

# Drugs for pain management in dentistry

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## Abstract

Pain is one of the most common reasons patients seek dental treatment. It may be due to many different diseases/conditions or it may occur after treatment. Dentists must be able to diagnose the source of pain and have strategies for its management. The '3-D's' principle – diagnosis, dental treatment and drugs – should be used to manage pain. The first, and most important, step is to diagnose the condition causing the pain and identify what caused that condition. Appropriate dental treatment should then be undertaken to remove the cause of the condition as this usually provides rapid resolution of the symptoms. Drugs should only be used as an adjunct to the dental treatment. Most painful problems that require analgesics will be due to inflammation. Pain management drugs include non-narcotic analgesics (e.g., non-steroidal anti-inflammatory drugs, paracetamol, etc) or opioids (i.e., narcotics). Non-steroidal anti-inflammatory drugs (NSAIDs) provide excellent pain relief due to their anti-inflammatory and analgesic action. The most common NSAIDs are aspirin and ibuprofen. Paracetamol gives very effective analgesia but has little anti-inflammatory action. The opioids are powerful analgesics but have significant side effects and therefore they should be reserved for severe pain only. The most commonly-used opioid is codeine, usually in combination with paracetamol. Corticosteroids can also be used for managing inflammation but their use in dentistry is limited to a few very specific situations.

**Key words:** Dentistry, pain, analgesics, non-steroidal anti-inflammatory drugs, NSAIDs.

**Abbreviations and acronyms:** ACTH = adrenocorticotrophic hormone; CNS = central nervous system; NSAIDs = non-steroidal anti-inflammatory drugs.

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## INTRODUCTION

There are many reasons patients attend dental practices. These include regular check ups, scheduled visits for planned treatment, for advice about a problem, and because the patient is experiencing pain or other symptoms that concern them.<sup>1</sup> The presence of pain is perhaps the most common reason for an unscheduled visit to the dentist and most general dentists would probably see at least one or two patients with pain almost every working day.

Pain that leads a patient to seek dental advice or treatment may be a result of many different diseases or conditions of the dental, oral, facial or nearby structures. Dental-related pain may also occur after treatment by a dentist. Hence, dentists must be able to diagnose the source and nature of the pain and they must be familiar with strategies for the management of dental, oral, facial and post-operative pain.

The '3-D's' principle should always be used to manage pain in dental practice.<sup>2</sup> The '3-D's' should be followed in the correct order: (1) diagnosis; (2) dental treatment; and (3) drugs.

The first, and most important, step for managing pain is to diagnose the disease or condition causing the pain and to identify what has caused that disease or condition. The process of making a diagnosis should be considered as an 'information gathering' exercise. The information is obtained by taking thorough medical and dental histories, discussing the presenting problem in detail with the patient, carrying out a very thorough clinical examination and conducting the appropriate tests. The history and discussions with the patient should enable the clinician to formulate a provisional diagnosis so the clinical examination and diagnostic tests can be targeted towards confirming the diagnosis and identifying which tooth or other tissues are involved. It will not always be necessary to perform every possible diagnostic test, but clinicians should be sure to choose tests that are relevant to the presenting complaint. Once the information has been gathered, the clinician should collate it and decide on the definitive diagnosis. The diagnostic process requires that the dental clinician has a very thorough knowledge of the various diseases and conditions that may affect the oral and dental tissues, as well as the surrounding structures, and any systemic diseases that may manifest in the mouth.

The diagnosis of any disease or condition is incomplete if its cause has not been determined. The cause may be simple (such as caries for pulp disease) and may only require routine dental treatment or it may be complex (such as a medical syndrome or disease) and require management other than just dental treatment.<sup>3-6</sup> Identification of the cause of the disease is essential since the cause must be removed as an integral part (and usually the first stage) of the management of the disease. If the cause is not removed, clinicians should not expect to see full or rapid recovery from the presenting condition. In addition, if the cause is not removed the patient's presenting condition may be converted from an acute and painful condition to a chronic state with reduced or no symptoms but with

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the disease still present and slowly progressing. Indeed, pre-existing pain conditions serve as a risk factor for patients continuing to report pain after endodontic treatment, even under clinical conditions that suggest healing is occurring.<sup>7</sup>

Once the diagnosis and its cause have been established appropriate dental treatment can be undertaken. This will usually lead to rapid resolution of symptoms. The use of drugs to manage pain should be restricted to those situations that really do require them, and the drugs should only be used as an adjunct to the dental treatment.

The majority of painful dental problems that require analgesics will be due to inflammation of one of the oral, dental or associated tissues. This inflammation may be a result of various factors such as infection, trauma and following an operative procedure. If the pain is caused by infection, local dental treatment with or without antibiotics will be required. If the problem is purely inflammatory in origin, an anti-inflammatory drug would be indicated. In some cases, analgesics may be more appropriate, either alone or in conjunction with other medications. It is important to note that analgesics do not have any therapeutic effect on the underlying disease and they essentially only act by blocking the pain sensation being experienced by the patient. Hence, they should only be adjuncts to other treatment.

Drugs available for acute pain management belong to two major groups: the non-narcotic analgesics (e.g., non-steroidal anti-inflammatory drugs and paracetamol) and the opioids (or narcotics). The most commonly used non-narcotic analgesics in dentistry are aspirin, ibuprofen and paracetamol, all of which are available as 'over the counter' medications. The non-steroidal anti-inflammatory drugs (NSAIDs) are very useful and provide good to excellent pain relief. This is largely due to their combined anti-inflammatory and analgesic action. Paracetamol is a very effective analgesic but it has very little anti-inflammatory action. It is therefore not classified as an NSAID. The opioids are powerful analgesics but they have significant side effects and should be reserved for severe pain only. The most commonly used opioid in dental practice is codeine, usually in combination with paracetamol in commercial preparations. Corticosteroids are another group of drugs that can be used for managing inflammation (and hence pain) but their use in dentistry is limited to just a few very specific situations.

The remainder of this review article will discuss the important pharmacological aspects of the NSAIDs, paracetamol, opioids and corticosteroid drugs and will provide guidelines for dentists to use these drugs appropriately for the management of pain.

## Non-steroidal anti-inflammatory drugs (NSAIDs)

### Mechanisms

Despite more than 100 years of clinical experience with the prototypic NSAID aspirin, controversy persists

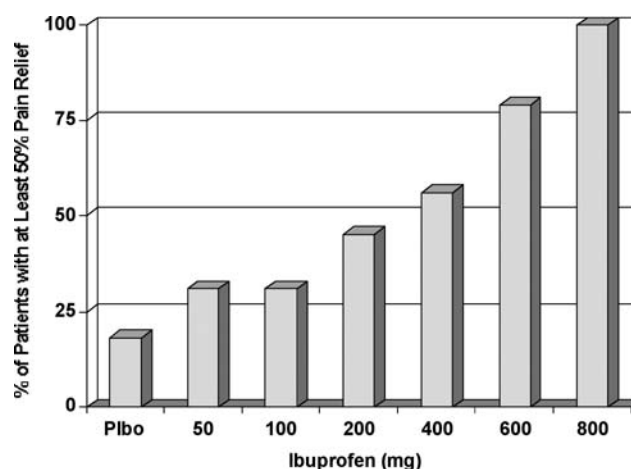


Fig 1. Dose-related analgesic effect of ibuprofen for treating acute inflammatory pain. Data are taken from the The Oxford League Table of Analgesic Efficacy<sup>37</sup> and represent a meta-analysis of randomized clinical trials where post-operative patients were treated with either placebo (Plbo) or with ibuprofen (50-800mg) and the results are plotted as the percentage of treated patients who report at least 50 per cent relief from their pain (N = 76 – 4700 patients/group).

over the mechanism(s) of action of these drugs.<sup>8</sup> A major hypothesis familiar to many clinicians is that NSAIDs produce analgesic and anti-inflammatory actions by inhibition of cyclo-oxygenase, thereby reducing the synthesis of arachidonic acid metabolites such as prostaglandins and thromboxanes.<sup>8</sup> However, more recent studies suggest that this important class of analgesics has other actions including inhibition of free radical formation, cytokine synthesis or major cellular signaling pathways mediating inflammatory responses.<sup>9,10</sup> Recognition of these multiple mechanisms has led to the appreciation that the NSAIDs may have other important therapeutic indications such as inhibition of the growth of cancers.<sup>11,12</sup> This area of research is rapidly expanding and given the recent recognition of adverse effects attributed to the COX-2 inhibitors,<sup>13</sup> it is likely to continue as a major area of scientific inquiry.

### Trials/efficacy

Prostaglandins play a key role in the development of inflammation and pain. Therefore it is predictable that the NSAIDs have clinical efficacy for reducing acute dental pain and inflammation. In support of this point, numerous double-blind placebo-controlled clinical trials have demonstrated that the NSAIDs are effective for reducing pain due to surgical,<sup>14-17</sup> periodontal<sup>18,19</sup> and endodontic<sup>20-29</sup> procedures. Moreover, systematic reviews of these studies<sup>20,21</sup> support the clinical recommendation that NSAIDs should be the analgesics of first choice in patients who can tolerate this class of drugs.<sup>2</sup>

Many NSAIDs – including ibuprofen,<sup>18,22,23,30-32</sup> aspirin,<sup>33,34</sup> diflunisal,<sup>35</sup> etodolac,<sup>35</sup> mefenamic acid,<sup>33</sup> ketoprofen,<sup>15,22</sup> ketorolac<sup>27,28</sup> and flurbiprofen<sup>26</sup> – have been shown to produce significant reductions in dental pain using randomized, double-blind placebo-

controlled clinical trials. However, for purposes of this review, ibuprofen will be selected as a commonly used standard for NSAID treatment of acute dental pain.

Since ibuprofen has been evaluated in many clinical trials, a wealth of data is available about its analgesic efficacy. In general, there is no difference in analgesic responses to ibuprofen between male and female patients when managing post-operative pain.<sup>36</sup> Meta-analyses indicate that ibuprofen produces greater analgesia than paracetamol/codeine combinations.<sup>17</sup> Another meta-analysis of ibuprofen<sup>37</sup> indicated that it produces a dose-related analgesia over the range of 200-800mg, as shown in Fig 1. Thus, increasing the dose of ibuprofen will produce an increasing magnitude of analgesia. Of course, adverse effects are also dose-related. A prudent clinician must balance the analgesic needs of their patient with the risk of producing adverse effects.

Ibuprofen is readily absorbed after oral administration and peak blood levels occur about one to two hours after ingestion.<sup>38</sup> Recent studies suggest that ibuprofen kinetics are strongly associated with a genetic polymorphism of the liver enzyme cytochrome P450, with patients having the CYP-2C8 and CYP-2C9 polymorphisms exhibiting a reduced ability to clear ibuprofen (and, therefore, possibly having an increased risk of experiencing adverse effects of ibuprofen).<sup>39</sup> Although genetic testing is not routinely conducted for this polymorphism, there is an increasing recognition of the importance of each patient's particular genotype in modifying their response to medications. This knowledge is likely to have increasing impact on clinical care in the future.

Ibuprofen has been evaluated in several different formulations. One recent modification is the use of gel caps that provide faster absorption and therefore a quicker onset for meaningful analgesia that occurs about 25-30 minutes after ingestion.<sup>15,40-42</sup> Another recent advance in formulation includes a muco-adhesive patch that permits intra-oral delivery of ibuprofen.<sup>43</sup> Other modifications to ibuprofen include the addition of other drugs such as hydrocodone or oxycodone (which enhances ibuprofen analgesia but with a concomitant increase in adverse effects)<sup>30,44</sup> and paracetamol (1000mg) to ibuprofen (600mg). This latter combination has been shown to significantly improve pain relief after endodontic treatment when compared with ibuprofen (600mg) alone.<sup>23</sup> This increase in ibuprofen-related analgesia has been observed in several clinical pain models.<sup>45</sup>

### **Adverse effects**

Although the NSAIDs are extremely effective for the management of acute dental pain, several adverse effects can occur. The adverse effect profile of the acute administration of ibuprofen includes gastro-intestinal complaints and somnolence.<sup>46</sup> Acute (3-day pre-operative) administration of ibuprofen does not appear to produce any detectable increase in post-operative

bleeding as measured by the occurrence of a haematoma or ecchymosis following third molar extraction.<sup>31</sup> Evidence exists to suggest that a cumulative consumption of NSAIDs (but not aspirin) over a lifetime increases the risk of end-stage renal disease.<sup>47</sup> In addition, recent studies suggest that the COX-2 inhibitors, and possibly some of the traditional NSAIDs, may produce prothrombic cardiovascular effects.<sup>48</sup>

### **Summary of pharmacology**

NSAIDs such as ibuprofen are effective for treating acute pain and inflammation related to endodontic, surgical, restorative or periodontal procedures.

### **Recommended drugs, doses and regimes**

Ibuprofen should be considered the drug of first choice for management of acute inflammatory pain in patients who can tolerate this class of drug. Conventional oral formulations are very effective over a dose range of 200-800mg (not to exceed a total daily dose of 3200mg). Although the 800mg dose produces maximum analgesic effects, clinicians should only consider this dose if the benefit for treating severe intense pain outweighs the increased risks of adverse effects. Under most conditions, 400-600mg of ibuprofen taken every six hours is very effective for treating moderate inflammatory pain. Rapid absorption formulations (for example, ibuprofen in gel caps) may have particular applications in clinical conditions involving emergency pain patients and the combination of 600mg of ibuprofen with 1000mg of paracetamol taken every six hours increases pain relief compared with ibuprofen taken alone.<sup>23</sup>

### **Paracetamol and paracetamol-opioid combinations**

#### **Mechanisms**

Paracetamol (also known as acetaminophen in some countries) acts primarily in the central nervous system (CNS) although neither the site nor the mechanisms of action have been clearly established.<sup>49</sup> It has analgesic and anti-pyretic effects, and it is a weak inhibitor of the cyclo-oxygenase sub-groups COX-1 and COX-2. Paracetamol readily crosses into the cerebrospinal fluid. Within the CNS it works by inhibiting prostaglandin synthesis in the hypothalamus, preventing release of spinal prostaglandin and inhibiting nitric oxide synthesis in macrophages. At therapeutic doses it does not inhibit prostaglandin in the peripheral tissues so there is very little, if any, anti-inflammatory action.<sup>49,50</sup>

#### **Trials/efficacy**

Paracetamol has been used extensively in many trials that have documented its efficacy and demonstrated that higher doses are more effective than lower doses. For example, 1000mg of paracetamol taken every six hours produced analgesia comparable to ibuprofen (600mg taken every six hours) after surgical extraction of impacted third molar teeth<sup>34</sup> and a systematic review

of randomized clinical analgesic trials (with over 1000 patients/group) indicated that paracetamol used in doses of 975-1000mg produced a 28 per cent improvement in the relative analgesic benefit when compared with lower doses (600-650mg) of paracetamol.<sup>52</sup>

Paracetamol can be combined with codeine (an opioid – see below) for greater analgesia.<sup>51</sup> Commercial preparations are available with varying amounts of codeine added to the paracetamol – typically 8mg, 9.75mg, 10mg, 15mg or 30mg combined with 500-600mg paracetamol. At least 25-30mg of codeine<sup>51</sup> is considered to be required for effective analgesia so the efficacy of the lower dose preparations is somewhat uncertain, if at all effective, especially if a preparation containing only 8-10mg is used since typically patients take two tablets for a total of only 16-20mg of codeine. However, if the compounds containing 30mg codeine are used, very effective analgesia can be obtained with a combination of actions from the paracetamol and the codeine (especially if a double dose is taken as is usually required to have adequate paracetamol for pain relief).

The addition of doxylamine, an antihistamine with a 'calmative' action, can further increase the effectiveness of analgesia obtained with paracetamol/codeine compounds.<sup>51</sup> The exact mechanism of action is not clear although it is likely to be due to a combination of actions – the antihistamine helping to reduce inflammation as well as helping the patient to cope better due to its calmative action.<sup>51</sup>

### **Adverse effects**

Since paracetamol is metabolized in the liver, patients with liver disease need to take care. Paracetamol can cause liver damage, even with normal therapeutic doses, but fortunately this is rare.<sup>49,50</sup> Other patients who may have increased toxicity are those with a high alcohol intake and those taking enzyme-inducing drugs (e.g., anti-epileptics and rifampicin).<sup>50</sup>

Recent research suggests a relationship exists between the toxicity of chronic paracetamol (end-stage renal disease) and the history of lifetime consumption of the drug.<sup>47</sup> Less is known about toxicity and dosage interval or duration of acutely administered doses although it appears more likely to be toxic if the daily dose exceeds 4000mg in adults. Despite this, it has been suggested that the use of 6000mg per day for a short period of time may have therapeutic benefit without unduly increasing risks.<sup>47</sup>

Paracetamol may cause prolongation of prothrombin time in patients taking anticoagulants and it can occasionally cause urticarial or erythematous skin rashes, fever or blood dyscrasias.<sup>49</sup>

An overdose of paracetamol is defined as a single dose of more than 100mg/kg of body weight. Overdose will produce hepatotoxicity, hypoglycaemia and acute renal tubular necrosis.<sup>50</sup> In adults, a dose of 7.5-15mg/kg is considered potentially toxic. The smallest fatal dose recorded in adults was 18mg/kg.<sup>50</sup> Overdose

should be considered as a medical emergency and the patient should be admitted to hospital for urgent treatment.

### **Summary of pharmacology**

Paracetamol is rapidly absorbed from the stomach so its peak blood levels are reached within 30-60 minutes.<sup>49</sup> It is non-toxic at therapeutic concentrations – usually reaching 5-20 micrograms/ml in plasma, compared to its toxic concentration of 150 micrograms/ml.<sup>50</sup> Elimination half-life is about two hours and protein binding is insignificant.<sup>49</sup> It is metabolized in the liver and the metabolites are excreted via the kidneys.<sup>49</sup> Tolerance and dependence have not been reported, and paracetamol does not cause the same gastric irritation or the other complications associated with aspirin and other NSAIDs.<sup>49,50</sup>

### **Recommended drugs, doses and regimes**

There are numerous brands and formulations of paracetamol commercially available and most are available 'over the counter'. Typical preparations contain 500mg of paracetamol in tablet or capsule form, but syrups, elixirs and suppositories are also available. The usual recommended adult dose of paracetamol is 500-1000mg every four to six hours (up to a maximum of 4000mg per day).<sup>50</sup> Modified dosing schedules apply to some preparations as they may be 'slow-release' formulations.

Paracetamol is one of the most common analgesics used in children. The recommended dose for children is 15mg/kg orally every four hours.<sup>50</sup> The maximum daily dose should be limited to 90mg/kg up to a total of 4000mg. It can also be used rectally in children with a dose of 20mg/kg.

### **Paracetamol and codeine compounds**

There are several brands and formulations of these compounds available. Most contain 500mg of paracetamol but the amount of codeine varies and could be 8mg, 9.75mg, 10mg, 15mg or 30mg. The dose used is usually based on the paracetamol component but dentists should be cognizant of the presence of the codeine and its possible side effects so it should not be ignored. Typically, a dose of 500-1000mg of paracetamol would be used and this implies two tablets/capsules for most commercial preparations. If two tablets are used this implies that the codeine dose would be doubled. The same precautions and contraindications apply to the compound preparations as those that apply for paracetamol and codeine when either drug is used alone.

Doxylamine is added to some paracetamol + codeine preparations for increased analgesia. The usual dose of doxylamine in commercially-available preparations is 5mg. Patients being prescribed this triple compound should be warned of drowsiness and they must be advised not to drive a car and not to operate machinery.



They should also be advised to avoid work or other situations where they need to be fully alert. The recommended doses to be used are the same as above for paracetamol and the paracetamol + codeine combination.

## **The opioids (narcotics)**

### **Mechanisms**

The opioids produce analgesia by activation of opioid receptors. Three major families of opioid receptors have been cloned: the mu, kappa and delta opioid receptors.<sup>53</sup> The mu opioid receptor is activated by most clinically used opioids including codeine, hydrocodeine, oxycodone, hydrocodone, tramadol and morphine. The kappa opioid receptor is activated by drugs such as pentazocine and buprenorphine. No currently approved drugs are selective for the delta receptor. Opioid analgesia occurs by activation of opioid receptors expressed on neurons in supraspinal sites, spinal sites and in peripheral tissue.<sup>2,52</sup> In general, the opioid receptors are thought to inhibit neuronal activity and their analgesic efficacy is attributed in part to the observation that opioid receptors are expressed at most of the major pain processing areas in the central nervous system. Consequently, systemic administration of opioids produces analgesia by inhibiting pain transmission at multiple areas in the neuraxis.

Opioids are well recognized to produce variable responses in patients, with some patients reporting considerably greater analgesia than others, even after administration of identical doses. The variability in patient response is an important clinical problem and forms the basis for recommendations that analgesics be prescribed based on patient report rather than on prior expectations of the clinician.<sup>2</sup> The basis for this variability in analgesia is unclear but it is thought to involve both environmental (e.g., psychosocial status, secondary gain, etc), pathophysiological (e.g., liver function, enzyme/receptor expression) and genetic factors. Considerable interest has been raised by pharmacogenetic analysis of opioid analgesia. For example, patients with certain polymorphisms to the cytochrome P450 enzyme (i.e., CYP 2D6) are completely resistant to codeine analgesia (since they cannot convert codeine to morphine), and they are partially resistant to tramadol analgesia.<sup>54</sup> In addition, several polymorphisms to the opioid receptors have been discovered and are associated with altered responses to opioid analgesics or altered reports of pain intensity.<sup>54-56</sup> Gender is another interesting genetic factor associated with altered opioid responsiveness. Several studies have reported that women demonstrate significantly greater analgesia to kappa opioids (e.g., pentazocine) than men.<sup>57</sup> In addition, a meta-analysis of third molar extraction studies concluded that women report significantly greater pain levels compared with men.<sup>36</sup> Given these factors, clinicians should prescribe drugs based on the patient's reported pain levels. Although a patient's report of pain is not an exact

value, it is a useful alternative to prescribing fixed doses to all patients as this invariably leads to some being over-medicated and others experiencing unnecessary pain due to being under-medicated.

### **Trials/efficacy**

Numerous clinical trials have evaluated the analgesic effects of opioids including codeine, tramadol, oxycodone, pentazocine etc. For the purposes of this review, codeine and tramadol will be selected as prototype opioids. When used in dose ranges appropriate for ambulatory patients, both of these drugs should be considered only as adjunctive analgesics and not as primary analgesics. In one meta-analysis, the administration of 60mg of codeine produced only a 15 per cent analgesic response (i.e., 15 per cent of 1305 patients reported at least 50 per cent pain reduction) and this response did not differ from a placebo tablet (18 per cent response in >10 000 patients).<sup>37</sup> In this same meta-analysis, tramadol produced dose-related analgesia at 50mg (19 per cent of 770 patients reported at least 50 per cent pain relief), 75mg (32 per cent of 563 patients reported at least 50 per cent pain relief), 100mg (30 per cent of 882 patients reported at least 50 per cent pain relief), and 150mg (48 per cent of 561 patients reported at least 50 per cent pain relief).<sup>37</sup> These figures should be compared with 200mg of ibuprofen which produced a 45 per cent analgesic response in 1414 patients.<sup>37</sup> Since NSAIDs are generally well-tolerated, there is strong support for the conclusion that ambulatory acute dental pain patients are best treated with NSAIDs or paracetamol as the primary analgesic and the addition of a narcotic should be reserved for situations when additional analgesia is required but where substantially increased side effects are likely.<sup>58</sup>

Opioids are frequently combined with paracetamol<sup>59</sup> or more recently with ibuprofen in treating acute dental pain. The combination of 600-650mg of paracetamol with 60mg of codeine produces very effective analgesia in post-operative pain patients.<sup>58,60</sup> In one meta-analysis, there was a 38 per cent analgesic response in 1886 patients given 600-650mg of paracetamol alone (response defined as 50 per cent of greater reduction in pain), whereas the addition of 60mg of codeine increased the analgesic response to 42 per cent in 1123 patients.<sup>37</sup> Thus, these opioids should only be considered adjunctive analgesics.

Tramadol used alone,<sup>61</sup> combined with acetaminophen<sup>62-66</sup> (i.e., paracetamol) or co-administered with flurbiprofen<sup>26</sup> produces significant analgesia, although questions regarding its use and effectiveness have been raised in the Australian and New Zealand literature.<sup>67,68</sup>

### **Adverse effects**

The adverse effect profile of the opioids is well recognized and includes nausea, emesis and respiratory depression.<sup>66,67,69</sup> Concern has also been raised about opioid abuse and its impact in the dental setting.<sup>70</sup>

### **Summary of pharmacology**

Opioids are highly effective analgesics but they also have a concomitant high incidence of side effects. In the clinical setting of treating ambulatory acute dental pain, opioids are used in low dosages that provide relatively minor adverse effects at the cost of reduced analgesia. Given their relative ratio of therapeutic benefits versus risks, the opioids should not be considered as the analgesic of first choice in this setting. Instead, opioids should be used as adjuncts to non-narcotics that are given at maximally effective dosages (i.e., 1000mg paracetamol). A meta-analysis of the analgesic literature supports this last point. In one meta-analysis there was a 42 per cent analgesic response in 1123 patients given 600-650mg of paracetamol with 60mg of codeine (response defined as 50 per cent reduction in pain), whereas increasing the non-narcotic dosage to 1000mg of paracetamol combined with 60mg of codeine increased the analgesic response to 57 per cent in 197 patients.<sup>37</sup>

### **Recommended drugs, doses and regimes**

Given the above data, the general recommendation is to consider opioids as adjunctive drugs. Patients who can tolerate NSAIDs such as ibuprofen should be first given maximally effective doses based on the patient's pain report. Patients who cannot tolerate NSAIDs should be given paracetamol combinations with codeine as discussed above.

### **Corticosteroids**

Systemic corticosteroids are rarely indicated in dentistry but they can at times be useful for the management of inflammation. Their use should be reserved for situations where the correct diagnosis has been made, the dental treatment has been provided adequately, no other anti-inflammatory medication has helped and the medical history does not reveal any contraindication to their use. They should also only be used when there are no signs of infection and no possibility of an infection developing. Such situations include emergencies (adrenal crisis, anaphylaxis and allergic reactions), severe post-operative swelling, following severe trauma, periapical nerve sprouting and acute apical periodontitis following removal of an acutely inflamed pulp, severe muscle inflammation associated with temporomandibular dysfunction, and for some oral ulcerations and mucosal lesions that cannot be managed with topical medications.<sup>71</sup>

### **Mechanisms**

Corticosteroids can be either glucocorticosteroids or mineralocorticosteroids. Only glucocorticosteroids inhibit immune and inflammatory responses, therefore the latter group will not be discussed in this review. Cortisol is the primary glucocorticoid and it is produced and secreted by the adrenal cortex. Its release is regulated by a complex pathway known as the hypothalamic-hypophyseal portal system which

produces adrenocorticotrophic hormone (ACTH).<sup>72</sup> Several synthetic glucocorticoids have been produced and their relative activity and potency vary. Prednisone and prednisolone are four times more potent as anti-inflammatory agents than cortisol, whilst triamcinolone is five times more potent and dexamethasone is 25 times more potent. The adrenal cortex produces approximately 10mg/day of cortisol in non-stressed adults and under severe stress this may increase more than 10-fold.<sup>72</sup>

Glucocorticoids act to reduce inflammation by inhibiting the production of multiple cells and factors involved in the inflammatory response (see Marshall<sup>72</sup> for a full review). They decrease vasoactive and chemoattractive factors, decrease secretion of lipolytic and proteolytic enzymes, decrease extravasation of leukocytes to areas of tissue injury and decrease fibrosis. Glucocorticoids also act against the immune response by inhibiting cytokine production. The multiple sites of action of the glucocorticoids has been proposed as the reason for their greater anti-inflammatory and, possibly, greater analgesic effects than the NSAIDs which typically are more selective and only act on one site.<sup>72</sup>

Glucocorticoids have been shown to be very effective in reducing the periapical inflammatory response following endodontic treatment,<sup>73,74</sup> and studies have shown anti-inflammatory effects in untreated irreversible pulpitis.<sup>75</sup> They have also been shown to reduce bradykinin levels and post-operative pain<sup>76</sup> and oedema in the oral surgery third molar extraction model used in many pain studies.<sup>72</sup>

### **Summary of pharmacology**

The glucocorticoids circulate in the blood with 90 per cent or more being reversibly bound to plasma protein. The half-life of cortisol is about 90 minutes and the synthetic forms vary (e.g., prednisone – 60 minutes, prednisolone – 200 minutes, triamcinolone – 300 minutes, dexamethasone – 300 minutes). Metabolism takes place in the liver and they are excreted in the urine.<sup>72</sup>

When glucocorticosteroids are taken systemically, they can potentially affect many organ systems and tissues. However, such effects are usually only associated with supraphysiological doses taken over a long period of time (usually more than two weeks). Schimmer and Parker have stated that 'a single dose of glucocorticoid, even a large one, is virtually without harmful effects and a short course of therapy (up to one week) in the absence of any specific contraindications is unlikely to be harmful'.<sup>72</sup>

### **Trials/efficacy**

Many studies have been reported in the dental literature to report the efficacy of corticosteroids in the reduction of pain, especially post-endodontic treatment. Some of these have used topical, or intra-dental, routes of administration whilst others have used

oral or parenteral routes. Topical and intra-dental uses have been reported to be very effective, and usually better than the comparative regimes of other medicaments and/or oral drugs in reducing post-operative pain in many studies.<sup>77-83</sup> Systemic administration of steroids has been reported in several studies<sup>84-86</sup> using prospective, randomized, double-blind placebo-controlled study designs. All of these studies reported significant reductions in post-operative pain at various time intervals and they also reported that there was significantly less need for additional analgesic medications.

### Adverse effects

Clinicians must be aware that corticosteroids not only reduce inflammation but they also suppress the immune response. This may have adverse effects on the patient's health and well-being. Wherever possible, the topical use of corticosteroids is preferred since the immunosuppressive effects are much less severe.<sup>72</sup>

The glucocorticosteroids should be avoided in patients with systemic fungal infection and known hypersensitivity to the drug being prescribed.<sup>71,72</sup> They should be used with caution in patients with ulcerative colitis, pyogenic infections, diverticulitis, peptic ulcers, diabetes mellitus, ocular herpes, acute psychosis and tuberculosis. They can cause mild psychological disturbances such as euphoria, insomnia and nervousness but can also cause severe problems such as manic depression and schizophrenic psychosis. These problems are usually related to the size of the dose and the duration.<sup>71,72</sup>

It is important for the dentist to monitor the patient's progress whilst taking corticosteroids since many oral and dental inflammatory conditions are the result of, or are associated with, an infection of some kind (i.e., bacterial, fungal or viral) which may rapidly exacerbate once the inflammatory and immune responses have been suppressed by the corticosteroid. Conditions not resolving within a few days may also warrant referral for specialist assessment and management.

### Recommended drugs, doses and regimes

A simple and relatively safe corticosteroid that can be used for oral and dental inflammatory conditions is dexamethasone. It should only be used as an adjunct to dental treatment and not as the sole means of managing the pain. Dexamethasone is available as 4mg tablets. The usual oral dosing regime is an 8mg loading dose, followed by 4mg every eight hours for two to three days up to a maximum of five days. If the problem has not improved within this time period, then the dentist should review, and possibly revise, the diagnosis and consider other treatment strategies and whether some other condition may be the cause of the inflammation.

### Dose regimens

When attempting to manage a patient's pain via pharmacologic means, clinicians should appreciate that

the presence of pain increases the probability of further pain developing due to the complex neural pathways and the release of various neuropeptides. This hypersensitivity reaction generally occurs centrally but it is due to peripheral input.<sup>87</sup> Hence, it is easier, and better for the patient, to prevent pain rather than to allow it to develop and then try to control it. As a result, if it is predictable that the patient will suffer pain (e.g., post-operatively), pre-emptive pain relieving medication should be prescribed. The minimum effective dose should be used and the drug should be taken at the appropriate regular intervals as a 'course' of medication rather than on an 'as needed' basis. Hence, prescriptions should not be written with the term '*prn*' (i.e., *pro re nata*). Rather, prescriptions should stipulate the appropriate dose and frequency, including the maximum daily dose. The use of medications on an 'as needed' basis should be reserved for severe new pain or breakthrough pain in a patient already taking analgesics on a regular basis.<sup>87</sup>

### CONCLUSIONS

The ability to effectively manage pain represents a critical skill of the prudent practitioner. Pain management strategies include the '3-D' approach that provides a systematic way of evaluating and managing the acute dental pain patient using combined non-pharmacologic and pharmacologic strategies. This review has focused on oral analgesics as a component of the pharmacologic strategy for pain control following the establishment of the diagnosis and the delivery of appropriate dental treatment. From this perspective, patients should be treated with NSAIDs or paracetamol (for those patients who cannot tolerate NSAIDs) as the 'first choice' drugs at doses that are proven to be effective in the literature and with a perspective of balancing the patient's analgesic requirements with the potential for adverse effects. Opioids should be considered adjunctive drugs that act to enhance overall analgesia at the cost of increased adverse effects. Corticosteroids can be used in specific situations where the pain is inflammatory in origin, where there is no infection and where there are no contraindications to the chosen drug being used.

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