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RECENT ADVANCES

Best Use of New and Established Therapies for Allergic Rhinitis

Allergic rhinitis (AR) is an IgE-mediated inflammatory disease of the nasal mucosa, triggered by exposure to airborne allergens, and is associated with atopic dermatitis, food allergy, and asthma.[1] Symptoms primarily include rhinorrhea, nasal blockage, and sneezing though ocular symptoms can also occur. The standard treatment for AR begins with the avoidance of the allergen.[2] If symptoms persist despite avoidance strategies, newer generation oral antihistamines (AHs) are the first line option. They are the most commonly used treatment method, being safe and efficacious. Intranasal corticosteroids (INCS) are also recommended as 1st line treatment and in fact, show greater efficacy than oral AHs. Combination intranasal therapies with antihistamines and corticosteroids also exist which can provide more significant relief.[2]

Oral AHs have been the most utilized class of medications consisting of first and newer-generation AHs.[3] First generation AHs are associated with central nervous system side effects like sedation and mental impairment and anticholinergic side effects such as dry mouth, dry eyes, urinary retention and constipation.[3] Newer generations are safer and are used as first-line AHs.[4] The CNS effect of 1st generation AH resembles and exacerbates those produced by alcohol and by other CNS active chemicals.[4] Infants and children who experience accidental or intentional overdose may present with paradoxical excitation, including irritability, delirium, respiratory depression, and coma.[5]

Cardiac toxicity was previously an under-recognized risk of 1st generation AHs. Diphenhydramine and hydroxyzine interfere with cardiac K^+ channels involved in action potential repolarization. As a consequence, these drugs may cause dose-related prolongation and a form of polymorphic ventricular dysrhythmia called 'torsade de pointes.[6]

The safety of newer generation AHs came onto the Canadian market in the 1980s.[6] Prescription event monitoring studies in England comparing the risk of drowsiness and sedation between newer-generation AHs have proven there is a low risk of sedation for cetirizine, desloratadine, fexofenadine and levocetirizine.[7] It is worth mentioning that two 2nd generation AHs, astemizole and terfenadine, have been associated with prolonged cardiac QT intervals and "torsade de pointes" at high doses. Both drugs have been off the market for over 20 years.[7]

It is a misconception that older AHs have a faster onset of action than newer agents. In a double-blind placebo-controlled trial comparing cetirizine and loratadine to chlorpheniramine, both were found to have a faster onset and a longer duration of action.[8]

New advances in AH have focused on rupatadine and bilastine. Rupatadine is a novel substance which, in addition to being an H_1 antagonist, is also a potent platelet-activating factor (PAF) inhibitor and bilastine that is highly selective for the H^1 receptor, has a fast onset of action with a long duration of action.[9]

Intranasal antihistamines

Intranasal antihistamines (INAHs) ensure drug delivery to the nasal mucosa, enhancing local anti-allergic and anti-inflammatory

effects while minimizing systemic exposure to therapy.[10] The 2016 allergic rhinitis and its impact on asthma (ARIA) guidelines recommend using intranasal antihistamines (e.g. olopatadine, and levocabastine) in intermittent but not persistent AR.[10]

Intranasal corticosteroids

ARIA guidelines recommend INCS as the best option for mild, moderate to severe AR.[10] The significant disadvantages of INCS are patient adherence and the length of time they take to reach maximal effect.

Leukotriene receptor antagonists

They block the activity of cysteinyl leukotrienes, a potent inflammatory mediator of AR symptoms.[11] Montelukast, alone or in combination with an AHs, gave a gradual increase in nasal symptom improvement within 6 weeks of treatment. More recent studies have suggested the presence of neuropsychiatric side effects with the use of montelukast, and as such, the U.S. Food and Drug Administration has discouraged its use as a first-line therapy for mild AR.[11]

Intranasal antihistamine and intranasal corticosteroid combination

Combining an INAH and an INCS, azelastine hydrochloride/fluticasone propionate (AZE/FP) is a novel formulation in a single spray. Patients benefit from the additive effects and there is possible improvement in adherence to therapy by delivering the two agents in a single device.[12] Moreover, the single spray application provides more uniform distribution and greater retention in the nasal cavity than sequential sprays of AZE and FP.

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DRUG SAFETY

Drug Induced Photosensitivity

Drug-induced photosensitivity refers to the development of cutaneous disease as a result of the combined effects of a chemical and light.[1] Photosensitive adverse events are usually categorized as either photo-toxic or photo-allergic, and additionally as either topical or systemic. While this classification is based on different pathophysiological mechanisms, several features illustrate the contrast between them, including incidence, immunization, onset after exposure, and clinical appearance.[2] These reactions are due to cellular damage from the altered medicine in sun-exposed areas and are dose-dependent. Clinical presentation varies from mild burning and stinging to exaggerated sunburns with erythema and oedema of the sun-exposed areas. Hyperpigmentation may also occur.[3] Photoallergic reactions have an immunological basis. UV radiation transforms the medicine into an antigen that triggers an allergic response. The presentation is generally of eczematous dermatitis which can spread across the whole body beyond the exposed areas.[3,4]

The rash may or may not be itchy. Medications can also cause onycholysis (the nail plate lifting off the nail bed). This is known as photo-onycholysis.

Common photo-sensitizing medications are:[5]

1. Antibiotics: Tetracyclines, Fluoroquinolones (eg, Ciprofloxacin), Sulfonamides
2. Nonsteroidal anti-inflammatory drugs (NSAIDs): Ibuprofen, Naproxen, Ketoprofen, Celecoxib
3. Diuretics: Frusemide, Bumetanide, Hydrochlorothiazide
4. Retinoids: Isotretinoin, Acitretin
5. Hypoglycaemics: Sulfonylureas (e.g, glipizide, glyburide)
6. Antipsychotics: Phenothiazines (e.g. Chlorpromazine, Fluphenazine), Thioxanthenes (e.g. Chlorprothixene)
7. Targeted therapies: Vemurafenib (50%), Dabrafenib, Imatinib, Vandetanib.
8. Other drugs: Amiodarone, Diltiazem, Quinine, Quinidine, Hydroxychloroquine, Enalapril, Dapsone, Voriconazole.

The clinical features of drug-induced photosensitivity vary according to the photosensitising agent involved and the type of reaction it causes in the skin. The reaction can be phototoxic and/or photoallergic.

Phototoxic reactions result from direct damage to tissue caused by light activation of the photosensitising agent, whilst photoallergic reactions are a cell-mediated immune response in which the antigen is the light-activated photosensitising agent.

Photoallergic reactions occur less commonly than phototoxic reactions and are mostly caused by photosensitising topical agents. Although some oral photosensitising medications can cause photoallergic reactions, most cause phototoxic reactions. A handful of medications can cause both phototoxic and photoallergic reactions.

The clinical features differ between phototoxic and photoallergic reactions.

Phototoxic reactions[6]

- Skin reaction occurs minutes to hours after exposure to the agent and light
- Appears as an exaggerated sunburn reaction (reddening and swelling)
- Vesicles, blisters and bullae may occur in severe reactions (pseudoporphyria)
- May or may not be itchy
- Less commonly, the skin may change colour, for example, a blue-green pigmentation is associated with amiodarone
- The reaction is limited to sun-exposed skin
- Photo-onycholysis (separation of the distal nail plate from the nail bed) may arise with many oral photosensitising medications and may be the only sign of phototoxicity in dark-skinned individuals

Photoallergic reactions[7]

- Eczematous, itchy type reaction occurs 24-

72 hours after exposure to agent and light

- May spread to areas that have not been sun-exposed
- Hyperpigmentation does not occur

The main goal of treatment is to identify the photosensitising agent and if possible to avoid it. In cases where medication is being taken to treat an existing condition and cannot be discontinued, patients should be advised to follow strict sun protection strategies, including wearing sun protective clothing and using high protection-factor, broad-spectrum sunscreen.[8]

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DRUG SAFETY

Non-steroidal antiinflammatory drugs (NSAIDs): Risks of maternal, fetal and neonatal adverse effects in pregnancy

The Medsafe has announced that the product information for nonsteroidal anti-inflammatory drugs (NSAIDs) are to be updated and aligned regarding the risks of maternal, fetal and neonatal adverse effects for the use in pregnancy. The Medicines Adverse Reactions Committee (MARC) reviewed the safety of NSAID use in pregnancy. NSAIDs used in early pregnancy is associated with an increased risk of miscarriage and congenital malformation; NSAIDs used in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment; and NSAIDs used in the third trimester may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth. Health-care professionals are advised that NSAIDs are contraindicated in the third trimester of pregnancy; NSAIDs should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment during the first or second trimester, use should be limited to the lowest effective dose and shortest duration possible. Health-care professionals should enquire about NSAID use in women who are pregnant or planning pregnancy and advise them not to self-medicate with these medicines during pregnancy.

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