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Review Article

The role of acemetacin in pain management

Asemetazinin ağrı tedavisindeki yeri

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Abstract

Analgesics can be divided into three main groups as non-opioid, opioid, and adjuvant treatment options. In this review, the place of acemetacin, which is among the non-steroidal anti-inflammatory drugs (NSAIDs) in the non-opioid group, in pain treatment was evaluated. Acemetacin is a prodrug and acts by converting to indomethacin in the body. Clinical studies have shown that acemetacin is an effective and safe treatment option for acute and chronic pain. The main gastrointestinal side effects of acemetacin are complaints such as loss of appetite and nausea, and the severity of the side effects is usually mild to moderate. In conclusion, acemetacin is a good option that is effective orally, has a sufficient analgesic effect, has a low gastrointestinal side effect profile, and does not cause tolerance and addiction in pain treatment.

Keywords: Acemetacin, Pain, NSAID

Öz

Analjezikler, opioid dışı, opioid ve adjuvan tedavi seçenekleri olmak üzere üç ana gruba ayrılabilir. Bu derlemede, opioid dışı grupta yer alan non-steroid anti-inflamatuar ilaçlar (NSAİİ) arasında yer alan asemetasinin ağrı tedavisindeki yeri değerlendirilmiştir. Asemetasin bir ön ilaçtır ve vücutta indometazine dönüşerek etki eder. Klinik çalışmalar asemetasinin akut ve kronik ağrı için etkili ve güvenli bir tedavi seçeneği olduğunu göstermiştir. Asemetasinin başlıca gastrointestinal yan etkileri iştahsızlık ve mide bulantısı gibi şikayetlerdir ve yan etkilerin şiddeti genellikle hafif ila orta şiddettedir. Sonuç olarak asemetasin, oral yoldan etkili olan, yeterli analjezik etkiye sahip olan, düşük gastrointestinal yan etki profiline sahip olan ve ağrı tedavisinde tolerans ve bağımlılığa neden olmayan iyi bir seçenektir.

Anahtar Kelimeler: Asemetasin, Ağrı, NSAID

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Key Points

1. Asemetacin is a potent NSAID with strong COX-2 and weak COX-1 inhibition, providing effective analgesic and anti-inflammatory effects.
2. Compared to other NSAIDs, asemetacin has a lower risk of gastrointestinal side effects and renal toxicity due to its prodrug properties and lipoxin production.
3. Asemetacin is used for conditions like osteoarthritis, rheumatoid arthritis, and postoperative pain, but further large-scale clinical studies are needed to confirm its efficacy.

Introduction

Pain is defined as an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (1). Prolonged exposure to chronic pain can lead to further health problems that diminish the quality of life (2). Pain can negatively affect the immune system, delay healing, and cause sleep disorders, nutritional problems, concentration and communication disorders. For good pain management, pain should be regularly questioned and evaluated at every encounter. Each patient should be individually assessed, and the most appropriate pain relief method should be determined for the patient. The treatment plan should be arranged according to the cause, severity, type, and nature of the pain.

Non-pharmacological methods (exercise, massage, acupuncture, music therapy, etc.) are available in pain management, but pharmacological methods are often the first and most frequently used treatment options. Medications should be personalized, administered at regular intervals, preferably orally, and the least invasive route should be chosen as much as possible. Side effect control must be performed, and the entire process should be shared with the patients and caregivers. An ideal analgesic should be effective when administered orally, have sufficient analgesic effect, and not cause tolerance or dependence.

Analgesics can be divided into three main groups: non-opioid, opioid (weak opioids tramadol, codeine; strong opioids morphine, fentanyl, hydromorphone, etc.), and adjuvant (glucocorticoids, antidepressants, etc.) treatment options. In this article, the role of acemetacin, a non-steroidal anti-inflammatory drug (NSAID) within the non-opioid group, in pain management will be evaluated.

Non-Steroidal Anti-Inflammatory Drugs

NSAIDs play a central role among analgesic and anti-rheumatic drugs (3). The analgesic and anti-inflammatory effects of NSAIDs are mainly due to their inhibition of prostaglandin synthesis. Arachidonic acid is synthesized from cell membrane phospholipids by phospholipase A. The formation of prostanoids (PGI2, PGD2, PGE2, PGF2α, TXs) from arachidonic acid is catalyzed by the cyclooxygenase enzyme. It is known that there are at least two different cyclooxygenase isoforms. Cyclooxygenase-1 (COX-1) is an enzyme that structurally exists in many cells and synthesizes prostanoids related to many physiological processes. Cyclooxygenase-2 (COX-2) is an enzyme that can be induced by various factors such as proinflammatory cytokines and mitogens (bacterial lipopolysaccharides, interleukin-1, and others) in inflammation regions (4). Both categories are useful for managing pain (5). In addition to providing pain relief by reducing edema and inflammation due to their anti-inflammatory effects, NSAIDs also have a direct analgesic effect independent of this, and all NSAIDs have analgesic effects to some extent (3). The analgesic mechanisms of NSAIDs involve inhibiting the synthesis of PGI2 and PGE2, which are hyperalgesic pain mediators in peripheral tissues, and partially inhibiting the synthesis of prostaglandins in pain-related synapses in the central nervous system (6). NSAIDs form the basis of treatment for inflammatory arthropathies like rheumatoid arthritis, osteoarthritis, and pain and stiffness associated with musculoskeletal disorders, providing symptomatic relief to thousands of patients (7-9). Clinicians routinely prescribe NSAIDs for mild to moderate pain (10,11). They are the most frequently prescribed analgesic drugs worldwide, and their efficacy in treating acute pain has been well demonstrated (10). NSAID treatment should aim to provide effective analgesia with the lowest possible incidence of side effects (8). However, their clinical use is significantly limited due to their tendency to cause ulceration and bleeding in the gastrointestinal system (12). Observational studies have shown that the use of NSAIDs is associated with approximately a fourfold increase in the risk of upper GI bleeding/perforation (13). These side effects of NSAIDs significantly increase hospitalizations, mortality rates, and healthcare costs.

NSAIDs are classified into two groups based on their effects on the cyclooxygenase enzyme: non-selective cyclooxygenase inhibitors and selective COX-2 inhibitors. All NSAIDs cause some gastrointestinal side effects (pain, diarrhea, bloating) (5). However, selective COX-2 inhibitors only inhibit the COX-2 enzyme and therefore cause less gastric ulceration (5) and bleeding than non-selective NSAIDs, and they are reported to have a more favorable side effect profile in the gastrointestinal system compared to non-selective NSAIDs (14). Other side effects of NSAIDs include abnormal liver function tests, hematological effects, non-allergic angioedema, bronchospasm, or urticaria (5). Renal and cardiovascular effects associated with NSAIDs are seen particularly in elderly adults, patients with renal dysfunction, and patients with cardiovascular disease (5).

Drug interactions should also be considered when using NSAIDs. If the patient is taking aspirin for cardioprotective reasons, simultaneous use of NSAIDs should be avoided. The combined use of NSAIDs and aspirin negates the antiplatelet effect of aspirin and increases the risk of thromboembolic events (5). The use of COX-2 inhibitor NSAIDs should be avoided in patients at risk of stroke (5).

Asemetazine

Pharmacokinetic and Pharmacodynamic Properties

Asemetazine is the glycolic acid ester of indomethacin, a potent NSAID developed by Boltze and colleagues (10,12,15,16). Asemetazine is a prodrug and exerts its effect by being converted to indomethacin in the body (16). It has been suggested that its lower gastrointestinal side effects compared to indomethacin are due to its action as a prodrug (12). However, in vitro, studies have reported that asemetazine, in addition to being converted to indomethacin, directly affects the cyclooxygenase enzyme (12,17). The lower gastric and renal toxicity profile of asemetazine has been attributed to its strong COX-2 inhibition and weak COX-1 inhibition effect (12). Moreover, the gastric tolerability and gastroprotective effect of asemetazine are likely due to the production of lipoxins by acetylating COX-2 in the gastric epithelium, similar to acetylsalicylic acid (17).

When taken orally, asemetazine is rapidly absorbed, metabolized, and converted to indomethacin (18,19). It has been found that the peak plasma concentrations of asemetazine and its metabolite indomethacin are reached 2.4 to 4 hours after oral administration (20). After reaching steady-state concentrations (7 days), the elimination half-life for asemetazine in young and elderly groups was found to be 1.1 hours and 1.0 hours,

respectively; for indomethacin, it was 7.1 and 7.2 hours (20). The recommended dose is 30 to 60 mg once to three times a day or 90 mg extended-release capsules twice a day with meals (21). Daily doses above 180 mg should not be administered for more than 7 days (21).

The main pharmacodynamic properties include strong COX-2 and weak COX-1 inhibition, inhibition of prostaglandin release, inhibition of histamine release from mast cells, analgesic effect, anti-inflammatory effect, and gastroprotective effect.

What Diseases Is It Used For?

Asemetazin is indicated for the treatment of symptoms and signs of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, as well as acute gout arthritis, acute musculoskeletal pain, postoperative pain, and dysmenorrhea (21). Clinical studies have shown that asemetazin is an effective and safe treatment option for acute and chronic pain (16).

In the randomized controlled study by Chou and Tsai on 42 patients with osteoarthritis, it was reported that asemetazin had similar efficacy to indomethacin and was better tolerated, especially in relation to the gastrointestinal system (22). In a study by Saul and colleagues comparing asemetazin and indomethacin in the treatment of rheumatoid arthritis, the drug effects were similar, and gastrointestinal and central nervous system side effects were significantly less in those using asemetazin (7). In a clinical study conducted by Rechziegler and von Bernuth in patients with rheumatic diseases, the analgesic effect of asemetazin was found to begin most frequently between the 40th minute and 2nd hour following oral intake, and during the seven-day treatment, both spontaneous pain and pain with movement either disappeared or improved in 90% of all patients (3). In the randomized controlled study by Leeb and colleagues, it was shown that in the short-term treatment of patients with osteoarthritis, asemetazin caused a significant reduction in pain, increased function of the affected joint, and significantly improved quality of life (14).

In a 1981 study conducted with a small sample size, it was evaluated for efficacy against symptoms of acute upper respiratory tract infection, and both asemetazin and indomethacin were found to be effective against symptoms thought to be associated with fever, such as fever, headache, muscle and joint pain, and general weakness (18). The maximum antipyretic effect was achieved 3 hours later, and the average body temperature remained at the lowest level for 4 hours (18). Studies demonstrating its efficacy in the treatment of hemicrania in children, adolescents, and adults are also available (23,24).

However, there are also authors who report that its efficacy in some pain treatments has not been sufficiently investigated (10). In a Cochrane review investigating the use of single-dose analgesics for postoperative pain, no controlled clinical trials related to the use of asemetazin were identified (10). The authors of this study reported that there is a lack of studies clearly demonstrating the analgesic efficacy in the most basic acute pain studies and that its use in other indications should be used with caution (10).

Side Effects

The primary side effects of NSAIDs are the unwanted effects on the gastrointestinal system. The primary gastrointestinal side effects of asemetasin include complaints such as loss of appetite and nausea, and the severity of these side effects is generally mild to moderate (14,18,25). Rarely, it may cause gastrointestinal side effects such as gastrointestinal bleeding, ulcers, changes in stool color, and diarrhea (21). The side effect rate reported in Rechzieglerin's study is 3.3% (3). Additionally, many studies have reported that asemetasin causes less stomach damage compared to other NSAIDs (17). While selective COX-2 inhibitors are associated with higher cardiovascular risk, non-selective COX inhibitors are associated with higher gastrointestinal risk (11). There have been reported cases of both hypertension and hypotension with the use of asemetasin. In a long-term study, hypotension, edema, chest pain, and thrombophlebitis were reported in 1 out of 280 cases (21). In the same study, itching was observed in 19 out of 280 cases, sweating in 3, eczema in 2, erythema in 1, exanthema in 1, and hair loss in 1 (21). In the case report by Cebeci and colleagues, drug eruptions due to asemetasin use were reported (26). Sometimes, headache, dizziness, drowsiness, or sleepiness may be seen with asemetasin (21). Anxiety, confusion, psychosis, hallucinations, depression, peripheral neuropathy, and irritability are less frequently reported side effects associated with asemetasin treatment (21). Visual disturbances such as diplopia and blurred vision have been reported, and with long-term use of asemetasin, pigmentary retinopathy and corneal opacities may occur (21). Individual cases of acute renal failure associated with asemetasin treatment have been reported (21). Symptoms that can be interpreted as concomitant drug interactions at a rate of 0.1% have been observed (3).

Use in Elderly and Specific Patient Groups

Elderly patients are more sensitive to the side effects of NSAIDs (8). Studies show that there is no drug accumulation in elderly patients with asemetasin use and that the need for dose adjustment is low in elderly patients from a pharmacokinetic perspective (20,21). Comparing the results of use in young and elderly individuals reveals that both groups metabolize asemetasin similarly (4). Elderly patients, patients with cardiovascular disease, or patients with renal dysfunction, who frequently need to use NSAIDs, will benefit more from drugs with lower renal excretion (e.g., asemetasin, diclofenac, and etodolac) (11). A study conducted with 60 milligrams of asemetasin daily for seven days showed no statistically significant difference in the pharmacokinetic profiles of patients with varying degrees of renal failure (20 to 70 mL/min) and patients with normal renal function. This indicates that dose reduction is not necessary in patients with renal failure (21). Patients undergoing polymedical treatment, elderly patients, and patients with chronic alcohol abuse will be at a lower risk of side effects with NSAIDs undergoing phase 2 liver biotransformation (e.g., asemetasin and diclofenac) (11).

Conclusion

Applying effective treatment against acute, traumatic, and rheumatic origin pain and inflammation, providing an antipyretic effect, reducing the morbidity and mortality associated with NSAIDs, facilitating compliance with the treatment, ease of dosage and application, rapid onset of action, and low cost are generally accepted results for asemethazine (4). Consequently, asemethazine is a good option in pain treatment, as it is effective

orally, has sufficient analgesic effect, has a low gastrointestinal side effect profile, and does not cause tolerance or dependency. However, there are many studies with large sample sizes in the literature on the use of NSAIDs in pain treatment. More studies are needed to evaluate the effectiveness of asemethazine in different indications of pain treatment. Due to its safe and effective use over the years and its relatively less data in the current literature, this subject could be a research target for researchers.

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Author Contributions	Author Initials
SCD Study Conception and Design	HC, MA, EKA
AD Acquisition of Data	HC, MA
AID Analysis and Interpretation of Data	MA, EKA
DM Drafting of Manuscript	HC, MA, EKA
CR Critical Revision	HC, EKA

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