



REVIEW ARTICLE

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Peptic ulcer in nephrotic syndrome patients due to steroid therapy

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ABSTRACT



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Peptic ulcers comprise gastric and duodenal ulcers. Complications of peptic ulcers include bleeding, perforation, and obstruction. Bleeding is a major problem of peptic ulcers, as it is at times fatal. Peptic ulcer bleeding is diagnosed and treated by upper gastrointestinal (GI) endoscopy. Oral glucocorticosteroids (referred to hereafter as corticosteroids) are commonly prescribed for symptom control in patients receiving palliative care. A recent study has shown that one-third of patients admitted to an inpatient hospice unit were receiving corticosteroids. This frequency in prescribing exposes a large number of patients to the potential side effects known to be associated with corticosteroids, including weight gain, impaired glucose tolerance, and proximal myopathy. H. pylori infection is a risk factor for PUD in aspirin and NSAID users.

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Introduction

Peptic ulcers comprise gastric and duodenal ulcers. Complications of peptic ulcers include bleeding, perforation, and obstruction (Milosavljevic et al., 2011). Bleeding is a major problem of peptic ulcers, as it is at times fatal (Leontiadis et al., 2013). Peptic ulcer bleeding is diagnosed and treated by upper gastrointestinal (GI) endoscopy (Kim et al., 2012). Known causes of peptic ulcer bleeding are the long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs), anti-platelet agents, anti-coagulants, and infection with Helicobacter pylori (Huang et al., 2014). NSAIDs are commonly used for rheumatic and orthopedic diseases. Rheumatic diseases have an autoimmune basis and affect connective tissue (Bahadur et al., 2011). This inflammation damages tissue and impairs the patient's quality of life (Grateau et al., 2013). To suppress the autoimmune basis of the disease, corticosteroids, and immunosuppressive agents are used (da Mota et al., 2010). Tumor necrosis factor blockers, biological modifiers, are also used to suppress the autoimmune response (Radner H et al., 2015). It is well

known that corticosteroids trigger peptic ulcer bleeding by making the gastric mucosa susceptible to ulceration by gastric acid (van der Goes et al., 2014). However, the correlation between immunosuppressive agents and upper GI bleeding has remained to be determined. For the prevention of peptic ulcer bleeding, proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs) are used (Tuskey et al., 2013). PPIs and H2RAs increase the pH of gastric acid, prevent damage to the gastric mucosa and promote the healing of peptic ulcers. PPIs are superior to H2RA in preventing peptic ulcer bleeding due to stress in patients in intensive care (Alhazzani et al., 2013). However, the efficacy of the prevention of peptic ulcer bleeding has remained elusive in patients with long-term administration of PPIs or H2RAs. The association between upper gastrointestinal complications and intake of nonsteroidal anti-inflammatory drugs (NSAIDs) has been extensively evaluated and reviewed (Gabriel et al., 1991). In some studies, corticosteroids have been suggested to reinforce the risk associated with NSAIDs (Hernández-Díaz et al., 2000). However, the literature on corticosteroids as an independent risk factor for upper gastrointestinal



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complications in the general population is limited, and often we learn about them from secondary analyses included in research on NSAID.

Oral glucocorticosteroids (referred to hereafter as corticosteroids) are commonly prescribed for symptom control in patients receiving palliative care (Hanks et al., 1983). A recent study has shown that one-third of patients admitted to an inpatient hospice unit were receiving corticosteroids (Bruera et al., 1983). This frequency in prescribing exposes a large number of patients to the potential side effects known to be associated with corticosteroids, including weight gain, impaired glucose tolerance, and proximal myopathy (Needham et al., 1992). The relationship between corticosteroids and peptic ulceration remains controversial, but there continues to be clinical concern related to the possible increase in morbidity and mortality (Grahame-Smith et al., 1984).

Previous history of peptic ulceration Conn and Blitzer analyzed studies that excluded patients with a history of peptic ulceration and compared them with studies that included patients with prior peptic ulcers. In the group receiving corticosteroids, 0.1 % of those with no previous history developed a peptic ulcer, compared with 4.8 % of those who had a history of peptic ulceration ($p < 0.001$) (Conn et al., 1985).

Risk factors with corticosteroids

Overall, the evidence suggests that corticosteroids are related to peptic ulceration and the associated major gastrointestinal side effects. The following should be considered as high-risk factors: a total dose of corticosteroid (over 140 mg dexamethasone or 1000 mg prednisolone), previous history of peptic ulcer, advanced malignant disease, and concomitant use of NSAIDs and corticosteroids. The major complications of hemorrhage and perforation may occur with relatively few symptoms and should be considered in those patients on corticosteroids who develop unexplained tachycardia. For patients who have two or more are prescribed corticosteroids and it may not be appropriate for those patients who are in the terminal phase of their illness. For patients who have two or more risk factors, prophylaxis should be considered. If a patient is prescribed corticosteroids and has two or more risk factors, but is not taking NSAIDs, there is some evidence to suggest that H₂ antagonists are of benefit. Until further research shows that other drugs are more efficacious, H₂ antagonists remain the preferred treatment in this situation. If, however, a patient has two or more risk factors, including NSAIDs, then misoprostol is the drug of choice (Ellershaw et al., 1994)

The ability of corticosteroids to promote the development of peptic ulcers is an old concept, mainly based on the evidence provided by experimental and pharmacological studies, still widely accepted by clinicians. A recent

survey carried out in the Czech Republic has shown that 82 % of physicians believe that cortisone is ulcerogenic (Martínek et al., 2010). From an experimental point of view, this has been established and corticosteroids are known to inhibit the biosynthesis of gastric cytoprotective prostaglandins while suppressing as well the production of gastric-damaging leukotrienes. In animal studies, both gastric mucus production and gastric bicarbonate secretion are impaired by steroid administration, which results in a weakening of gastric mucosal defenses. (Guslandi et al., 1992) In addition, steroids impair angiogenesis and epithelial repair mechanisms in experimental ulcers (Carpani et al., 1985). However, for reasons not quite clear, the real incidence of steroid-induced ulcers in the clinical setting is much lower than what could be expected based on the experimental data. In the past three different meta-analyses have been performed (Luo et al., 2003) the most recent and larger dating back to 1994 indicates that steroid-treated patients have a relative risk for gastric and duodenal ulcers not significantly different from untreated controls (Luo et al., 2004)

H.pylori infection is a risk factor for PUD in aspirin and NSAID users (Huang et al., 2002). However, no studies are showing that H. pylori infection is an aggressive factor for PUD in steroid users. A previous study showed that H. pylori infection was not a risk factor for PUD in autoimmune disease patients receiving low-dose oral steroid therapy (Luo et al., 2002). Another study also showed that H. pylori infection did not increase gastric mucosal injury in SLE patients receiving pulse methylprednisolone therapy (Chang et al., 2009). Dr. Jiing et al. studied only one of the 60 nephrotic patients who developed PUD. Though the subject had H. pylori infection, there were too few ulcer patients to analyze whether H. pylori infection played an important role in PUD in nephrotic patients receiving prednisolone therapy. Though patients with chronic renal failure and hemodialysis have a higher prevalence of PUD (Sugimoto et al., 2009) there are no reports demonstrating that nephrotic patients or nephritic patients have a higher PUD rate. Dr. Jiing et al., the study cannot conclude that 3-month medium-dose corticosteroid therapy does not increase PUD. There were several limitations in this study. First, only patients with relatively low gastrointestinal risks were enrolled due to ethical reasons. Patients who had current PUD (one subject during screening), who took aspirin or NSAIDs (three subjects during screening), or who had a history of surgery for PUD complications (zero in this study) were excluded. Second, the study was limited to 60 nephrotic patients who needed steroid therapy nephritic patients without steroid therapy were compared as a control group. Further studies enrolling more subjects including healthy subjects, elderly patients, or other disease patients who need steroid therapy are needed to clarify whether steroid therapy is ulcerogenic or not for the human upper gastrointestinal tract. Third, there

was only one ulcer subject in the study group and, therefore, it was impossible to evaluate the role of *H. pylori* infection for PUD in steroid users in this study. The study concluded as follows In conclusion, a 3-month medium-dose corticosteroid therapy (60 mg prednisolone day⁻¹) caused few endoscopic ulcers (1.6 %) and no related complications in nephrotic patients, which was comparable with the occurrence of endoscopic ulcers (3.3 %) and complications (0 %) in nephritic patients without prednisolone therapy. Corticosteroid therapies seem not to increase PUD in nephrotic syndrome patients. Further larger studies are needed to clarify the role of corticosteroids in PUD (Kuo-Wei Hsiang et al., 2013).

Conclusion

Unfortunately, the quality of the clinical studies employed to perform the analyses was rather poor (no double-blind conditions, no information about concomitant medications, and no distinction between gastric and duodenal ulcers), which did not allow the firm, definitive conclusions. However, there should be monitoring of patients required while giving a high dose of steroids as they may have highly life-threatening conditions or mild to moderate reactions. Still, we need to require high-quality research to identify the side effects related to steroid therapy.

Conflict of interest

The author declares that there is no conflict of interest

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