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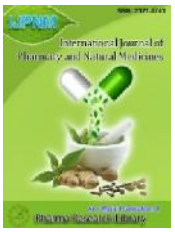

Review Article **Open Access**

A Review on NSAIDS Induced Pulmonary Disorders

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A B S T R A C T

Nonsteroidal anti-inflammatory drugs (NSAIDs) are identified as the most widely prescribed and self medicated group of drugs all around the world, as they are frequently used in different age groups, for the management of inflammation, fevers and pain of different etiologies. As these drugs are exposed by a large population, makes them the second cause of unwanted reactions. NSAIDs can cause drug allergic reaction, which may includes, urticaria, less commonly pneumonitis and meningitis, angioedema, anaphylaxis and exacerbation of underlying respiratory disease. Aspirin-exacerbated respiratory disease (AERD) is a clinical factor, which includes aspirin and other NSAIDs induced respiratory reactions in with sinusitis, asthma and chronic rhinitis. Among the population, the prevalence of these reactions varies between 0.1% and 0.3%. As the sign and symptoms vary, the mechanisms of each of them may vary accordingly, but the mechanism of AERD can be related to arachidonic acid metabolism. The clinical spectrum of NSAIDs includes Allergic Hypersensitivity, Non-allergic Hypersensitivity, Respiratory Hypersensitivity, Cutaneous Hypersensitivity, and Non-allergic Anaphylaxis. Diagnosis can be done by collecting clinical history, Skin prick and intra-dermal tests, Patch test, photo patch tests, Basophile activation test, Lymphocyte transformation test, Aspirin-induced release of LTC4, ASPI TEST and Oral challenge test. When the patient is diagnosed as AERD, the prior management includes the limitation or complete avoidance of COX-1 inhibiting drugs or aspirin desensitization and continuous aspirin therapy. Pharmacological treatment with high-dose Corticosteroids, Antihistamines, Anti-IgE antibodies, long-acting agonist, β cysteinyl leukotrienes receptor antagonists and surgical procedures are recommended.

Keywords: Non steroidal anti-inflammatory drugs, Cyclo-oxygenase, Desensitization

A R T I C L E I N F O

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are identified as the most widely prescribed and self medicated group of drugs all around the world, as they are frequently used in different age groups, for the management of inflammation, fevers and pain of different etiologies. As these drugs are exposed by a large population, makes them the second cause of unwanted reactions, following the beta lactam antibiotics. Pharmacology textbooks define NSAIDs as a chemical compounds, that antagonize inflammation through the inhibition of a group of enzymes known as cyclo-oxygenases (COXs). [1] Some drugs, like pyrazolones and acetaminophen, were previously not included into this classification as they didn't inhibit COX enzymes. Recently, new COX iso enzymes have been identified, such as COX-2b and COX-3, and they can selectively antagonize these drugs, and thus these drugs suites to the NSAID group.[2,3]As soon as the introduction of acetylsalicylic acid into the medical use, the first adverse reaction was reported by Hirschberg[4] in 1902 later by Widal in 1922[5], followed by Samter and Beer[6], which was called as aspirin-intolerant asthma, aspirin-induced asthma, aspirin-exacerbated respiratory disease (AERD) or aspirin triad (or tetrad), which consist of several lower and upper respiratory disorders like asthma, nasal polyposis, aspirin sensitivity and rhinosinusitis.[7]

Aspirin- induced asthma can be defined as the acute broncho constriction, skin flushing and rhinorrhea in asthma patient after the aspirin administration.[8] The aspirin-induced and steroid resistance asthma usually occurs 30 minutes to three hours.[9] Even if, the name is relates to aspirin, it also affected patients who have cross sensitive to all NSAIDs which inhibit cyclo-oxygenase enzymes. A newer clinical research articles show a clear evidence of having impact on non small cell lung cancer and H1N1 pneumonitis.[10] Among the population, the prevalence of these reactions varies between 0.1% and 0.3%.[11] NSAIDs action includes,… inhibiting the activities like (a) COX iso enzymes and (b) the enzymes that cause prostanoid biosynthesis from arachidonic acid. Some NSAIDs COX-1 selective inhibition and COX-2 partial inhibition (e.g., indomethacin, aspirin, naproxen, and diclofenac), thereby, inhibiting production of protective prostaglandins. Newer NSAIDs that inhibit COX-2 primarily (e.g., meloxicam, nimesulide) or specifically (e.g., rofecoxib, celecoxib), these can reduce the inflammatory prostanoids, and only slightly decrease protective prostaglandin production.[12] NSAIDs can be classified according to their selectivity for COX isoenzymes as Weak COX inhibitors (Salsalate, Acetaminophen), COX-1 and COX-2 inhibitors (Acetylsalicylic acid, Piroxicam, Indomethacin, Sulindac, Ibuprofen, Tolmetin, Naproxe, Fenoprofen, Ketoprofen Meclofenamate, Diflunisal, Mefenamic acid, Diclofena, Oxaprozin, Etodolac, Nabumetone, Ketorolac,Flurbiprofen), Preferential COX-2 inhibitors (Meloxicam, Nimesulide),Selective COX-2 inhibitors (Celecoxib, Parecoxib, Valdecoxib, Rofecoxib, Lumiracoxib, Etoricoxib).[13]

According to Nomenclature Committee of the World Allergy Organization, drug hypersensitivity are the clinical manifestations that are initiated by the exposure to a drug at a dose normally tolerated by non-hypersensitive persons and a Drug allergy refers to immunologically mediated drug hypersensitivity reactions. These may be either immunoglobulin E (IgE)-mediated (immediate) or non IgE-mediated (delayed). Non allergic hypersensitivity reactions can be defined as the adverse drug reactions that are not mediated by immunological mechanisms.[14]

2. Clinical Spectrum

A) Allergic Hypersensitivity

Classification Based On Allergic Hypersensitivity:

The Hypersensitivity to NSAIDs can be classified according to time of onset and the sign and symptoms into acute and delayed.

I. Acute actions start after several hours of drug administration and include

Respiratory reaction, Cross reacting urticaria and angioedema, Urticaria, angioedema and anaphylaxis induced by multiple NSAIDs Urticaria, angioedema and anaphylaxis inducedby a single NSAID. The conditions of Allergic Hypersensitivity to NSAIDs include

a) Respiratory reactions.

This type of patient may present the conditions like, chronic disease characterized by chronic rhinosinusitis, severe persistent and steroid-dependent asthma, with or without nasal polyposis, acute asthma exacerbations may be related to aspirin or other classic NSAIDs administration. These attacks can cause severe or life-challenging reactions. Genetic polymorphism has been related with these manifestations.

b) Cross reacting urticaria and angioedema

Genetic polymorphisms, LTC4 synthase, the high affinity receptor for IgE, 5-lipooxygenase, and genes coding for HLA antigens have been observed in these patients.

c) Urticaria, angioedema and anaphylaxis induced by multiple NSAIDs.

NSAIDs can induce acute urticaria, angioedema or systemic reactions that do not affect any other morbid condition. This type of hypersensitivity is more common in facial angioedema and atopic individuals. This condition also trigger with A444-C allele of LTC4 synthesis.

d) Urticaria, angioedema and anaphylaxis induced by a single NSAID:

These reactions are more common in patients with food or drug allergy, previous history of atopic disease.

II. Delayed reactions begin after 24 hours of NSAID exposure.

These include cell (T-lymphocyte)-mediated type IV hypersensitivity reactions which may be:

Organ specific b) Multi systemic diseases.

Delayed reactions can occur by a single or multiple cross-interacting NSAIDs, and they are expressed as organ specific and they include:

i) Skin:

Contact and photocontact dermatitis, Maculopapular

exanthemas, Bullousreaction (Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis), acute generalized, fixed drug eruptions, exanthematous pustulosis.

- Lung: Pneumonitis.
- Central nervous system: Aseptic meningitis.
- Liver: Hepatitis
- Kidney: Nephritis [13]

B) Nonallergic Hypersensitivity:

Non allergic hypersensitivity reactions include respiratory tract and skin and non allergic anaphylaxis.

C) Respiratory Hypersensitivity:

Aspirin-exacerbated respiratory disease (AERD) can be presented as asthma, rhinosinusitis, nasal polyposis, and aspirin or NSAID hypersensitivity.

D) Cutaneous Hypersensitivity:

The cutaneous hypersensitivity includes cross-interacting angioedema and urticaria in patients with or without chronic unknown urticaria.

E) Nonallergic Anaphylaxis:

Can also be called as pseudoallergic or anaphylactoid reaction, it is observed in cross-reactive patients.

Clinical Presentation

Chronic asthma, refactory rhinitis, hypertropic esnophillic rhinosinusitis, Chronic nasal symptoms like nasal congestion, anosmia, nasal polyposis, Watery discharge, Significant fall in inspiratory nasal flow, decreased sense of smell, periorbital odema, injection of conjunctiva and asthmatic symptoms like wheezing, cough, dysponea, and chest tightness. Additional symptoms like facial flushing or erythema, laryngospasm, abdominal cramps, epigastic pain, and hypotension.

Risk Factors

a) **Non modifiable risk factors:** Female gender, Young adulthood, advanced age and Genetic and epigenetic factors.
b) **Modifiable risk factors:** Atopy, Intermittent NSAID use for acute pain management [15], Pre-existing hyperreactive lung disease, Smoking, Respiratory infections, Onset of nasal congestion with anosmia, Progression to chronic pan sinusitis, Nasal polyps which re-grow rapidly after surgery and Nocturnal nasal obstruction with sleep deprivation fatigue [16, 17].

Complications:

- Chronic, severe, corticosteroid dependent asthma
- Myocardial ischemia [18, 19]
- Ocular complications [20]

Pathogenesis

As thesign and symptoms vary, the mechanisms of each of them may vary accordingly. The general mechanism of AERD includes the COX-1inhibition which results in arachidonic acid metabolism shunting towards the 5-lipooxygenase pathway and increased cysteinil leukotriene synthesis. [21] Several observations are made to prove this theory, which includes:

a) By the drugs that inhibiting the COX-1the respiratory reactions are triggered, while the COX-2 specific inhibitors do not have any role with AERD.[22, 23, 24]
b) The induced airway symptoms, which can be correlated with the effectiveness of the drug to inhibit COX1.[25, 26]

- The symptoms in AERD patients, who are induced to aspirin, are able to inhibit the leukotriene synthesis and leukotriene receptor antagonists partially.[27]
- After the aspirin challenge there is an increase in patient'sbaselineurinary LTE4 levels which can be correlate with the severity of pulmonary reactions.[28,29]
- The amount of leukotrienes in nasal and bronchial secretions increases during Aspirin challenge.[30, 31]

COX-1 inhibition

NSAIDs can inhibit the synthesis of prostaglandins (PGs), especially PGE2 and thus increases cysteinyl leukotrienes level (LTA, LTB, LTC, LTD). PGE2 releases the inflammatory mediators from mast cells, and recruits immune cells to inflammatory sites and thus it has a protective effect against broncho constriction.[25, 26] Whereas, cistern leukotrienes induces platelet activation, broncho constriction, cell recruitment, and airway inflammation.[32-37]

IgE-mediated allergic reactions

NSAIDs can increase the production of specific IgE antibodies, which bind to high-affinity receptors on basophils and mast cells and provide multivalent binding sites for drug antigens. When the drug antigen binds with IgE antibodies, the basophils or mast cells are stimulated to release the mediators (e.g., histamine) and produce new mediators.[38]

T cell-mediated mechanisms

By T cell activation, NSAIDs can cause delayed-type reaction. The mucous membrane identifies and transport drug antigen complexes to the regional lymph nodes, by the maturation signals which results from the drug-related disease or trauma, stress, dendritic cells in the skin. Dendritic cells introduce the drug antigens to T lymphocytes and stimulate the synthesis of antigen-specific T cells, in the lymph node. Simultaneously, drug antigen-specific T cells can migrate to the target tissue and on re-exposure of drug can cause the secretion of cytokines and cytotoxins. [39, 40]

Oxidative stress

Oxidative stress is the generation of pro-inflammatory mediator synthesis and (chemokines and cytokines) can aggravate the mucin secretion, bronchospasm, and airway inflammation.[41]

3. Management

When the patient is diagnosed as AERD, the prior management includes the limitation or complete avoidance of COX-1 inhibiting drugs or aspirin desensitization and continuous aspirin therapy. By the avoidance of cyclooxygenase-1 inhibiting NSAIDs, prevents the occurrence of serious asthma exacerbations and an alternative NSAIDs (weak COX-1 inhibitors) such as acetaminophen, salsalate, floctafenine, dextro propoxyphene, opioids, hyoscine, ergotamine, sodium

salycilate, choline-magnesium trisalicylate, salicylamide or COX-2 inhibitors (coxibs) for relief of fever, pain or inflammation after challenge in the medical settings.[45] Aspirin desensitization can be done to the patients who require continuous anti- thrombotic or anti- inflammatory therapy, such as those with heart disease, chronic inflammatory disorders severe and corticosteroid-dependent AERD.[46] As there is an increased risk of cardiovascular side effects, COX-2 inhibitors are not recommended for chronic use, especially in patients with previous history of coronary or cerebrovascular disease. Pharmacological treatment with high-dose topical (nasal, inhaled) and systemic corticosteroids, leukotriene receptor antagonists, and 5-lipoxygenase inhibitors, antibacterials, and antifungals are recommended.[47]

Anthihistamines can be used for the management of acute, severe cutaneous reactions. In frequent asthmatic exacerbations, anti-IgE antibodies, may be beneficial for controlling the upper and lower respiratory symptoms.[48] The IgE antibodies like omalizumab, benralizumab, and mepolizumab can be given for these patients.[49] Patients with moderate to severe asthma, and medium to high doses of inhaled corticosteroids, long-acting β agonist cysteinyl leukotrienes and receptor antagonists (Montelukast, Zafirlukast) ±5 Lipooxygenase inhibitors (Zileuton) should be maintained to control lower respiratory symptoms.[50] The upper airway symptoms related to chronic rhinitis or nasal polyps should be controlled to improve bronchial symptoms, either medically using intranasal corticosteroids or surgically (Sinus drainage, polypectomy) if necessary.[51]

Other drugs that can cause pulmonary diseases:

β-Lactam antibiotics (Amoxicillin, Penicillin, Ampicillin, Cephalosporins, Cephalosporin administration to penicillin allergic patients, monobactams (aztreonam), Penicillin administration to cephalosporin allergy patients, carbapenems), antimycobacterial drugs, non–β-lactam antibiotics, diabetes medications, Human immunodeficiency virus (HIV) medications, cancer chemotherapeutic agents, disease-modifying antirheumatic drugs (DMARDs), modifying drugs for dermatologic diseases, immunomodulatory agents for autoimmune diseases, perioperative agents, Opiates, blood and blood products, Corticosteroids, Heparin, Protamine, Local anesthetics, angiotensin-converting enzyme (ACE) inhibitors, Radiocontrast media (RCM), biologic modifiers (Anti–TNF-drugs, Cytokines, Monoclonal antibodies, Anticancer monoclonal antibodies, Omalizumab).[52]

4. Conclusion

NSAIDs can cause a wide range of adverse reactions to drugs that can be clinically interpreted in different manner. Desensitization is required for the successfull management of AERD condition. Continuous research efforts are required for the improvement in patho physiology and the phenomenon called “silensitization”dese and treatmet possibly prevention that are needed for the better management. For a better understanding of the functional and genetic/epigenetic pathogenic mechanisms, it will be helpful in the development of new diagnostic methods and effective management.

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