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REVIEW

Rhinosinusitis and allergy: a relationship of random meetings

D Wolmarans, SF Steyn, L Brand

Centre of Excellence for Pharmaceutical Sciences, Department of Pharmacology, Faculty of Health Sciences, North-West University, Potchefstroom, South Africa
Corresponding author, email: dewet.wolmarans@nwu.ac.za

Rhinosinusitis

Sinusitis, more aptly referred to as rhinosinusitis, can be described as a symptomatic inflammatory condition of the paranasal sinuses and the nasal cavity.[1] Generally, the condition is regarded as acute (ARS) if lasting up to 4 weeks, sub-acute when lasting between 4 and 12 weeks, and chronic (CRS) if symptoms present for more than 12 weeks.[2]

Common symptoms of ARS include purulent nasal drainage which is *accompanied by* nasal obstruction and/or facial pressure pain. Clear mucous drainage is mostly associated with viral upper respiratory conditions and must be distinguished from the purulent, cloudy drainage associated with sinusitis. If upper respiratory infection is excluded, viral ARS can be separated from bacterial ARS on the basis of duration and prognosis; viral ARS should be diagnosed if the condition does not worsen, but rather improve within 10 days from the onset of symptom presentation, while bacterial ARS is considered if symptoms are present for longer than 10 days since day of onset or worsens within 10 days after initial improvement.[2] Moreover, as opposed to most other bacterial infections of the human body, *fever is neither a required clinical sign of bacterial ARS, nor an accurate marker that can be applied to distinguish between viral and bacterial ARS,* although it may be present.[3] Although other symptoms, e.g. malaise, reduced sense of smell, maxillary pain, and increased ear pressure are often associated with ARS, neither of these is required for diagnosis.[4]

CRS can be diagnosed with high sensitivity if any two or more of any of the symptoms that usually manifest in ARS, persist for longer than 12 weeks.[5] However, symptomological overlap with other conditions, e.g. allergic and non-allergic rhinitis, vasomotor rhinitis, and nasal septal deformities, is common and hence consideration of potential differential diagnoses is important. As opposed to ARS, CRS is primarily an inflammatory condition and although acute flares in viral or bacterial infection may complicate the illness, it is not the etiological foundation of the condition.[2] In contrast, recurrent ARS, defined as at least 4 episodes of ARS within a 12-month period, is generally caused by viral or bacterial infection and therefore, should be approached differently.

The clinical relationship between allergy and rhinosinusitis is quite ambiguous.[6] In fact, allergic rhinitis is generally not a contributing factor in ARS but may influence the etiology and prognosis of CRS. Further, it is the involvement of systemic, rather than local intranasal markers of inflammation that seem to provide insight into the mechanisms underlying both conditions. Indeed, nasally inhaled allergens *are mostly unable to cross into the paranasal sinuses.*[7] However, once inhaled, allergens can also be processed by macrophages and eosinophils which in turn involve allergen-specific T-cell immune responses[8] that will persist until the triggering allergen is neutralised. That said, patients who are chronically susceptible to rhinosinusitis present with persistently inflamed mucous membranes, irrespective of the actual presence of allergens in the nasal cavity.[9,10]

The treatment of rhinosinusitis with or without comorbid allergy

Intranasal saline irrigation

Intranasal saline irrigation (not saline sprays) is regarded as first-line intervention for both ARS and CRS. In this regard, hypertonic, rather than isotonic solutions may be more beneficial to thin and clear mucus and prevent worsening of the condition. Not only do nasal irrigations assist the intranasal cilia from clearing mucus, but it also facilitates the removal of inflammatory mediators, e.g. histamine and prostaglandins.[11] Further, saline irrigation is equally recommended for both viral and bacterial ARS as well as for the supportive treatment of CRS due to its low incidence of adverse effects.[12]

Antibacterial therapy

Antibacterial treatment for acute and chronic sinusitis includes amoxicillin-clavulanic acid combination, erythromycin, cefuroxime, doxycycline, co-trimoxazole, or moxifloxacin for a total of 10 to 14 days.[13,14] Although efficacy of all the mentioned compounds have been demonstrated in the treatment of sinusitis, the increasing development of resistant organisms and

antimicrobial stewardship awareness necessitate the optimal use of these drugs, only if and when necessary. A recent study reported that the majority of sinusitis prescriptions average a 10-day treatment period.[15] This is of note as previous work suggests short-course antibiotic treatment regimens (up to 7 days) induce similar efficacy and outcome than long-term (≥ 2 days longer than short-course) regimens,[16] while being without the increased risk for antibiotic-associated side effects.[17] Amoxicillin has a favourable side-effect profile and is therefore considered the first-line treatment option in chronic (and acute) sinusitis patients.[14] Mono-therapy amoxicillin remains effective in low-risk patients, whereas the combination with clavulanic acid is recommended in patients where bacterial resistance is more likely (smokers, patients recently treated with antibacterials and/or where high rates of community resistance have been reported)[3,18] as well as in children and elderly patients.[14] As alluded to earlier, macrolides are often prescribed in penicillin-allergic patients.[14]

Importantly, healthcare practitioners should evaluate each patient individually before prescribing antibiotics for sinusitis, as such intervention is unnecessary in the majority of patients.

Corticosteroid therapy

Corticosteroids benefit patients with both ARS and CRS, bearing in mind that such therapy be co-administered with oral antimicrobial therapy in the case of bacterial ARS.[2] Intranasal corticosteroids have proven efficacy in the maintenance treatment of allergic rhinitis, acute post-viral sinusitis as well as chronic rhinosinusitis. Collectively, corticosteroids attenuate the expression and release of pro-inflammatory cytokines from airway epithelial cells and are effective in reducing the number of inflammatory and immunoreactive cells.[19,20] Further, at the recommended doses they are safe to use, mostly being devoid of adrenal suppressive effect.[21]

Antihistamines

Although not indicated for use in bacterial ARS[2] – in fact, they can complicate disease prognosis – all antihistamines are equally effective against the symptoms of allergic rhinitis and in some cases rhinosinusitis, but differ with regard to their chemical structures, clinical pharmacology and toxicology.[22,23]

Oral and topical second generation H_1 antihistamines are commonly used as a first-line intervention for the symptoms of allergic rhinitis, including sneezing, nasal itching, rhinorrhoea[24]; however, they have modest effects on nasal congestion, which often predominates in persistent allergic rhinitis. Although differing in chemical structure, all of the newer, second-generation antihistamines demonstrate high affinity for H_1 receptors and therefore present with equal efficacy, anti-inflammatory potential (not necessarily linked to their H_1 blocking activity) and a reduced side-effect profile.[23,25] However, that they differ on a chemical level is important to explain differences in their pharmacokinetic properties.[25] Most of the currently available second generation H_1 antihistamines are lab-synthesised derivatives from parent antihistaminergic compounds, which may have had undesirable central nervous system (CNS) and cardiotoxic adverse effects if administered as is. However, the single greatest advantage of using the second-generation antihistamines as opposed to their first-generation predecessors, is the reduced risk for CNS-related adverse effects that characterised therapy with the first-generation compounds.

In terms of their administration to patients with non-bacterial rhinosinusitis, it is interesting to note that all H_1 antihistamines have anti-inflammatory effects, mediated via their inhibition of histamine-activated NF-κB synthesis, a transcription factor involved in the synthesis of pro-inflammatory cytokines and adhesion molecules.[26] This results in reduced nasal congestion and hyperreactivity when administered according to a regular daily dosing schedule, an effect not clinically evident if given on an as-needed basis.[26] Against this background, the relatively novel H_1 antihistamine, rupatadine, displays an additional ability to block platelet activating factor receptors, thereby decreasing platelet aggregation which contributes to its anti-inflammatory effect.[27,28] Continuous treatment with the H_1 antihistamines over a longer period of time proves to be more beneficial and effective than on-demand treatment.[29]

The leukotriene receptor antagonists

Montelukast is an orally active compound, initially developed for the prophylactic treatment of asthma and the only antileukotriene approved for the treatment of allergic rhinitis. The drug binds with high affinity and selectivity to the leukotriene-1 receptor, thereby inhibiting the physiologic actions of leukotrienes in the upper respiratory system.[30] The drug also reduces the number of circulating eosinophils, suggesting that it acts on a systemic level to reduce the physiological sequelae of allergic inflammation.[30] Moderate evidence for the efficacy of antileukotrienes in the treatment of CRS with nasal polyposis exists, especially in combination with topical and/or oral corticosteroids.[31] Unfortunately, post-marketing reports of neuropsychiatric adverse effects, including depression, aggression, insomnia, irritability, and nightmares,[32] have prevented the drug from being registered as an over-the-counter therapy for allergic rhinitis and rhinosinusitis.[33]

Immunotherapy

Immunotherapy is only indicated in patients with moderate to severe refractory allergic rhinitis and CRS. Furthermore, subcutaneous omalizumab is currently the only monoclonal IgE antibody registered in South Africa in this category. By binding to high levels of circulating, allergy-associated IgE-antibodies, omalizumab removes IgE antibodies from the circulation, thereby reducing its potent ability to cause mast cell degranulisation and subsequent allergic reactions.[34]

Decongestants

Whether administered locally or systemically, decongestants induce nasal vasoconstriction via alpha (α)-adrenoceptor stimulation, thereby reducing hyperaemia and mucosal swelling, leading to increased airflow and overall improvement of nasal breathing. Due to the reduction in nasal blood flow,

plasma exudation and nasal discharge is also decreased, altogether contributing to the decongestant properties.[35] Oral decongestants include *direct*- (i.e. phenylephrine) and *indirect* acting (i.e. pseudoephedrine) sympathomimetics. However, due to their general non-selectivity and systemic absorption, their α-adrenoceptor stimulating effects are not limited only to the nasal cavity. In fact, side effects generally associated with systemic decongestants, include, but are not limited, to hypertension, insomnia and appetite suppression.

Topical decongestants could be a more attractive treatment strategy in treating nasal congestion. In this regard, topical decongestants include the α-adrenoceptor agonist imidazoles, xylometazoline and oxymetazoline. Despite differences in receptor affinity (xylometazoline being a full agonist to the α_{2B}-adrenoceptor, and oxymetazoline a more potent and full agonist at the α_{2B}-adrenoceptor with additional weak α_{1A}-adrenoceptor partial agonist properties),[36] both drugs induce fast-acting decongestant effects with similar duration of action.[37] Nevertheless, the overall higher affinity for the α_2-adrenoceptor subtype of topical decongestants, relative to α_1, facilitates an improved side-effect profile compared to systemic and non-selective decongestants. In fact, α_2-adrenoceptor agonists might have a greater constricting effect on nasal veins, as opposed to the equipotent constricting effects of non-selective adrenoreceptor decongestants.[35] This could partly be due to the dominating α_2-adrenoceptor-mediated vasoconstricting effects, relative to the α_1-adrenoreceptor effect, within the nasal cavity.[38] In fact, the α_2-adrenoceptor agonist, clonidine, was originally developed as a decongestant,[39] but due to its systemic effects, most notably hypotension and bradycardia, its decongestant potential was deemed inferior. Importantly, topical decongestants are not free from side effects, and although being a debated topic,[40-42] prolonged use of topical decongestants are commonly associated with rhinitis medicamentosa – rebound congestion.[41,43]

Summary

In this article, we summarised the major clinical aspects of acute and chronic rhinosinusitis. We further highlighted the fact that contrary to general perception, allergic rhinitis and rhinosinusitis are in fact two fundamentally distinct conditions, that may overlap to some extent and co-present in some patients under certain circumstances. That said, the pharmacological treatment of these conditions overlaps significantly. As such, we also elaborated on the different available drug classes and explained from a mechanistic perspective how they may be used to improve overall disease prognosis.

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