Desensitization of hypersensitivity to acetylsalicylic acid in a 63-year-old patient – case report

DESENSYTYZACJA W NADWRAŻLIWOŚCI NA KWAS ACETYLOSALICYLOWY U 63-LETNIEJ PACJENTKI - OPIS PRZYPADKU

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Streszczenie

Wstęp: Reakcje nadwrażliwości na niesteroidowe leki przeciwzapalne (NLPZ) występują nawet u 1,9% populacji europejskiej, stanowiąc istotny problem kliniczny. Możliwe objawy nadwrażliwości na NLPZ obejmują pokrzywkę, obrzęk naczynioruchowy, a także choroby, które mogą ulec zaostrzeniu takie jak astma lub przewlekłe zapalenie zatok z polipami. Przy braku alternatywnej metody leczenia wobec ASA, jedyną opcją terapeutyczną pozostaje desensytyzacja. Procedura ta polega na indukowaniu tymczasowego stanu tolerancji na lek wywołujący reakcję nadwrażliwości.
Opis przypadku: 63-letnia kobieta z chorobą wieńcową serca została skierowana do Kliniki Alergologii Uniwersyteckiego Szpitala Klinicznego w Opolu w celu przeprowadzenia procedury odczulania ASA, z powodu braku innych, korzystniejszych opcji terapeutycznych. W wywiadzie zgłaszała obrzęk powiek, nosa i warg po przyjęciu ibuprofenu 8 lat wcześniej oraz identyczną reakcję rok później po zażyciu ASA. Od tego czasu pacjentka unikała przyjmowania jakichkolwiek NLPZ. Odczulanie przeprowadzono według protokołu Silbermana do dawki całkowitej 150 mg, z dawką podtrzymującą 75 mg/dobę. Pacjentkę wypisano do domu ze skierowaniem do Kliniki Kardiologii oraz zaleceniem zdrowego trybu życia i codziennego przyjmowania ASA.
Wnioski: Procedura desensytyzacji umożliwia wdrożenie optymalnego leczenia nawet u pacjentów z nadwrażliwością na NLPZ. Przedstawiony przypadek kliniczny potwierdza skuteczność odczulania i jego przydatność w codziennej praktyce klinicznej.

Słowa kluczowe: działania niepożądane, kwas acetylosalicylowy, nadwrażliwość, NLPZ, aspiryna, desnsytyzacja, nadwrażliwość na leki

Summary

Introduction: Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) affect up to 1.9% of the European population, constituting a significant clinical problem. Possible symptoms of hypersensitive drug reaction (HDR) to NSAIDs include urticaria, angioedema, and co-existing clinical conditions that might be excerbated: bronchial asthma or chronic sinusitis with nasal polyps. When no alternative treatments to ASA exist, desensitization remains the only therapeutic option. It involves inducing a temporary state of tolerance to the drug that causes HDR.
A 63-year-old woman with coronary heart disease was referred to the Allergology Department of the University Clinical Hospital in Opole to undergo an ASA desensitization procedure due to the lack of another, more beneficial option for cardiac treatment. She reported a history of swelling of the eyelids, nose and lips after taking ibuprofen eight years earlier and an identical reaction a year later, after taking ASA. Since then, the patient avoided taking any NSAIDs. Desensitization was performed according to the Silberman protocol to a total dose of 150 mg, with a maintenance dose of 75 mg/day. The woman was discharged home with a referral to the Cardiology Department for further treatment and a recommendation for a healthy lifestyle and daily intake of ASA.
Conclusions: The desensitization procedure allows for the most beneficial treatment, even in patients suffering from hypersensitivity to NSAIDs. The presented clinical case confirms the effectiveness of desensitization and its usefulness in everyday clinical practice.

Key words: side effects; acetylsalicylic acid; hypersensitivity; NSAIDs; aspirin; desensitization; drug hypersensitivity

© Alergia Astma Immunologia 2025, 30(2): 72-78
www.alergia-astma-immunologia.pl
Przesłano: 12.03.2025
Recenzja: 17.04.2025
Zaakceptowano: 06.05.2025

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Introduction

Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is an increasing clinical problem. These drugs are among the most frequently used in the world, approximately 30-50 million people use them daily. Their high prevalence is due to their documented anti-inflammatory, analgesic and antipyretic effects, as well as their widespread availability [1,2]. These drugs are available to consumers without restrictions and without qualified advice from a pharmacist or doctor in non-pharmacy outlets, such as grocery stores, drugstores or gas stations [2,3]. NSAIDs work by inhibiting cyclooxygenases (COX). Non-selective NSAIDs that inhibit COX-1 are much more likely to cause symptoms of hypersensitivity, unlike selective COX-2 blockers (coxibs) which are better tolerated [4]. Due to their multidirectional mechanism of action, the use of NSAIDs is associated with the risk of side effects, which include, among others, disorders of the stomach and intestines, liver and bile ducts, nervous system, cardiovascular and renal complications [1,5]. Among NSAIDs, acetylsalicylic acid (ASA) holds a special place, which, apart from its analgesic and anti-inflammatory properties, is widely used in cardiology and neurology for secondary prevention after cardiovascular events [6] There is a significant variation between European countries in the prevalence of NSAID-induced respiratory hypersensitivity reactions - the mean prevalence of NSAID-induced dyspnea was 1.9% in a European multicentre study [7]. It was lowest in Skopje, (0.9%) and Amsterdam (1.1%), and highest in Poland (4,4-4,9%) [7]. The study of Kasper et al. [8] report that the frequency of aspirin-induced asthma equals 1.9% of polish bronchial asthma patients (0.1% of the adult population) [8]. Clinically, non-allergic acute hypersensitivity to NSAIDs may manifest as: urticaria and/or angioedema (NIUA, NSAIDs-induced urticaria or angioedema), NSAIDs-exacerbated cutaneous disease (NECD) in patients with urticaria, NSAIDs-exacerbated respiratory disease (NERD) in patients with asthma [4,9]. Allergic reactions to NSAIDs comprise IgE-mediated single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) and T-cell mediated single-NSAID-induced delayed reactions (SNIDR), e.g fixed drug eruption, SJS/TEN, nephritis [9]. NSAIDs, including ASA, may cause exacerbation of respiratory symptoms in nonimmunologically mediated manner - this is referred to as NSAID-exacerbated respiratory disease (NERD) or aspirin-exacerbated respiratory disease (AERD). In the literature, these names were often used interchangeably, however they both represent the same disease. [10,11]. In a study by Andersén et al. [10] involving 16,000 Finnish people, NERD affected 1.4% of those surveyed. NERD may occur not only due to exposure to medications [4,10,12]. The most common symptoms of NERD include runny nose, sneezing, loss of smell, nasal congestion and the so-called "aspirin triad". Historically, it was called Samter's triad which consists of three characteristic clinical symptoms: aspirin intolerance, bronchial asthma and nasal polyps [4,13]. NERD diagnosis can be made based on the clinical picture [14]. The gold standard for confirming the diagnosis is an oral challenge test with ASA [15]. When alternative treatment methods have been exhausted, the use of another drug is not possible, and the use of NSAIDs is necessary in the patient's therapy, a desensitization procedure may be used. It involves inducing a temporary state of tolerance to the drug that caused the hypersensitivity reaction [16]. In the case of ASA, desensitization is only possible in patients with NERD and in patients with NIUA. In patients with NERD, desensitization is recommended in cases of recurrent inflammation of the nasal and sinus mucosa, to prevent polyp regrowth after surgery, and to reduce the need for systemic corticosteroids (in both NERD and NIUA). It is also indicated when long-term treatment with aspirin (as antiplatelet therapy) or regular use of NSAIDs for pain or inflammation is necessary. [12,17]. An absolute contraindication to desensitization is a history of a severe or life-threatening anaphylactic reaction after taking ASA or another NSAID, pregnancy, breastfeeding, and the lack of guarantee that the patient will take ASA regularly and non-adherent patients [16]. A relative contraindication is the use of ß-blockers or ACE inhibitors, an ongoing infection or another coexisting condition constituting a contrain [16,18]. The procedure should be performed in a hospital allergology department, where immediate intervention by the anesthetic team is possible. ASA is administered orally, starting with the lowest dose in the protocol chosen and gradually increasing it. Patients with asthma who undergo desensitization to ASA require higher target doses than those who are desensitized for cardiovascular indications. Typically, individuals desensitized for cardiovascular reasons are required to achieve optimal drug tolerance at a range of 75-100 mg [18]. To maintain the desensitization effect, it is necessary to take the drug regularly, as tolerance lasts for several hours, and 48 hours after taking the last dose, evaluation for resuming the procedure is recommended [17,19,20]. This article is a case report of a patient who was hypersensitive to ASA and underwent effective desensitization.

A case report

A 63-year-old woman was referred to the Allergology Department of the University Clinical Hospital in Opole for potent desensitization with acetylsalicylic acid. The patient was referred from the Cardiology Department of another hospital, where she was hospitalized due to symptoms of chest tightness that had been present for 2 years. After coronary angiography, a hemodynamically significant lesion of the LAD branch was detected, but angioplasty was withheld. During that hospitalization, it was not possible to find a treatment alternative to ASA that would bring the same clinical benefit. The patient was admitted to the Allergology Department without delay, on an expedited basis, due to information from the Cardiology Department indicating that the coronary angiography required prompt intervention. The patient had the following diagnoses: "chronic coronary syndrome, arterial hypertension grade 2 according to European Society of Cardiology (ESC), impaired glucose tolerance (IGT), thyroiditis, hypercholesterolemia and chronic bronchitis." She was permanently taking clopidogrel 75 mg/day, metoprolol 50 mg/day, ramipril 2.5 mg/day, budesonide + formoterol: 320 + 9 ug/day. The patient had smoked 20 cigarettes per week for 30 years she declared that she stopped smoking 5 months ago.

In medical history, the patient took orally NSAID - ibuprofen eight years ago. A one hour after administrating the drug, swelling appeared on the eyelids, descending through the nose to the mouth. There was no shortness of breath, pruritus or hives. The patient was hospitalized, and as a result treatment with systemic steroids and antihistamines was used, the

reaction subsided after 3-4 hours. One year later, when the patient took aspirin at a dose of 75 mg due to chest pain, the same symptoms of an immediate reaction appeared, despite taking a low dose of the drug. After this incident, the patient ceased using NSAIDs and experienced anxiety regarding the potential use of medications from this group. Without cardiological indications, she would not have opted for allergological diagnostics. She did not consent to any possible drug provocation with ASA. Considering the clinical picture, including the absence of respiratory symptoms and reactions to two different NSAIDs, NIUA was diagnosed. Informed about the procedures, patient was positively inclined only towards attempting desensitization with the smallest possible ASA dose that would allow her to undertake cardiological treatment.

In the laboratory tests performed in the Allergology Department, significant abnormalities in morphology revealed leukocytosis (12.45 G/l) with a predominance of neutrophils (6.68 G/l), increased inflammatory parameters: CRP 44.61 mg/l (ULN: < 5mg/l), IL-6 17.2 pg/mL (ULN < 7 pg/ml), positive antibodies against thyroglobulin (anti-Tg) - 368.3 IU/ml (ULN: < 115 IU/ml) and antibodies against thyroid peroxidase (anti-TPO) - 138.0 U/ml (ULN: <34 U/ml). Helicobacter pylori antigen was detected in stool examination. An ultrasound of the thyroid gland revealed focal and nodular lesions that could correspond to the radiological picture of immune thyroiditis. An abdominal ultrasound was also performed, where no detectable pathologies were found.

Due to the history of otherwise unspecified chronic bronchitis, the bronchodilator responsiveness test with spirometry (400ug of salbutamol) was performed (Fig. 1). Given the clinical picture and post-bronchodilatator FEV1/FVC < 0,7, according to the GOLD guidelines, chronic obstructive pulmonary disease (COPD) was diagnosed.

	Predicted	LLN	Pre	%Pre	Post	Z - score
FVC [L]	2,80	2,1	2,63	94%	3,35	1,2
FEV1 [L]	2,21	1,65	1,40	63%	1,56	-1,9
FEV1/FVC [%]	79,34	66,92	53,15	67%	46,54	-3,9
MEF75 [L/s]	5,05	2,83	1,82	36%	1,78	-2,4
MEF50 [L/s]	3,41	1,6	0,75	22%	0,56	-2,6
MEF25 [L/s]	0,54	0,21	0,19	35%	0,13	-2,5
TPEF [sec]			0,21		0,14	
FET [s}			13,99		20,99	

Fig. 1. Results ofthe bronchodilator responsiveness test.

FEV - Forced expiratory volume
FEV1 - Forced Expiratory Volume in 1st Second
FEV_1/ FVC - The percentage of the FVC expired in first second
MEF75 - Mean expiratory flow rate at 75% of vital capacity
MEF75 - Mean expiratory flow rate at 50% of vital capacity
MEF25 - Mean expiratory flow rate at 25% of vital capacity
TPEF: Time to Peak Expiratory Flow Rate expressed in milliseconds
FET - Forced Expiratory Time
LLN- Lower Limit of Normal

The treatment was modified by adding tiotropium at a dose of 18 ug/day. A rapid clinical improvement was observed, what correlated with the improvement of ventilation values in the follow-up examination (Fig. 2).

	Predicted	LLN	Pre	%Pre	Z - score
FVC [L]	2,80	2,1	3,66	131%	1,9
FEV1 [L]	2,21	1,65	2,06	93%	-0,4
FEV1/FVC [%]	79,34	66,92	56,26	71%	-2,7
MEF75 [L/s]	5,05	2,83	2,75	55%	-1,7
MEF50 [L/s]	3,41	1,6	1,23	36%	-2
MEF25 [L/s]	0,54	0,21	0,17	31%	-2
TPEF [sec]			0,12		
FET [s}			14,86		

Fig. 2 – Spirometry parameters after six days from treatment modification.

The patient underwent three oral challenge tests as part of the selection of safe analgetics: acetaminophen (paracetamol) up to 500 mg, nimesulide up to 100 mg and celocoxib up to 100 mg. No symptoms of hypersensitivity were observed (FEV1 value in the control spirometry before the selection of safe medications was >70% of the expected value).

On the 6th day of hospitalization, desensitization was performed according to the Silberman protocol, with 5 mg, 10 mg, 20 mg, 40 mg, 75 mg of ASA administered orally every 30 minutes to a total dose of 150 mg, with a maintenance dose of 75 mg/day [21]. The desensitization was performed in standard ward setting. The patient was observed by medical staff throughout the entire process. Before each subsequent dose of the drug, blood pressure, heart rate, and oxygen saturation were measured; the patient was also physically examined with particular attention paid to possible symptoms of airway obstruction. During desensitization procedure the patient did not report any symptoms and there were no abnormalities in physical examination.

The patient was discharged home in good condition with recommendations regarding the need to take a maintenance dose of ASA 75 mg/day to maintain the effect of desensitization, salbutamol as a rescue medication due to the diagnosis of COPD, a healthy lifestyle and further treatment in the primary care clinic and allergy clinic. It is still contraindicated to take NSAIDs, except for those proven during hospitalization. The patient was also advised to continue diagnostics and therapy in the Cardiology Department. The patient has opted to undergo regular follow-up appointments at an allergology clinic closer to her residence due to the considerable distance to our outpatient clinic. She was advised to notify our Department if any complications arise post-desensitization procedure. To date, no issues have been reported.

Discussion

ASA is a drug commonly used in the treatment of cardiac diseases, therefore it is extremely important to identify patients hypersensitive to ASA and implement appropriate therapeutic options for them. Recent data shows that ASA intolerance affects 1.5 - 2.6% of patients undergoing cardiac treatment [21-22]. Other antiplatelet

medications, including clopidogrel, prasugrel, and ticagrelor, are often used in cardiovascular treatment, especially when ASA is not tolerated or when dual antiplatelet therapy (DAPT) is necessary. These drugs work by blocking the P2Y12 receptor, which inhibits platelet aggregation. Ticagrelor is generally preferred for its quicker action and fewer drug interactions compared to clopidogrel. However, these medications can increase bleeding risk and are frequently prescribed alongside ASA for patients with acute coronary syndromes (ACS) or following percutaneous coronary intervention (PCI) to minimize the risk of clot formation [22]. Classification of hypersensitivity to NSAID-s differ non-allergic reaction such as: NERD, NNECD, NIUA and allergic: SNIUAA, SNIDR [9]. The history of desensitization dates back to the 1930s, when Widal et al. [23] first described its use in clinical practice [21,23]. Currently, several dozen desensitization protocols are used, with various indications, routes of ASA administration, cumulative doses and execution procedures with most of them including only stable patients [18,23].

The protocols varied both in number of doses and in time from few hours up to 10 days in van Nguyen protocols [21]. All the protocols proved its safety and effectiveness in the achivement of ASA tolerance and there is no relevant difference in intravenous and oral desensitazation. The variability in desensitization protocols and final doses of ASA are primarily driven by the distinct clinical indications and therapeutic objectives. In patients with cardiovascular diseases, the goal of desensitization is to achieve tolerance to low-dose ASA (typically 75–100 mg daily) to ensure adequate antiplatelet effects. In contrast, patients with NERD are desensitized to higher doses of ASA (commonly 300–650 mg or more) to achieve anti-inflammatory effects and prevent polyp recurrence.

Consequently, the choice of protocol and final maintenance dose is tailored to the patient's specific clinical condition and the therapeutic aim, as corroborated by studies conducted by Verdoia et al. [21] and Chopra et al. [24]. Research indicates that protocols involving a higher number of doses (those exceeding six doses of ASA) are associated with improved success rates compared to those with fewer doses. Furthermore, statistical analysis reveals no significant differences in outcomes between protocols of longer duration (exceeding two hours) and those of shorter duration. This suggests that both the quantity and temporal aspects of ASA administration may influence the potential for effective desensitization. [21,24].

Numerous studies confirm the effectiveness and safety of the desensitization procedure. Chopra et al. [24] performed a systematic review of studies available in PubMed which shows that the effectiveness of this procedure in patients with acute heart failure is estimated at 98.3% [24].

Studies by Verdoia et al. [25] also confirms safety and effectiveness of desensitization in over 90% of patients, specifically to patients with ischemic heart disease, such as those with coronary artery disease. [21,25].

In this case, it was decided to proceed with the Silberman protocol as the patient refused to take a high dosage of ASA. This protocol is one of the shortest, lasting only 2.5 hours [26]. The procedure was initiated early in the morning, allowing the team of experienced allergists to observe the patient during regular working hours.

In the described case, we faced the challenge of recognizing chronic bronchitis, which was repeatedly noted in the patient's medical history without further specification. Spirometry at admission, despite the use of inhaled medications, was abnormal. Given the entire clinical picture, history of smoking, and post-bronchodilatory FEV1/FVC < 0.7, COPD was diagnosed. COPD should be considered in patients presenting with dyspnea that worsens over time and with exercise, is persistent; recurrent wheeze, chronic cough, recurrent lower respiratory tract infections, and risk factors such as tobacco smoke, smoke from home cooking/heating fuels, occupational exposure. [27]

Beta-blockers are relatively contraindicated during desensitization because, while they do not increase the frequency of systemic reactions, if such reactions do occur, they may be more severe, and the effectiveness of adrenaline can be diminished. Scientific research indicates that patients using beta-blockers with a history of myocardial infarction (MI) and congestive heart failure (CHF) experience higher mortality rates due to anaphylaxis, but their overall life expectancy is improved. Furthermore, withholding beta-blockers could result in rapid onset of cardiac symptoms. Some studies suggest that angiotensin-converting enzyme inhibitors (ACEIs) should also be withheld during desensitization due to increased risk of systemic reaction and its association with angioedema; Silberman proposed to discontinuation of beta-blockers, while McMullan et al [28] and deLuca et al [29] proceeded without further adverse effects [30-32].

Considering the patient's entire clinical picture, it was decided to proceed with desensitization while skipping only one morning dose of the beta-blocker and proceed with ACEI on the day of the procedure and continuing regular therapy the following day.

Most ASA desensitization protocols do not require premedication, including the Silberman protocol. In patients who have undergone desensitization, the expression and sensitivity of CysLT receptors are reduced. Studies show that the uncommon adverse reactions responded quickly to standard treatment. However, premedication may be considered for patients with a history of unsuccessful desensitization attempts in the past. Usually premedication consists of antihistamines, antileukotrienes and steroids [33].

Conclusions

1. The general availability, growing prevalence and multidirectional mechanism of action of ASA have contributed to their spread in many areas of medicine and everyday life [6]. However, their use is associated with numerous side effects and the possibility of hypersensitivity reactions. The clinical picture of hypersensitivity to NSAIDs is varied. Syndromes such as NIUA and NERD may be an indication for the desensitization procedure. The only absolute contraindication to the described procedure is a severe or life-threatening anaphylactic reaction after taking ASA or another NSAID. The desensitization protocol enabling the use of cardiac doses of ASA is the Silbermann protocol, in which the principle is the supply of increasing doses of

ASA up to a total dose of 150 mg, with a maintenance dose of 75 mg/day.

2. Performing desensitization provides an opportunity to select the most optimal treatment for patients suffering from hypersensitivity to NSAIDs and should be a component of a comprehensive approach to the diagnosis and treatment of drug hypersensitivity. This procedure is relatively safe and effective, which is confirmed by numerous scientific studies. If a maintenance dose of ASA is used regularly, the safety and effectiveness of the therapy are over 90%. The therapy also contributes to improving the quality of life of patients by enabling the continuation of cardiac treatment in patients who have experienced cardiovascular event and a specific drug is necessary to further control the course of their disease.

3. The described clinical case demonstrates the validity of multidisciplinary care for patients with cardiovascular diseases, increasing awareness of the need for cooperation between specialists from the fields of cardiology and allergology in the event of a hypersensitivity reaction to ASA, in the absence of alternative methods of treating the underlying disease. Moreover, the case confirms the effectiveness of the desensitization procedure and its validity in everyday clinical practice.

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