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REVIEW ARTICLE

Gastrointestinal Toxicity of Nonsteroidal Anti-inflammatory Drugs in Maxillofacial Trauma Patients: A Review

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ABSTRACT

NSAIDs are widely prescribed for the treatment of pain and inflammation and is well accepted and recommended by World Health Organization (WHO), but their use is associated with adverse gastrointestinal effects, ranging from dyspeptic symptoms and peptic ulcers to more serious complications. Elderly patients are at high risk of experiencing NSAID-induced gastrointestinal tract injury and should be considered candidates for prophylactic pharmacological therapy. NSAIDs cause damage in the upper gastrointestinal (GI) tract by impairing the ability of the mucosa to resist and respond to injury. Many of these effects of NSAIDs can be attributed to their ability to suppress mucosal prostaglandin synthesis. This review focuses on several of the important recent observations that have improved our understanding and the safety of NSAIDs in the gastrointestinal tract.

Keywords: NSAIDs, Gastrointestinal toxicity, Maxillofacial trauma.

INTRODUCTION

The use of non-steroidal anti-inflammatory drugs (NSAIDs) as a first-line therapy for pain and inflammation is well accepted and recommended by World Health Organization (WHO)[1]. NSAIDs are one of the most widely used drugs over the world. It is estimated that everyday 30 million people worldwide use NSAIDs for anti-inflammatory and analgesic effects [2]. In maxillofacial settings, NSAIDs are recommended for pain relief in case of accidents/trauma [3].

NSAIDs are beneficial in relieving the pain associated with soft-tissue injuries. In severe pain associated with muscle spasms, NSAIDs are generally used in combination with skeletal muscle relaxants [4]. Moreover; these medications do not alter the perception of sensory modalities other than pain. Hence, they are free from the issues of drug dependence and CNS side-effects unlike opioids[4]. The beneficial effect of NSAIDs is masked by its gastrointestinal (GI) side-effects [3]. Patients on NSAIDs are at increased risk of upper GI complications that range from dyspepsia to peptic ulcers and GI bleeding. Approximately 60% of NSAIDs users at high-risk of NSAIDs complications, fail to receive adequate gastroprotection[5]. Gastroprotective strategies are effective in reducing the risk of GI complications in chronic NSAIDs users. Proton pump inhibitors (PPIs) are likely to prevent the development of peptic ulcer disease in patients using NSAIDs.

GI complications: 'Silent epidemic'

NSAIDs are the choice of drugs in musculoskeletal injuries as these conditions are considered to be inflammatory in nature [3]. The most important mechanism of the anti-inflammatory action of NSAIDs; is inhibition of the cyclooxygenase (COX) enzymes that catalyze the biosynthesis of prostaglandins (PGs) and arachidonic acid. PGs are mediators of inflammation. COX-1 being a constitutive enzyme plays a role in 'housekeeping' processes, such as the protection of mucosa in the GI tract and vasodilatation in the kidney. On the contrary, COX-2 is an inducible enzyme that is up-regulated only in inflammatory conditions [6]. Consequently, one of the serious drawbacks of NSAIDs is GI toxicity that is widely associated with traditional NSAIDs. The GI complications range from gastric pain, dyspepsia development and drug intolerance to clinically significant gastroduodenal ulcer complications; such as bleeding, obstruction and perforations. The pathogenesis of the mucosal injury and bleeding is depicted in Figure 1[7]. Complications related to

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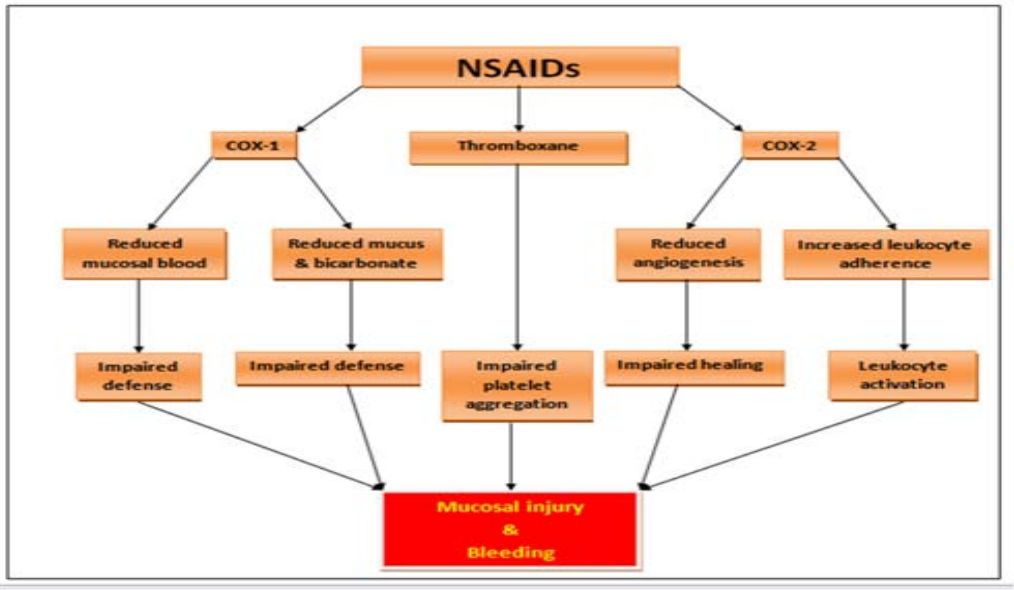
NSAIDs influence the medical outcomes, health-related quality-of-life (QoL) and health-care expenditures considerably [8].

A study reported that almost 6% of hospitalizations were due to adverse drug reactions and NSAIDs account for approximately 25% of all reported adverse events [9]. These complications, mainly upper GI complications, were found common in patients with chronic use of NSAIDs, but could also occur in short-term treatment (with few doses). Traditional NSAIDs account for almost 12,000 ulcer bleeding incidences and 1200 deaths per annum in the United Kingdom [10]. Similarly, in USA it is the estimated that serious GI complications account for about 107,000 hospitalizations and 16,500 deaths per year [11]. Moreover, the economic burden pertaining to this issue accounts for an annual cost over 2 billion USD [12]. Further, the upper GI symptoms associated with NSAIDs can have a considerable impact on the QoL, productivity at work and routine daily activities [13].

Individuals who have GI bleeding while taking NSAIDs have a significantly higher mortality than those with GI bleeds who are not taking NSAIDs. GI bleeding secondary to NSAIDs use is reported as the fifteenth leading cause of death in the United States [14]. Data published since 1997 suggest that mortality in patients suffering from an upper GI bleed or perforation is approximately 1 in 5 among those exposed to NSAIDs [15]. Despite this high mortality, NSAIDs induced gastrotoxicity remains a 'silent epidemic' with many physicians and most patients being unaware of the magnitude of the problem.

Therefore, with a higher possibility of the manifestation of these complications; adherence to prescription guidelines and preventive approaches, and proper monitoring of patients on the medications are vital in improving the safety and tolerability profiles of NSAIDs [4]. (**Fig 1**)

Fig 1: NSAIDs induced GI mucosal injury and bleeding



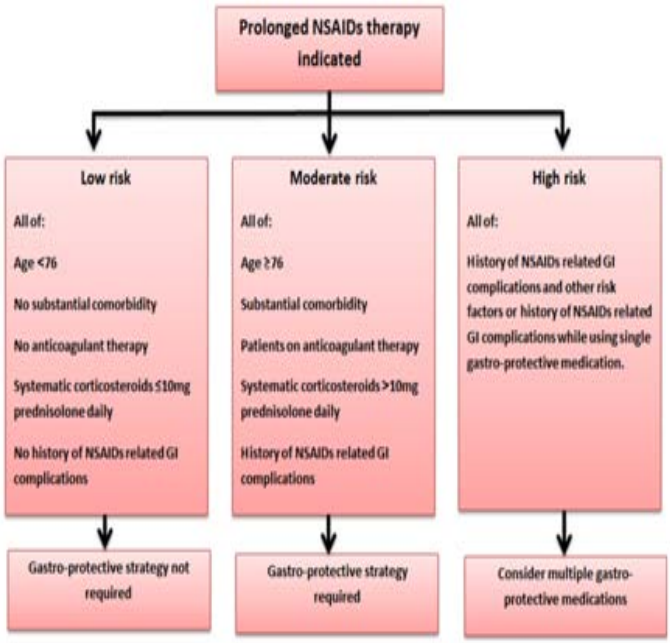
Managing NSAID-associated toxicity

Despite current guidelines recommending prescription of Gastroprotective drug among high-risk groups, the rate of concomitant prescribing of Gastroprotective agents in NSAIDs users is low. The need for gastroprotection can be made based on the existing risk factors (**Fig 2**). The simplest approach to managing NSAID associated dose or switch to a less toxic NSAID. However, dose reduction might lead to suboptimal drug concentrations in the blood and consequently the control of pain and inflammation is compromised. Therefore, concomitant use of GI supportive therapies is often required with NSAIDs.

One option is to prescribe a PG analogue to replace the missing gastroprotective PGs; however such treatment is associated with a high incidence of side-effects [16]. Alternatively, PPI and/or H_2 – receptor antagonists can be used to decrease gastric acidity and acid-related GI damage. The H_2 –receptor antagonists, at standard doses, fail to prevent NSAID associated gastric ulcers, which are more common than NSAID associated duodenal ulcers [17]. In contrast, co-therapy with a PPI has been shown to provide effective and well-tolerated prophylaxis against NSAID associated gastric complications [18]. Prescribing COX-2 selective NSAID is also an alternative approach used by many physicians. However, a study showed no significant difference in risk reduction attained by a COX-2 selective NSAID alone, compared with a non-selective NSAID+PPI. Further, the combination of a COX-2 selective

NSAID+PPI was associated with the greatest reduction in the risk of GI complications [19].

Fig 2: Decision algorithm for gastroprotective strategies for NSAID users



Balancing the risks of NSAIDs with PPI

The Third Canadian Consensus Conference recommends the use of PPIs with NSAIDs in patients at increased GI risk [20]. PPIs like omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole are the co-prescribed drugs of choice with NSAIDs as they effectively reduce GI adverse events and provide long-term safety.

- As reported in various studies, PPIs significantly reduced the risk of both endoscopic duodenal and gastric ulcers compared to placebo [21].
- Several studies have shown that COX-2 inhibitors reduce the risk of clinically important ulcer complications [22]. However, the rate of re-bleeding in such study was relatively high suggesting that in high risk participants, neither strategy was sufficient [19].
- The ASTRONAUT (Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID- Associated Ulcer Treatment) study compared omeprazole 20 mg daily to ranitidine 150 mg twice-daily and reported that omeprazole was superior to standard dose ranitidine for the prevention of both gastric and duodenal ulcers[18].
- NSAID+PPI also showed better drug adherence compared to NSAID+ H_2 – antagonist therapy [23].

SUMMARY

- NSAIDs are key to the clinical management of a wide range of inflammatory conditions including trauma.
- Several complications, mainly GI erosion and bleeding are secondary to chronic use of NSAIDs.
- The burden of such GI complications not only influences healthcare resources, but the patient themselves who may experience discomfort resulting in limitation of daily activities and reduced QoL.
- Despite current guidelines recommending gastroprotective drug among high risk groups, the rate of concomitant prescription of gastroprotective agents in NSAID users is low.
- Therefore, co-prescription of gastroprotective agents/antacids is highly recommended with NSAIDs. Efficacy of PPIs is widely reported and accepted in this regard.

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