Review Article

NSAID HYPERSENSITIVITY – AN ALLERGIST’S PAIN

Jonny G Peter

Groote Schuur Hospital Drug Allergy Clinic, Division of Allergology and Clinical Immunology, Department of Medicine, University of Cape Town

Email | Jonny.Peter@uct.ac.za

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are a chemically diverse class of drugs that inhibit the cyclo-oxygenase pathway, decreasing pro-inflammatory prostenoid synthesis. They cause a number of adverse reactions and are one of the most common causes of drug hypersensitivity with ~2% of the general adult population reporting an NSAID allergy. Accurate diagnosis and clinical phenotyping is necessary to ensure patient safety, initiate appropriate therapy and limit the unnecessary restriction of different NSAIDs. Detailed history and oral provocation testing is usually sufficient for diagnosis and management, with in vitro and skin testing of very limited added value. Classification requires that the allergist distinguish immediate and delayed reactions; single-drug reactors from COX-1 cross-intolerance; as well as the presence of any associated cutaneous or respiratory disease. Management involves either specific NSAIDs or avoidance of all COX-1 inhibitors; guideline-driven management of associated cutaneous and respiratory disease, and, where indicated, aspirin desensitisation.

INTRODUCTION

NSAIDs antagonise inflammation through inhibition of cyclo-oxygenases (COX-1 and -2) – the enzymes responsible for the production of prostenoids (prostaglandins and thromboxanes) that mediate tissue inflammation, pain and fever. They are a diverse class of chemically distinct drugs (see Figure 1), grouped according to a shared chemical structure, and then stratified by their relative selectivity for COX-1 or COX-2 isoenzymes.

NSAIDs cause a number of adverse effects, most commonly mild gastric irritation (‘on-target’ side-effect). ‘Off-target’ drug hypersensitivity reactions to NSAIDs are also common, affecting up to 1.9% of the general adult population.1 Moreover, in populations with chronic rhinosinusitis, asthma and chronic urticaria, the prevalence of NSAID hypersensitivity might be as high as 30%.2 In the United States, ~15% of all outpatient allergy referrals are for drug allergies and nearly one-third are NSAIDs-related, second only to antibiotic allergies in frequency. NSAIDs are responsible for more than half of all cases of drug-induced anaphylaxis.1

The diagnosis and management of NSAID hypersensitivity can be challenging. The spectrum of symptoms can vary widely, while the pathophysiology remains incompletely understood. Diagnostic in vitro and skin testing are not validated, and are of limited use, meaning that oral provocation is considered part of the diagnostic criterion in most cases where the phenotype is not clear on clinical history alone. This review aims to outline the current classification of NSAID hypersensitivity, defining and briefly discussing the clinical manifestations, diagnosis and management of each subtype. The reader should then be well positioned to classify and manage the five illustrative cases from our multidisciplinary drug allergy clinic (see Table I). The views outlined in this review are consistent with the international collaborative efforts outlined in Kowalski et al and Laidlaw et al.1–3

CLASSIFICATION

Several subtypes of NSAID hypersensitivity have been defined, based on the timing, clinical pattern of symptoms, and the presence or absence of cross-reactivity to other NSAIDs. An additional criterion – the presence of underlying chronic skin or respiratory tract disease is also important. International drug-allergy working groups have provided a current framework by which reactions can be generally classified into one of five reaction types (see Table IIA-E).
MULTIPLE NSAID-EXACERBATED URTICARIA/ANGIOEDEMA IN PATIENTS WITH UNDERLYING CUTANEOUS DISEASE

**Definition and mechanisms**

A number of patients with chronic urticaria and/or angioedema will have an increased frequency and/or severity of cutaneous disease when using COX-1 inhibitors. These patients are classified as having NSAID-exacerbated cutaneous disease (NECD) (see Table IIA). This is a cross-reactive process whereby exposure to any COX-1 inhibitor worsens the patients’ cutaneous disease. The ability of different doses of COX-1 inhibitors to trigger exacerbation of disease does seem to reflect their in vitro inhibitory potency against the COX-1 isoenzyme.\(^4\)

The pathophysiology of NECD relates directly to COX-1 inhibition, likely via a decreased synthesis of prostaglandin E\(_2\) – a mast-cell stabiliser; and simultaneous increased release of cysteinyl leukotrienes by inflammatory cells.\(^5\)

Increased urinary leukotriene E\(_4\) levels, both at baseline and during a positive aspirin challenge, have been demonstrated in NECD.\(^6\) This is not IgE-mediated. A genetic predisposition is likely also involved; for instance, a variant of the FC\(_{ε}\)R1\(_{α}\) subunit gene (FCER1A- 344C>T) is more common in patients with NECD.\(^7\)

**Clinical manifestations**

Patients with NECD present with immediate reactions to NSAIDs (minutes to approximately four hours). Hypersensitivity reactions are limited to the dermis and subcutaneous structures such as their underlying chronic urticaria and angioedema. There should not be systemic symptoms consistent with anaphylaxis, for example hypotension, although there have been reports of respiratory symptoms (eg bronchoconstriction). In addition, there is no clear association with underlying asthma, rhinosinusitis or blood eosinophilia. The prevalence of NECD among patients with chronic spontaneous urticaria is up to 30%.\(^8\)

Notably, in some patients NSAIDs sensitivity may precede the development of chronic urticaria making classification difficult. A detailed history should illustrate reactions to all COX-1-inhibiting NSAIDs, and the presence of ongoing symptoms despite avoidance of all NSAIDs. NECD patients are generally tolerant of highly selective COX-2 inhibitors.\(^9\)

**Diagnosis and challenge**

The first step in the diagnosis is confirmation of chronic idiopathic urticaria; which by definition is the spontaneous development of urticaria that has been continuously

---

### Classification of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Common NSAIDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Selective COX Inhibitors</strong> (Traditional NSAIDs)</td>
<td>Aspirin, Paracetamol (Acetaminophen), Ibuprofen, naproxen, ketoprofen, diclofenac, indomethacin, phenylbutazone, oxybutazone, ketorolac</td>
</tr>
<tr>
<td><strong>Selective COX-2 Inhibitors</strong></td>
<td>Celecoxib, meloxicam, nabumetone</td>
</tr>
<tr>
<td><strong>Preferential COX-2 Inhibitors</strong></td>
<td>Nimesulide, etoricoxib, parecoxib</td>
</tr>
<tr>
<td><strong>Aryl Acetic Acid Derivatives</strong></td>
<td>Diclofenac, aceclofenac</td>
</tr>
<tr>
<td><strong>Propionic Acid Derivatives</strong></td>
<td>Ibuprofen, naproxen, ketoprofen</td>
</tr>
<tr>
<td><strong>Oxicam Derivatives</strong></td>
<td>Piroxicam, tenoxicam</td>
</tr>
<tr>
<td><strong>Indole Derivatives</strong></td>
<td>Ketorolac</td>
</tr>
<tr>
<td><strong>Pyrazolone Derivatives</strong></td>
<td>Phenybutazone, oxybutazone</td>
</tr>
<tr>
<td><strong>Pyrrolo-Pyrole Derivatives</strong></td>
<td>Ketorolac</td>
</tr>
<tr>
<td><strong>Para-Aminophenol Derivatives</strong></td>
<td>Paracetamol (Acetaminophen)</td>
</tr>
</tbody>
</table>

---

**Figure 1: Classification and chemical structure of NSAIDs**

**CLASSIFICATION OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)**

**REVIEW ARTICLE**

[Current Allergy & Clinical Immunology](https://www.currentallergyandclinicalimmunology.com) | September 2017 | Vol 30, No 3

---

163
or intermittently present for at least six weeks. Clinical history usually confirms reactivity to multiple NSAIDs including aspirin. If unclear, an oral aspirin-provocation test is indicated, and should be performed during a symptom-free period (ideally two weeks). A single blind, placebo-controlled two-day aspirin challenge can be performed. On Day 1, the patient receives placebo to determine baseline activity and, on Day 2, the patient receives escalating dose of aspirin (75 mg, 150 mg, 300 mg and 450 mg) at 1.5–2-hour intervals. The majority of patients will have a reaction within 1–2 hours after a single dose of 300 mg. Skin testing is unhelpful, although a positive autologous serum skin test, together with a reaction history confirms the diagnosis; basophil activation testing, for example FLOW CAST is also not validated for NECD.

Management
There are three aspects to the management of patients with NECD:
1. the underlying chronic urticaria needs to receive adequate treatment;
2. avoidance of all COX-1 inhibiting NSAIDs, and
3. use of highly selective COX-2 inhibitors as needed.

Interestingly, NSAIDs reactivity can wane as chronic urticaria goes into remission, and in certain patients re-exposure can then be considered. In addition, in patients needing low-dose aspirin for secondary prevention in ischaemic heart disease, both strategies of pretreatment with antihistamine, as well as successful desensitisation have been reported, although breakthrough urticaria and angioedema is common.

MULTIPLE NSAID-EXACERBATED URTICARIA/ANGIOEDEMA IN OTHERWISE ASYMPTOMATIC PATIENTS

Definition and mechanisms
NSAID-induced urticaria and/or angioedema (NIUA) is defined as the development of urticaria and angioedema on exposure to any COX-1 inhibitor in the absence of any history of chronic urticaria/angioedema (see Table IIb). Similar to the proposed mechanism in NECD, the pathophysiology relates to an abnormal balance of inflammatory prostenoids triggered in predisposed individuals following COX-1 inhibition. Genetic variants of both leukotriene C4 synthetase (LTC4 – 444A>C) and thromboxane synthase (TBXAS1 rs6962291) have been associated with NIUA in different populations.

What is of interest is that aeroallergen sensitisation is common in patients with NIUA (up to 60%), and therefore there may be a role of underlying atopy.

Clinical manifestations
The majority of patients with NIUA present with urticaria and facial angioedema within one hour – and up to 24 hours – after the ingestion of different COX-1 inhibitors. Angioedema, without urticaria, especially after ibuprofen

### TABLE I: ILLUSTRATIVE CASES FROM THE CLINIC

<table>
<thead>
<tr>
<th>CLINICAL HISTORY</th>
<th>TESTING</th>
<th>CHALLENGE OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>52-year-old male</td>
<td>FlowCAST for Aspirin Aspirin Diclofenac K-fenak (Diverse CAST) All negative</td>
<td>Admitted to ICU for challenge Day 1 Aspirin challenge up to 300 mg Day 2 Ibruprofen challenge up to 400 mg Both successful</td>
</tr>
<tr>
<td>55-year-old female</td>
<td>CAST ELISA negative to Lys-Aspirin</td>
<td>No challenges performed</td>
</tr>
<tr>
<td>44-year-old female</td>
<td>FlowCAST testing to Diclofenac Ibruprofen K-fenak (Diverse CAST) Carboxymethylcellulose All negative</td>
<td>Positive oral provocation with different diclofenac preparation (angioedema and urticaria) Negative challenge to aspirin</td>
</tr>
<tr>
<td>55-year-old female hiker</td>
<td>Nil</td>
<td>Straight to oral aspirin desensitisation (see Table III)</td>
</tr>
</tbody>
</table>
Recurrent nasal polyposis with ×3 FESS; marked anosmia
Atopy: Moderate with moderate persistent asthma
45-year-old male tolerated all NSAIDs and subsequently used ibuprofen including throat swelling; no hypotension or bronchospasm; previously
55-year-old female hiker chronic urticaria flare
Angioedema on aspirin and ibuprofen exposure during most recent
Subsequently, relapses of four-six months with chronic urticaria time and developed angioedema
2005: three-month period of daily urticaria; given diclofenac during this normal baseline level
Sept 2015 – Awoke with shoulder pain, took celecoxib 200 mg; 30 Possible sulphonamide allergy – unknown reaction sensitisation
Atopy – mild atopic dermatitis and allergic rhinitis; HDM and grass
55-year-old female
Jan 2017 – Diclofenac ×1 followed by anaphylaxis requiring out-of-
facial tingling
June 2016 – Diclofenac ×2 followed 20 minutes later with redness and
No chronic medical history, no atopy
52-year-old male

TABLE I: ILLUSTRATIVE CASES FROM THE CLINIC

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TIMING OF REACTION</th>
<th>CLINICAL SYMPTOMS</th>
<th>CROSS-REACTIVITY AMONG NSAID CLASS</th>
<th>ASSOCIATED/UNDERLYING DISEASE</th>
<th>PUTATIVE MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Multiple NSAID-exacerbated urticaria/angioedema in patients with underlying cutaneous disease (NECD)</td>
<td>Acute</td>
<td>Urticaria/angioedema</td>
<td>Yes</td>
<td>Chronic spontaneous urticaria</td>
</tr>
<tr>
<td>B</td>
<td>Multiple NSAID-induced urticaria/angioedema in otherwise asymptomatic patients (NIUA)</td>
<td>Acute</td>
<td>Urticaria/angioedema</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>C</td>
<td>Single NSAID-induced anaphylactic reactions (SNIUAA)</td>
<td>Acute</td>
<td>Anaphylaxis, Urticaria/angioedema</td>
<td>No</td>
<td>Atopy</td>
</tr>
<tr>
<td>D</td>
<td>Aspirin- or NSAID-exacerbated respiratory disease (AERD or NERD)</td>
<td>Acute</td>
<td>Rhinitis, nasal congestion, bronchoconstriction, asthma exacerbation</td>
<td>Yes</td>
<td>Asthma/rhinosisinusitis/ nasal polyps</td>
</tr>
<tr>
<td>E</td>
<td>Delayed reactions to NSAIDs (SNIDR)</td>
<td>Delayed (&gt;24hrs)</td>
<td>Varied: maculopapular drug eruptions, fixed drug eruptions, bullous skin reactions, maculopapular drug eruptions</td>
<td>Single or cross-reactive</td>
<td>None</td>
</tr>
</tbody>
</table>

and diclofenac is most frequently reported. Among patients with NSAID-associated peri-orbital angioedema, sensitisation to house-dust mite allergen is common, suggesting a possible link with atopy for this subtype.3
Previously it was reported that up to 40% of patients thought to have NIUA went onto develop chronic spontaneous urticaria (CSU); however, more recent data suggest that the proportion of NIUA patients with CSU is not different from that among health controls.10

**Diagnosis and challenge**

Clinical history of skin reactions to at least two NSAIDs with different chemical structures, and no history of underlying cutaneous disease has a high sensitivity for the diagnosis of NIUA. If the offending drug was not aspirin, or the history was unclear, oral-provocation testing with aspirin is recommended. This will allow the allergist to differentiate NIUA from single NSAID-induced urticaria/angioedema (SNIUAA). Skin testing is not indicated unless SNIUAA is considered; basophil-activation testing, for example FLOW CAST utility is unknown.

**Management**

Similarly to patients with NECD, avoidance of all COX-1 inhibitors is recommended. Patients will normally tolerate weak COX-1 inhibitors (eg paracetamol and selective COX-2 inhibitors). Successful aspirin desensitisation has been reported in a small series of patients, with durable tolerance of aspirin for up to two years.11

**SINGLE NSAID-INDUCED ANAPHYLACTIC REACTIONS**

**Definition and mechanisms**

These immediate reactions to NSAIDs are the ‘odd man out’. Anaphylaxis, urticaria and/or angioedema to single NSAID agents (or chemically related ones) are well described (SNIUAA, see Table IIC). Most literature is limited to case reports. The reason these are the unusual of the acute reactions is that the pathomechanisms are more consistent with IgE-mediated type-1 hypersensitivity. Reports have shown increased tryptase during reactions; skin testing or serum assays for certain reactions have confirmed the presence of IgE sensitisation, although in the majority of cases no IgE antibodies have been found.1

The complexity of the pathophysiology has been further highlighted by demonstration of hapten modification of albumin by NSAIDs in patients with SNIUAA, as well as a glucuronide acyl modification of different lysine residues of albumin by diclofenac and acetaminophen.12

In our setting, the most common NSAIDs responsible for SNIUAA are diclofenac, ibuprofen and naproxen. Importantly, these patients will be tolerant of aspirin or other chemically different NSAIDs. Anaphylaxis, or urticaria and angioedema secondary to COX-2 inhibitors is rarely reported. However, of published reactions to COX-2 inhibitors, celecoxib causes the majority (and one of our illustrative cases). Celecoxib is nonarylamine benzensulfonamide derivative and therefore cross-reactivity to patients with existing sulfa hypersensitivity has been postulated as the aetiological link.13 However, data from larger epidemiological studies suggest that patients with a history of hypersensitivity to sulphonamide antibiotics are simply more likely to have allergic reactions to other medications, rather than a specific cross-reaction with sulphonamide nonantibiotics.14

**Clinical manifestations**

Consistent with a likely IgE-mediated hypersensitivity, these reactions occur within minutes or up to one hour
after ingestion. Urticaria and angioedema occur most frequently, but anaphylaxis occurs in approximately one-third of patients.\textsuperscript{2} In comparison to patients with NECD, angioedema can affect both skin and mucosa of the larynx and therefore may be life-threatening.

**Diagnosis and management**

The diagnosis and offending drug can usually be identified through clinical history alone. Supporting evidence such as increased tryptase is very useful as it aids classification, lowering the likelihood of NSAID cross-reactivity. Skin and in vitro basophil-activation testing may be useful to confirm reactivity to the offending drug, but there are no large studies of skin-testing reagents to validate their use. Provocation testing to the offending drug is rarely, if ever, indicated. However, it is important that these patients are challenged with aspirin (if not the offending drug) or another class of NSAIDs, so that cross-reactivity can be excluded and patients do not lose access to the entire class of drugs. Management involves strict avoidance of the culprit agent and any structurally similar NSAID. There are no reports of successful desensitisation to the anaphylaxis-inducing NSAID, and given the number of alternatives, desensitisation should rarely, if ever, be attempted.\textsuperscript{1}

**ASPIRIN EXACERBATED RESPIRATORY DISEASE**

**Definition and mechanisms**

Aspirin exacerbated respiratory disease (AERD) has been known by many different names including Widal syndrome and the Samter’s triad of asthma, recurrent eosinophilic nasal polyposis and respiratory reactions triggered by aspirin and other COX-1 inhibitors. The mechanisms underlying the chronic nature of AERD are incompletely understood, but involve the arachidonic acid pathway. Abnormal trafficking through this pathway leads to a chronic overproduction of pro-inflammatory eicosanoids, including by cysteinyl leukotrienes (cysLTs) and prostagaldins (PG) D\textsubscript{2}, and underproduction or diminished response to the anti-inflammatory PGE\textsubscript{2}. There are marked differences in the baseline and NSAID-exacerbated urinary levels of leukotriene E\textsubscript{4} and PGD\textsubscript{2} between AERD and aspirin-tolerant patients.\textsuperscript{15,16} In addition, patients overexpress CysLT receptors. Mast cells as well as platelet-adherent neutrophils are responsible for the production of cysLTs, and this leads to extensive eosinophilic inflammation within the sinus and bronchial mucosa, as well as acute symptom worsening on exposure to COX-1 inhibitors.\textsuperscript{1}

**Clinical manifestations**

AERD usually begins in early adulthood (third and fourth decades) with severe and persistent rhinitis with nasal polyposis; anosmia is common and disabling. Patients then progress to develop asthma and intolerance to COX-1 inhibitors. A history of reactions to NSAIDs may or may not be present. A typical reaction involves an onset within 30–120 minutes of ingestion, starting with worsening nasal symptoms – rhinorrhea or acute congestion, ocular erythema and then worsening bronchoconstriction. Interestingly, one-third of AERD patients develop extrapulmonary symptoms including gastrointestinal symptoms such as pain, nausea and diarrhoea, and cutaneous features such as flushing or pruritic macular eruption on the limbs.\textsuperscript{1}

**Diagnosis and challenge**

AERD is the most common NSAID hypersensitivity. Nevertheless, AERD is often missed by clinicians, as of all patients with a diagnosis of asthma, the prevalence is less than 3%. However, a prevalence of 15% and 10% among patients with severe asthma and chronic rhinosinusitis with nasal polyps respectively, is reported, and these are the patient groups in whom the diagnosis should be actively sought.\textsuperscript{17} In clearcut cases of asthma, recurrent nasal polyps and at least two previous NSAID-induced respiratory reactions, at least one of which was within the past five years, the diagnosis can be made on history alone. However, about 15% of patients are unaware of their NSAID intolerance.\textsuperscript{1} Furthermore, patients using Leucotriene receptor antagonists, such as Montelukast, may mask NSAID-induced reactions to the point where patients deny NSAID hypersensitivity. These patients should be considered for an aspirin challenge.

Oral and intranasal provocation testing protocols are available.\textsuperscript{1} Challenges can induce bronchospasm and should therefore be performed under direct the supervision of an experienced physician with the facilities to treat emergent reactions. Internationally, many of these procedures are done as an out-patient, but my own preference is for an in-patient challenge. For the challenge, the patients’ asthma must be stable with an FEV\textsubscript{1} of at least 60–70% of predicted; they must be off β-blockers, ACE-inhibitors, Leucotriene-modifying agents and antihistamines (for one week). Oral-challenge protocols usually involve a four-dose protocol (32.5 mg, 75 mg, 150 mg and 300 mg aspirin) with 90 minutes between doses. Lung function is measured every 90 minutes before proceeding with dose escalation. A ‘positive’ challenge is a decrease in FEV\textsubscript{1} of 15% or more from baseline and/or at least two of the following symptoms: nasal congestion, rhinorrhea, sneezing, nasal or eye itching, or eye-redness and tearing. Extrapulmonary symptoms are recorded, but in the absence of respiratory symptoms they are insufficient to confirm the diagnosis of AERD. Intranasal ketorolac is an alternative challenge method with less severe bronchoconstriction than oral challenge, but a sensitivity of only 78%.\textsuperscript{1}

**Management**

Patients need to receive conventional asthma medications according to international guidelines. Leucotriene-modifying drugs are recommended and have shown benefits in managing both upper and lower respiratory disease; Zileuton – a five-lipoxygenase inhibitor seems to offer greater benefit, especially on upper-
**TABLE III: ASPIRIN DESENSITISATION PROTOCOLS**

<table>
<thead>
<tr>
<th>Oral aspirin desensitisation for AERD</th>
<th>Ketoctac alternative challenge and modified oral aspirin challenge</th>
<th>Rapid aspirin desensitisation protocol for patients with IHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1</strong> (Day 0 may include a placebo day)</td>
<td>Day 1*</td>
<td>Day 1</td>
</tr>
<tr>
<td>1. Admit to ward for review of history, medication</td>
<td>8:00 AM 1 spray (1 in one nostril)</td>
<td>Admit to coronary care unit/intensive care unit for procedure</td>
</tr>
<tr>
<td>2. Informed consent</td>
<td>8:30 2 sprays (1 in each nostril)</td>
<td>1. Detailed history of reactions documented, send off CAST ELISA for aspirin</td>
</tr>
<tr>
<td>3. Baseline spirometry, FEV₁ should be at least 1.5 L and &gt;60% of predicted.</td>
<td>9:00 4 sprays (2 in each nostril)</td>
<td>2. Stop β-blocker of 24 hours</td>
</tr>
<tr>
<td>4. Montelukast 10 mg PO daily</td>
<td>9:30 6 sprays (3 in each nostril)</td>
<td>3. Informed consent</td>
</tr>
<tr>
<td>5. IV access</td>
<td>10:30 60 mg aspirin*</td>
<td>4. IV access</td>
</tr>
<tr>
<td>6. Mix 300 mg aspirin in 150 mL water (2 mg/mL concentration)</td>
<td>12:00 60 mg aspirin*</td>
<td>5. Mix 300 mg aspirin in 150 mL water (2 mg/mL concentration)</td>
</tr>
<tr>
<td>7. Then check BP, pulse and PEFR prior to commencement</td>
<td>3:00 PM Instructions and discharge</td>
<td>6. Then check BP, pulse and PEFR prior to commencement</td>
</tr>
<tr>
<td>8. First dose administered 10 mL (20 mg)</td>
<td><strong>Day 2</strong></td>
<td>7. First dose administered 2 mL (4 mg)</td>
</tr>
<tr>
<td>9. 1-hrly check any cutaneous, nasal, laryngeal or respiratory symptoms</td>
<td></td>
<td>8. 30 minutes later check any cutaneous, nasal or lung symptoms</td>
</tr>
<tr>
<td>10. Measure FEV₁ hourly</td>
<td></td>
<td>9. Check PEFR, BP and PR</td>
</tr>
<tr>
<td>11. At three hours, if normal proceed second dose administered 20 mL (40 mg)</td>
<td></td>
<td>10. If above normal proceed with next dose of 5 mL (10 mg)</td>
</tr>
<tr>
<td>12. 1-hrly check any cutaneous, nasal, laryngeal or respiratory symptoms</td>
<td></td>
<td>11. Repeat steps 8 and 9 after further 30 mins</td>
</tr>
<tr>
<td>13. Measure FEV₁ hourly</td>
<td></td>
<td>12. If above normal proceed with next dose of 10 mL (20 mg)</td>
</tr>
<tr>
<td>14. At six hours, if normal proceed third dose of the day 30 mL (60 mg)</td>
<td></td>
<td>13. Repeat steps 8 and 9 after further 30 mins</td>
</tr>
<tr>
<td>15. 1-hrly check any cutaneous, nasal, laryngeal or respiratory symptoms</td>
<td></td>
<td>14. If above normal proceed with next dose of 20 mL (40 mg)</td>
</tr>
<tr>
<td>16. Measure FEV₁ hourly</td>
<td></td>
<td>15. Repeat steps 8 and 9 after further 30 mins</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
<td>16. If above normal proceed with next dose of 40 mL (80 mg)</td>
</tr>
<tr>
<td>17. Baseline spirometry</td>
<td></td>
<td>17. Repeat steps 8 and 9 after further 30 mins</td>
</tr>
<tr>
<td>18. Montelukast 10 mg PO daily</td>
<td></td>
<td>18. If above normal proceed with next dose of 50 mL (100 mg)</td>
</tr>
<tr>
<td>19. Mix 300 mg aspirin in 150 mL water (2 mg/mL concentration)</td>
<td></td>
<td>19. Repeat steps 8 and 9 after further 30 mins</td>
</tr>
<tr>
<td>20. Then check BP, pulse and PEFR prior to commencement</td>
<td></td>
<td>20. If above normal proceed with next dose of 75 mL (150 mg)</td>
</tr>
<tr>
<td>21. First dose administered 50 mL (100 mg)</td>
<td></td>
<td>21. Observe for a further three hours in CCU for reactions</td>
</tr>
<tr>
<td>22. 1-hrly check any cutaneous, nasal, laryngeal or respiratory symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Measure FEV₁ hourly</td>
<td></td>
<td>22. Discharge and ensure patient understands that aspirin must be taken daily thereafter or tolerance will be lost</td>
</tr>
<tr>
<td>24. At three hours, if normal proceed second dose administered 80 mL (160 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. 1-hrly check any cutaneous, nasal, laryngeal or respiratory symptoms</td>
<td></td>
<td>If reactions develop:</td>
</tr>
<tr>
<td>26. Measure FEV₁ hourly</td>
<td></td>
<td>1. Call for assistance if required (doctor-on-call)</td>
</tr>
<tr>
<td>27. At six hours, if normal proceed third dose of the day 150 mL (300 mg)</td>
<td></td>
<td>2. Drugs to be used include: solucortef (200 mg IVI stat), salbutamol nebulisation (for chest tightness), and adrenaline (0.01 mg/kg; adult: 0.5 mg IMI stat)</td>
</tr>
<tr>
<td>28. 1-hrly check any cutaneous, nasal, laryngeal or respiratory symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29. Measure FEV₁ hourly</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reactions can be:**
- Naso-ocular alone
- Naso-ocular and a 15% or > decline in FEV₁ (Classic reaction)
- Lower respiratory reaction only (FEV₁ declines by >20%)
- Laryngospasm with or without a, b, c (flat or notched inspiratory curve)
- Systemic reaction: hives, flush, gastric pain, hypotension

**Additional information**
1. Patients are instructed to continue oral and topical corticosteroids and long-acting bronchodilators.
2. Patients are instructed to discontinue their antihistamines, decongestants and short-acting inhaled beta-agonists prior to aspirin challenge.

Contraindications to aspirin desensitisation include pregnancy, unstable asthma, gastric ulcers or bleeding disorders.
airway symptoms than Montelukast and is currently under-prescribed. Nasal polyps need to be managed in conjunction with ENT surgeons, as high-dose aspirin therapy following desensitisation does not cure existing polyps, but only prevents polyp recurrence. AERD patients who have not undergone aspirin desensitisation need to be counselled to strictly avoid COX-1 inhibitors. Paracetamol has very weak COX-1 inhibition and is therefore usually well tolerated, however, in about one-third of AERD patients, some reaction can occur at doses of 1 000 mg or higher. Similarly, reactions to COX-2 inhibitors have been reported, although for the majority of patients these drugs are safe.

Aspirin desensitisation followed by high-dose aspirin therapy should be considered in all patients with confirmed AERD. Oral and intranasal desensitisation protocols are outlined in Table III. Multiple studies have confirmed that high-dose aspirin will provide most AERD patients with improvement of upper and lower respiratory tract pathology, and allow a reduction in corticosteroid use and repeat sinus surgeries. Half of desensitised patients will maintain symptom improvement on 325 mg twice daily, whereas the other half required 650 mg twice daily for efficacy; the side-effect profiles with the two dosages were similar. About a quarter of patients will either not experience improvement of symptoms or be forced to discontinue therapy due to side-effects, usually gastrointestinal. At present we have no biomarkers to identify which AERD patients will not benefit.

**ASPIRIN DESENSITISATION IN ISCHAEMIC HEART DISEASE**

Hypersensitivity to aspirin can be a major problem in patients with ischaemic heart disease. In the setting of an acute coronary syndrome, patients with a history of aspirin hypersensitivity should undergo urgent desensitisation. Our protocol is outline in Table III and is consistent with published data. A recent audit across ten allergy centres and 147 patients found a failure rate of only 1.4%. Patients with chronic stable ischaemic heart disease where aspirin therapy is considered, allergists can decide whether the patients history necessitates aspirin challenge or desensitisation, and the timing thereof.

**DELAYED REACTIONS TO NSAIDS**

**Definition and mechanisms**

A number of delayed reactions (>24 hours after exposure) to different NSAIDs are well described. Reactions are most frequently cutaneous, but systemic reactions involving other organs are reported. The pathomechanisms of delayed reactions are considered to be type-IV hypersensitivity mediated by drug-specific cytotoxic T-cell or NK cells.

**Clinical manifestations**

Maculopapular (exanthematous) eruptions are the most common delayed cutaneous adverse effect of NSAIDs, with the main offending agents being ibuprofen, pyrazolones, diclofenac and celecoxib. NSAIDs are also an important cause of fixed-drug eruptions (FD). FDEs involve one or more circular-to-oval erythematous patches that develop following systemic drug exposure and heal with hyperpigmentation. Re-exposure results in recurrence at the site of original presentation with or without additional patches. Cross-sensitivity among NSAID groups causing FDEs varies, being reported for -oxicams but not propionic acid derivatives. Severe cutaneous adverse reactions (SCAR), such as SJS/TEN, AGEP and DRESS, can be caused by NSAIDs, with reactions to -oxicams, celecoxib and ibuprofen reported. Contact dermatitis is also described to certain NSAIDs. Topical ketoprofen and etofenamate are the two most common causes of photocontact dermatitis in Europe, eliciting a papulovesicular, puritic eruption in the sun-exposed area.

NSAIDs have also been reported as causative agents in hypersensitivity pneumonitis, aseptic meningitis, for example ibuprofen and nephritis.

**Diagnosis and challenge**

Diagnosis of delayed reactions to NSAIDs is based on drug exposure with the symptoms, morphology and location of skin lesions and/or other organ involvement. Histology may be useful in difficult cases, as well as the use of scoring tools such as Naranjo. Patch and in vitro diagnostic tools are not standardised or well-validated, however, they can offer utility; photopatch tests are indicated to diagnose photoallergy. Drug provocation may be useful for less severe reaction or to exclude cross-reactivity, but is contraindicated in patients with severe reactions.

**Management**

All offending NSAIDs should be promptly discontinued. In SCAR reactions early withdrawal of offending drug can decrease mortality. Symptomatic treatment usually involves topical or systemic corticosteroids and antihistamines. For further details on the management of SCAR, readers are referred to our recent review. Rechallenge and desensitisation does not play a role in the management of these patients.

**CONCLUSION**

NSAIDs are a diverse group of drugs consumed in huge quantities daily. They are common culprits in drug allergy, and a frequent reason for consulting an allergist. An understanding of the chemical groups, different phenotypes and putative pathomechanisms all aid in making management decisions around which patients need NSAID avoidance, challenge or desensitisation.

**DECLARATION OF CONFLICT OF INTEREST**

The author declares no conflict of interest.

This article has been peer reviewed.
NOTICE OF 
ALLSA ANNUAL GENERAL MEETING 
16H30 Saturday 16th September 2017 
Boardwalk Hotel, Port Elizabeth

AGENDA

1. Welcome
2. Minutes of previous meeting
3. Matters arising
4. Treasurer’s report
5. Secretary’s report
6. Portfolio Reports
   • Journal
   • Research
   • Education/Training
   • ALLSA Handbook
7. Reports by working Groups
   • Journal
   • Research
8. General

Current Allergy & Clinical Immunology | September 2017 | Vol 30, No 3