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COMMON NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND ORTHODONTIC PAIN

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ABSTRACT

Orthodontic therapy is associated with pain and discomfort, which usually appear at every stage of the treatment, causing patients to ask the dentist for a prescription with pharmacological agents or to resort to non-prescription drugs. This brief review summarizes some of the main characteristics for four non-steroidal antiinflammatory drugs (acetylsalicylic acid, acetaminophen, ibuprofen and meloxicam) frequently used to alleviate orthodontic pain, the first three of them having the advantage of being OTC drugs.

KEYWORDS: acetylsalicylic acid, acetaminophen, ibuprofen, meloxicam, orthodontic pain

INTRODUCTION

Pain is defined by the International Association for Pain Study (1994) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Being a subjective reaction, it presents large individual variations [1].

The main factors that influence it are age, sex, individual threshold of pain

supportability, emotional state, stress, cultural differences and previous painful experiences [2,3].

72% -100% of patients report the presence of pain during orthodontic treatment which reduces their health-related quality of life, speech and masticatory ability [4], this being one of the reasons for the therapy's discontinuation [4,5]. Fixed appliances were reported to be more painful than removable appliances [2].

The most frequently used medications are non-steroidal anti-inflammatory drugs (NSAIDs) [2,6], some of them, like acetylsalicylic acid, acetaminophen and ibuprofen, being easily accessible to patients as 'over the counter' (OTC) drugs [7].

ORTHODONTIC PAIN

Orthodontic pain is an inflammatory reaction initiated by orthodontic force-induced vascular occlusion followed by a cascade of inflammatory responses, including vascular changes, the recruitment of inflammatory and immune cells, and the release of neurogenic and pro-inflammatory mediators [8,9].

Expression of many biomarkers (cytokines, thrombospondin-1, pentraxin-3, matrix metalloproteinases, osteoprotegerin, TNF-α) was studied in gingival crevicular fluid during orthodontic treatment [10,11] to better understand the intricate processes generated under the mechanical stress, some of them being well known involved in the pathology of chronic inflammatory diseases [12]

Moments of pain occurring in fixed orthodontic therapy are: the onset of orthodontic treatment (both due to the application of the separation elastics for the mounting of the orthodontic rings and due to the dental movement itself from the initial stage); after reactivating the appliance; when intermaxillary elastics are used; when using temporary anchor devices (mini orthodontic implants); during and after removing the device (debonding) [13].

The initial phase of orthodontic dental movement always involves an acute inflammatory reaction [14,15], which translates clinically with difficulties in mastication and painful sensation. This first acute inflammatory process lasts for 1-2 days and is predominantly exudative, with plasma and leucocytes being extracted from capillaries in the areas of stress. It is followed by a chronic, mainly proliferative process involving fibroblasts, endothelial cells, osteoblasts and alveolar bone marrow cells [16].

Prostaglandin, TNF-α, interferon-gamma (IFN-γ), macrophage-colony-stimulating factors (M-CSF) and vascular

endothelial growth factor (VEGF) stimulate and amplify local inflammation in the incipient stages of orthodontic pain [17-20]. IL-6, TNF-α, IFN-γ and M-CSF are active in stimulating osteoblasts and osteoclasts that participate in alveolar bone remodelling and subsequent teeth movement [21,22]. M-CSF stimulates both the conversion of monocytes into macrophages and the recruitment and differentiation of osteoclasts, which increase local inflammation and painful sensation [20].

ACETYLSALICYLIC ACID

Acetylsalicylic acid (*aspirin*), first synthesised in 1853 [23], is the most used NSAIDs in history [23,24], not only for its analgesic and antipyretic effects, but also for its cardioprotective and antiplatelet properties when administered in a low-dosage (75-300 mg/day) [24].

Its mechanism of action is targeted on cyclooxygenase (COX) enzyme, binding irreversibly with both its isoforms [23] and inhibiting the secretion of prostaglandins, prostacyclin and thromboxane from arachidonic acid [24], therefore it has anti-inflammatory, antipyretic and analgesic effects, it reduces vasodilation and oedema, but it can also provoke gastric discomfort, dyspepsia, constipation, ulceration, sodium and fluid retention and cardiovascular adverse reactions [23-25].

Acetylsalicylic acid is rapidly hydrolysed in 15 minutes and absorbed from the stomach and upper small intestine, reaching the anti-inflammatory plasma salicylate level within 1-2 hours [26], after it undergoes a high hepatic first-pass metabolism [25].

Acetylsalicylic acid is promoted using various formulations as slow or fast release forms, enteric coated forms, effervescent or chewable forms, and even topic forms [25-27]. Tablets should be administrated just after they are removed from their packaging because acetylsalicylic acid degrades rapidly on contact with air, which could generate a smell of vinegar from its conversion to acetic acid crystals [25]. It is recommended always to take this drug sitting upright and with plenty of water, due to its irritant effect on the esophagus and its contribution in worsening gastroesophageal reflux [26].

Acetylsalicylic acid can also provoke dizziness, tinnitus, compensated respiratory alkalosis which represent a classic intoxication called salicylism [23,26] and is particularly contraindicated in children and young teenagers under 16 years old because it has a risk of 40% mortality determined by Reye's syndrome, a rare hepatic encephalitis [23,25,26]. Acetylsalicylic acid is also responsible for asthma-induced-reaction,

rhinitis, bronchospasm which develop more in middle-aged women [25,28] and Stevens-Johnson syndrome in adults, which is fortunately very rare [23]. It is not indicated in the third trimester of pregnancy as acetylsalicylic acid may cause premature closure of the fetal ductus arteriousus [25].

ACETAMINOPHEN

Acetaminophen or paracetamol is a first-line non-opioid, synthetic analgesic therapy for pain disorders [29], such as osteoarthritis in elderly patients due to its low cardiovascular risks and as dental or postoperative pain in children for its safety profile [24,25]. It is useful in mild to moderate pain such as headache, postpartum pain, myalgia [24,25], gout pain when it can be associated with uricosuric agents [25].

While acetylsalicylic acid is contraindicated for children [23,24,26], paracetamol is a safe alternative for viral conditions [26] and it is recommended not only as an analgesic, but especially as an antipyretic [23], under different flavours [25] as solutions and syrups for children and under various formulations such as suppositories for new-borns [26]. Acetaminophen can also be used in pregnancy for its action of relieving pain, lethargy, malaise and fever, as a benefit in comparison with acetylsalicylic acid [23,24].

It was synthesised more than a century ago [23] and was first discovered as a metabolite of phenacetin, a prodrug used once for its analgesic properties, but which proved to be highly nephrotoxic and was withdrawn [23,26]. This is why acetaminophen is considered to have very low potential for interactions with other drugs and an established efficacy profile [29].

Acetaminophen is not a true NSAID and it does not have anti-inflammatory action, because it does not inhibit COX-1 or COX-2, although it centrally inhibits through COX-3 the secretion of vasodilator and renal prostaglandins PGE_1 and PGE_2 [25,26,30], a mechanism which determines its antipyretic effect [30]. In addition, its analgesic effect is caused by a peripherical blockage of the chemoreceptors for bradykinin, a mediator involved in tissue oedema, irritation and inflammation [23,24,30,31]. Acetaminophen is well absorbed after oral administration, on an empty stomach [26], achieving a peak concentration after 2 hours [25]. It is used every 4 to 6 hours as 10-15 mg/kg/dose in children, not exceeding 60 mg/kg/day and as 650 mg/dose in adult, a maximum dosage of 4 g/day [25] should not be exceeded because it can cause hepatotoxicity through its toxic metabolite N-acetyl-p-bezoquinone imine (NAPQI) [24,25].

Specialists should make patients aware of the multitude of formulations which contain paracetamol such as cold and flu preparations or other OTC and should advise them to keep an appropriate control of the dosage, in order to avoid hepatic adverse reactions and even acute liver failure [25]. It is important to monitor heavy alcohol drinkers when administering OTC preparations because they are more susceptible to paracetamol poisoning [25]. Even though it is safer to administer paracetamol in pregnancy than acetylsalicylic acid, it can lead to asthma or allergic disease in children between 28 months and 7 years old [24].

IBUPROFEN

Ibuprofen was first introduced in 1960s [32] and it is one of the most commercialised non-prescription NSAIDs, after acetylsalicylic acid and acetaminophen, for its analgesic, anti-inflammatory and antipyretic effects [23,24] because its chemical structure is derived from propionic acid which means it is better tolerated [24,25]. Even though is inhibits both forms of COX, Reye's syndrome has not been reported, so ibuprofen is available in syrup form, with different flavourings [26] or chewable tablets for children and it can be used in viral conditions [25]. Those formulations can improve compliance in children [25].

Specialists recommend ibuprofen, which is a mixture of racemic substances [25], for adults, in 200-400 mg every 4-6 hours in acute painful conditions, postsurgical dental pain, osteoarthritis, musculoskeletal pain, migraines [23,24,26], and in doses of 2,4 g/day ibuprofen is equivalent to 4 g of acetylsalicylic acid in anti-inflammatory effect [26]. Food does not change its bioavailability, but it is highly hepatic metabolized, through the family of P450 liver enzymes, therefore caution is needed in patients with liver failure [24,25]. The adverse effects of ibuprofen are the classic ones for all NSAIDs which include: gastrointestinal disease, ulceration, oedema, dizziness, nervousness, rash, tinnitus, bronchospastic reactivity [25,26] but it is important to mention that gastrointestinal risk is lower than that with acetylsalicylic acid [23,25]. It is also mentioned that it has an increased prothrombotic activity which leads to higher cardiovascular risk [23,25].

MELOXICAM

Meloxicam is a modern NSAID [23], first introduced in 2000 [33], beneficial in all types of musculoskeletal and postoperative pain, a selective COX-2 inhibitor which provides good anti-inflammatory and

analgesic actions with less gastric damage and it is better tolerated [23,24]. Meloxicam is an enol carboxamide, a derived-oxicam chemical structure [24,25], and has the advantage of long half-life of 20 hours [25], one dose of 7,5 mg or 15 mg administered per day, but it takes longer time to reach a steady state and to relief pain [23,25,26]. Oxicams represent a group of the 1,2-benzothiazine compounds which were first synthesized in 1923 [33].

Meloxicam is used in acute or chronic inflammation associated with prostaglandin synthesis, but it has a different adverse reactions profile due to the fact that it inhibits with higher selectivity the inducible COX-2 [23,25]. Because of its special mechanism of action, meloxicam has higher safety upon gastrointestinal segment, decreases the production of vascular prostaglandin PGI_2 [25], but does not decrease the production of thromboxane TxA_2 at its usual doses, so on the other hand it can increase incidence of oedema and hypertension [24,25].

Some related structural compounds as rofecoxib and valdecoxib, previously marketed, were withdrawn because they increased cardiovascular thrombotic events [25,26], so there should be caution administering meloxicam in geriatric patients, with high risk of cardiovascular events [25]. On the other hand, they are safer than other classic NSAIDs like acetylsalicylic acid, ibuprofen or diclofenac, in elderly people regarding to hepatic function, gastrointestinal events and perioperative bleeding complications [34,35].

ACETYLSALICYLIC ACID, ACETAMINOPHEN, IBUPROFEN, MELOXICAM AND ORTHODONTIC PAIN

Despite all the adverse reactions and given their availability, NSAIDs are among most commonly used drugs, with approximately 30 billion OTC doses, administered annually in the United States [24]. NSAIDs are involved as mild pain-killers in the management of dental and orthodontic procedures as root canal treatment, operative procedures, extractions, stomatitis, gums lesions [27,36], and they can also be associated with topical anaesthetics [26].

Specialists recommend OTC acetylsalicylic acid 0.3 g - 1 g orally every 4 hours [25] as a treatment for acute mild-to-moderate dental or musculoskeletal pain, dysmenorrhoea, postoperative pain, headaches and even migraines [23,26,27].

There are people who prefer to apply acetylsalicylic acid tablets directly on the swollen gum, to avoid gastrointestinal adverse reaction due to oral administration, but it could provide local gum irritation and even

severe ulceration, so this method should be discouraged [26].

It is very important for doctors and pharmacists to alert patients to discontinue administrating acetylsalicylic acid (even if it is used in small thrombophylactic dosage) [23,24] seven days before planned dental surgery or any advanced dental procedures, in order to avoid increased bleeding [24,25,37].

Recently, a fast release acetylsalicylic acid formulation with the inclusion of sodium carbonate as desintegrant has been used in a study of comparison between same dosage of acetylsalicylic acid and paracetamol (1000 mg) and has demonstrated that meaningful dental pain relief was achieved in approximately 42 minutes for both analgesics [27].

Patients with acute dental pain or post-operative dental pain have recently benefited in clinical trials of combinations between ibuprofen and caffeine or acetaminophen, in fixed-dose formulas, which have proven a higher efficacy in relieving inflammatory signals and a higher concentration of the drug at the necessary site [32,38,39]. What is more important is that pre-medication in paediatric population with ibuprofen and acetaminophen, which have similar potential in pain reduction during teeth separation [40,41], can lower the pain levels after teeth replacement, which may encourage children to receive regular dental control [40].

In dentistry, acetaminophen is an analgesic as effective as acetylsalicylic acid or ibuprofen [42], and it has been recommended in the past years for orthodontic pain, after applying teeth separators [30]. Ibuprofen, another classic NSAID [24], can delay orthodontic movement besides relieving pain, so separators can turn out ineffective in first days, acetaminophen representing a better alternative [30]. Acetaminophen can substitute the need for NSAIDs in patients who suffer of gastrointestinal reflux or serious haemorrhage [23] and even though acetaminophen is an exception to the general NSAID ”stereotype”, it can be succesfully used in relieving dental inflammation, pain and swelling [23,25].

Intravenous meloxicam administered in maximum dosage of 60 mg has been safer and has proven a higher analgesic effect than oral ibuprofen in 400 mg dosage after dental impaction surgery [35]. There are no studies yet regarding the usage of meloxicam in pregnancy or in children, so it is not recommended to administer in patients under 18 years [25].

Meloxicam has a higher tolerability, efficacy and safety as an anti-inflammatory, analgesic and antipyretic agent than other classic NSAID and acetaminophen and it can

be used intraoperative or postoperative dental surgery, extractions, root canal procedures [25,26,35] and most important, it reduces the need for supplying with opioid analgesia [35].

Reducing pain also leads to the removal of anxiety associated with dental treatments [43], including orthodontic appliances, needed to correct dento-maxillary anomalies like deep bite syndrome, open occlusion syndrome and maxillar compresion syndrome with protrusion [44].

Increasing success in orthodontic therapy could be obtained with better pharmacological management of pain which is achieved by high patients' multiple medication adherence [45,46], and also through access facilitated by the reimbursement lists with small copayments range from 0% to 80% [47].

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