

# Combination ibuprofen and acetaminophen analgesic products for dental pain management

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Combination analgesic products have been the mainstay of treatment of moderate to severe dental pain for many years. Formulations containing both an opioid analgesic, such as oxycodone, and a non-opioid analgesic, such as acetaminophen, are widely used in dentistry and have demonstrated greater efficacy in providing pain relief than either ingredient used individually.<sup>1</sup> However, since an opioid analgesic ingredient may increase the risk of adverse effects such as central nervous system depression, respiratory depression, and gastrointestinal upset, combination analgesic products that contain only non-opioid ingredients are attractive alternatives.

Non-opioid analgesics useful in the treatment of dental pain include acetaminophen (Tylenol) and nonsteroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen). Many patients believe that since these agents are available without a prescription, they are inferior to analgesics available only by prescription in their ability to relieve dental pain. However, many studies have concluded that the opposite is true.<sup>2,3</sup> In addition, recent studies have demonstrated the potential advantages of a product which combines these 2 ingredients.<sup>4,6</sup>

Acetaminophen is often referred to as *APAP*, an acronym for its chemical name (N-(4-*acetyl*)-p-aminophenol), or as *paracetamol* outside the United States. It has analgesic and antipyretic activity that is equivalent to that of aspirin, but very weak anti-inflammatory effects when compared with aspirin or NSAIDs. Although acetaminophen is not a true anti-inflammatory drug, it can be effective in treating pain resulting from inflammation. While its exact mechanism of action is not fully understood, it is thought that acetaminophen, like aspirin and the NSAIDs, inhibits prostaglandin synthesis. However, there is evidence that acetaminophen may be much more active in the central nervous system as a result of multiple unknown mechanisms of action.<sup>7</sup>

For patients in whom aspirin and NSAIDs are contraindicated, acetaminophen is usually the drug of choice. The most serious adverse effect associated with the use of acetaminophen is drug-induced hepatotoxicity due to acute or chronic overdose of the drug.

When used as monotherapy, acetaminophen has been shown to be a superior analgesic for the relief of postoperative pain.<sup>2</sup> Acetaminophen at a 1000 mg dose has been shown to be more effective than placebo in reducing pain after third molar extractions.<sup>8</sup> However, especially at high doses, acetaminophen's analgesic effect is limited in the treatment of moderate to severe postoperative pain resulting from other types of dental procedures.<sup>2,9</sup>

Acetaminophen has long been considered the "safe" analgesic because it produces few side effects at typical adult doses, though studies have demonstrated some clinically significant drug interactions and adverse drug reactions. It has been shown

that at high doses acetaminophen may interact with warfarin, resulting in a significantly higher internationalized normal ratio (INR).<sup>10</sup> In addition, while it is well known that acetaminophen may cause acute liver toxicity in supratherapeutic doses, even high therapeutic doses of acetaminophen may still result in sub-clinical liver injury.<sup>11,12</sup>

This information suggests that acetaminophen's analgesic effect would be optimized and its potential for producing adverse reactions and drug interactions minimized if it were used in lower doses. This would perhaps be possible in combination with another analgesic, such as an NSAID.<sup>13</sup> Such a combination would improve analgesic efficacy without increasing the risk of adverse drug reactions.

NSAIDs themselves have long been considered first line therapy in the treatment of dental pain. NSAIDs inhibit the formation of cyclooxygenase-2 (COX-2), the enzyme responsible for the production of certain prostaglandins which, in turn, produce pain, fever, and inflammation. Unfortunately, NSAIDs also inhibit the formation of cyclooxygenase-1 (COX-1), the enzyme responsible for the production of other prostaglandins which are responsible for numerous beneficial effects, such as the production of the gastrointestinal mucous lining, regulation of normal platelet activity, bronchodilation, and maintenance of adequate blood flow to the kidneys. As in the case with acetaminophen, the therapeutic and adverse effects of NSAIDs are dose-related, and the use of lower doses in a combination product would be considered advantageous.<sup>13,14</sup>

There is no definitive evidence to support the conclusion that one NSAID is superior to another in its ability to relieve dental pain. Studies have demonstrated that NSAIDs are equally efficacious compared to acetaminophen and acetaminophen/codeine in reducing pain after dental surgery.<sup>15,16</sup> There is a substantial amount of evidence which shows that the NSAID ibuprofen, at 200 mg and 400 mg doses, is an effective pain reliever, equal or superior to acetaminophen in treating postoperative dental pain.<sup>3</sup> Numerous studies comparing ibuprofen to placebo found that ibuprofen provided greater pain relief in patients with moderate to severe postoperative dental pain and with similar adverse effects.<sup>3</sup>

Monotherapy with ibuprofen has been shown to be equal or superior to monotherapy with acetaminophen in the management of dental pain.<sup>3</sup> However, because monotherapies may provide incomplete pain relief, combinations of these 2 analgesics have been researched extensively.<sup>13,14</sup> Acetaminophen and ibuprofen have similar yet different mechanisms of action, so a combination of the 2 agents may offer a synergistic approach to pain relief.<sup>13</sup> Although there is as yet no nonprescription analgesic product available in the US that combines acetaminophen with ibuprofen, studies have compared combinations of acetaminophen with various NSAIDs.<sup>4</sup>

Historically, the therapeutic superiority of the combination of acetaminophen and ibuprofen over either drug alone was controversial, but current evidence now suggests that a combination of acetaminophen and ibuprofen may offer superior analgesia compared with either monotherapy.<sup>17</sup> In a 2010 study by Mehlich et al, concurrent ibuprofen and acetaminophen appeared to provide significantly better analgesic efficacy compared with ibuprofen or acetaminophen alone for acute postoperative dental pain in adolescents and adults.<sup>5</sup> Daniels et al found that a single-tablet combination of ibuprofen (200 mg)/acetaminophen (500 mg) provided highly effective analgesia that was comparable with or superior to other combination analgesics currently indicated for strong pain.<sup>6</sup> In another 2010 study by Mehlich et al, ibuprofen (200 mg)/acetaminophen (500 mg) and ibuprofen (400 mg)/acetaminophen (1000 mg) were significantly more effective than comparable doses of ibuprofen or acetaminophen alone in treating moderate to severe acute dental pain and were significantly more effective than placebo in providing sustained pain relief.<sup>18</sup>

Several nonprescription combination analgesics contain caffeine. While caffeine is not thought to possess any analgesic properties on its own, in combination with traditional analgesics such as acetaminophen, ibuprofen, and aspirin, it is believed to enhance analgesic efficacy. Studies have demonstrated that the addition of caffeine to these analgesics provided an increase in the number of patients who experienced improved pain relief.<sup>19</sup> As a result, a combination analgesic containing acetaminophen and ibuprofen that contains caffeine as an adjunct may improve the efficacy of the product.

Such acetaminophen and ibuprofen combination products would not be without risks. It has been reported that among elderly patients requiring analgesic/anti-inflammatory treatment, use of a combination of acetaminophen and an NSAID increased the risk of GI bleeding compared with either agent alone.<sup>20</sup> Additionally, a recent warning by the FDA notified health care professionals and patients that acetaminophen has been associated with a risk of Stevens-Johnson syndrome, and toxic epidermal necrolysis.<sup>21</sup> The use of NSAIDs has also been associated with the risk of these rare but serious skin reactions, so a product which combines both of these ingredients may theoretically increase this risk.<sup>22</sup>

Combining 2 analgesic agents with similar yet different mechanisms of action may offer a synergistic approach to providing dental pain relief while minimizing adverse effects. Recent studies have consistently demonstrated that a combination analgesic containing acetaminophen and ibuprofen is more effective in treating dental pain than the individual ingredients when administered alone.

## Author information

In addition to his daily practice in the pharmacy profession, Mr. Viola is also an educator, published author, and professional speaker in the fields of dentistry, dental hygiene, and dental assisting.

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