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Nimesulide-induced hepatotoxicity – a case report and literature review

Hepatotoksyczność nimesulidu – opis przypadku i przegląd piśmiennictwa

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Summary

Background. Nimesulide is a drug from the NSAID group with a multidirectional mechanism of action. It is one of the preferred COX-2 inhibitors with a potent anti-inflammatory and analgesic effect in moderate pain, prescribed for painful osteoarthritis and primary dysmenorrhea. It is recommended for patients requiring a strong analgesic effect and may be more beneficial than other NSAIDs because of the lower risk of gastrointestinal bleeding. Nevertheless, its use has many contraindications and arouses controversy in the medical community, as it may have a hepatotoxic effect. ***Material and methods.*** We describe a case report of a 63-year-old woman who experienced an adverse reaction of abdominal pain resulting from impaired liver functions during the therapy with nimesulide. ***Results.*** The symptoms resolved after discontinuation of nimesulide, introducing dietary changes and a drug containing phospholipids. ***Conclusions.*** The described case confirms the risk of gastrointestinal adverse reaction in the form of impaired liver functions during the therapy with nimesulide. *Geriatria 2021; 15: 274-278. doi: 10.53139/G.20211532*

Keywords: nimesulide, adverse drug reactions, abdominal pain, hepatotoxicity

Streszczenie

Wstęp. Nimesulid to lek z grupy NLPZ o wielokierunkowym mechanizmie działania. Jest to jeden z preferowanych inhibitorów COX-2 o silnym działaniu przeciwzapalnym i przeciwbólowym w leczeniu bólu o umiarkowanym nasileniu, przepisywany w przypadku bolesnej choroby zwyrodnieniowej stawów i pierwotnego bolesnego miesiączkowania. Jest zalecany pacjentom wymagającym silnego działania przeciwbólowego i może okazać się bardziej korzystny w porównaniu z innymi lekami z grupy NLPZ ze względu na mniejsze ryzyko krwawień z przewodu pokarmowego. Niemniej jednak jego stosowanie ma wiele przeciwwskazań i budzi kontrowersje w środowisku medycznym, gdyż może mieć działanie hepatotoksyczne. ***Materiał i metody.*** Przedstawiamy przypadek 63-letniej pacjentki, u której wystąpiły działania niepożądane w postaci bólu brzucha wynikającego z pogorszenia funkcji wątroby w trakcie stosowania nimesulidu. ***Wyniki.*** Objawy ustąpiły po zaprzestaniu terapii nimesulidem i wprowadzeniu zmian w diecie oraz leku zawierającego fosfolipidy. ***Wnioski.*** Opisany przypadek potwierdza ryzyko wystąpienia działania niepożądanego w postaci upośledzenia funkcji wątroby, jako następstwa terapii nimesulidem. *Geriatria 2021; 15: 274-278. doi: 10.53139/G.20211532*

Słowa kluczowe: Nimesulid, działania niepożądane leku, ból brzucha, hepatotoksyczność

Introduction

Nimesulide (N-(4-Nitro-2-phenoxyphenyl)-methanesulfonamide), a non-steroidal anti-inflammatory drug (NSAID), is a potent anti-inflammatory, antipyretic and analgesic drug for moderate pain. Nimesulide was discovered in 1971, and the first marketing authorization for it was issued in 1985 in Italy. This drug is indicated for the treatment of acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhea; however, it should only be prescribed as second-line treatment. Nimesulide has a pleiotropic effect in patients with inflammatory

pain. Due to the numerous actions that effectively eliminate the symptoms of inflammation, it is a drug with high efficacy in the treatment of receptor pain with an inflammatory component. Moreover, nimesulide has also been associated with antitumor activity. Nimesulide is a weak acid (pKa = 6.5) characterized by the presence of an active sulfonanilide group. It is a relatively selective cyclooxygenase (COX)-2 inhibitor, which works by inhibiting the activity of cyclooxygenase, an enzyme involved in the synthesis of prostaglandins [1-4]. It significantly modifies the inflammatory environment, contributing to the increased effectiveness of the anti-inflammatory and analgesic effect by: inhibiting the aggregation and migration of neutrophils, inhibiting the synthesis and release of histamine, inhibiting the generation of oxygen free radicals at the site of inflammation, inhibiting the activity of nitric oxide synthase, inhibiting the production of platelet-activating factor, inhibiting the synthesis of metalloproteinases, inhibiting cytokine-induced inflammation, in particular interleukin 6, inhibition of synthesis and release of substance P, inhibition of phosphodiesterase IV, and direct supraspinal analgesic effect. Therefore, it is a drug with a multidirectional mechanism of action, as it can act on various inflammatory mediators and metabolic pathways activated in inflammation [3]. The mechanism of action of nimesulide is mainly based on the inhibition of COX-2 – it is blocked by the drug approximately 20 folds more than COX-1, however weaker than selective (specific) COX-2 inhibitors. Compared to selective COX-2 blockers, nimesulide appears to have the advantage of inhibiting COX-1 to some extent, as COX-1 production may be induced in the ongoing inflammatory process. In contrast, the anti-inflammatory effect of selective COX-2 inhibitors at therapeutic doses does not extend to the blocking of COX-1. It has been shown that nimesulide's anti-inflammatory and analgesic effects are not solely based on the preferential inhibition of COX-2. This drug also reduces the production and release of tissue-damaging oxygen free radicals by neutrophils and phagocytes. It lowers their production by inhibiting the activity of myeloperoxidase and phosphodiesterase type IV in leukocytes. It leads to, i.a., reduction in the activity of phospholipase A2 responsible for the release of arachidonic acid- a substrate for the production of prostanoids under the influence of COX- from phospholipids of cell membranes. Therefore, nimesulide blocks the production of eicosanoids both by indirect inhibition of phospholipase A_2 activity and by direct inhibition of COX-2. Nimesulide also reduces the release of lysozyme and β-glucuronidase. It also inhibits the synthesis and release of pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α) and IL-6. This drug has also been shown to activate glucocorticoid receptors, enhancing the anti-inflammatory effects of glucocorticosteroids. Nimesulide also has a chondroprotective effect (significant in the treatment of rheumatic diseases in which the articular cartilage is destroyed), as it reduces the production of plasminogen activators and the interleukin-1 (IL-1) stimulated production of metalloproteinases (MMPs) such as stromelysin and collagenase, which destroy the cartilage extracellular matrix. Since nimesulide can block COX-1, this medication also has the ability to inhibit platelet aggregation. Thus, in comparison with selective COX-2 inhibitors, nimesulide may be more beneficial in patients with coexisting diseases requiring the use of anticoagulants [4]. In Poland, nimesulide is available by prescription in a dose of 100 mg in the form of granules for oral suspension [2]. After oral administration, more than 80% of the dose is absorbed from the gastrointestinal tract, reaching maximum serum concentrations within 1-4 hours. It is 99% bound to proteins (mainly albumin). Therefore, the free drug concentration in patients with impaired liver function may increase several times. There is no significant influence of the patient's age on the drug's pharmacokinetics and its metabolites. Dose adjustment is only necessary for patients over 80 years of age. Dosage should also be reduced in the case of advanced renal failure. In the case of particularly severe hepatic failure, it is advisable to refrain from treatment with nimesulide. Nimesulide is almost completely metabolized in the liver; about 80% of metabolites are excreted in the urine, and the remaining 20% in the feces within 3 days. The half-life ranges from 2 to 5 hours. The drug penetrates the synovial fluid. The available data also seems to suggest that nimesulide accumulates relatively selectively in the foci of inflammation, which is extremely important in rheumatic diseases with an inflammatory component [4]. Important features of nimesulide are: rapid onset of analgesic effect, a large volume of distribution, which in practice translates into good penetration into the inflamed area, and a low risk of interactions, especially pharmacokinetic with other concurrent drugs. An additional feature of nimesulide, considering its analgesic effect, is also an antihyperal-

gesic effect. It has a practical importance for patients who have arthritis and has been proven in clinical trials by comparing nimesulide with other drugs from the NSAID group. Nimesulide is generally well-tolerated, but similarly to other NSAIDs, it should be used in the lowest effective doses for the shortest period necessary to control symptoms, as there is a risk of adverse reactions. Adverse effects can include headache, dizziness, somnolence, gastrointestinal upset, nausea, abdominal discomfort, diarrhea, peripheral edema and hypersensitivity reactions. One of nimesulide's adverse effects, which is of greatest concern, is hepatotoxicity [3, 5, 6]. In the article, we present a case report of a patient who experienced abdominal pain and liver injury during the therapy with nimesulide.

Case report

A 63-year-old female patient reported to a general practitioner due to abdominal pain. Two months earlier, the patient developed knee pain after a fall, initially treated with paracetamol in a dose of 2-4 g/ day. The lack of a satisfactory analgesic effect resulted in the discontinuation of paracetamol and the introduction of topically applied diclofenac. Due to persistent pain in the knee, the patient reported to the family doctor several times. After one week, diclofenac was discontinued, and oral administration of nimesulide at a dose of 100 mg/ day was commenced. The interview conducted before the modification of the therapy excluded simultaneous exposure to the hepatotoxic substances, medications, drugs, alcohol addiction, and active gastric or duodenal ulcer disease. For several years, the patient had been using an effective and safe antihypertensive therapy (amlodipine 5 mg/ day, ramipril 5 mg/ day). Abdominal pain appeared after two weeks of the therapy with nimesulide. Laboratory tests revealed increased levels of aspartate aminotransferase ASPAT (240 U/ l) and alanine aminotransferase ALAT (124 U/ l). The patient was ordered to discontinue nimesulide, use a drug containing phospholipids, and make dietary changes (eating a few smaller, easily digestible meals at regular intervals every 2-3 hours). The laboratory tests performed after a week showed correct values of ASPAT (14 U/ l) and ALAT (28 U/ l).

Discussion

Nimesulide is used in the pharmacotherapy of acute pain, including post-traumatic pain and pain syndromes of the musculoskeletal system, especially in exacerbating pain with an inflammatory receptor mechanism. It is worth recalling that in pain therapy, nimesulide can be combined with opioid analgesics, metamizole, chondroitin and glucosamine to obtain a synergistic effect that helps treat pain. Moreover, in the case of using nimesulide, there is a low risk of interactions with other concurrent drugs, which is an essential aspect of treating patients with multiple diseases [3]. Nimesulide differs from other selective COX-2 inhibitors and classical non-steroidal anti-inflammatory drugs (NSAIDs). The pharmacological profile of nimesulide is peculiar and distinct from the other COX-2 selective inhibitors, suggesting the involvement of other molecular mechanisms besides inhibition of COX-2 derived prostaglandins. Nimesulide is called a COX-2 preferential NSAID, as apart from its overall effect on COX-2, it has a balanced action on both cyclooxygenases. Nimesulide is characterized by the short onset of action, as its gastrointestinal absorption is rapid and complete. The effectiveness of this drug in pain control is due to its fast distribution in the synovial fluid, where it persists longer than in the blood. Nimesulide is recommended in cases when paracetamol occurs ineffective in the treatment of pain [7]. However, there are some contraindications to the use of this medication. Some of them are: history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) to acetylsalicylic acid or other NSAIDs; concomitant exposure to substances with potential hepatotoxic effects; active gastric or duodenal ulcer, previous, recurrent episodes of ulcer or gastrointestinal bleeding, history of central nervous system bleeding, and other active bleedings and disorders associated with bleeding, severe coagulation disorders, heart failure, kidney problems, and liver dysfunction. Nimesulid is not allowed for children under 12 and women during the third trimester of pregnancy and breastfeeding [2]. It should not be taken together with aspirin (increased risks of gastrointestinal and hepatic adverse effects), warfarin (may increase anti-coagulant effect), furosemide (may decrease the oral bioavailability and the natriuretic and diuretic response to furosemide), angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (may decrease the action of these and other antihypertensive drugs). It may also be displaced from binding sites with fenofibrate, salicylic acid, and tolbutamide and may interact with lithium, probenecid and ciclosporin. Nimesulide inhibits the isoenzyme CYP2C9; thus, the serum levels of drugs that are sub-

strates of this enzyme may increase during the use of this medication [2, 8]. Although the anti-inflammatory effect mechanism of nimesulide is similar to other classic NSAIDs, this drug has been recognized as one exerting lower risk of upper gastrointestinal bleeding and protective effect on classic NSAID-induced ulcers, thanks to its preferential activity on COX-2 (comparing to celecoxib and rofecoxib, which are more selective to COX-2, and fail to prevent ulcers) [3, 7, 9]. However, its gastrointestinal safety cannot be ascribed only to a COX-1 sparing effect. Nimesulide's efficacy depends upon a wide spectrum of actions due to the combination of effects on immune and non-immune cells [1, 3, 7]. On the other hand, the most common adverse effects of nimesulide and other NSAIDs are gastrointestinal complaints, and more specifically- injury to gastrointestinal mucosa leading to haemorrhagic lesions and ulcers. The major concern on the use of nimesulide has been the potential liver toxicity. For that reason, nimesulide has been withdrawn from the market in several countries since its use has been associated with a higher risk of hepatotoxicity than other NSAIDs, increasing with dosage and exposure duration [1]. Gastrointestinal adverse effects of classic NSAIDs cannot be related to the COX-1 inhibition alone. Nimesulide seems to be an atypical NSAID, different from non-selective and selective COX-2 inhibitors [9]. The mechanism is probably related to the combined COX-1 and COX-2 inhibition, causing reduced blood flow and increased leukocyte adherence to mesenteric venules. COX-inhibitors may have negative effects probably by causing an imbalance between prostaglandins and leukotrienes/ 5-hydroxyeicosatetraenoic acid (5-HETE) intestinal production and, consequently leading to the disruption of epithelial barrier function, which is a key element for gastrointestinal health [1]. Nimesulide induced hepatotoxicity was first reported in 1997. A number of observational studies that evaluated the safety profile of nimesulide were published; in the world's literature, there are more than 100 cases of clinically apparent liver injury with jaundice linked to nimesulide, even the fatal ones [5-6]. Merlani et al. described a case of a 57-year-old female patient with chronic lumbago who died from the sequelae of acute liver failure induced by nimesulide medication [10]. McCormick et al. reported a case of a 58-year old female who developed fulminant hepatic failure after treatment with nimesulide – the patient had liver transplantation, but she died of multiorgan failure and primary graft non-function 12 h after surgery. Histology of the native liver revealed massive hepatic necrosis [11]. According to a study of Kwon et al., nimesulide was significantly associated with hepatotoxicity in a meta-analysis of five observational studies- rates of reported hepatotoxicity were significantly higher in patients using nimesulide, compared to those treated with other NSAIDs. Of a total of 33 patients approximately 45% either required liver transplantation or died due to fulminant hepatic failure; one third developed hepatotoxicity within less than 15 days of nimesulide administration. The reports indicate that the time to onset has ranged from a few days to 6 months and the usual latency of 4 weeks. The reports usually involved typically hepatocellular pattern of enzyme elevations, and cholestatic forms to a lesser extent. Most cases of liver injury resolve a few days after stopping the treatment with nimesulide. The mortality rate of nimesulide-associated acute hepatitis with jaundice ranges from 10% to 20%; however, the studies using systematic evaluation methods to quantitatively assess the safety profile of nimesulide related to hepatotoxicity in peer-reviewed journals are still lacking [5-6]. Widespread controversy over the safety of nimesulide has led to various regulatory decisions on restrictions its use in various European countries. The use of this medication was restricted or withdrawn from the market in 2002 in Spain and Finland, followed by several other countries [6]. However, the overall risk of liver damage (based on cohort studies) in patients using NSAIDs is relatively low. Hepatotoxicity due to nimesulide therapy occurs mainly in patients with concomitant risk factors for hepatocyte damage before starting treatment. It is worth recalling that the risk of liver damage increases approximately six times in patients receiving more than one NSAID simultaneously, compared to the group not receiving such a combination [3]. Moreover, during the therapy with nimesulide a particular caution should be paid while taking drugs such as anti-convulsants (e.g. valproic acid), anti-fungals (e.g. ketoconazole), anti-tuberculous drugs (e.g. isoniazid), tacrine, pemoline, amiodarone, methotrexate, methyldopa, amoxicillin/clavulanic acid, as they may induce additive hepatotoxic effects [8]. Because nimesulide is a drug intended to treat acute pain, the maximum duration of its continuous use should not exceed 15 days. Patients should also be advised to contact their physician if symptoms suggesting a gastrointestinal complication develop (e.g.

abdominal pain, nausea, vomiting, generalized itching of the skin, jaundice, anorexia) [3].

Conclusion

The therapy with nimesulide raises many controversies. Nevertheless, the choice of nimesulide should be taken into account when a strong analgesic and anti-inflammatory effect is required in patients at risk of damage to the upper gastrointestinal tract and kidneys, as it entails a lower risk of gastrointestinal bleedings compared to other NSAIDs. However, nimesulide should be prescribed only in the absence of concomitant risk factors for hepatotoxicity, as the therapy with this drug may carry a significant risk of liver injury.

Conflict of interest
None

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