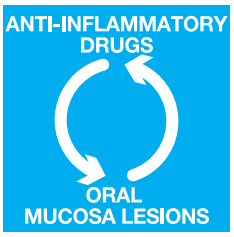
GENGIGEL®
Hyaluronic Acid

ORAL HEALTH & ANTI-INFLAMMATORY DRUGS

FACT FILE

HOW CAN ANTI-INFLAMMATORY DRUGS AFFECT ORAL HEALTH?

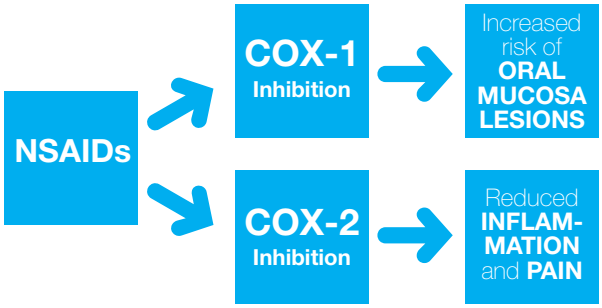
Oral health management is closely related to overall well-being and health maintenance; however, oral diseases, such as periodontitis, gingivitis, oral mucosal lesions, continue to be a major health problem worldwide, limiting the performance of daily actions – such as eating, drinking, speaking - and causing pain. This has a negative impact on people's physical health and on overall quality of life [Villanueva-Vilchis, 2016]. Healthy behaviours, especially daily brushing, flossing, and controlled sugar consumption, are the most effective prevention against the development of most oral diseases. However, epidemiological data show that oral diseases are widespread and therefore therapeutic strategies (pharmacological or surgical dental procedures) are necessary to correct them. Medications for the management of oral conditions include antibiotics, antifungals, immunosuppressive, and anti-inflammatory drugs. Anti-inflammatory drugs are widely used for oral disease therapy due to their ability to quench the underlying inflammatory pathways. Additionally, their analgesic and antipyretic effects relieve pain and fever, recurring symptoms of oral diseases. Despite their popularity, anti-inflammatory drugs have several systemic side effects i.e. osteoporosis, increased susceptibility to infection, hypertension, hyper-glycemia, and local side effects - such as mucosal lesions and gingival bleeding (Buchman 2001; Nagi 2014]. Anti-inflammatory drugs can mitigate inflammation and pain, but they can also cause oral disorders resulting in a lower quality of life if left untreated. Among them, non-steroidal anti-inflammatory drugs (NSAIDs), widely prescribed in different medical fields, including dentistry, because of their efficacy in reducing inflammation and pain, have been associated with the occurrence of lesions of the oral mucosa (Bilodeau et al. 2019; Nagi 2014; Singgih et al. 2020).



HOW CAN NSAIDs AFFECT ORAL DISEASES?

NSAIDs are one of the most commonly used classes of drugs for the treatment of inflammatory and painful conditions, (i.e. chronic pain, rheumatoid arthritis, postoperative pain).
This class of anti-inflammatory drugs acts as inhibitor of the two subtypes of cyclooxygenase (COX-1 and COX-2), enzymes involved in the biosynthesis of prostaglandins (PGs) from arachidonic acid. COX-1 and COX-2 have different functions and tissue distribution:

- COX-1 is constitutively expressed in most tissues and generates PGs for the body's housekeeping functions, such as the integrity of the gastric mucosal, platelet homeostasis, and the regulation of renal blood flow
- COX-2 is an inducible enzyme found predominantly in the kidneys and central nervous system. It synthesizes pro-inflammatory PGs that mediate pain and inflammation at the site of tissue damage



It is known that pro-inflammatory prostaglandins are involved in the pathogenesis of many oral diseases and this explains why this class of drugs is routinely prescribed in clinical dental practice (Nagi et al. 2014; Yang 1989). Even though the use of NSAIDs is widespread, their potential side effects must be taken into consideration. Best known adverse effects include ulcer formation and gastric haemorrhage, cardiovascular complications, and renal toxicity (Harirforoosh et al. 2013). In addition, oral health can be negatively affected by NSAIDs. Indeed, several studies outline the correlation between lesions of the oral mucosa - responsible for the perception of pain and discomfort - and administration of NSAIDs (Bagan et al. 2004; Healy and Thornhill 1995; Siegel and Balciunas 1991). The molecular mechanism leading to oral damage has yet to be fully clarified although a reduction in mucoprotective prostaglandins due to cyclooxygenase inhibition seems to be involved (Bilodeau et al. 2019). Nevertheless, NSAIDs remain the first choice in the treatment of inflammation and pain relief. Therefore, a therapeutic strategy that limits and/or eliminates NSAID-induced damage, such as oral mucosal lesions, may help improve the discomfort associated with their use and people's overall quality of life.

WHY RESORTING TO NON-DRUG TREATMENTS?

Over the past few years, it has become clear that oral health has a wide impact on overall health.
First-line treatments for oral diseases include non-pharmacological interventions such as effective daily oral hygiene with mouthwashes, fluoride-containing toothpastes and even plaque biofilm and tartar deposit removal through scaling and root planing (Wilder and Bray 2016). Nevertheless, oral inflammation is a common condition and anti-inflammatory drugs, particularly NSAIDs, remain widely used medicines in clinical dental practice as they can reduce oral inflammation and pain. However, they can also lead the occurrence of oral diseases (Buchman 2001; Nagi et al. 2014). Topical treatment of non-keratinized sulcular epithelium was found to deliver high concentrations of pharmacological agents to the periodontal tissue, gingiva, periodontal ligament, alveolar bone, and cementum (Casale et al. 2016). Recently, Sánchez-Fernández et al. showed that the topical application of high molecular weight hyaluronic acid (HMW-HA) in patients with peri-implantitis reduced inflammation and peri-implant crevicular fluid concentrations of the proinflammatory cytokine IL-1β suggesting that HMW-HA may be an effective therapeutic option to control the progression of this disease (Sánchez-Fernández et al. 2021). Hence, resorting to non-drug treatments might be a first line protection also for NSAID-induced oral damage.

WHY HIGH MOLECULAR WEIGHT HYALURONIC ACID?

HA is a natural and unbranched polymer belonging to a group of heteropolysaccharides called glycosaminoglycans (GAGs) diffused in the epithelial, connective and nervous tissues of vertebrates (Fraser et al. 1997). HA is major component of the ECM, particularly abundant during embryogenesis, in tissues undergoing rapid growth and development, during repair and regeneration, and in association with aggressive malignancies (Erickson et al. 2012). HA has many different functions, including maintenance of tissue homeostasis and cell surface protection, but it is also involved in many physiological processes, such as cell attachment, migration and proliferation, wound healing, and regulation of immune response and inflammation (Kavasi et al. 2017). High molecular weight hyaluronic acid (HMWHA) is deposited in normal tissues and interacts with other components of the ECM to control the ECM structural organization and signaling. In addition, endogenous HMWHA possesses enhanced anti-angiogenic, anti-inflammatory and immunosuppressive properties (Kavasi et al. 2017). The amphophilic nature of HMWHA allows this molecule to trap large amounts of water while binding to hydrophobic molecules such as cell membrane lipids. This property is relevant to the control of hydration and helps to delay the passage of viruses and bacteria through the hyaluronan-rich pericellular zone, as well as during inflammatory processes (Chen and Abatangelo 1999). Clinical studies have shown that HA accelerates the healing of various types of wounds, including burns, epithelial surgical wounds, and chronic wounds (Shaharudin and Aziz 2016).

Why Gengigel®?

Gengigel® is a specific and innovative treatment for gingivitis and periodontitis that relies on the action of its main component, HMWHA to make the product strongly bioadhesive, an effect that may be enhanced by using a calibrated mixture of additional glycopolymers. Because of its adhesive properties, Gengigel® sticks to the oral mucosa long enough to promote the activation of physiological tissue repair processes which improve the healing response and reduce healing time. In addition, the presence of high molecular weight hyaluronic acid helps Gengigel® maintain the balance of extracellular fluids and promotes the resorption of oedema in inflammatory conditions, rapidly reducing the associated pain. Last but not least, it protects the oral mucosa by preserving the micro-environment of the mucosal surface and by regularizing the growth of bacterial flora. The evidence on Gengigel® includes clinical data from high-quality prospective, comparative studies (Polepalle et al. 2015; Gupta 2017; Al-Shammari et al. 2018). The studies covered different Gengigel® indications, including treatment of clinical signs associated with periodontal disease or gingival inflammation following surgical periodontal therapy. In all cases, patients were treated with the gel formulation, either in a single application at the time of surgery, or with multiple applications following periodontal surgery/treatment. Gengigel® proved to be an effective treatment in controlling the inflammatory process and gingival bleeding at various stages of periodontal disease.

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