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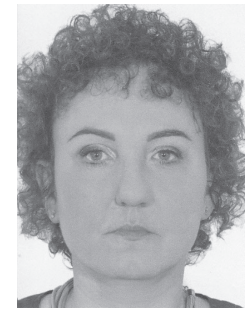
Aceclofenac-induced gastrointestinal adverse reactions – a case report and literature review



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Abstract

Background. Back pain is a prevalent ailment (experienced by almost every adult), which has made it a civilization problem, especially in highly developed countries. Aceclofenac is an oral nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory and analgesic properties widely used for the treatment of ailments such as low back pain, scapulohumeral periarthritis, extraarticular rheumatism, odontalgia, osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Aceclofenac is generally well tolerated. Although it is considered to have a better gastrointestinal profile than other NSAIDs, it may induce gastrointestinal adverse reactions. Material and methods. We describe a case report of a 36-year-old patient who experienced gastrointestinal adverse reactions in the form of nausea, indigestion, and abdominal pain, during the treatment with aceclofenac. Results. Aceclofenac was discontinued, mesoprolol was recommended at 20 mg/day, and the analgesic therapy was modified - oral tramadol and paracetamol were introduced. Conclusions. The described case confirms the risk of gastrointestinal complications following the administration of aceclofenac. *Anestezjologia i Ratownictwo 2023; 17: 19-24. doi:10.53139/AIR.20231703*

Keywords: Aceclofenac, NSAIDs, back pain, adverse drug reactions, gastrointestinal adverse reactions

Introduction

Back pain is one of the most prevalent and well--documented health problems. It is a general term for pain felt on the dorsal side along the body's vertical axis. Pain can occur in any section of the spine, but it is usually located in the lumbosacral section (low back pain) [1]. Although its burden is often considered trivial, back pain may cause activity limitation, significant rates of disability, and absenteeism from work in people around the World. In recent decades the apparent increase in disability caused by low back pain decades occurred in low-and middle-income countries. This condition entails high medical and socioeconomic costs [2,3]. In 2017, the estimated prevalence of people with low back pain was 7.5%, which means that 577 million people were affected at that time [2]. It is estimated that over 70% of the population up to 40 years of age experienced pain in the lumbar region. In turn, pain in the cervical spine is the second most common pain syndrome and affects up to 50% of the population [4]. Back pain can result from a broad range of potential etiologies, but most commonly, it is mechanical or non-specific [3,5,6]. The course of back pain can be acute (lasting about four weeks), chronic (lasting more than three months), and recurrent. Recurrent pain is acute pain and occurs after an asymptomatic period in patients who have experienced episodes of pain in a similar location [7,8]. Environmental factors increasing the risk of back pain include smoking, diabetes, blood vessel diseases, infections, old age, chronic stress, depression, overweight, and primarily, reduced physical condition [1,9,10]. However, it is believed that biomechanical causes related to static and dynamic overloading of the joint and ligament apparatus of the spine play the most vital role in the formation of pain syndromes. The most important mechanical risk factors are heavy lifting or frequent

lifting, subjecting the body to vibration (driving), frequent bending or twisting of the trunk, and long--term uncomfortable postures. Also, an incorrect posture while sitting (when the lumbar and thoracic spine are incorrectly positioned) greatly impacts the development of back pain. Attention should also be paid to the work-associated overloading of the spine and frequent non-compliance with the rules of work hygiene [1,10]. Back pain and associated dysfunction syndrome are now considered lifestyle diseases, along with hypertension and diabetes [10]. Management of low back pain and identifying effective treatments are constantly developing, yet still remain challenging for researchers and clinicians because of large variations in the manifestations, possible causes, course, prognosis, and consequences in terms of activity interference and quality of life [11]. Apart from that, the overuse of imaging, opioids, and surgery remains a widespread problem [12]. Lifestyle, adherence to the principles of prophylaxis, and conservative treatment greatly impact the inhibition of the disease process. It is important to lead an active lifestyle to maintain an appropriate weight, muscle strength, and joint mobility. Knowledge and application of the principles of ergonomics at work and during everyday activities help to avoid overloading the spine [1]. Back pain management guidelines endorse triage to identify the cases of low back pain caused by medically serious pathology requiring specialistic diagnosis. Many patients require little, if any, proper medical care. As non-specific low back pain does not have a known pathoanatomical cause, the treatment is symptomatic and focused on reducing pain and its consequences. Currently, two treatment strategies are used- a stepped approach with simpler care at the beginning that progresses if the patient does not respond, and simple risk prediction methods to individualize the amount and type of care provided [12]. Conservative treatment should include physiotherapeutic treatment, psychotherapy, education, and pharmacotherapy. According to American College of Physicians (ACP) recommendations, acute or subacute low back pain should be treated with non-drug therapies such as superficial heat, massage, acupuncture, or spinal manipulation. If drug therapy is needed, nonsteroidal anti-inflammatory drugs (NSAIDs) or skeletal muscle relaxants are advised [13]. Pharmacotherapy is used in the acute phase to support the patient's return to usual activities as soon as possible. In the case of chronic low back pain, pharmacotherapy should be implemented if it is considered potentially helpful to improve activating measures, or when the patient still has an intolerable functional impairment due to pain despite the appropriate performance of these measures. The evidence showing that treatment with drugs relieves acute and chronic non-specific low back pain is moderate with a low-to-intermediate effect size. Moreover, long-term pharmacotherapy entails relevant risks, including major adverse effects [14]. One of the analgesics prescribed for musculoskeletal disorders is aceclofenac.

Case report

In this report, we describe a case of a 36-year-old patient, not chronically ill, with a normal BMI, who came to the general practitioner because of lower back pain. The patient has a sedentary lifestyle, but he has been doing housework for several days requiring heavy lifting. On the second day, the patient experienced pain in the lumbosacral region, which became the reason for the inability to work and the deterioration of the quality of life. Due to pain, the patient used paracetamol in a daily dose of 3g and an ice compress for two days. Because of the lack of improvement on the third day, the patient started using topical NSAIDs (ibuprofen, naproxen). On the fifth day of pain onset, oral aceclofenac was introduced at 200 mg/day. Modifying the therapy resulted in reduced back pain; however, on the third day of oral treatment with aceclofenac, the patient experienced gastrointestinal complaints - nausea, indigestion, and abdominal pain, which persisted throughout the duration of the drug treatment (5 days). After consultation with the doctor, aceclofenac was discontinued, mesoprolol was recommended at 20 mg/day, and the analgesic therapy was modified - oral tramadol, and paracetamol were introduced.

Discussion

Aceclofenac, a derivative of aminophenylacetic acid, belongs to the group of nonsteroidal anti-inflammatory drugs. It was first approved in the EU in 1990, and since then, it has been approved for use in 69 countries worldwide [15-16]. Aceclofenac is recommended for the treatment of inflammatory and painful processes, including low back pain (LBP), odontalgia, scapulohumeral periarthritis, extraarticular rheuma-

tism, osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis (AS). The authorized indications may vary between countries [17]. Aceclofenac is a potent inhibitor of cyclooxygenase (COX), which is a key enzyme in synthesizing prostaglandins and thromboxanes with selectivity for COX-2. The drug has little effect on COX1 [16,17]. In vitro studies have shown that aceclofenac inhibits inflammatory mediators such as PGE2, interleukin 1β (IL1β), IL6, and TNFα, which are involved in developing chronic inflammation, including synovitis. One of the important mediators of inflammation inhibited by aceclofenac is IL1 [16]. Aceclofenac was proven to inhibit prostaglandin synthesis in synovial fluid from patients with acute knee osteoarthritis and in peripheral blood leukocytes from patients with osteoarthritis [18]. A study by Alvarez-Soria found that a dose of 100 mg twice daily for 3 months inhibited COX-2 synthesis in the knee synovial membrane of 30 patients with osteoarthritis scheduled for total knee replacement surgery compared with patients with osteoarthritis who refused to take NSAIDs (control group). Aceclofenac reduced PGE2 in the synovial fluid and protein expression at the synovial membrane [19]. Another study by Alvarez-Soria showed that 3-months treatment with aceclofenac in 30 patients with osteoarthritis scheduled for knee replacement surgery decreased IL-1β-induced release of PGE2 and decreased the synthesis of COX-2 and microsomal prostaglandin E synthase (mPGES)-1 in the cartilage and chondrocytes. Moreover, aceclofenac reduced IL-1β-induced expression of TNFα and IL-1β in cultured osteoarthritis chondrocytes [20]. After oral administration, the drug is absorbed at 100%, and the maximum concentration is reached 1.25-3 hours after administration (Tmax); food does not affect the degree of drug absorption, but it must not be forgotten that Tmax is prolonged. After penetrating the synovial fluid, aceclofenac concentrations reach approximately 57% of those in the plasma. Aceclofenac is almost completely protein bound (>99%), and its volume of distribution is approximately 25 L. Aceclofenac is metabolized in the liver by CYP2C9. Rapid biotransformation of the drug in hepatocytes results in the formation of 4'-hydroxyaceclofenac and several minor metabolites, including 5-hydroxyaceclofenac, diclofenac, 4'-hydroxydiclofenac. The drug does not accumulate and is characterized by a short biological half-life (T0.5), which is about 4 hours, which facilitates the elimination of the drug during the day and translates into shorter gastrointestinal tract exposure time. Aceclofenac is mainly excreted as glucuronides in the urine (70-80%). The elimination parameters of the drug do not change in elderly patients; therefore, it does not require dose adjustment in this population. It is worth noting the possibility of converting the parent substance into active metabolites in places of inflammation, which significantly prolongs and increases the anti-inflammatory effect of aceclofenac [15,16]. Aceclofenac is generally well tolerated, with a safety profile consistent with that expected of NSAIDs; however, it causes fewer adverse effects from the upper gastrointestinal tract (bleeding, perforation) than conventional NSAIDs. The efficacy and tolerability of aceclofenac (200 mg/24 h) and paracetamol (3000 mg/24 h) were evaluated in patients with knee osteoarthritis (n = 168). The Visual Analogue Scale (VAS) was used to assess the severity of pain in patients, and the Lequesne scale was used to determine the severity of osteoarthritis. The frequency of adverse effects was comparable in both analyzed groups, but a more effective analgesic treatment was demonstrated for aceclofenac. Similar clinical effects were observed when aceclofenac at 100 mg/12 h was compared to diclofenac at 75 mg/12 h [16]. Aceclofenac in a dose of 100 mg twice daily has also been efficacious in patients with low back pain. Schattenkirchner et al. performed a randomized, double-blind, multicenter non-inferiority study in patients with uncomplicated acute lumbosacral pain suffering from degenerative spinal disorders. The trial included 227 patients randomized to receive either aceclofenac 100 mg twice daily (n = 100) or diclofenac resinate 75 mg twice daily (n = 105) for up to 10 days. The study's outcome revealed that aceclofenac was non-inferior (primary endpoint) and superior to diclofenac in terms of analgesic efficacy; however, the between-group difference in the score was not considered clinically relevant [21]. The most common adverse events reported in clinical studies and during the post-marketing experience with aceclofenac were gastrointestinal disorders (dyspepsia, abdominal pain, nausea, and diarrhea), dizziness, and increased hepatic enzymes. Rarely, there were also reports of peptic ulcers or GI bleeding (≥1/10,000 to <1/ 1000) and very rare intestinal perforation (<1/10,000), which may be fatal at times, particularly in the elderly [22]. It seems that aceclofenac is tolerated better than several other NSAIDs, such as naproxen, piroxicam, indomethacin, and ketoprofen, and has a tolerability profile

generally resembling that of tenoxicam and paracetamol [15]. The analysis of all spontaneous adverse reactions recorded in the pharmacovigilance database of the World Health Organization Collaborating Center for International Drug Monitoring during the first year after the introduction of the drugs in the UK, revealed that the incidence rate (adverse reactions/106 defined daily dose) of total adverse reactions with aceclofenac was lower than with meloxicam or rofecoxib. Moreover, this analysis showed that aceclofenac had lower incidences of GI bleeding, abdominal pain, and arterial hypertension than meloxicam or rofecoxib and a lower incidence of liver toxicity, thromboembolic cardiovascular events, arterial hypertension, and edema than rofecoxib [23]. According to a large (n =10,142 patients), 12-month prospective, observational study in patients with rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis receiving aceclofenac (n = 7890) or diclofenac (n = 2252), the overall incidence of adverse events was significantly lower in aceclofenac than in individuals taking diclofenac. Both diclofenac and aceclofenac were generally well tolerated, with mild or moderate adverse reactions- the most common adverse effect of both drugs were mild or moderate gastrointestinal reactions (dyspepsia, abdominal pain, diarrhea, nausea), which occurred in significantly fewer aceclofenac than diclofenac recipients. Central Nervous System adverse drug reactions (ADRs) occurred in less than 3% of patients in the two treatment groups, with a higher incidence in patients taking aceclofenac than diclofenac - there were higher incidences of dizziness, depression, and headache with aceclofenac [24]. The results of a 6-week randomized controlled trial by Pareek et al. showed that mild or moderate gastrointestinal adverse events (GI AEs) (including dyspepsia, abdominal pain, and nausea) were experienced by fewer patients receiving aceclofenac (n =284) than diclofenac (n = 285) [25]. Patel et al. aimed to analyze the effects on pain, function, and safety of aceclofenac compared with other NSAIDs or pain relief medications in patients with osteoarthritis. They performed a meta-analysis of seven randomized clinical trials, and no significant difference between aceclofenac and comparators (diclofenac, naproxen, piroxicam, and paracetamol) was found in terms of the occurrence of adverse events (AEs), withdrawal rates, adverse events-related withdrawal rates or withdrawal rates due to GI AEs. This analysis also confirmed a lower relative risk of GI AEs in patients taking aceclofenac compared to diclofenac and piroxicam [26]. NSAIDs have also been associated with renal, cardiovascular, and dermatological adverse events. However, in the case of aceclofenac, there were uncommon to very rare occurrences of cardiac disorders (cardiac failure -rare- and palpitations -very rare- occurrences), renal disorders (e.g., increased blood urea and blood creatinine- uncommon), and skin and subcutaneous tissue disorders (e.g., pruritus, rash and dermatitis- uncommon) [22]. Considering recommendations for the use of aceclofenac in the elderly, dosage modifications are not required as the pharmacokinetics of this drug are not significantly altered in this population. However, older patients are at higher risk of impaired renal, cardiovascular, or hepatic function, bleedings from the gastrointestinal tract, ulceration, or perforation, and are more likely to receive concomitant medication, which may increase the risk of interactions and adverse reactions. Particular caution should be exercised when NSAIDs are used concomitantly with systemic corticosteroids, anticoagulants (e.g., warfarin), selective serotonin-reuptake inhibitors, or antiplatelet agents, as the risk of GI bleeding or ulceration may be increased [15]. Jeong et al. aimed to evaluate the overall incidence and patterns of adverse events, the effectiveness of aceclofenac controlled-release (CR), and the differences in incidence rates of the AEs in the Korean population. The study included 14,543 subjects, who were administered one tablet of aceclofenac CR (200 mg once a day) and were observed for four weeks post-administration. Among the patients, 143 AEs were reported in 125 subjects, and of these, 121 adverse drug reactions were reported in 107 participants. No serious adverse events were reported. The most commonly reported adverse events were gastrointestinal disorders, such as heartburn and gastrointestinal disorders (66/14,543 subjects, 73 cases). The incidence rates of AEs occurred higher in females, inpatient treatment, individuals with concurrent disorders, and those receiving concomitant medications, respectively. The study confirmed that for aceclofenac CR no severe adverse reactions were observed (exceeding those previously reported for conventional drug formulation safety results in routine clinical practice settings) [27]. Aceclofenac is generally well tolerated and appears to have a more favorable gastrointestinal profile than other NSAIDs. Thus, this drug seems a useful option for managing pain and inflammation across a wide range of painful conditions.

Summary

The most effective treatment of low back pain should be a multidisciplinary rehabilitation intervention of a psychobiosocial nature. However, in some cases, pharmacotherapy is in favor. Aceclofenac is a nonsteroidal anti-inflammatory drug, efficacious in treating a broad range of musculoskeletal disorders. The advantages of aceclofenac include preferential selectivity towards cyclooxygenase 2 (COX-2) induced during inflammation and only slight inhibition of the constitutive function of COX-1. Although aceclofenac is an effective medication with a favorable safety profile, especially regarding gastrointestinal adverse effects, gastrointestinal symptoms may occur as in the described case. Thus, the physician must carefully weigh the risks and benefits of pharmacotherapy when starting pharmacotherapy with aceclofenac.

Conflict of interest
None

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