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General

A Comprehensive Review of Celecoxib Oral Solution for the Acute Treatment of Migraine

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A migraine is a clinical diagnosis with a presentation of one or more severe unilateral or bilateral headache(s) often preceded by an aura and typically accompanied by nausea, vomiting, photophobia, and/or phonophobia. This neurological disease is often debilitating and greatly affects the quality of life of those it inflicts. In fact, a recent study conducted by the Global Burden of Disease and published in The Lancet Neurology revealed that migraines ranked second to only back pain as the most disabling disease. Triggers for migraines have ranged from female sex, low socioeconomic status, and diet to loud noises, sleep hygiene, and stress. Along with its clinical presentation, laboratory tests and imaging help rule out other potential causes of the headache and lead to a diagnosis of migraine. Migraines are typically divided into three phases: prodromal, headache, and postdrome. The pathophysiology of each phase remains under investigation, with differing theories regarding their pathways. Existing therapies are abortive therapies for acute migraines or preventative therapies. Abortive therapy consists of NSAIDs and triptans. Preventative therapies include tricyclic antidepressants, calcium channel blockers, beta-blockers, and anticonvulsants. In this review, we focus on the role of NSAIDs and the COX-2 inhibitor, celecoxib oral solution, for the abortive treatment of acute migraines.

INTRODUCTION

Migraine is a chronic neurological disease that affects numerous people of varying ages, races, and socioeconomic statuses. Migraine is a severe headache that can be described as primarily unilateral or bilateral, commonly accompanied by nausea, vomiting, aura, photophobia, and phonophobia.[1] Further classification of these migraines includes chronic migraines (e.g., greater than 15 days per month) and episodic migraines (e.g., less than 15 days per month).[2] Clinical history is usually all that is needed to diagnose migraines.

Initially, migraines were thought to be related to dysfunction in energy metabolism; however, further advancements showed that it is likely a multifocal condition that includes varying neuronal pathways and genetic predispo-

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sitions.[1,3,4] One major pathway that is thought to cause the characteristic pain of migraines is the trigeminovascular pathway. The activation of these neuronal pathways leads to characteristic head pain associated with migraines.[1] In addition, multiple other structures, including nuclei in the brainstem, the hypothalamus, and the thalamus, play a role in initiating migraines and the other symptoms that accompany migraines.[4]

The increased understanding of the pathophysiology of migraines has led to an increase in treatment options for this chronic disease. Treatment of migraines aims to lessen the severity of symptoms, decrease the recurrence rate, and increase patient functionality.[1] The main two categories of pharmacological treatment include abortive and preventative therapy. Initial treatment for migraines is with abortive therapy, which consists of acetaminophen, nonsteroidal anti-inflammatory drug (NSAID), triptans, dihydroergotamines, opioids (e.g., butorphanol, codeine, tramadol, and meperidine), and antiemetics (e.g., chlorpromazine, droperidol, metoclopramide, and prochlorperazine).[5] Preventative therapy is initiated if a patient has four or more headaches a month or has failed abortive therapy.[6] Current preventative medications include beta-blockers (e.g., atenolol, metoprolol, nadolol, propranolol, and timolol), anticonvulsants/antiepileptics (e.g., divalproex sodium or topiramate), antidepressants (e.g., amitriptyline and venlafaxine), calcitonin gene-related peptide inhibitors, and onabotulinumtoxinA.[6] Although there are many treatments for migraines, research is continuously being performed to identify other treatment strategies to control this devastating disease better.

The present investigation, therefore, evaluates a new abortive treatment using a celecoxib oral solution. Celecoxib is an NSAID that selectively inhibits cyclooxygenase-2 (COX-2). In a study conducted by Lipton et al., celecoxib oral solution was more effective at migraine termination than placebo with decreased risk of GI side effects associated with other NSAIDs.[7] This review further aims to evaluate the pathophysiology and side effects of celecoxib oral solution for migraine treatment.

EPIDEMIOLOGY

According to the National Health Interview Survey (NHIS) conducted in 2018, migraines affect 15.9% of people in the US. This number has steadily increased from 2016, were 15.3% of people in the US were affected. Further breakdown showed that 21% of females and 10.7% of males in the US had migraines.[8] In addition to women having a higher prevalence, they also report more severe features with increased pain and disability from migraines.[9] Although women have a higher prevalence than men, this is not always the case across different age groups. In children, migraines are more prevalent in males until puberty, in which the ratio trends upward in favor of females.[8] Other factors that play a role in the epidemiology of migraines include socioeconomic status and race. According to the NHIS, between 2012 and 2018, unemployment, poverty, lack of insurance, and lower education were all contributing factors in people with migraines. Different races also played a role, with higher prevalence in American Indians or Alaska natives and the lowest prevalence in Asians.[8]

IMPACT AND PATIENT BURDEN

The effects of migraines are vast and are seen by their high prevalence. However, the burden does not stop with patients. Families, as well as other aspects of society, are also affected by this disease such as loss of work. According to the Global Burden of Disease (GBD) study, low back pain is the only condition more disabling than migraines.[10] Other studies have found that migraines led to more workdays missed and decreased productivity during migraine episodes.[11] Multiple studies have used the Migraine Disability Assessment (MIDAS) to evaluate the level of productivity and disability that patients with migraines face. This questionnaire consists of 5 items that are graded 1-4, with 4 being severe disability and one being little or no disability.[12] Using the MIDAS, studies showed decreased productivity and work absences during migraine episodes.[13]

Additionally, Buse et al. found that patients with chronic migraines had decreased activity with kids and family, decreased ability to perform daily household chores, and decreased ability to play with children. This study also showed that children of patients with migraines without spouses were affected more than patients that had spouses.[14] Thus, the effects of migraines on the patients, their families, and the society around them have led to extensive research in the treatment and management of this disease.

RISK FACTORS AND TRIGGERS

There are not many studies that evaluate the risk factors of migraines. Previous studies have shown that women, persons with low socioeconomic status, and lower education are all at increased risk of migraines.[15] The research on triggers of migraines to date has been extensive and includes diet, environmental factors, physiologic factors, behavioral factors, and pharmacological factors. Some of the most common dietary triggers include alcohol, dehydration, aspartame, tyramine found in wine and cheese, phenylethylamine found in some chocolates, flavonoids, and nitrates. Environmental triggers can include loud noises and weather. Physiologic triggers include hypoglycemia, hypoxia, infection, and hormones such as estrogen. Behavioral factors that can lead to migraines are sleeping habits, mental fatigue, and stress. Finally, pharmacological factors like nitroglycerin have also been associated with increased migraines.[16] Thus, many factors play crucial roles in the initial development of migraines and triggers that can initiate an acute episode.

DIAGNOSIS AND CLINICAL PRESENTATION OF MIGRAINE

CLINICAL PRESENTATION

Migraine is one of the most common chronic neurological disorders in the world, comprised of intermittent, episodic

head pain in conjunction with various other symptoms. The gap in knowledge and understanding regarding this disorder is considerably prevalent in the world of Neurology and medicine today.[1] Migraine is commonly perceived to be headaches; however, their presentation varies widely throughout the population.[17] The timeline of a migraine can be divided into three separate phases: prodromal, headache pain, postdrome.[18] These three phases each have defining characteristics, although they can present differently across a patient population.[18] The prodromal phase is largely the most studied phase of the migraine, given its clinical relevance in diagnosis and prevention.[19] This phase has a very diverse presentation but can be broadly categorized into four main groups: hormonal, mood and fatigue, migrainous and sensory, and autonomic symptoms.[18] This phase typically presents anywhere from hours to days before the headache begins. Symptoms common in the prodrome include confusion, disorientation, yawning, fatigue, cravings, thirst, photophobia, tinnitus, tearing, conjunctival injection, diaphoresis, and rhinorrhea.[18] Headache pain usually begins thereafter, presenting with a throbbing headache, often unilateral, as well as nausea, emesis, and sensitivity to light, sounds and smell.[20] These symptoms continue up until seventy-two hours after their onset.[18] The postdrome is the final phase of the migraine attack, lasting anywhere from twenty-four to forty-eight hours. This phase is typically comprised of fatigue, decreased mental acuity, inability to concentrate, nausea, and bodily aches.[18] While each phase of an attack has important and distinct features, the prodromal phase is arguably the most interesting, given its potential to assist in the prevention, diagnosis, and abortion of a migraine once it has begun.[20]

DIAGNOSIS

Diagnosis of migraines is clinically significant in that it determines whether the headache is related to a primary or secondary cause. Many of the diagnostic tests, such as EEG, lumbar puncture, neuroimaging, and blood testing, allow physicians to rule out secondary causes of headache, while concurrently ruling in migraine as a diagnosis.[21] Neuroimaging is one of the most common diagnostic modalities used in diagnosing migraine. CT and MRI are both used; however, both have benefits and drawbacks. CT is more readily available and has less radiation exposure. MRI, however, is often preferred given its increased sensitivity to detect soft tissue masses, vascular malformations, and white matter disease.[21] While it does expose the patient to higher levels of radiation, it is still preferred over CT for imaging.[21] EEG is another diagnostic modality, although it confers a little clinical benefit in migraine diagnosis. EEG was initially the test of choice prior to the use of neuroimaging to diagnose migraines.[21] It should be noted that with the increased usage of CT and MRI, EEG has fallen out of favor.[21] However, it is still used occasionally to rule out seizure disorders in patients complaining of a headache.[21] Lumbar puncture is another modality used in migraine diagnosis. While this modality is secondary to neuroimaging, it is still performed if there is suspicion of an infectious cause such as meningitis, or other causes such as pseudotumor cerebri.[21] There are many risks associated with this procedure, including low CSF pressure headache.[21] Blood tests are the final diagnostic tool utilized in migraine diagnosis. These are generally inconclusive; however, they can be used to rule out causes of headache, such as vasculitides, HIV, Lyme disease, rheumatoid arthritis, infectious mononucleosis, Lupus, and thyroid disorders.[21]

PATHOPHYSIOLOGY

Migraine attacks are subdivided into three major phases: prodromal, headache, and postdrome. Each of these phases has specific qualities and symptoms that have led investigative efforts into their pathophysiology. The prodromal phase, which presents days before the actual headache, has symptoms such as confusion, disorientation, yawning, fatigue, cravings, thirst, photophobia, tinnitus, tearing, conjunctival injection, diaphoresis, and rhinorrhea.[18] These symptoms indicate a possible correlation between structures of the brain such as the limbic system, hypothalamus, and brainstem and the symptoms observed.[22,23] One mechanism proposed is through activation of nociceptors on the meninges due to increased parasympathetic activity.[22, 23] Various autonomic symptoms persist throughout the course of a migraine attack, creating the suspicion that migraine triggers alter the parasympathetic tone, thereby activating nociceptors.[22,23] The parasympathetic system, when activated, may release neurotransmitters creating a signal cascade to meningeal nociceptors.[22,23] Another proposed theory is the regulation of nociception from the thalamus to the cortex. The thalamus receives signals from various nociceptors in the brain that are thought to be modulated by neurotransmitters.[22] These neurotransmitters, depending on their properties, can help modulate or prohibit pain signals from traveling through the brain. The aura, which is typically included in the prodromal phase, are neurological deficits that are reversible, localized, and last for more than five minutes.[23] This phenomenon is thought to be a “cortical spreading depression”, which depicts a slow neuronal depolarization through the cortex triggering cortical inhibition which ultimately leads to the symptoms of an aura.[23] The headache phase is comprised of unilateral, throbbing head pain lasting up to seventy-two hours after they start.[19] This phase is correlated to a disturbance in the trigeminovascular pathway of the brain. This pathway contains sensory fibers from the trigeminal nerve, ultimately traveling to the central brain and back out to the somatosensory processing regions.[23] This largely explains the clinical symptoms of a migraine headache, including pain in various cranial regions such as the periorbital, occipital, and cervical regions.[23] Additionally, this also explains symptoms such as photophobia and phonophobia.[23] The activation of the nociceptors in this pathway induces the release of CGRP and subsequent activation of the trigeminovascular system.[23] The postdromal phase, which concludes the migraine attack, is very understudied, which little information surrounding it. Although the

symptoms of this phase have been defined, very little knowledge surrounding the pathophysiology is known.

TRADITIONAL TREATMENT OPTIONS

ACUTE THERAPIES

Acute therapy for migraines has evolved over the years to include a wide variety of abortive drugs. While general, nonspecific therapies such as NSAIDs have been used for years, treatment is now trending towards more specific, targeted agents. Arguably the most popular of the bunch is triptans, which target the 5-HT1B and 5-HT1D receptors in the brain.[24] Many of these have severe cardiovascular and cerebrovascular side effects.[25] CGRP receptor antagonists are a newer class of drugs that have been developed for use in migraines. This class seems to have a milder side effect profile, as compared to the triptans, however, CGRP receptor antagonists are still relatively new.[24] Another class of drugs, the 5-HT1F receptor agonists, have recently been developed. These receptors have been hypothesized to be found within the trigeminovascular pathway, making them an excellent target for newer therapies. This class of drug also possesses a much milder side effect profile.[24]

PREVENTATIVE THERAPIES

Preventative therapies for migraines include drugs such as tricyclic antidepressants, calcium channel blockers, beta-blockers, and anticonvulsants.[25] These drugs have class A evidence that supports their usage as prophylactic therapy.[24] However, most of these have a significant side effect profile in their patients. This diminishes patient compliance and ultimate therapeutic efficacy in the long run.[24] Newer preventative therapies such as monoclonal antibodies to CGRP and its receptor are currently in phase II of clinical trials. Many of the clinical trials comparing the efficacy of current preventative therapies to mAB therapy demonstrate similar outcomes for both categories of drugs.[25] Given these mABs are still being studied in randomized controlled trials, many questions surrounding their efficacy, side effects and long-term usage are still unanswered.[25]

CELECOXIB

DEFINITION

Non-steroidal anti-inflammatory drugs or NSAIDs are widely prescribed for the treatment of several rheumatologic disorders, due to their ability to provide pain relief.[26] NSAIDs, such as diclofenac and naproxen, exhibit their analgesic effect through the inhibition of the cyclooxygenase enzyme.[26] The COX enzymes are important in the synthesis of prostaglandins, which play a role in the pain and inflammation seen in many rheumatologic conditions.[27] The enzyme has two isoforms, COX-1 and COX-2, which differ in their expression and function. The COX-1 isoform is constitutively expressed and synthesizes prostaglandins (PG) involved in normal cellular functions such as gastrointestinal mucosal protection and maintenance of vasculature.[28] The other isoform, COX-2, is inducible and plays a role in inflammation and pain in certain disease processes.[27,29] By inhibiting the COX enzyme, NSAIDs inhibit the synthesis of prostaglandins, decreasing inflammation and pain.[26,27] However, since traditional NSAIDs inhibit both isoforms, they also interfere with the homeostatic functions of the constitutively expressed COX-1. This results in GI toxicity related to inhibition of COX-1 and subsequent decrease in GI protection.[29] This toxicity can range from symptoms of dyspepsia and heartburn to more severe mucosal lesions.[26,28] In an effort to avoid the GI side effects associated with inhibition of COX-1, COX-2 has become a drug target to selectively decrease inflammation and pain.[30] Consequently, the selective COX-2 inhibitors were developed to provide similar analgesic effects while avoiding the gastrointestinal toxicity associated with traditional NSAIDs.[26,28] These selective COX-2 inhibitors, a subgroup of NSAIDs, are known as coxibs and include the drugs celecoxib, rofecoxib, parecoxib, etoricoxib, and lumiracoxib. Celecoxib is a reversible and selective inhibitor of COX-2 and is currently the only selective COX-2 inhibitor available in the US.[31,32] It was the first of the coxibs to be approved by the US Food and Drug Administration for the treatment of osteoarthritis and rheumatoid arthritis in 1999.[33] In addition to acetaminophen and other NSAIDs, celecoxib is recommended as first-line in the treatment of these conditions.[9,10] Celecoxib also has several off-label uses for a variety of conditions including ankylosing spondylitis and gout.[10] It has also been used as an adjunct to surgery, reducing the number of polyps in familial adenomatous polyposis[32]

MECHANISM OF ACTION

Celecoxib is a diaryl-substituted pyrazole compound, and its chemical designation is 4-[5-(4-methyl phenyl)-3-trifluoromethyl-1H-pyrazoyl-1-yl]benzenesulfonamide.[11] Celecoxib exerts its inflammatory effects through the selective inhibition of the COX-2 enzymes and as a result, the synthesis of prostaglandins. The formation of these prostaglandins depends on the availability of arachidonic acid (AA), which is released from cellular phospholipids following mitogenic stimulation of the cell membrane. Either secretory (sPLA2) or cytoplasmic (cPLA2) phospholipases release these arachidonic acids (AA), which are then converted to produce prostanoids in a series of reactions catalyzed by the COX enzymes.[32] The COX enzymes catalyze this reaction in two reactions, with the first converting AA to PGG2, and the second reducing PGG2 to PGH2. Then the PGH2 molecule is converted by PG synthases to different metabolites including PGE2 and prostacyclin, and thromboxane.[32] The structure of both isoforms of the COX enzyme are similar, as both have three folding units and a long hydrophobic channel that leads to their respective active sites. The main difference is a substitution of isoleucine in COX-1 for the smaller amino acid valine in COX-2 at position 523, leaving a gap in the COX-2 isoform 12. This results in a larger active site in the COX-2 isoform than the COX-1 active site, allowing for larger molecules, such as selective COX-2 inhibitors, to bind. The COX-2 iso-

form also has a secondary binding site that also contributes to the accessibility of the active site by allowing the binding of the COX-2 inhibitor sulfur-containing sidechain 13. Celecoxib binds both parts of the enzyme, its methyl phenyl ring of binds to one site of COX-2 and the benzenesulfonamide ring binds the other site 12. This binding of the phenylsulfonamide moiety to these sites prevents the activation of COX-2, inhibiting its ability to catalyze the reactions that produce prostaglandins. As a result, this binding prevents the resulting inflammation and pain associated with COX-2 12.

PHARMACOKINETICS AND PHARMACODYNAMICS

Following oral administration, celecoxib is rapidly absorbed, achieving peak serum concentration in about three hours, and in the presence of a high-fat meal, plasma levels will peak in 4-5 hours,[7,8] Like most traditional NSAIDs, celecoxib is highly protein-bound, mainly to albumin.[32,34] The fraction of unbound drug remains constant at 2.6% up to concentrations of 4000µg/L.[34] At steady state, it has a volume of distribution of about 400 L.[29] Celecoxib is currently available in an oral capsule; its bioavailability is not known due to the lack of an intravenous solution to compare.[12] The COX-2 inhibitor undergoes extensive metabolism in the liver primarily through cytochrome P450 (CYP2C9).[8] It undergoes methyl hydroxylation to form hydroxycelecoxib by CYP2C9, with less than 3% of the drug excreted unmetabolized.[32] The cytosolic alcohol dehydrogenases ADH1 and ADH2 oxidize hydroxycelecoxib further to carboxycelecoxib. UDP glucuronosyltransferases then conjugate carboxycelecoxib with glucuronic acid, forming 1-O-glucuronide.[32,35] The metabolites of celecoxib, which are the primary alcohol, carboxylic acid, and glucuronide conjugate, have not been shown to inhibit either isoform of the COX enzyme.[8,12] Celecoxib has an average plasma half-life of about 8-12 hours.[8] Hepatic function affects plasma concentrations, with mild to moderately impaired liver function resulting in plasma concentrations being doubled. Also, patients over the age of 65 have altered plasma concentrations, as much as 40% higher when compared to concentrations in younger people 8. Celecoxib's main routes of excretion are through feces and urine, with less than 2% excreted unchanged in the urine and 2.6% in feces.[32,34,36] CYP2C9 is the primary catalyst in the metabolism of celecoxib and polymorphisms in this enzyme confer some variability in the drug response.[32] The co-administration of CYP2C9 inducers can decrease the plasma concentration of celecoxib, these include drugs like carbamazepine, barbiturates, and rifampicin.[8] CYP3A4 also has a small role in celecoxib metabolism.[8]

SAFETY & EFFICACY

Celecoxib was originally licensed by the US Food and Drug Administration (FDA) for use in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). Thus, the safety and efficacy of the drug are well studied.[37] When compared to non-selective NSAIDs, celecoxib is consistently found to be equal in pain relief with fewer gastrointestinal adverse effects,[38] with no effect on platelet aggregation unlike non-selective NSAIDs,[39] and with similar renal effects.[40] An early study of celecoxib as a treatment for osteoarthritis showed similar efficacy of the drug compared to naproxen, the treatment of choice at the time.[41] Since then, it has been evident that celecoxib is as equally effective as an analgesic and anti-inflammatory drug when compared to its NSAID counterparts.

The efficacy of celecoxib as an anti-inflammatory and analgesic agent can be seen in several large studies produced since its approval for the treatment of OA and RA. A 2018 study on the effect of selective COX-2 inhibitors compared to non-selective COX-2 inhibitors on the incidence of heterotopic ossification (HO) following total hip arthroplasty (THA) demonstrates no significant difference between the two groups in overall HO incidence ($p= 0.203$).[42] Heterotopic ossification is the formation of extra-skeletal bone in soft tissue and muscle and has an incidence of 30-40% following THA.[43,44] HO is important when comparing the efficacy of the two drugs because HO can be used as a metric of inflammation. Patients who develop HO following trauma demonstrate a strong systemic inflammatory response.[44] NSAIDs, diphosphonates, and low dose irradiation are currently used the main prophylaxis for HO development after THA.[42] The 2018 meta-analysis included 8 clinical trials with 1636 patients.[42] One of the clinical studies specifically compared ibuprofen with celecoxib. In a subgroup analysis of this study, celecoxib was significantly reduced the incidence of HO when compared to ibuprofen ($p= 0.004$).[42] This study is indicative of celecoxib's efficacy as an anti-inflammatory agent. Celecoxib is equally effective as non-selective NSAIDs but is also equally effective in comparison to other selective COX-2 inhibitors (meloxicam and rofecoxib).[45]

A 2021 study exploring the efficacy of celecoxib as prophylactic analgesia for patients undergoing laparoscopic transabdominal preperitoneal inguinal hernia repair (LTAPP) compared the drug to transversus abdominis plane (TAP) blocks for postoperative analgesia.[46] This study found that while the numerical rating scale (NRS) score was greater at 24 hours post-operation and the time to first request of an analgesic was longer in the group that received TAP blocks, it was not significantly different from the group receiving 200mg celecoxib 2h before surgery.[46] This study is yet another indication of celecoxib's efficacy as an analgesic.

The Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION) trial is an important study when discussing the safety of celecoxib and this data has been further used to evaluate the cost-effectiveness of celecoxib compared to ibuprofen and naproxen. It has been determined that celecoxib is a long-term cost-effective treatment for osteoarthritis.[47] By evaluating cost parameters such as monthly treatment acquisition and cost per adverse event, the study determined that celecoxib is a more cost-effective treatment due to the reduction in adverse events. Further analysis of the data determined celecoxib to be 81% more cost-effective

than ibuprofen and 50% more cost-effective than naproxen at $40,000 quality-adjusted life years (QALY).[47] Cost-effectiveness is a critical quality of a drug to assess, and this study indicates the increase in cost-effectiveness is largely due to the reduction in toxicities and their associated costs.

An additional consideration in the safety and efficacy of celecoxib is the consideration that its use could reduce the use of other analgesics, particularly opioids. Adding celecoxib to the regimen of OxyContin and Pregabalin in the treatment of cancerous pudendal neuralgia led to improved patient pain, a better quality of life, and a reduction of the use of OxyContin.[48] In addition to the addictive properties of OxyContin, there are adverse reactions such as constipation and urinary retention that can be avoided with a lower dose of the opioid.[48] It is just as pertinent to account for the benefits associated with adding celecoxib to a multi-drug regimen.

ADVERSE EVENTS

The PRECISION trial is an excellent recent study that outlines the adverse effects associated with celecoxib use. The trial demonstrated similar cardiovascular event incidence in the use of celecoxib (noninferiority < 0.001 for celecoxib vs. ibuprofen, noninferiority < 0.001 for celecoxib vs. naproxen), significantly less GI side effects (p = 0.002 for celecoxib vs. ibuprofen, p = 0.01 for celecoxib vs. naproxen), significantly less renal events compared to ibuprofen (p=0.004), and similar all-cause mortality between celecoxib, ibuprofen, and naproxen (noninferiority < 0.001 for celecoxib vs. ibuprofen, noninferiority < 0.001 for celecoxib vs. naproxen).[49]

As with other non-selective NSAIDs, celecoxib shares an increased risk of cardiovascular events such as death, myocardial infarction, heart failure, and stroke. A placebo-controlled trial in 2003 demonstrating evidence of increased cardiovascular adverse events in rofecoxib caused the FDA to withdraw the drug.[49] After this evidence, there was much controversy surrounding the safety of all selective COX-2 inhibitors. A follow-up placebo-controlled trial demonstrated a dose-dependent increase in these outcomes associated with doses of celecoxib that were higher than recommended.[50] A meta-analysis performed in 2006 supported this evidence.[51] There is no "safe dose" in the use of rofecoxib as well as diclofenac.[51] Celecoxib doses of 200 mg or less demonstrate no increased risk of cardiovascular risk, doses 400 mg and greater are unsafe as they do significantly increase the risk of cardiovascular adverse events.[51] Theoretically, the addition of aspirin (a COX-1 inhibitor) to the regimen of selective COX-2 inhibitors should help to reduce the cardiovascular and thromboembolic risk, but this effect has not been seen in studies.[52] According to these results, the COX-2 selectivity of the drugs is responsible for the dose-dependent toxicities seen in previous studies. This has yet to be explained, however. The 2016 PRECISION trial results help to quell the controversy surrounding this class of drugs. The trial evidence that the cardiovascular risk associated with celecoxib use at moderate doses is similar (noninferiority < 0.001) to the non-selective NSAIDs which are widely used.[49]

The avoidance of GI side effects with selective COX-2 inhibitors was a primary reason for the research that led to their development.[53] Even so, the risk of gastrointestinal adverse events is still present with the use of selective COX-2 inhibitors with an overall incidence of 25- 28% in those treated with celecoxib compared to an incidence of 19% with placebo.[54] As celecoxib is a selective COX-2 inhibitor, it is more protective against gastrointestinal side effects, such as gastric ulcers, that occur in non-selective NSAID use due to COX-1 inhibition.[54] Celecoxib was shown to have a significantly lower risk for gastrointestinal adverse effects than naproxen (p=0.004) and ibuprofen (p=0.002).[49] Participants in a 2005 study taking celecoxib reported less vomiting, abdominal pain, dyspepsia, and clinical ulcers and bleeds when compared to a larger array of non-selective NSAIDs (ibuprofen, naproxen, diclofenac, and loxoprofen).[38] Celecoxib was also determined to be the least costly treatment option for patients with intermediate to high gastrointestinal risk in patients with OA and RA when compared to NSAID use with the addition of histamine 2 blockers, misoprostol, or proton pump inhibitors.[55]

Other rare, but important adverse events noted with celecoxib use include a case study of an 86 year old Caucasian woman who experienced intracerebral hemorrhage following the acute use of celecoxib and clopidogrel for 3 weeks.[56] There is no clear evidence of the interaction between these two drugs, but it is important to note a potential CYP2C9 pharmacokinetic interaction due to celecoxib undergoing metabolism by CYP2C9 and clopidogrel being a CYP2C9 in vitro studies.[56] A 2004 case study reports the presentation of methemoglobinemia in an 84-year-old African American male one month after receiving celecoxib for osteoarthritis of knee joints.[57] While acute methemoglobinemia has been reported with use of other drugs including sulfonamides, this was the first case of methemoglobinemia with a probable relationship to celecoxib.[57] It is important to also be aware of these rare adverse events associated with celecoxib use as well as the more common adverse events such as cardiovascular risk and gastrointestinal effects.

GUIDELINES FOR USE

Several studies have been conducted to illustrate the effectiveness of celecoxib on different forms of headaches. Celecoxib is proven to be effective in the treatment of migraine headaches, hemicrania continua, and withdrawal headaches from medication overuse.[58-60] Naproxen sodium has been a mainstay of acute migraine treatment for some time with its efficacy and cost-efficiency well proven. In a 2007 study, celecoxib was proven to be as equally effective in the treatment of acute migraine as naproxen sodium and demonstrated significantly less gastric pain.[59] A 400 mg dose of celecoxib is equivalent in efficacy to 550mg of naproxen sodium for the treatment of acute migraine attacks.[59] The current recommendation for treatment of hemicrania continua (HC), a form of chronic daily headaches, is indomethacin; however, celecoxib has been looked into as an alternate treatment for those with contraindications to indomethacin use, such as in patients with

renal failure, gastric ulcers, and bleeding disorders.[60] 3 out of 5 people in a 2002 study reported effective headache relief from celecoxib in the treatment of hemicrania continua.[58] It is suggested as a second-line treatment for HC for refractory cases or those with contraindications to indomethacin.[60] Another form of headache that could be effectively treated by celecoxib is medication overuse headaches (MOH). The treatment guideline for MOH, or analgesic rebound headache, is the withdrawal of the medication either in a gradual or abrupt manner. Often the withdrawal of the medication induces a rebound headache, to which no consensus has been drawn for acute treatment. Some studies suggest prednisone as an appropriate therapy, but a 2015 study compares the efficacy of prednisone to celecoxib.[61] Celecoxib was found to be more effective in reducing headache intensity and should be considered for a bridge therapy in medication overuse headache and withdrawal.[61]

SUMMARY & CONCLUSION

In summary, migraines can be a debilitating condition affecting 15.9% of people in the United States.[62] Pharmacologic treatment for both abortive and preventative therapy includes a myriad of drugs, but there is still potential for research for more effective treatments with fewer adverse effects. Clearly, celecoxib, a reversible and selective COX-2 inhibitor, could be an excellent abortive treatment for the headache phase of migraine attacks.[63] By decreasing the activity of the COX-2 isoform without affecting the COX-1 isoform, celecoxib can reduce inflammation while retaining normal cellular functions of gastrointestinal mucosal protection and maintenance of vasculature.[64] CYP2C9 is the primary catalyst for Celecoxib metabolism and as such, patients with reduced hepatic function and those over the age of 65 should be aware of the elevated plasma concentration of the drugs.[62,63] Co-administration of CYP2C9 inducers and inhibitors can affect the distribution of the drug as well.[62] The largest benefit of the use of celecoxib over non-selective NSAIDs is the reduction of gastrointestinal side effects due to its selectivity of the COX-2 isoform.[38] Numerous studies have been conducted comparing celecoxib to other anti-inflammatory drugs and forms of analgesia. Celecoxib was found to be more effective than ibuprofen in the prevention of Heterotropic Ossification, equal to transversus abdominis plane blocks for postoperative analgesia in a 2021 study, and more cost-effect than other NSAIDs in the treatment of osteoarthritis due to the reduction in adverse effects.[42,46,47] The most important adverse effects associated with celecoxib use are cardiovascular events, but the risk of cardiovascular events with the use of celecoxib is similar to the risk with the use of non-selective NSAIDs as well.[49] In addition to its proven safety and efficacy in the use of osteoarthritis, celecoxib is equally effective in the treatment of migraine headaches, hemicrania continua, and withdrawal headaches from medication overuse when compared with naproxen sodium, the current mainstay of treatment.[58-60] The present manuscript reviews both historically important literature about the use of celecoxib as well as more recent studies that indicate the efficacy of celecoxib in the use of acute migraine therapy.

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