

Steroid ulcers: Any news?

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Abstract

Steroid ulcers, although a common feature in experimental studies, seldom develop in clinical practice, as observed by the meta-analyses carried out in the 90s. Corticosteroids alone become ulcerogenic only if treatment lasts longer than one month and the total administered dose exceeds 1000 mg. On the other hand concomitant intake of non-steroidal anti-inflammatory drugs results in a synergistic, highly damaging effect on the gastroduodenal mucosa. Thus, despite the survival of the steroid ulcer myth in the medical culture, pharmacological protection against steroid-induced peptic ulcers is a rare necessity while the best prophylactic strategy still remains to be determined.

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Key words: Corticosteroids; Peptic ulcer; Proton pump inhibitors

Core tip: Although the myth of steroid ulcers still survives among general practitioners, the incidence of ulcers in patients receiving corticosteroids is so low that concomitant gastric protection is not necessary except in patients on long-term, high-dose steroids or taking concomitant non-steroid anti-inflammatory drugs.

STEROID ULCERS

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^[1].

From an experimental point of view, this has been clearly 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 defences^[2]. In addition steroids impair both angiogenesis and epithelial repair mechanisms in experimental ulcers^[3-5].

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 on the basis of the experimental data.

In the past three different meta-analyses have been performed^[6-8], the most recent and larger dating back to 1994^[8] clearly indicates that steroid-treated patients have a relative risk for gastric and duodenal ulcers not significantly different from untreated controls. Unfortunately the quality of the clinical studies employed to perform the analyses was rather poor (no double blind conditions, no information about concomitant medications, no distinction between gastric and duodenal ulcers), which did not allow firm, definitive conclusions.

Thus, in spite of the “definitive” review articles ap-

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peared on the subject^[2,8] the myth of steroid ulcers still survives, also because, during the last twenty years or so, neither additional, perspective clinical studies nor other meta-analyses have been carried out. Admittedly, due to the low incidence of steroid ulcers in the clinical setting, it would be hard to conduct studies in this area unless an extremely large number of patients are recruited. This has not been done and most likely won't ever be done due to the lack of both sufficient interest by the scientific community and commercial motivation by the drug industry.

All in all, it would seem that corticosteroids rather than directly cause ulcers can, in keeping with experimental studies^[3-5], hamper the healing process of ulcers caused by other agents, namely anti-inflammatory drugs (NSAIDs)^[2,9].

Epidemiological studies have proved that NSAIDs are significantly more ulcerogenic than steroids but that the association of the two types of drugs has a truly synergic and lethal effect, increasing of 3 to 6 times the relative risk^[10,11]. Yet corticosteroids themselves can become ulcerogenic if treatment lasts for more than one month, with a total intake higher than 1000 mg of prednisolone^[6]. Elderly people (aged more than 65 years) seem to be more exposed to the risk of developing peptic ulcers.

A recent retrospective study examining the risk of gastrointestinal bleeding with low-dose aspirin alone and in combination with other drugs, has shown that the risk is increased when a high dose (but not low/medium dose) of corticosteroids is co-administered^[12].

Pharmacological prevention of steroid ulcers in clinical practice does not seem, therefore, justified in the large majority of patients under corticosteroid treatment. Subjects undertaking a high-dose long-term steroid administration would deserve concomitant pharmacological "protection", but evidence-based information about the best therapeutic measures is wanting.

Proton pump inhibitors (PPI) are often prescribed but no controlled studies in this area are available.

Indirect evidence, obtained by analyzing sub-populations in NSAID-treated patients suggests that the prostaglandin derivative misoprostol might be effective in counteracting the possible gastric toxicity of cortisone^[13]. However this hypothesis, although consistent with the results of experimental studies on the effects of steroids on ulcer repair^[3] remains largely unproven.

The results of the recent above mentioned survey^[1] show that about 60% of gastroenterologists, compared with only 30% of the other physicians, refrain from prescribing any concomitant "gastroprotective" medication when low doses of steroids are employed. By contrast, when higher doses (*i.e.*, 1 mg/kg prednisone) are prescribed, more than 70% of gastroenterologists and about 90% of the other physicians also carry out empirical pharmacological prevention with PPI.

In conclusion, the body of knowledge on the possible ulcerogenic effects of steroid treatment in humans has

grown very little in the last years. The more recent clinical studies (and subsequent meta-analyses) available in the scientific literature date back to the 90s and the experimental studies performed in the last two decades have added precious little to what was already known in the past.

Due to the apparent lack of interest by clinical researchers, the myth of steroid ulcers, although based on a very weak and disputable clinical evidence, still survives. In daily practice development of peptic ulcers in steroid-treated patients remains a very infrequent event, for which pharmacological protection is seldom required and the most effective drug prevention is still undetermined.

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