Safety and Efficacy of Ibuprofen in Children: A Review

By

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

The thesis was completed without doing any unethical acts. This study does not involve with any animal or human trials.

Abstract

This study aims to compile data from numerous recent investigations on the pharmacological characteristics, therapeutic applications, and safety of ibuprofen. Ibuprofen is frequently used to treat fever, discomfort, and inflammatory symptoms around the world. The evidence regarding ibuprofen's modes of action is examined in light of the drug's effectiveness on reducing fever, pain, and inflammation as well as its negative side effects. Considering the recent restriction for codeine in children under the age of 12, there aren't many pharmaceuticals permitted to relieve pain in these individuals. The most popular medications for this purpose are paracetamol and the NSAID ibuprofen. This overview's objective was to evaluate ibuprofen's therapeutic applicability in children based on its pharmacological characteristics. The effectiveness and adverse effects related to the use of ibuprofen as an analgesic in the pediatric population have been the subject of a critical assessment of the paediatric literature over the past 20 years. Children who experienced musculoskeletal pain, ear pain from acute otitis media, toothaches, and inflammatory diseases of the mouth and throat found relief from pain with ibuprofen. The medication provides a suitable and effective substitute for pain relief following surgery, including tonsillectomy and adenoidectomy. Ibuprofen has minimal side effects and unpleasant reactions. Although rare instances of GI toxicity may happen, it has the lowest gastrointestinal (GI) toxicity of all NSAIDs. In a clinical setting where an inflammatory pathophysiology is present, the decision on the medication to be taken in cases of fever or pain should be made in favor of ibuprofen.

Keywords: Ibuprofen; Pain; Children; Anti-inflammatory; Analgesia; Adverse reactions.

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Dedication

This paper is dedicated to my dear parents.

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List of Acronyms

OTC	Over-the-counter

NSAID	Nonsteroidal anti-inflammatory drug
CV	Cardiovascular
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
GI	Gastrointestinal
ADME	Absorption, distribution, metabolism, and excretion
CYP2C8	Cytochrome P4502C8
CNS	Central nervous system
CSF	Cerebrospinal fluid
PGe2	Prostaglandin E2
PGI2	Prostaglandin I2
EMA	European Medicine Agency
FDA	Food and Drug Administration
ED	Emergency department
PED	Pediatric emergency department
AOM	Acute otitis media
JIA	Juvenile idiopathic arthritis
GFR	Glomerular filtration rate
BUN	Blood urea nitrogen

JRA	Juvenile rheumatoid arthritis
ASA	Acetylsalicylic acid
GAS	Group A -hemolytic Streptococci

Chapter 1 Introduction

1.1 Background

Ibuprofen is an analgesic, antipyretic, and anti-inflammatory drug that has been widely used to reduce fever, relieve pain and treat inflammation. Ibuprofen belongs to the class of non-steroidal anti-inflammatory drugs and is a non-prescription over-the-counter (OTC) used to relieve the symptoms of acute pain, fever, and inflammation. OTC ibuprofen is probably the least toxic compared aspirin and paracetamol (Moore et al., 1999). Ibuprofen the mildest NSAID with the fewest adverse effects that have been clinically used for a long time Ibuprofen was first made available by prescription only in the UK in 1969 and then throughout the world in the 1970s (Ashraf et al., 1999). Starting doses of ibuprofen can be as low as 400 mg and the maximum prescribed dose of ibuprofen is up to 2,400 mg per day for the relief of musculoskeletal pain and inflammation, and other painful conditions (Rainsford, 2009). In the 1970s it was often prescribed either as a first-line NSAID or as a substitute drug therapy for aspirin, indomethacin, or phenylbutazone for treatment of arthritic conditions as it showed greater therapeutic efficacy and lower gastrointestinal adverse effects (Altman et al., 2015). One of the defining characteristics of ibuprofen's early success and the growing assurance that it was safe based on cautious use (Rainsford, 2009). Ibuprofen is associated with xtremely rare adverse reactions (e.g., Stevens-Johnson and Lyell's syndromes, renal or hepatic failure, necrotizing fasciitis), as well as some that are more typical to the class of NSAIDs (Rainsford, 2009). The most recent of these are cardiovascular (CV) conditions, which were brought to light by the occurrence of myocardial infarction and cardio-renal symptoms in patients taking the more recent class of NSAIDs, the coxibs [rofecoxib, valdecoxib, and to some extent celecoxib (Ostor & Hazleman, 2005). This led to

regulatory organizations all over the world looking into the possibility that all NSAIDs could produce a CV and cardio-renal symptoms, a factor that is still a cause for worry for some coxibs and other NSAIDs. Newer NSAIDs have also presented several challenges, particularly the 20 to 30 new NSAIDs introduced between the 1970s and the 1980s and the widely publicized introduction of the selective cyclooxygenase-2 (COX-2) inhibitors (coxibs) in 1999. COX-2 has later identified as the primary prostaglandin synthesizing enzyme expressed in inflammatory and pain pathways (Bjarnason et al., 2007). Surprisingly, over half of the NSAIDs introduced to the clinic since the 1970s have been withdrawn mostly due to unacceptable and unpredictable toxicities. In this context, ibuprofen has overcome these obstacles of the negative effects of other drugs' failures and related safety issues, specifically the risks raised by the coxibs. These problems have primarily affected NSAIDs available exclusively by prescription, while they may also have affected NSAIDs sold over-the-counter (OTC). Acetaminophen, also known as paracetamol, has been a significant rival, particularly in the OTC market (Peterson, n.d.-a), in the treatment of osteoarthritis. Ibuprofen and paracetamol are equally efficient at reducing fever in non-prescription OTC pediatric use, however, the current research indicates that a combination of these two medications may be especially helpful in really painful or febrile illnesses (Hay et al., 2008). Ibuprofen and paracetamol may have additive or even synergistic effects because of their conceivably different mechanisms of action. The usage of paracetamol is linked to fewer gastrointestinal (GI) and renal side events than those seen with ibuprofen and thus the combined use may be more effective in reducing pain with reduced side effects of ibuprofen in children (Bjarnason et al., 2007).

Of note, NSAIDs such as naproxen and ketoprofen have been rivals to ibuprofen and both of these medications have greater anti-inflammatory and prostaglandin inhibitor potencies compared to ibuprofen but are linked to a higher risk of severe upper GI responses (Milsom

et al., 2002). Therefore, in this context, ibuprofen stands as a more preferred option by physicians as a pain reliever for children. In general, over the 4 decades from the launch of ibuprofen as a prescription drug and the more than 2 decades following its introduction for over-the-counter sale, ibuprofen has proven to be safer and more effective with reduced adverse effects compared to other NSAIDs and pain-killers.

1.2 Rationale and Aim of the Review

Ibuprofen at low doses (400 mg to 1200 mg) is associated with lower possibilities of serious gastrointestinal (GI) adverse effects with a much lower chance of developing hepatic disease, especially the irreversible liver damage observed with the use of paracetamol and negative effects that arise from the use of aspirin. The favourable pharmacokinetic properties of ibuprofen, particularly the short elimination half-life of the drug, with no production of pathological metabolites (e.g. covalent modification of liver proteins by the quinine–imine metabolite of paracetamol or irreversible acetylation of biomolecules by aspirin) thus resulting in low toxicity with ibuprofen use make ibuprofen a more feasible option for use in children. The combined action of ibuprofen in reducing inflammation by inhibiting the enzymes cyclooxygenase COX-1 and COX-2 with lower residence time within the body resulting in reduced side effects such as low GI, cardiovascular and renal risks overall highlights the efficacy and safety of ibuprofen use, especially in children.

Therefore, the current review aims to provide an overview of the pharmacological properties and mechanism of action of ibuprofen along with its clinical use, overall highlighting its efficacy and safety for reducing pain, fever and inflammation in children.

Chapter 2: Pharmacodynamic & Pharmacokinetics of Ibuprofen

2.1 Pharmacodynamic characteristics

Ibuprofen was developed in 1969 as a safer alternative to aspirin and is the first member of the propionic acid derivative class of NSAIDs. Despite new molecular findings, it continues to be the most often used and prescribed NSAID in both the adult and pediatric populations. Over time, it rose to the top spot for both prescription and over-the-counter NSAID use. (Davis et al., 2017). Ibuprofen is a combination of stereoisomers. Its composition is split evenly between R(-) ibuprofen, a less potent prostaglandin synthesis inhibitor, and S(+) enantiomer, the pharmacologically active prostaglandin inhibitor(Dawood & Khan-Dawood, 2007). Approximately 40–50% of the R(-) enantiomer consumed orally undergoes metabolic conversion into the active S(+) form in the liver and intestine. However, the presence of the R (-) isomer may help partially explain the drug's excellent safety profile by contributing to its pharmacological capabilities, particularly its anti-inflammatory properties. It is understood that NSAIDs' effectiveness is due to their ability to inhibit cyclo-oxygenase-1 and cyclo-oxygenase-2 (COX-1 and COX-2), which catalyze the conversion of arginine to prostaglandins. The production of pain, heat, and inflammation is then aided by prostaglandins. Arachidonic acid is used by COX-1 and COX-2 to produce prostaglandin H. This product is further altered by several enzymes to produce bioactive prostanoids like prostacyclin, thromboxane A2, and prostaglandins D2, E2, and F2. These prostanoids have an impact on reproductive, immunological, cardiovascular, gastrointestinal, and renovascular function (Ostor & Hazleman, 2005), (Figure 1). Ibuprofen is a non-selective balanced inhibitor of the inducible COX-2 enzyme as well as the constitutive COX-1 enzyme. The widespread consensus is that most cells contain COX-1, which is accountable for prostanoids' (PGs, tromboxaneA2) production. Numerous physiological processes, such

as blood flow, gastric and renal function, as well as hemostasis, are regulated by prostaglandins. The main source of prostanoids involved in inflammation and pain is COX-2, which is activated by cytokines, shear stress, and cancer-promoting agents. However, both enzymes help to produce prostanoids, which play a significant role in physiology (Dawood & Khan-Dawood, 2007). The dose range of ibuprofen currently being used causes the inhibition of both COX-1 and COX-2 >80%, according to in vitro and in vivo tests. This suggests a direct link between the medication effect and the inhibition of prostanoid production. Ibuprofen, however, has a competitive and reversible inhibitory effect on both cyclooxygenase (COX) isoforms. This applies to side effects as well. When ibuprofen is digested and removed, the reversibility of the inhibition allows for a quick restoration to constitutive prostaglandin synthesis. This will restore their activities in tissues like the kidneys and stomach, hence lowering the risk of adverse ibuprofen effects (Carmody & Charlton, 2013).

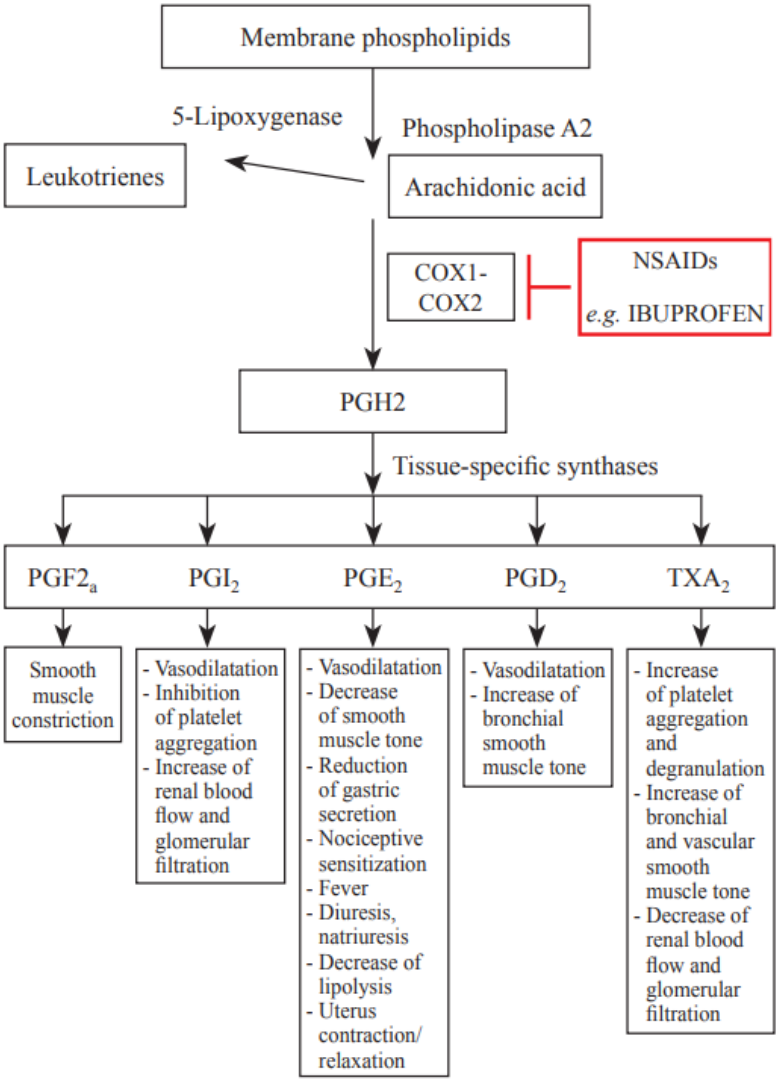

Figure 1: *Pharmacodynamic Characteristics of arachidonic acid metabolism, and site of action of ibuprofen (Rainsford, 2009).*

2.2 Pharmacokinetic profile of oral ibuprofen

Ibuprofen's pharmacokinetics have been extensively studied in adults and have been rather well described in pediatric patients as well. There are no significant changes in the pharmacokinetics and antipyretic effects of ibuprofen between children >3 years old and adults, despite the possibility that the physiological development of newborns and children may have a significant impact on the ADME of medications (Har-Even et al., 2014). Ibuprofen's half-life, volume of distribution, and clearance all change over time (with increasing values) starting in the newborn period and continuing until children's ages 1-3 years, when they start to take on adult values. Ibuprofen's pharmacokinetics and antipyretic impact in infants and children were researched by Kauffman et al., who concluded that these effects were not affected by age (Ziesenitz et al., 2017). The patient's age has a big impact. It appears that there are no significant variations between children and adults in the pharmacokinetics and antipyretic effects of ibuprofen. Ibuprofen is well absorbed from the upper GI tract when taken orally, and in children who are fasting or have an empty stomach, peak plasma levels can be reached in under an hour (45 minutes). Ibuprofen absorbs more slowly and inconsistently if taken after meals, and the peak plasma concentration is reached between one and two hours later. Recent studies indicate that earlier peak concentrations and faster absorption may result in more effective symptom alleviation. To lower the danger of stomach irritation and erosion, it is crucial to reconsider taking ibuprofen with meals (Bjarnason et al., 2007).

At therapeutic doses, ibuprofen is extensively (>98%) bound to whole human plasma and purified albumin. One of the reasons for the relatively reduced risk of GI problems compared to other NSAIDs may be due to the drug's very short plasma half-life (t1/2 of about 2 hours). Children's elimination half-lives are shorter than those of newborns (de Martino et al., 2017).

As evidenced by the decreased S+ levels recorded in comparison to adults, it has been reported that the conversion of R- to S+ is changed in newborns younger than 6 months of age. However, a recent study by Ziesenitz14 evaluated the safety and efficacy only in a juvenile population under 6 months of age, and it concluded that, despite certain pharmacokinetic differences, the medication can be safely taken if dosed taking into account body weight (Ziesenitz et al., 2017). Ibuprofen is metabolized primarily via the P450 cytochrome enzyme complex (Cyp2C8, Cyp2C9, and Cyp2C19), as well as by glucuronic acid conjugation.

Within 24 hours of the previous dose, the metabolites are then eliminated through the kidneys. None of the metabolites have been discovered to be poisonous or to have any pharmacological effects. This indicates a lack of build-up risk for active metabolites. Ibuprofen's capacity to enter the CNS and its presence in free (i.e., non-protein bound) quantities in the CSF are both important pharmacokinetic characteristics of its analgesic and antipyretic effects (Har-Even et al., 2014).

Chapter 3 Therapeutic Applications of Ibuprofen in paediatrics

3.1 Ibuprofen in pediatric fever management

An adaptive physiological response is a fever. The body's response to exogenous and endogenous pyrogens is an increase in temperature, which is thought to be beneficial in infectious, inflammatory, and neoplastic disorders because it enhances the body's response. Over 30% of requests for child medical examinations are related to fever, even though fever is a common clinical sign in the pediatric age and its degree does not immediately correlate with the clinical severity and/or importance of the causative etiology (Chiappini et al., 2017). For this reason, even though recommendations specify that antipyretics should only be used to treat young patients' feelings of malaise (perceived as anguish or discomfort), medication use in cases of pyrexia remains consistent during the early years of life. Ibuprofen and paracetamol are the only antipyretics for children that are advised (Lesko et al., 2001). Because of the high cost-benefit ratio, the possibility of side effects, and the risk of masking underlying infectious, inflammatory, or malignant diseases and delaying the diagnosis, acetylsalicylic acid is not recommended for the risk of Reye's Syndrome (a serious, potentially fatal condition characterized by encephalopathy and liver disease) (Hay et al., 2008).

Ibuprofen, an antipyretic, has demonstrated quickness of action (starts working in just 15 minutes), the persistence of the impact up to 8 hours, and efficacy in the treatment of malaise brought on by a rise in body temperature, notably in the first 24 hours (Shepherd & Aickin, 2009)

3.2 Ibuprofen as analgesic

Acute pain is a common symptom of diseases in children. Children are especially vulnerable to inadequate pain management. Untreated childhood pain has been linked to long-term concerns like anxiety, hyperesthesia, and fear of receiving medical treatment as well as short term issues like slower healing. Due to difficulties in evaluating it and their dread of taking painkillers, children's pain is frequently underdiagnosed and later undertreated. This is also true for ibuprofen, where under dosage is common, as evidenced by various statistics (Ichihara et al., 1999)

The effectiveness of NSAIDs as analgesics depends on both their anti-inflammatory activity and their capacity to delay or reverse peripheral sensitization. A variety of stimuli, including heat, pressure, and acid, can activate nociceptors, which are specialized peripheral terminals of primary afferent fibers (Ichihara et al., 1999). When tissue is injured or inflamed, certain non-neuronal cells release prostaglandins including PGe2 and PGI2 that lower nociceptors' activation thresholds and result in peripheral sensitization. The peripheral component of NSAIDS' analgesic benefits is based on the reversal of peripheral sensitization brought on by inflammatory mediators. Ibuprofen can therefore start working right away to reduce peripheral nociceptor sensitivity and to start lowering the inflammatory response that would otherwise result in more pain. Furthermore, it has been proposed that COX-1 and COX-2 play a crucial role in the transmission of nociception in the spinal cord (Walker & Carmody, n.d.).

The drugs used to treat acute pain in children are split into opioids, which should only be used in cases of moderate-to-severe pain, and not opioids (paracetamol and NSAIDs), which should be used in cases of mild-to-moderate pain. The etiology of the pain (nociceptive, neuropathic, psychogenic, mixed), its duration (acute or chronic, episodic or recurrent), and

the concomitant clinical factors must all be taken into account when choosing a treatment plan (deficiency of metabolization or elimination) (Barbagallo & Sacerdote, 2019). There are a variety of factors to be considered, including the anticipated length of the therapy and how well the child and family will adjust to it. The administration method should be as straightforward and pleasant as feasible (the oral route is typically the first one suggested for children). Limiting the occurrence of predictable pain as much as feasible during treatment involves giving analgesics at predetermined times when necessary. A pain-relieving strategy should be set up, comprising therapy at regular intervals, and one based on the use of reinforcement or rescue dosages. This plan will be determined based on the severity of the suffering and the length of the medication's pain-relieving effect (Kokki, n.d.). Ibuprofen is increasingly being used to treat pain in children, especially those who are "fast metabolizers," while also taking into account the mounting evidence of potential side effects of opioid use in children (sedation, risk of respiratory depression, nausea and vomiting, constipation). Due to recorded incidences of obstructive sleep apnea in youngsters after tonsillectomy, the European Medicine Agency (EMA) has restricted the use of codeine to children older than 12 years. Additionally, a recent FDA warning advised against using codeine in teenagers between the ages of 12 and 18 who are obese or have illnesses like severe lung disease or obstructive sleep apnea, which may raise the risk of life-threatening breathing issues (Da et al., 2011). Children who experience acute pain most frequently have a sore throat, ear pain, headache, toothache, post-traumatic musculoskeletal pain, arthritis, and pain following surgery. Ibuprofen is the NSAID that has been examined the most for the treatment of acute pain in children in general as it displayed a good safety profile and showed efficacy. When a sustained inflammatory component is present, it has generally been observed to be at least as effective as paracetamol or even more effective. It must be noted that paracetamol has no anti-inflammatory effects while ibuprofen has both anti-

inflammatory properties with pain-killing effect.

Ibuprofen and paracetamol both had similar reported mild adverse effects, according to a systematic review that evaluated the safety profiles of three groups of oral medications, including paracetamol, nonsteroidal anti-inflammatory drugs, and opioids, to manage acute nonsurgical pain in children (18 years) treated in ambulatory settings (Da et al., 2011). Ibuprofen is the only NSAID that can be used in 3-month-old newborns even though other NSAIDs are also authorized for use in children (for example, ketoprofen over 6-year-old children). Ibuprofen should be taken orally in doses of 10 mg/kg every 6 to 8 hours to treat acute pain; the maximum cumulative daily dose is 30 mg/kg.

3.3 Musculoskeletal pain

Bruises, sprains, fractures, and other acute musculoskeletal traumatic injuries are among the most common reasons for admitting kids to emergency rooms. Ibuprofen has proven to be effective in the treatment of post-traumatic musculoskeletal pain in youngsters. In a study, 336 children aged 6 to 17 with pain from a musculoskeletal injury (to the extremities, neck, or back) that occurred within the previous 48 hours before presentation in an emergency room were given single oral doses of paracetamol (15 mg/kg), ibuprofen (10 mg/kg), and codeine (1 mg/kg) (Clark et al., 2007). At 60 minutes, patients in the ibuprofen group experienced a pain score improvement that was noticeably greater than those in the codeine and paracetamol groups. However, after 30 minutes, there was no discernible difference between the three groups. In addition, children with fractures experienced superior pain alleviation (54% of instances), which may be related to ibuprofen's anti-inflammatory properties (Clark et al., 2007).

When 134 kids between the ages of 5 and 17 reported to the pediatric emergency department

(ED) with an uncomplicated (nonoperative) limb fracture randomly assigned them to receive either morphine (0.5 mg/kg) or ibuprofen (10 mg/kg) orally for 24 hours following discharge (Poonai et al., 2014). There was no discernible difference in the analgesic efficacy of the two medicines, but pain scores did improve. The opioid, however, was connected to more frequent side effects. In a pediatric emergency department, carried out a prospective, randomized controlled research. The two medications were equally beneficial in reducing child-reported pain and parent-reported sleep quality among the 72 kids who finished the research (Shepherd & Aickin, 2009). To ascertain whether ibuprofen use is linked to a higher incidence of problems with bone repair in kids who have fractures children who came with a fractured limb to the pediatric emergency department (PED) between the ages of 6 months and 17 years were the subject of a retrospective study 338 (42%) of the 808 patients that were a part of the final study had ibuprofen exposure and no correlation between ibuprofen intake and the emergence of a bone healing problem was observed (DePeter et al., 2017). Consequently, ibuprofen is sought to be the medication of preference for analgesia in kids with simple extremities fractures.

3.4 Ear pain and acute otitis media

Ibuprofen is frequently used to treat ear pain in children by international and national standards (Barbagallo & Sacerdote, 2019). It is possible to delay antimicrobial medication for 48–72 hours during an incident of acute otitis media (AOM), instead beginning an analgesic treatment right once, taking into account the fact that antibiotic treatment does not provide symptomatic relief during the first 24 hours (Barbagallo & Sacerdote, 2019). Older children with mono- or bilateral AOM with mild symptoms, as well as children between the ages of 6 months and 2 years with a monolateral and non-serious form, can be managed with watchful waiting if the parents agree to it and follow-up is ensured. This strategy helps lessen

the costs and negative effects of antimicrobial therapy and bacterial resistance to antibiotics. This strategy helps lessen the costs and negative effects of antimicrobial therapy and bacterial resistance to antibiotics (Peterson, n.d.). 219 children (aged 1-6.75 years) with unilateral or bilateral otoscopically verified AOM were included in a DB-RCT (Clark et al., 2007). Three parallel oral treatment groups were created randomly from them. Children were given ibuprofen, acetaminophen, and placebos over the course of 48 hours. The researchers showed that acetaminophen and ibuprofen both reduced ear discomfort to the same extent. These findings were supported by a recent Cochrane systematic review of the literature, which compared the efficacy of paracetamol or NSAIDs, either alone or in combination, for pain management in children with AOM (Da et al., 2011). The review demonstrated the equivalency between paracetamol and ibuprofen, for short-term use, in treating ear pain at 24 and 48 hours with no differences related to the adverse events, using the GRADE system to grade the overall quality of evidence. When ibuprofen is used with antibiotic treatment for AOM caused by Streptococcus pyogenes, some results on experimental animals would suggest a better outcome. This observation seems acceptable given that the majority of the harm produced by this bacteria is elicited in the production of Th1-derived proinflammatory cytokines by human peripheral blood mononuclear cells. However, clinical studies are required to support this finding (Dawood & Khan-Dawood, 2007).

3.5 Sore throat and pharyngotonsillitis

Guidelines advise using the appropriate analgesic and antipyretic treatment (with ibuprofen or paracetamol) to reduce fever and relieve discomfort in children with acute pharyngotonsillitis. Both paracetamol and ibuprofen were found to be equally beneficial in treating the signs and symptoms of tonsillitis and pharyngitis in children in two double-

blind, randomized clinical trials (DB-RCTs)[46, 47]. A recent meta-analysis evaluating the safety and effectiveness of ibuprofen and paracetamol in pediatric patients with acute pharyngotonsillitis supported these findings. Ibuprofen should be used because of its anti-inflammatory effects in situations when there is a greater degree of inflammation, such as exudative pharyngotonsillitis or when lymphadenitis is present (Chiappini et al., 2012).

3.6 Headache

Ibuprofen and paracetamol are the two medications most frequently used in children to treat acute headaches. Ibuprofen is effective in relieving headache pain in children and adolescents within two hours of dosing, according to numerous research. In double-blind crossover research of migraine kids between the ages of 4.0 and 15.8 were enrolled. Randomly chosen single oral doses of 15 mg/kg of paracetamol, 10 mg/kg of ibuprofen, and placebo were given to each kid for three attacks. In under two hours, ibuprofen reduced discomfort, and the majority of patients experienced pain relief. Paracetamol was beneficial to almost as many people. When compared to ibuprofen, which peaks at around 1 to 2 hours, paracetamol, which achieves peak plasma levels in around 0.5 to 1 hour, tends to be more effective after that time. Ibuprofen was found to be more beneficial overall in the trial, according to an intention-to-treat analysis (Hämäläinen et al., 1997). Ibuprofen's superiority over paracetamol in this clinical setting hasn't been substantiated, according to a recent systematic assessment of the literature.

3.7 Arthritis and other rheumatic diseases

Ibuprofen might be thought of as the preferred medication for pediatric pain that has an inflammatory component due to its anti-inflammatory properties. An example of a chronic inflammatory condition that benefits from the usage of NSAIDs are juvenile idiopathic

arthritis (JIA) (Giannini et al., n.d.). Inflammation is the mechanism that keeps the tissue damage present in various disorders, not the disease itself. The most prevalent and severe JIA symptom, pain, has a significant impact on how people feel and behave physically, socially, and emotionally. Despite receiving adequate doses of disease-modifying antirheumatic medications, children with arthritis nevertheless feel clinically considerable pain. In this clinical setting, ibuprofen has been used for a long time to treat pain and inflammation in children. In a multicenter, double-blind, 12- week trial comparing the effectiveness and safety of a liquid formulation of ibuprofen at a dosage of 30 to 40 mg/kg/day versus those of aspirin at a dosage of 60 to 80 mg/kg/day, ninety two kids with juvenile rheumatoid arthritis were randomly assigned to treatment (Giannini et al., n.d.). There were no discernible intergroup variations in response rates or the degree of articular markers of disease activity improvement. Aspirin-treated children were more likely to stop taking it early due to side effects. 84 more juvenile rheumatoid arthritis patients with this condition subsequently enrolled in a 24-week, multidose (30, 40, and 50 mg/kg/day), open study of ibuprofen suspension. The three groups' favorable reaction rates were comparable, and throughout the 24 weeks, advancement was seen. Regarding adverse events of the upper gastrointestinal tract, a dose-response association was seen (Grimaldi-Bensouda et al., 2010). Children with juvenile chronic arthritis participated in a multicenter controlled open research to evaluate the safety, effectiveness, and acceptability of ibuprofen syrup. The study included 46 kids, whose ages ranged from 18 months to 13 years (mean 6.8 years). Depending on the condition and the patient's disease control, the dosage was initially 10 mg/kg/day and then increased to a maximum of 40 mg/kg/day (Giannini et al., n.d.). The usage of NSAIDs, such as ibuprofen, in children with arthritis, was severely examined. Children with arthritis are typically evaluated differently than adults since they report less pain. Ibuprofen, indomethacin, and salicylates are typically used to treat systemic juvenile

chronic arthritis fever. Salicylates and indomethacin were no more efficacious but more harmful than diclofenac, ibuprofen, tolmetin, and naproxen for the management of joint problems. NSAIDs are well tolerated by kids (Joseph et al., 2019). Gastrointestinal symptoms appeared to be less frequent than in adults, and renal damage was uncommon. Ibuprofen's pharmacokinetic and pharmacodynamic properties allow for a quick onset of action and an excellent effectiveness profile in various therapeutic settings. Ibuprofen dosages of 20–30 mg/kg per day have been proven to help treat pain and lower fever in children, whereas dosages of 30 mg/kg per day can be used safely in the symptomatic treatment of JIA (Giannini et al., n.d.).

Ibuprofen therapy was effective in treating transitory synovitis of the hip, which is a common cause of hip pain in preschoolers and younger school-age children and is characterized by limping, hip discomfort, and refusal to walk symptoms without a fever. 36 kids, ages 1 to 12, received either ibuprofen (N = 17) or a placebo (N = 19) treatments. Ibuprofen medication was shown to shorten illness duration by 2.5 days while posing no major side effects (Clark et al., 2007).

3.8 Post-surgical pain

Studies have demonstrated that surgical pain left untreated can increase clinical complications, lengthen hospital stays, and increase mortality. Underestimating the psychosocial effects of pediatric post-surgical pain may also be detrimental. Unfortunately, many hospitals address juvenile postoperative pain ineffectively; as a result, more kids than adults receive less medicine after the same kind of treatment (Pediatrica et al., 2019). Lack of training and expertise due to concern over potential negative effects, a low number of analgesics licensed for use in children, and an imperfect understanding of pain

pathophysiology are only a few of the factors that contribute to insufficient pain treatment in children (compared to adults). Ibuprofen, among NSAIDs licensed for use in children, has undergone the most research and has proven to have the highest safety and effectiveness profiles. Ibuprofen is considered to be more successful in preventing pain than treating it once it has already started, thus being proactive is advised. The best pain management results come from giving ibuprofen as soon as feasible and continuing it regularly for whatever long the pain is anticipated to linger (Walker & Carmody, n.d.). This idea can be used to effectively treat post-surgical pain. Since there have been recent restrictions on the use of codeine, particularly in this clinical setting, ibuprofen has been taken into consideration for the management of pain following juvenile tonsillectomy and/or adenoidectomy. A pro-drug called codeine is converted to morphine in the liver by the enzyme cytochrome P450. Because of its convenient oral and rectal forms, it was once a commonly administered opioid in the pediatric age (Chiappini et al., 2017).

One of the most frequent operations on children is adenotonsillectomy, which can have major postoperative morbidities besides pain, such as bleeding (between 3% and 5% of pediatric tonsillectomy patients experience bleeding following tonsillectomy on average). Nonsteroidal anti-inflammatory medicines, as previously mentioned, help reduce postoperative pain, however, some surgeons are still unsure about the possibility of postoperative bleeding. There is a possibility for qualitative effects on platelet function due to the normal NSAID mode of action, which results in the suppression of thromboxane A2 production. Results from four meta-analyses of recent literature on post-tonsillectomy bleeding and risk with NSAIDs are inconsistent. NSAIDs did not significantly change bleeding episodes that required surgery (OR 1.32, 95% CI: 0.47-3.7) or did not (OR 1, 95% CI: 0.39-2.53), according to a Cochrane meta analysis of 201174 that was restricted to

pediatric patients and included quality studies (Har-Even et al., 2014).

Ibuprofen was not linked to increased bleeding, according to a new large case study. Ibuprofen use can therefore be deemed effective based on the available data, but additional research is required to confirm its safety and use in a clinical setting.

3.9 Osteochondrosis

Patients with an underdeveloped skeleton are said to have a range of illnesses collectively referred to as osteochondrosis. Osteochondrosis is caused by the growth plate and adjacent ossification centers developing improperly, being damaged, or being overused. Due to their increased vulnerability to developmental trauma and overuse injuries, boys are more frequently afflicted and symptoms typically start to show between the ages of 10 and 14. The bodily parts most commonly impacted by pain and incapacity include the hip, knee, foot, elbow, and back (Clark et al., 2007).

The most prevalent of these disorders, Legg-Calvé-Perthes, is brought on by an unidentified partial blockage of the blood flow to the developing femoral head. The Osgood-Schlatter disease, another osteochondrosis and a prevalent source of anterior knee pain in children are brought on by the patellar tendon's recurrent traction on the tibial tubercle's ossification center or apophysis, which results in subsequent inflammation and discomfort (Rainsford, 2009). There are several other types of osteochondrosis, including the Sever disease (or calcaneal apophysitis), the Sinding

Larsen-Johansson disease (affecting the inferior pole of the patella), the Freiberg disease

(dysfunctional ossification of the second metatarsal head), the Köhler bone disease (osteochondrosis of the navicular bone in the foot), the medial epicondyle. Absolute rest and osteoarticular unloading are the basis of the regimen. However, ibuprofen is frequently used to benefit from its anti-inflammatory and analgesic properties (Bjarnason et al., 2007).

Chapter 4 Safety and tolerability of Ibuprofen in children

Ibuprofen is the most used NSAID for treating inflammation, mild to moderate discomfort, and fever in children. It is also the only NSAID that has been recommended for use in children older than three months old due to its favorable tolerability profile. Ibuprofen has taken the role of acetylsalicylic acid in the treatment of inflammation since it was first marketed as an oral suspension for pediatric use, reducing the risk of Reye's Syndrome in kids suffering from viral illnesses. Italian post-marketing data show a rise from 28% in 2008 to 70% in 2015 in the percentage of pediatric ibuprofen packs purchased without a prescription (de Martino et al., 2017). The hazards of ibuprofen overuse as well as the proper use of the medication by parents and caregivers are raised by this medically unsupervised use of the dug. Ibuprofen, as previously mentioned, is not a selective COX inhibitor, and as a result, it may have minor adverse effects that affect the kidneys and digestive system more than other organ systems. Ibuprofen is the most effective and least hazardous NSAID in adults in recent reviews and meta-analyses, and a similar conclusion has also been seen in children (Davis et al., 2017).

Numerous pertinent articles, including reviews, randomized clinical trials, observational clinical studies, and case reports, show that ibuprofen is an effective non-prescription analgesic/antipyretic medication for usage in children and has a good tolerability profile. Ibuprofen has fewer negative effects than ketoprofen, which is recommended for kids above the age of 6. Patients under the age of 12 and those under the age of 16 should not take nimesulide, ketorolac, or acetylsalicylic acid, respectively. Ibuprofen has been shown by epidemiological studies and controlled clinical trials to be one of the NSAIDs with the lowest risk of serious gastrointestinal side effects (Altman et al., 2015). Because NSAIDs have the potential to decrease the renal synthesis of prostaglandins, there has been much thought over

the years regarding the dangers of renal side effects associated with the use of these medicines in children. However, in cases of hypovolemia, up-regulation of the renin-angiotensin system as well as of the catecholaminergic system results in systemic and renal vasoconstriction, which triggers the production of renal prostaglandins to maintain renal perfusion and glomerular filtration. In euvolemic states, prostaglandins have little effect on renal hemodynamics. NSAIDs have the ability to prevent this protective action, which causes unregulated vasoconstriction of the afferent arteriole, lowered GFR, and ultimately renal ischemia and acute tubular necrosis. According to the medical literature, it is quite improbable that ibuprofen by itself causes acute renal damage in kids with normal kidney function and an adequate circulation volume (Carmody & Charlton, 2013).

However, there have been a few isolated case reports of children with febrile infections treated with ibuprofen or other NSAIDs developing reversible renal insufficiency, primarily due to volume depletion (Joseph et al., 2019). Ibuprofen should be used with caution if you are dehydrated as a result of symptoms like vomiting or diarrhea, especially if a fever is present. In these situations, insensible fluid loss (such as perspiration) and the frequently existing problem with drinking liquids must be taken into account. Dehydration in children can be difficult to spot and may go unrecognized in its milder stages. Due to their smaller nephron mass and higher lifetime risk of kidney injury, children born prematurely or with low birth weight should be treated with ibuprofen with caution (Carmody & Charlton, 2013).

4.1 Renal effects in children

Over the years, several nephrologists, pediatricians, and other physicians have voiced concerns over the dangers of significant analgesic-related renal responses in children. Lesko and Mitchell (1995, 1999) made particular note of the fact that neither of the two extensive practitioner-based studies conducted as a part of the Boston University Fever Study showed any instances of acute renal failure in patients who received either ibuprofen (5 or 10 mg kg-1) or paracetamol (12 mg kg-') (Lesko & Mitchell, 1997). assessed blood urea nitrogen (BUN) and creatinine levels in a subset of 288 of the 795 babies or children who were hospitalized patients from the first study as indicators for renal effects of the medicines. In each of the three drug treatment groups, the mean BUN levels were 4 mmol L' and the mean creati-nine levels were 42 mmol L'. All of the hospitalized patients with concurrent dehydration showed a slightly increased prevalence of BUN values above 6,4 mmol L-1 and creatinine levels above 62 mol L-1. As was mentioned before in the discussion of the large-scale pediatric study (Ashraf et al., 1999). neither ibuprofen nor paracetamol was associated with any cases of renal failure or other significant renal conditions in the groups totaling 31,144 younger or older children that were evaluated. Ibuprofen and other NSAIDs have been linked to six recorded incidences of acute renal failure in children (Ulinksi et al., 2004). After 308 days after stopping the drug, all patients showed signs of recovery and the levels of serum creatinine returned to normal. As a result, it would seem that although ibuprofen and the other NSAIDs have known renal side effects, there is a low likelihood that these adverse events will affect children. Given that all NSAIDs concentrate in the renal tubular systems, dehydration (Leroy et al. 2007, among other conditions) can undoubtedly play a significant role in the incidence of renal consequences from all NSAIDs (Giannini et al., n.d.).

4.2 Hepatic effects in children

Large-scale hospitalized practitioner-based studies in children do not appear to have reported any liver effects, and neither have critical assessments of clinical trials (Bjarnason et al., 2007). Hepatitis has frequently been documented in studies using NSAIDs, such as ibuprofen and aspirin, in JRA or JIA patients (Giannini et al., n.d.), while others observed that liver function tests in these individuals were unaffected (Ansell et al., 1973). Unless concurrent hepatotoxic medications (e.g., paracetamol, methotrexate) are taken, the risks of liver responses, particularly in JRA or JIA, appear to be modest (Hay et al., 2008).

4.3 Skin reactions in children

Lesko and Mitchell (1995, 1990) found no hospitalizations for anaphylaxis in the extensive Boston University Fever investigations. However, three occurrences of erythema multiforme occurred in individuals who had taken ibuprofen, and one case happened in a patient who had taken paracetamol (Lesko & Mitchell, 1997). In their extensive experiment, others similarly reported that none of their patients had Stevens-Johnson syndrome (Ashraf et al., 1999).

4.4 Other adverse reactions

All NSAIDs are known to cause rare side effects, which have been recorded with ibuprofen at prescription-level doses and less commonly at OTC doses.

These include interactions with the immune, endocrine, and metabolic systems, the central

nervous system, and ocular effects (Rainsford, 2009). Other effects include thrombocytopenia, agranulocytosis, anemia, aseptic meningitis, and ananaphylactoid reactions. With the exception of allergies and aspirin-sensitive asthma, the majority, but not all, of these side effects are uncommon, especially when using ibuprofen at OTC levels.

Chapter 5 Contraindications to the use of ibuprofen in children

Ibuprofen interferes with the antiplatelet effect of acetylsalicylic acid (ASA), hence it should be avoided during the treatment of Kawasaki Syndrome with ASA. An acute, systemic inflammatory disorder involving vasculitis is known as Kawasaki disease. Ibuprofen should not be used to treat any present fever. Reducing inflammation and avoiding cardiac problems are goals of Kawasaki disease treatment. The administration of high-dose ASA (80 to 100 mg/kg per day divided into 4 doses) in conjunction with intravenous immunoglobulin therapy is advised by guidelines. The guidelines advise lowering the dose of ASA to 3 to 5 mg/kg once daily for 6 to 8 weeks after the fever has subsided for 48 to 72 hours. Low-dose ASA may be necessary for the rest of one's life if coronary anomalies like stenosis or aneurysms form and remain. The acetylation of the platelet COX1 that results in its irreversible inhibition is what gives aspirin its therapeutic effect in this clinical setting. NSAIDs like ibuprofen, which act as reversible COX-1 inhibitors in contrast to aspirin, may lessen the antiplatelet efficacy of aspirin by competing with it for the platelet COX-1 (Rainsford, 2009).

According to certain research, varicella patients taking NSAIDs seem to experience a higher rate of side effects. Group A -hemolytic Streptococci (GAS), which also causes necrotizing fasciitis (a fast progressing inflammatory infection of the fascia with subsequent necrosis of the subcutaneous tissues), is one of the most frequent complications of varicella (Bjarnason et al., 2007). In order to investigate the idea that NSAID use increases the incidence of invasive GAS infection, with a focus on necrotizing infections, in children with varicella, Lesko et al. carried out a prospective multicenter, case-control research. Instead of a change in bacterial defenses, the increased severity of NSTI in children treated with NSAIDs may be caused by the drug's masking effects and the therapeutic delay. More care would

need to be taken when administering ibuprofen to children who have varicella and impetigo due to the increased risk of complications, despite the drawbacks of a spontaneous reporting system and the extremely low number of cases (1.9% of all serious skin reactions reported during the same period) (Grimaldi-Bensouda et al., 2010).

Chapter 6. Conclusion and Future Perspectives

The recommendations made over the years all agree that ibuprofen, along with paracetamol, should be used to treat mild to moderate pain and fever in children. The recommended dosage is 20 to 30 mg per kilogram of body weight, given three times daily at intervals of 6 to 8 hours. Liquid formulations, such as solutions, syrups, suspensions, and emulsions, are ideal for younger pediatric patients (for example, those aged between birth and 8 years) who are unable to swallow capsules or tablets. For the formulation of compounds with bad tastes, suspensions may be particularly helpful because the formulation's palatability can be increased by reducing the amount of medication in solution. From 5.6 to 43 kg in bodyweight, the syrup formulation (100 mg/5 mL) can be administered (age 3 months-12 years). The use of oral formulations with a single concentration of ibuprofen reduces the chance of dose errors, which is another benefit. Utilizing taste-making technology, which involves coating ibuprofen particles to improve the flavor without significantly affecting the release of the active component, it is possible to increase compliance. Using tasty flavors (like banana and honey) helps kids agree more readily.

Ibuprofen is superior to other NSAIDs since it has the best pediatric safety and tolerability records. There is little evidence of gastrointestinal, hepatic, or renal side effects in the literature. Except in known cases of paracetamol- or NSAID-induced asthma, ibuprofen is not contraindicated in children with asthma. Ibuprofen is safe even when taken on an empty stomach, resulting in a quicker increase in plasma concentration. This mode of delivery results in a stronger effect that is more immediate and long-lasting, resulting in a reduced overall need for the drug. When compared to paracetamol, ibuprofen demonstrated faster (15 minutes) and longer (8–12 hours) antipyretic action, with the clear benefit of requiring less frequent administration. Additionally, some studies seem to show increased efficacy in

treating febrile illnesses, particularly in the first 24 hours. In terms of the analgesic impact, several studies demonstrate more efficacy than paracetamol (and comparable to the paracetamol/codeine relationship) in the treatment of post-traumatic musculoskeletal pain, toothache, and headache, particularly in the first two hours after commencing the therapy. Ibuprofen has been proven to be efficient and safe for post-surgical pain in pediatric patients, where it has also been widely investigated (children undergoing adenotonsillectomy have not showed an increased risk of bleeding). Ibuprofen is a safe and highly effective medication for treatment in a variety of severe, acute, and chronic inflammatory disorders, according to a considerable body of safety and efficacy evidence.

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