Asthma and Aspirin Exacerbated Respiratory Disease

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Abstract

Aspirin exacerbated respiratory disease (AERD) is a disease characterized by the triad of asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reaction to cyclooxygenase 1 inhibitors. The prevalence of AERD is estimated is reported to be: 7% in patients with asthma, 15% in patients with severe asthma, 24% in patients with life-threatening asthma, 10% in patients with nasal polyposis, and 9% in patients with unspecific chronic rhinosinusitis.

Aspirin and other nonsteroidal antiinflamatory drugs (NSAID) can cause hypersensitivity by different immunological mechanisms that can be classified into 5 categories: NSAID exacerbated cutaneous disease, NSAID induced urticaria or angioedema, single NSAID anaphylaxis, aspirin-exacerbated respiratory disease, single NSAID induced delayed reaction. The clinical picture, pattern of cross-reactivity, disease course, and course of desensitization may also be quite different. It is important to diagnose which disease phenotype is involved. This can be determined in most cases by history.

Due to distinctive symptoms, the diagnosis of AERD could often be based on reliable history. In patients with adult-onset asthma, recurrent nasal polyposis and multiple (two or more) reactions after a single NSAID or reactions after two different NSAIDs in the last 5 years the diagnosis could be based on history alone. However, in some cases, further diagnostic tests are necessary to avoid underdiagnosing or over-diagnosing the disease. Cross reactivity between NSAIDs in AERD is not associated with similarity of chemical structure, as it is in IgE mediated hypersensitivity, but it is associated with the strength of COX-1 inhibitions therefore the patient with AERD must avoid all the other drugs which are strong COX-1 inhibitors. Aspirin desensitization in AERD could be performed for two purposes: aspirin tolerance in cardiovascular indication or symptoms improvement in severe cases of chronic rhinosinusitis with nasal polyposis.

Keywords: aspirin, asthma, drug hypersensitivity, nonsteroidal antiinflamatory drugs

Introduction

Aspirin exacerbated respiratory disease (AERD) is a disease characterized by the triad of asthma, chronic rhinosinusitis with nasal polyposis, and respiratory reaction to cyclooxygenase 1 inhibitors. It was first described in the literature as a case report by French professors Widal and colleges in 1922[1]. Since then this condition has been given many different names from "Morbus Widal", "Samter's triad", "ASA induced asthma with nasal polyposis" and "NSAID-Exacerbated Respiratory Disease - NERD". Various specialists, including pulmonologists, otorhinolaryngologists, and allergists, treat patients with this condition.

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It is important to diagnose if the patient has an AERD, as NSAIDs are widely used as analgesic, antipyretic and cardio-protective drugs. NSAID asthma exacerbations in these patients may occur unexpectedly and may be severe[2]. Also, aspirin-associated asthma is a specific phenotype of eosinophilic asthma and with a different treatment decision. Asthma control can be improved by additional treatment with antileukotrienes and, in selected cases, by desensitization to aspirin. Therefore, it is important to define the tolerability of NSAIDs in all patients with asthma and nasal polyposis.

NSAID Hypersensitivity

Prevalence of hypersensitivity to NSAID is reported to be 1.6%[3]. Aspirin and other NSAIDs can cause hypersensitivity by different immunological mechanisms. Therefore, the clinical picture, cross-reactivity, disease course, and course of desensitization may also be quite different. It is important to diagnose which disease phenotype is involved. This can be determined in most cases by history.

NSAID hypersensitivity can be classified into 5 categories: NSAID exacerbated cutaneous disease (NECD), NSAID induced urticaria or angioedema (NIUA), single NSAID anaphylaxis, aspirin-exacerbated respiratory disease (AERD), single NSAID induced delayed reaction (SNIDR)[4-7]. Mixed pattern, called "blended reactions" represent the second most frequent entity in NSAID hypersensitivity simultaneously involving skin and airways[8] Immunological and clinical characteristics of various types of NSAID hypersensitivity are summarized in Table 1.

NSAID exacerbated cutaneous disease (NECD) occurs in patients who are suffering from chronic spontaneous urticaria. Approximately 12-30% of patients with chronic urticaria have worsening of their disease and occurrence of generalized hives and/or angioedema within 1-6 hours after application of NSAID. Skin symptoms may persist for several days. It is important to distinguish these symptoms from anaphylaxis. In NECD there are only cutaneous symptoms present, without systemic involvement. The intensity and the threshold dose for the reaction are changing through time and the course of the disease. The severity of the symptoms is also dose-dependent. Usually, NSAIDs are well tolerated when chronic spontaneous urticaria is in remission. Sometimes there are additional co-factors, such as viral disease, psychical or physical stress present, which aggravate the disease, and patients better tolerate NSAID without these co-factors. Therefore it is sometimes difficult to confirm the diagnosis with a drug provocation test, as results are not always replicable. Skin tests have no diagnostic value in NECD. NSAID exacerbated cutaneous disease is unpleasant, but it is not life threatening. Patients with NECD usually well tolerate selective COX-2 inhibitors and also the lower dose of aspirin (eg 100 mg as in antithrombotic treatment). However, desensitization to aspirin is rarely successful in NECD patients and patients should avoid all COX-1 inhibitors in therapeutic dose[5,6].

NSAID induced urticaria or angioedema (NIUA) occurs in patients without the underlying cutaneous disease, but similar to NECD patients develop isolated skin symptoms up to 24 hours after ingestion of at least two chemical unrelated NSAIDs. Again, there is no systemic involvement, in contrast to IgE mediated anaphylaxis. Sometimes NIUA occurs in patients several years before they develop chronic spontaneous urticarial, but this is not always the case. Cross reactivity is associated with the strength of COX-1 inhibitions and not with the chemical structure of NSAID. Also these patients tolerate well selective COX-2 inhibitors. In contrast to NECD patients, desensitization with aspirin is rarely successful in NIUA patients. When desensitized to aspirin, patients do tolerate also other NSAIDs[5,6].

Single NSAID anaphylaxis is different from both phenotypes of NSAID

Table 1. Immunological and clinical characteristics of various types of NSAID hypersensitivity.

Terminology	Aspirin-exacerbated respiratory disease (AERD)	NSAID exacerbated cutaneous disease (NECD)	NSAID induced urticaria or angioedema (NIUA)	Single NSAID anaphylaxis	Single NSAID induced delayed reaction (SNIDR)
Pathophysiology	COX-1 inhibition	COX-1 inhibition	Unknown, probably COX-1 inhibition	IgE mediated	T-cell mediated
Underlying disease	Asthma, nasal polyposis	Chronic urticaria	none	none	none
Cross reactivity	NSAID Cross reactive	NSAID Cross reactive	NSAID Cross reactive	selective	selective
Timing	30-180 min	1-6 h	up to 24h	immediate (up to 1h)	delayed
Symptoms	Bronchial obstruction, nasal congestion and/or rhinorrhea, wheezing, coughing, dyspnea	Urticaria and/or angioedema	Urticaria and/or angioedema	Anaphylaxis	Various delayed reactions
Desensitization	Successful	Rarely successful	Rarely successful	Successful	Contraindicated in most cases

hypersensitivity described above. The mechanism is IgE mediated immediate allergy. Therefore classical symptoms of anaphylaxis, with pruritus, flush, hives, angioedema, and systemic involvement with bronchospasm, hypotension, and gastrointestinal symptoms occur immediate, or within 1 hour after exposure to NSAID. The severity of the disease is usually not dose dependent. Patients usually react to other NSAIDs with similar chemical structures (and not with similar strength of COX-1 inhibition). Skin tests and also basophil activation tests may be useful in diagnosing this disease. Drug provocation test can confirm the diagnosis of allergy to culprit drug, but it is contraindicated in case of a very severe reaction. Drug provocation test is useful to confirm tolerance of alternative NSAID. Desensitization to culprit NSAID is possible, but usually not recommended as there are many alternatives on the market[5,6].

Single NSAID induced delayed reaction is rare. It occurs in patients with no underlying skin or respiratory disease. The onset of the disease is delayed, usually more than 1 day up to weeks after exposure to the NSAID. It has various clinical manifestations and various organ involvement such as maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS), fixed drug reaction, Steven Johnson syndrome, toxic epidermal necrolysis, drug induced nephritis, pneumonitis, etc. The pathomechanism include specific T cell stimulation. Diagnostic tests are specific and different for each clinical manifestation. Desensitization to aspirin is contraindicated in case of a severe delayed reaction[5,6].

Clinical Characteristics of AERD

The symptoms of AERD do not develop immediately after taking NSAIDs, but somewhat later, on average 30-180 min after administration[9]. This can sometimes make it difficult to identify the culprit of the reaction. The reaction starts with upper respiratory tract symptoms like nasal congestion and/or rhinorrhea, followed by lower airway symptoms like wheezing, coughing, and shortness of breath. In patients with not, well controlled asthma symptoms usually occur much quicker with more severe bronchospasm which may even lead to a fatal outcome[10-12]. The onset and severity are dose-related, lowest dose provoking a reaction for individual patients vary between 100-300 mg ASA[11-13].

Patients also frequently have chronic symptoms such as recurrent nasal polyposis with the need for frequent surgery, loss

of smell, and also similar upper and lower respiratory symptoms after intake of alcohol[11,12]. Symptoms usually appear 1-5 years before asthma develops[14].

Epidemiology

The prevalence of AERD is estimated is reported to be: 7% in patients with asthma, 15% in patients with severe asthma, 24% in patients with life-threatening asthma, 10% in patients with nasal polyposis, and 9% in patients with unspecific chronic rhinosinusitis[5,15,16]. Reported prevalence is likely to be underestimated due to low awareness of the disease.

Symptoms of AERD usually appears in patients with adult onset asthma between the age of 20-40 years[17,18]. AERD in children is rare. The ratio of male to female patients is 1:2[17]. AERD was previously not associated with atopy or any other respiratory allergy, although some newer studies report a higher prevalence of atopy in these patients[19,20]. Non steroidal anti-inflammatory drugs that most common cause respiratory reactions are: aspirin (80%), ibuprofen (41%), naproxen (4%)[13].

Pathophysiology

NSAIDs inhibit cyclooxygenase 1, increasing leukotriene production and decreasing the production of anti-inflammatory prostaglandins. Patients with AERD have higher levels of leukotrienes due to inflammation mediated by neutrophils, monocytes, and basophils, eosinophils, and mast cells. Increased leukotriene production with NSAID ingestion leads to bronchoconstriction, eosinophilic inflammation, increased mucus production in the bronchi. Also in nasal polyps tissue, there are elevated concentrations of leukotrienes[21,22].

Diagnostics

Due to distinctive symptoms, the diagnosis could be often based on reliable history. In patients with adult-onset asthma, recurrent nasal polyposis and multiple (two or more) reactions after a single NSAID or reactions after two different NSAIDs in the last 5 years the diagnosis could be based on history alone[11,12]. However, in some cases, further diagnostic tests are necessary to avoid underdiagnosing or over diagnosing the disease.

As the disease is not IgE mediated skin tests or measurements of specific IgE are not applicable. Several other approaches have been proposed and researched (like sulfidoleukotrienes release assay, 15-HETE test, basophil activation test) but are not used in clinical practice[25-25]. Therefore, unfortunately, there is currently no other clinically applicable in vitro test available to confirm the diagnosis. This means that the only testing available is drug provocation testing, which is time-consuming, complicated, and potentially dangerous, and should therefore only be carried out in experienced centers by experienced physician and trained nurse. Emergency treatment equipment should be at hand. Indications for performing drug provocation test with aspirin in suspected AERD are confirmation of AERD in patients with unreliable history and assessment of provocation dose before oral desensitization procedure[12,26]. Absolute contraindication for drug provocation tests are the history of severe anaphylactic reaction after any NSAID, unstable asthma, FEV1 ≤ 70%, recent respiratory infection, pregnancy, severe underlying disease such as cardiovascular, renal or liver disease[12,26]. There are different routes of aspirin administration for provocation tests: inhaled intranasal, oral and intravenous. Most commonly used are nasal and oral provocation tests[27]. Both have their advantages and disadvantages. Nasal inhalation of lysine-aspirin is safer and less time consuming in comparison to standard oral provocation tests. The nasal provocation test has a lower sensitivity (80-87%) compared to the oral test, which has a sensitivity of 89-90%. However, the specificity of both tests is high (93-100%)[12,26 28-32]. Inhalation challenge with

lysine-aspirin is as sensitive as oral one, but safer and faster to perform[11].

Nasal provocation is useful in patients with severe and unstable asthma and is at higher risk for severe obstruction. On the other hand, it is not useful in patients with severe nasal obstruction due to massive nasal polyposis as this reduces the sensitivity of the test[26]. At first, the test should be done with intranasal saline to exclude unspecific hypersensitivity. Then lysine aspirin up to 80 uL is installed into each nostril[33]. Assessment of the reaction includes a combination of objective symptoms such as rhinorrhea, sneezing, nasal congestion, and objective reduction of nasal flow measured with acoustic rhinometry, active anterior rhinomanometry, and peak nasal inspiratory flow[33]. As the sensitivity of nasal provocation is low, negative test should be followed by oral provocation. Oral provocation test is considered the gold standard in drug hypersensitivity. Although it has a high specificity, it still does not have 100% sensitivity, so in some cases, even a negative provocation test cannot completely rule out drug hypersensitivity. Drug provocation test is time-consuming, complicated, and potentially dangerous. It needs to be performed in a situation where emergency treatment is available, as well as intensive care unit. Medications for anaphylaxis, adrenaline, and antihistamines should be available on site. It should be performed under the supervision of experienced and trained personnel. When selecting an appropriate protocol for drug testing, it should be borne in mind that inadvertent desensitization to the drug may occur during the test, resulting in a false-negative result. Therefore, the doses and the interval between doses should be carefully selected. Ideally, the interval between doses of an oral drug provocation test should be 60 min and the amount of drug administered should be at least 2 times, but preferably 10x the previous dose.

Vital parameters, blood pressure, pulse, and saturation should be carefully monitored during provocation testing. It is also recommended that if AERD is suspected, spirometry or at least a PEF measurement should be performed before the next dose. The test is positive if at least one or more objective symptoms are present, such as upper respiratory tract reaction (rhinorrhoea, nasal congestion, sneezing, lacrimation), bronchospasm (dyspnoea, wheezing), laryngospasm, a drop of 20% in FEV1 or PEF. At the slightest symptom onset, the test should be stopped immediately and treated aggressively with antihistamines, nasal decongestants, bronchodilators, and adrenaline. There are several different protocols for oral aspirin provocation. The initial dose is typically 10-20 mg. The number of steps also varies, mostly in 5-8 steps. When AERD is suspected, it is important to remember that a reaction can occur up to 3 hours after the aspirin dose and therefore a longer observation period is required. In contrast to immediate IgE-mediated hypersensitivity testing where reactions usually occur immediately or within the first hour after drug administration, so observation up to 2 hours after the last dose is usually sufficient. Therefore, most protocols provide for a 2-day provocation protocol with aspirin. The median cumulative dose at which symptoms occur is 68-157 mg[34,35]. Upper respiratory tract symptoms and lacrimation are usually the first to occur. Bronchospasm is described in 35-90%. In addition to these, gastrointestinal symptoms (abdominal pain, nausea, vomiting), skin signs (erythema, pruritus, urticaria), and even hypotension have been described[26,36].

Risk factors predicting a more severe bronchial reaction include: patients not receiving additional anti leukotriene therapy, AERD symptoms lasting less than 10 years, reduced FEV1 already before the start of testing, history of asthma exacerbations requiring an emergency room visit[37]. There are also patients with a high clinical pretest probability of AERD but in whom the aspirin challenge test is negative. According to some studies, the

sensitivity of the provocation test is only 90%. In these patients, it is reasonable to repeat testing with a higher cumulative dose of aspirin at the time of discontinuation of antileukotriene therapy and systemic steroids.

Management of AERD

Cross reactivity between NSAIDs in AERD is not associated with similarity of chemical structure, as it is in IgE mediated hypersensitivity, but it is associated with the strength of COX-1 inhibitions. A patient must avoid all the other drugs which are strong COX-1 inhibitors: acetylsalicylic acid, piroxicam, sulindac, fenoprofen, oxazopirin, mefenamic acid indomethacin, ibuprofen, naproxen, ketoprofen, diclofenac, ketorolac, etodolac, nabumetone. Metamizole (dipyrone) is considered as week COX-1 inhibitor[8]. But majority of patients with AERD develop respiratory exacerbation with metamizole[38]. Patients should carry with them information about their drug hypersensitivity.

Weak COX-1 inhibitors such as paracetamol, meloxicam, and selective COX-2 inhibitors (celecoxib, etoricoxib, parecoxib) are well tolerated by most AERD patients. Central analgetics such as tramadol and opiates are also safe alternative[12,39]. Some patients also have respiratory symptoms after alcohol ingestion so alcohol avoidance should be advised to AERD patients[40]. Some patients even report respiratory symptoms after using spearmint flavored food like chewing gum or toothpaste, cows milk, and salicylate rich diet[41]. Patients with AERD do benefit with additional antileukotriens for asthma symptoms[42].

Aspirin Desensitization in AERD

Drug desensitization is a method of inducing a temporary tolerance and safely administering the drug to a patient who is allergic to it. The procedure is potentially dangerous and time-consuming and it is suitable for the selected patient in which there are no other equivalent alternatives. It can be used for IgE-induced hypersensitivity (eg anaphylaxis after antibiotics, monoclonal antibodies, or chemotherapeutics), for non-immune-mediated hypersensitivity (eg aspirin angioedema), or infusion reactions (eg chemotherapy or monoclonal antibodies). Desensitization is also possible for mild delayed reactions (eg maculopapular rash after antibiotics)[43,44].

The exact mechanism of action of desensitization is not yet fully understood. In vitro studies have shown that during desensitization both basophils and mast cells are temporarily unresponsive to desensitized antigen, while these cells may still respond to another antigen.

It has been suggested that aspirin desesnitization followed by maintenance of a daily dose of aspirin improves deregulation of arachidonic acid metabolism which leads to decreased airway inflammation and to clinical improvement[45]. The state of anergy to an antigen is temporary, the cells are responding after about two half-lives of the allergen. Desensitization can be performed in all patients with immediate hypersensitivity to the drug that have no alternative choice. It can theoretically be administered for any drug. The relative contraindications for desensitization are: unstable patient, uncontrolled asthma, severe heart failure, pregnancy. In these cases, it is necessary to evaluate risks and benefits. Desensitization is also not recommended when proper patient supervision and safety cannot be ensured[43,44].

Different protocols exist for performing desensitization, but all include the administration of ascending doses of aspirin at intervals of 90-120 minutes until a reaction or the target dose is reached within 1-3 days[46]. An example of desensitization protocol used in University Clinic Golnik is presented in Table 2. Aspirin desensitization in AERD could be performed for two purposes: aspirin tolerance in cardiovascular indication or symptoms improvement in severe cases of chronic

Table 2. Aspirin desensitization protocol used in University Clinic Golnik.

Step	Interval (min)	Aspirin dose
1	0	1 mg
2	30	2 mg
3	60	4 mg
4	90	8 mg
5	120	16 mg
6	150	32 mg
7	180	64 mg
8	210	100 mg

rhinosinusitis with nasal polyposis. In the first case is the target dose of 100 mg of aspirin, in the second case, the target dose varies from 325 mg up to 1300 mg[47,48]. In both cases, the selected aspirin dose must be taken daily to maintain tolerance. If the dose is missed for more than 48 hours, desensitization must be carried out again. In the majority of the patients, desensitization is successful, although up to one-quarter of the patients have reactions during the procedure[47]. Factors associated with successful desensitization are female sex, high blood eosinophil count, low sputum neutrophils, severe nasal symptoms[49]. If the reaction occurs, the patient should be treated, and then the desensitization process can be continued. The most common long term adverse effect is gastric irritation.

Aspirin desensitization in AERD is associated with beneficial effects mainly in symptoms of chronic rhinosinusitis. Use of intranasal corticosteroid and recurrence of nasal polyps are reduced, and there is also less need for revision surgery in these patients. Aspirin desensitization is less effective in reducing asthma symptoms, although one study did confirm minor improvement in FEV1, symptom and medication score[46,50].

There are several studies researching the effect of biological therapies on AERD with various outcomes. Omalizumab, anti-IL5 treatment, and dupilumab do have clinical effects on nasal polyposis, reducing the need for surgeries and nasal steroid use, however, there was no effect on NSAID hypersensitivity[17,52].

Summary

Aspirin, NSAIDs and pyrazolones should be avoided in patients with history of reaction after any of these drugs until allergy workup. Safe alternatives are paracetamol and opioids. Most patients tolerate COX-2 inhibitors, but this should be confirmed with drug provocation test.

In patients with asthma, nasal polyposis or chronic rhinosinusitis and convincing history of multiple reactions to Aspirin, NSAIDs or pyrazolones, no further diagnostic procedures are needed and strict avoidance is necessary. In patients with chronic urticaria, diagnostic provocation tests should only be performed in patients with indication for anti-inflammatory effects of NSAID as in rheumatologic diseases.

Aspirin is the drug of choice in some emergency situations (e.g. acute myocardial infarction). Patients with history of reaction after single NSAID and no history of asthma and/or chronic urticaria, should be offered Aspirin provocation test. If Aspirin is tolerated, patient could be offered further provocation tests with alternative NSAID. In patients with ischemic heart disease and NSAIH hypersensitivity, confirmation of tolerance or desensitization up to 100 mg is usually possible also in patients with asthma or chronic urticaria.

Patients with asthma, especially severe asthma and concomitant nasal symptoms and unknown tolerance to Aspirin, NSAID and pyrazolones should be warned of the potential for development of AERD later in life.

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