction between *H pylori* and NSAID as well as the histological characteristics of *H pylori*-induced or NSAID-related gastropathy, contributes to the eradication of duodenal or gastric ulcer and their complications. Clinical trails should focus on strategies for subgroups of NSAID patients with *H pylori* infection. Multiple centers, big samples, double blind and randomized controlled clinical trails with comparable methodology should be performed to farther elucidate the interaction and relationship between *H pylori* and NSAID.

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