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Mini Review

Acemetacin in Acute and Chronic Pain Management

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Abstract

Acemetacin is the carboxymethyl ester of indomethacin and is a pro-drug precursor compound, in other words, a prodrug. The pharmacologically active metabolite of acemetacin is also indomethacin. Acemetacin exerts its potent non-steroidal anti-inflammatory effects in the body as indomethacin. It is known that acemetacin is not only a prodrug of indomethacin, but also an agent with gastric protective mechanisms, possibly involving a reduction in leukocyte adhesion, and that acemetacin exerts gastric protective effects by exhibiting less efficacy on the COX-1 enzyme in the gastric mucosa compared to direct indomethacin use. It is clear that acemetacin is a valuable NSAID for acute and chronic pain.

Keywords: Acemetacin, indomethacin, non-steroidal anti-inflammatory drugs.

Introduction

Acemetacin is a derivative of indoleacetic acid (the carboxylmethyl ester form of indomethacin) and an analgesic from the non-steroidal anti-inflammatory drugs (NSAIs) group. It is indicated for the treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, acute gouty arthritis, acute musculoskeletal pain, postoperative pain and dysmenorrhea [1,2].

Acemetacin is the carboxymethyl ester of indomethacin and is a pro-drug precursor compound, in other words, a prodrug. The pharmacologically active metabolite of acemetacin is also indomethacin. Acemetacin exerts its potent non-steroidal anti-inflammatory effects in the body as indomethacin. It is known that acemetacin is not only a prodrug of indomethacin, but also an agent with gastric protective mechanisms, possibly involving a reduction in leukocyte adhesion, and that acemetacin exerts gastric protective effects by exhibiting less efficacy on the COX-1 enzyme in the gastric mucosa compared to direct indomethacin use. Due to the side effects of indomethacin, acemetacin was developed to obtain a safer drug and better gastric tolerability was achieved compared to indomethacin [2-7].

A 2008 study on the gastric and intestinal tolerability of acemetacin suggested that this may be related to the lack of induction of leukocyte-endothelial adhesion, which may be attributed to the reduced ability of acemetacin to elevate leukotriene-B4 synthesis and TNF-a expression compared to indomethacin, despite the rapid biological conversion of acemetacin to indomethacin after absorption [7].

180 mg/day of acemetacin and 75 mg/day of indomethacin have been shown to be clinically equivalent in efficacy in studies in which acemetacin acts as a prodrug of indomethacin as a glycolic acid ester, which is metabolized to indomethacin, which acts as a cyclooxygenase inhibitor and produces anti-inflammatory effects [3].

Overview of clinical evidence

In a case published in 2016, a 44-year-old male patient with multiple sclerosis (MS) who had transient osteoporosis of the hip with both hip joints 10 months apart and no history of corticosteroid use was presented. The patient was started on acemetacin 120 mg/day along with several medications and exercise. Two weeks after the start of treatment, the pain decreased, range of motion exercises were started and Acemetacin 120 mg/day was used for three weeks. At the follow-up three months later, the range of motion of the hip joint was found to be complete and painless. Ten months later, the patient presented to the outpatient clinic again with similar complaints in the opposite hip and was diagnosed with transient osteoporosis of the left hip. Acemetacin 120 mg/day was started again and a pair of caned braces was recommended. The patient's symptoms disappeared spontaneously after 20 days without the need for surgical intervention [8].

Also published in 2016, two 18 and 65-year-old patients with os trigonum syndrome and hindfoot pain were recommended to avoid activities requiring forced plantar flexion, ice application in the acute period, use of acemetacin 120 mg/day, use of ankle brace, and reduction of load on the foot. In the clinical follow-up of the patients after 2-3 weeks and 3 months, it was observed that their pain decreased [9].

Acemetacin (120 mg/day) was started as medical treatment in 2 patients diagnosed with spina bifida occultan accompanying painful bipartite patella and it was observed that their pain decreased 7 days after the treatment started [10].

Published in 2022, a patient with a rare diagnosis of idiopathic axillary web syndrome (AWS) was treated with acemetacin 60 mg twice daily [11].

In a case of spondyloepiphyseal dysplasia tarda accompanied by osteoporosis mimicking spondyloarthropathy, acemetacin 90 mg 1x1, tramadol retard 50 mg 1x1 and alendronate sodium at a dose of 70 mg/week for osteoporosis, calcium 1000 mg/day-880 IU vitamin D treatment were started as pharmacologic treatment and it was reported that the patient's complaints decreased significantly after these treatments [12].

Bone marrow edema syndrome is a condition of unknown etiology, characterized by sudden onset and self-limiting localized pain. On Magnetic Resonance (MR) imaging, hypointense and hyperintense signals on T1 and T2 sequences, respectively, are observed in non-specific bone edema that heals without sequelae. In a study involving 17 patients diagnosed with bone marrow edema syndrome between January 2014 and December 2016, it was reported that all patients had a history of sudden onset of foot and ankle pain and that patients who were started on acemetacin/indomethacin and vitamin D from the time of diagnosis would have effective results in their pain complaints [13].

The most common complication of muscle contusions is myositis ossificans. In the acute treatment of myositis ossificans, the principles of resting the affected area, applying cold, applying pressure and keeping the joint above the level of the heart are applied. In these cases, acemetacin can be used for pain in the acute phase [14].

In a 1991 study comparing acemetacin and indomethacin in the treatment of rheumatoid arthritis, the overall response to acemetacin was better than indomethacin, although not statistically significant, and tolerated gastrointestinal and central nervous system side effects were significantly less. It was concluded that acemetacin is effective in the treatment of rheumatoid arthritis but has significant advantages over indomethacin in terms of tolerability [15].

In addition, studies have shown that acemetacin is an effective treatment option in the treatment of osteoarthritis-related pain [3].

A German article published in 1984 described an open clinical study on the occurrence and duration of the analgesic effect of acemetacin in 20 patients suffering from arthrosis of the hip and knee joints. The data of this study reported a rapid onset and long duration of the analgesic effect in the majority of patients with acemetacin, as well as a very good tolerance to acemetacin. According to the results of this study, it is clear that acemetacin is a valuable NSAID for acute pain [16].

In a double-blind parallel-group follow-up study of 60 non-hospitalized patients with extra- articular rheumatism aged 18-67 years, it was found that the use of acemetacin/ indomethacin may significantly improve pain intensity (Table 1) and muscle tenderness (Table 2) in patients with acute pain with extra-articular rheumatism [17].

Table 1: Effectiveness of Acemetacin/indomethacin on Pain Severity in Non-Joint Rheumatism Patients with Acute Pain

Change in Pain Severity in Patients with Non-articular Rheumatism Presenting with Acute Pain						
	None	Mild	Moderate	Severe	Total number of patients	Average Score
Before the Study	0	2	16	6	24	2.2
1 week after treatment	1	14	8	1	24	1.4
2 weeks after treatment	2	15	7	0	24	1.2

[A]p<0.0I

Table 2: Effectiveness of Acemetacin/Indomethazine on Muscle Tenderness in Patients with Non-Joint Rheumatism with Acute Pain

Improvement in Muscle Sensitivity in Patients with Non-articular Rheumatism with Acute Pain						
	None	Mild Sensitivity	Moderate Sensitivity	Severe Sensitivity	Total number of patients	Average Score
Before the Study	0	15	8	0	23	1.3
1 week after treatment	1	16	6	0	23	1.2
2 weeks after treatment	1	17	5	0	23	1.2

[A]p<0.05

According to the results of a double-blind study in 31 patients with dysmenorrhea, acemetacin/indomethacin can significantly improve pain in 71% of patients (Table 3) [18].

Table 3: Improvement in Pain with Acemetacin/Indometacin Treatment in Patients with Dysmenorrhea

Improvement in Pain in Patients with Dysmenorrhoeae	
Very Good Improvement	7
Moderate Improvement	15
Mild Improvement	9

A double-blind comparative study with piroxicam in 28 outpatients with low back pain suggests that acemetacin/indomethacin may improve pain in outpatients with low back pain with significantly higher clinical efficacy (Table 4) [19].

Table 4: Improvement in Pain in Outpatients with Low Back Pain

Acemetacin/Indomethacin	Piroxicam
P < 0.001	P < 0.01

In a double-blind study of 28 patients with osteoarthritis involving one or more joints, it was observed that acemetacin/indomethacin treatment may significantly improve the complaints of patients (Table 5) [19].

Table 5: Improvement with acemetacin/indomethacin in the complaints of patients with osteoarthritis involving one or more joints.

Complaints Improved with Treatment in Patients with Osteoarthritis
Improvement in pain in the joints
Swelling in the joints
Joint stiffness
Limitation of movement

Among the clinical studies in which the use of acemetacin/indomethacin in postoperative pain management was reported to be an effective and safe treatment option, it was reported that acemetacin may be an effective and safe treatment option in the management of pain and inflammation after episiotomy, after varicose vein operation, after photorefractive keratectomy operation, after tooth extraction, after hysterectomy, after thoracotomy and after oral operations (Table 6) [20].

Table 6: Clinical Studies Related to the Use of Acemetacin in Postoperative Pain

Clinical Studies Associated With The Use of Acemetacin in Postoperative Pain	
Pain control after episiotomy	Irish Journal of Medical Science 1992; 161(8):493-7.
Pain management after varicose vein operation	Journal of International Medical Research 1978; 6(2):152-6. The Journal of International Medical Research 1974; 2:203-9 Current Therapeutic Research 1976; 20(2):134-41.
Pain management after photorefractive keratectomy	Ophthalmic Surgery and Lasers 1998;29(5):365-74
Pain management after tooth extraction	L'Information Dentaire 1983; 65(35):3241-5. Oral Therapeutics and Pharmacology 1987; 6(1):8-16. Current Therapeutic Research 1992; 51(6):937-45.
Pain management after hysterectomy	Acta Anaesthesiologica Scandinavica 1989; 33(6):498-501
Postoperative pain management	British Journal of Anaesthesia 1992; 69(3):304-6.
Pain and inflammation management after intraoral operations	European Journal of Rheumatology and Inflammation 1983; 6(3):259-65.
Pain management after thoracotomy	British Journal of Anaesthesia 1990;65(5):624-7

Hemicrania contunia (HC) is an uncommon, day-long, unilateral, primary headache syndrome with cranial autonomic symptoms. In a very recent Japanese case report published in October 2022, a 21-year-old woman who presented with cranial autonomic symptoms accompanied by persistent moderate headache in the right frontotemporal region was diagnosed with hemicrania continua (HC) according to the 3rd edition of the International Classification of Headache Disorders. As oral indomethacin was discontinued in April 2020, acemetacin, a prodrug of indomethacin, was administered (90 mg/day) and gradually increased to 180 mg/day over 2 months. Hemicrania continua with acute pain was successfully treated with acemetacin with no recurrence [21].

A systematic review of 22 articles on paroxysmal hemicrania in children and adolescents reported that almost all patients benefited from acemetacin/indomethacin. Although paroxysmal hemicrania (PH) is a primary headache disorder belonging to the trigeminal autonomic cephalalgias (TACs) group, it is also reported that the pain was quite severe in the cases included in this review [22].

Primary stabbing headache is a short-term, severe and recurrent headache syndrome, usually in the area corresponding to the first branch of the trigeminal nerve. Acemetacin/indomethacin is the first choice of treatment because of the good pain response [23-25].

According to the international classification of headache disorders, headache associated with sexual activity is defined as bilateral (in some cases unilateral) occipital or diffuse blunt pain. In a 2017 case report, male and female patients in their 30s were advised to take acemetacin/indomethacin 30-60 minutes before sexual activity. The patients stated that they used acemetacin/indomethacin twice as a preventive treatment, experienced sexual activity several times without taking medication, but did not experience headache. The patients had no similar complaints during the two-year follow-up. Acemetacin/Indomethacin can be used as prophylaxis (30-60 minutes before sexual activity) or after activity for acute treatment [25-31].

Headache triggered by coughing and straining without an intracranial disorder is called primary cough headache and, in its treatment, pulmonary problems that may cause cough should be investigated and treated first. For the first time, Mathew reported that acemetacin/indomethacin was effective in two patients with benign headache cough [32].

Acemetacin/indomethacin is the most effective option in primary exercise headache, which is a headache triggered by exercise. Although the mechanism of action is not fully understood, it is suggested that it acts by decreasing CSF pressure [32-35].

Frequently recurrent headaches that occur only during sleep and awaken from sleep, without characteristic accompanying autonomic symptoms (nausea, photophobia, phonophobia may be one of them) and cannot be attributed to another pathology are called hypnic headaches. Indomethacin is a more effective treatment option for prophylactic treatment, especially in the presence of unilateral pain and trigeminal autonomic symptoms [36,37].

Acemetacin/indomethacin therapy is often preferred as a short-term but effective treatment to control pain after hemorrhoidectomy [38].

In the study data comparing the effects of acemetacin and indomethacin on children and adolescents in the posttraumatic and postoperative period, the analgesic effect was good to very good in 76.7% of the patients treated with acemetacin, but only 66.7% in the indomethacin group, and the tolerability of acemetacin was very good [39].

Pain, which is the main source of dental anxiety, is undesirable by patients and clinicians. Therefore, pain control during and after root canal treatment is of great importance in endodontic practice. Many analgesics have been used to prevent pain after root canal treatment, with nonsteroidal anti-inflammatory drugs (NSAIDs) often being the first choice. In addition to ibuprofen, acemetacin can also be considered among the NSAID group of drugs [40].

In a case published in 1999, an 80-year-old woman with a history of severe osteoporosis and chronic polyarthritis was successfully treated with a fixed mandibular prosthesis supported by 6 implants, during which the patient was treated with acemetacin [41].

Conclusion

Clinical studies have shown that acemetacin is an effective and safe treatment option for acute and chronic pain [2-7].

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