Applications of ibuprofen

Ibuprofen

Ibuprofen is a nonsteroidal anti-inflammatory drug used for many purposes and is one of the most commonly used medications worldwide. Some of the reasons for which it is used include fever, pain, and inflammation. It was discovered in 1961 by Dr. Stewart Adams and launched in the United Kingdom in 1969 as Bufrin and launched in the United States in 1974 as Motrin; ten years later ibuprofen was approved for over-the-counter sale in the United States by the Food and Drug Administration and became the second nonsteroidal anti-inflammatory drug after aspirin to be available in this manner (1). Prior to this, pain relief was with aspirin and acetaminophen, both of which had been in use for many years. The discovery and development stemmed as a result for Dr. Adams' search for an alternative to aspirin, looking to find a drug with a higher potency and better toleration, particularly with the gastrointestinal system; he reported that his initial self-testing involved taking ibuprofen for a hangover with resulting relief (1). Dr. Adams intended to develop a drug that could be used to treat rheumatoid arthritis; corticosteroids were being used to treat the condition but there were many undesired side-effects, thus the search for a nonsteroidal alternative. Aspirin was helpful for rheumatoid arthritis but the aforementioned side effects involving the gastrointestinal system (damage to the gastric lining) created a desire for something better. Currently, ibuprofen is said to be one of the safest nonsteroidal anti-inflammatory drugs available (2).

Nonsteroidal anti-inflammatory medications generally work by inhibiting the cyclooxygenase (COX) enzymes (2). These enzymes are involved in

prostaglandin synthesis (COX enzymes convert arachidonic acid to prostaglandin H_2 which is then converted to other prostaglandins by various enzymes) (2). Prostaglandins are pain, fever, and inflammatory mediators and the inhibition of their synthesis is what leads to relief in patients who use these medications. Ibuprofen in oral form is the most common form, however it is also available in topical, intraocular, intravenous, intramuscular, and rectal forms. There are rapid release tablets and extended release forms available commercially (2). Ibuprofen in oral form is rapidly absorbed in the GI tract; peak concentrations in plasma and serum are seen within 3 hours of drug intake (2). In patients that were fasting extended release forms of ibuprofen were seen to be absorbed through the whole GI tract with the large bowel being the location that showed the highest level of ibuprofen absorption (2). In patients that had food prior, the extended release tablet stayed in the stomach and dissolved more slowly over a time period of seven to twelve hours (2). This resulted in slow increases in small bowel levels (2). Regardless of food intake, there was no difference in drug availability (2). Delayed in stomach emptying, caused by numerous factors including high sugar intake, can lead to delays in ibuprofen absorption (2). Topical ibuprofen leads to higher levels in fascia, muscles, and subcutaneous tissues (2).

Ibuprofen is generally found as a racemic mixture with both R and S enantiomer forms (2). In vivo, The R-enantiomer converts to the S-enantiomer; it is this form that is thought to be the more active form (2). This conversion occurs through a series of enzymes; acyl-CoA-synthetase converts the R-enantiomer to (-)-R-ibuprofen I-CoA, 2-arylpropionyl-CoA

epimerase converts the (-)-R-ibuprofen I-CoA to (+)-S-Ibuprofen I-CoA, and hydrolase converts the (+)-S-Ibuprofen I-CoA to the S-enantiomer (2). The rate of ibuprofen absorption can affect the rate of this conversion; the longer the ibuprofen remains in the conversion site, the more likely that the level of conversion will increase (2). Additionally, the bioavailability of the S-enantiomer was seen to be dose dependent (2). Either of the enantiomeric versions given alone reached higher maximum concentrations more rapidly than after the same dose of the racemic mixture however no major differences were seen in the pharmacokinetics (2). The brain is the site of fever reduction by ibuprofen; during the conversion of the R-enantiomer, R-ibuprofen I-CoA is formed which is highly lipophilic (2). This can cross the blood-brain-barrier and then convert into the S-enantiomer which is not as lipophilic (2).

Distribution volume increases with increasing dosages of ibuprofen with these volumes suggesting significant protein binding of the drug; it is bound to human plasma and albumin (2). Ibuprofen is distributed in the synovial fluid as high concentrations are seen following intake; concentrations were higher in serum than in synovial fluid for up to two and a half hours after intake but afterwards most patients and higher levels seen in the synovial fluid (2). It was seen that protein binding with ibuprofen occurred at higher levels in plasma than in the synovial fluid; this is because albumin and total protein concentrations are higher in plasma than in the synovial fluid (2). After topical application of ibuprofen, it was demonstrated that concentrations high enough to inhibit prostaglandin synthesis in

subcutaneous tissue, tendons, muscles, and joints were found similar systemic levels of the drug (2).

Along with the previously mentioned conversion of enantiomeric forms of ibuprofen, it is metabolized in the body forming various hydroxyl, carboxyl, and glucoronyl metabolites, all of which have virtually no pharmacological purpose; the most important catalyst in the formation of these metabolites is cytochrome P450 (2). Acyl glucuronides are metabolized from ibuprofen in conjunction with glucuronic acid; plasma concentrations of glucuronide in older patients are 4% of the initial concentration (2). Toxicity and other reactions (including anaphylaxis and other allergic reactions) are thought to be caused by bonding of the glucuronide to plasma protein (2). Ibuprofen has also been seen to be metabolized into 2, 4-carboxyphenylpropionic acid, which was found in dialysis fluid of kidney-failure patients (2). Patients with reduced renal function have been shown to have diminished clearance of ibuprofen (2).

General excretion of a drug and its metabolites occurs in both urine and feces. Following oral intake of ibuprofen, about eighty percent of the dosage is found in urine as the hydroxyl and carboxyl metabolites however some studies report this to be lower; it was initially reported that the amount excreted in urine was closer to 60% of the dose (2). The amount of ibuprofen excreted in urine was not significantly different between doses given intravenously and orally; the amounts were approximately 81% and 87% respectively (2). For oral doses, the percentage of initial dose excreted in urine did not differ dependent on dose for doses between 100mg and 1200mg—again, approximately 80% of the initial dose was excreted (2). It

had been thought for many years that ibuprofen is excreted in breast milk due to the high amount of protein binding but research actually shows that low levels of the drug are found in breast mild; infant exposure via breast milk is minimal and the American Academy of Pediatrics says that there are no contraindications to mothers using ibuprofen while breastfeeding (2). Overall clearance of ibuprofen from the body is dose dependent (2).

As mentioned previously, ibuprofen inhibits the activity of the COX enzymes which subsequently inhibits prostaglandin synthesis; clinical data has shown that the S-enantiomer inhibits the activity of COX-1 and COX-2 equally while the R-enantiomer inhibits COX-1 at a much lower rate than the S-enantiomer and shows no inhibition of COX-2 (2). This inhibition of the COX enzymes is non-selective and reversible (2). Ibuprofen has a recommended adult daily dosage of 200 to 400mg ever six hours. It has a large therapeutic range between ten to fifty mg/L and toxic levels over 100mg/L; high doses taken regularly for four years can result in serum levels of 50 to 100 mg/L (2). The half-life for ibuprofen is approximately two hours; to keep plasma concentrations at therapeutic levels, frequent dosing is often necessary (using extended release forms can limit the amount of times a patient needs to take the drug) (2). The half-life did not appear to be dependent on disease states except in cases of diabetes mellitus and high blood pressure, which both appeared to prolong the half-life of ibuprofen (2). Therapeutic responses within a normal range are often dose dependent as the pain relief offered by the medication is dependent upon serum levels; maximum pain relief was seen in various studies when serum concentrations were at the highest levels—this was seen approximately one hour post drug intake (2).

According to numerous studies, age (in children) did not cause differences in absorption rates, plasma concentration, or elimination of ibuprofen however the concentration in synovial fluid appears to be higher in younger patients than in adults after one dose (2). In elderly patients, the half-life of ibuprofen appears to be higher in some studies however when adjusted for body weight, these differences were found not to be significant; elderly patients also showed a lower clearance rate of the drug than younger patients (2). Other studies refuted this claim and stated that older ages have only small influences on the pharmacokinetics of the drug (2).

Dental procedures, such as root canal therapy (including initial treatment and non surgical retreatment) and apical surgery, initiate an inflammatory cascade that is mediated by prostaglandins previously mentioned. Among endodontists, ibuprofen (600mg four times per day) is the most commonly prescribed and recommended medication post-treatment when compared with acetaminophen and various narcotic medications (3). Additionally, due to the inflammatory nature of tooth pain, in clinical situations where patients presented in pain but no treatment was rendered, ibuprofen was again the most commonly recommended medication for management (3). Other studies from other specialties of dentistry and medicine have similar recommendations; 400 to 800mg of ibuprofen three or four times per day are recommended for inflammatory situations (2).

Endodontic treatment is sought after to relieve pain that is caused by bacterial invasion—this results in inflammation and infection. As mentioned earlier, treatment may result in diminished pain however residual symptoms may linger due to inflammation. An endodontist is involved in not only this

treatment, but management of symptoms and situations post operatively. Nonsteroidal anti-inflammatory medications such as ibuprofen play a vital role in the management of pain after routine procedures. For endodontic patients, preoperative pain is a very high indicator for post-operative pain resulting from inflammation; many studies show that ibuprofen is effective for this post-operative management—meta analysis concluded that both ibuprofen and a combination of ibuprofen and acetaminophen are more effective than placebo at six hours (4). The combination of ibuprofen and acetaminophen was not shown to be significantly different from ibuprofen alone (4). Among the endodontic literature, differences in results occur readily. A 2004 study had differing results from the findings mentioned and found that a combination of ibuprofen and acetaminophen was more effective than ibuprofen alone for the management of post-operative pain resulting from endodontic procedures; due to the anti-inflammatory effects of ibuprofen it is generally thought to be better at management of post-operative pain than acetaminophen alone (5). The prudent practitioner will use his/her best judgement and take into account a patient’s medical history, other medications/allergies, and the potential need for medication to manage post-operative symptoms prior to making recommendations or prescriptions.

Ibuprofen has been used for many years to manage pain in endodontic patients. In fact, its efficacy has been shown to be so good that it can mask symptoms and make diagnosis difficult (6). Accurate diagnosis is the first step to an endodontic procedure and if symptoms are masked and cannot be replicated, diagnosis is impossible. A study from the University of Minnesota

showed that ibuprofen altered testing in vital teeth by masking palpation 40% of the time, percussion 25% of the time, and cold testing 25% of the time on teeth with symptomatic irreversible pulpitis and symptomatic apical periodontitis however a “ bite stick” test did not seem to be affected (6).

Ibuprofen has a proven track record, is efficient and safe, and has many purposes. Its use in dentistry has been well researched and in the field of endodontics is the number one medication prescribed and recommended to patients who can tolerate it for post-operative pain. Its anti-inflammatory effects have led to its use for other conditions such as acne and Parkinson’s disease (2). Future research may look into more efficient forms (perhaps forms that don’t require enantiomeric conversion) or other anti-inflammatory medications with similar effects for patients who cannot tolerate nonsteroidal anti-inflammatory medications for one reason or another. For now, endodontists will continue to rely on ibuprofen as the first line medication for pre and post-operative symptoms associated with endodontic pain.

References

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