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SECOND-GENERATION PRESCRIPTION ANTIHISTAMINES IN CANADA: AN EVIDENCE-INFORMED REVIEW

Health Science

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ABSTRACT

Prescription antihistamines have been available in Canada for over fifty years, starting with first generation medications such as pyrilamine released during World War Two, with the first second-generation antihistamines commercially appearing in the 1980's. (1) Based on Canadian market growth assessments, antihistamines are an estimated $120 million market, representing over a dozen dedicated prescription and non-prescription (over-the-counter (OTC)) molecules. (2) There are a great number of other non-antihistamine molecules that have direct and indirect affinity for the histamine receptors. (3,4) Secondary to environmental, physiological and co-morbidities, this sector is experiencing an annual growth rate of just under 10%. (2) For registration trials, all antihistamines meet standards and are assessed for non-inferiority against an industry standard such as diphenhydramine. (5,6) Despite having confidence regarding non-inferiority across the antihistamines, it is important to go beyond this evidence-based parameter to a patient-focussed evidence-informed approach. (7) This is because not all prescription antihistamines, or necessarily any and all "non-inferiority" medications are created or work alike in the human body. Each molecule has their own molecular "fingerprint" that has physiological and immunological responses through slightly different mechanisms that go beyond histamine mitigation. (8) Evidence-informed medicine allows us to address triggers and cascade management leading to histamine release requires a robust multi-factorial assessment, which includes autoimmune, mast cell, cytokine, and environmental components. (9) Other factors that should be considered include patient specific goals, dietary habits, past allergen exposures, genetics, cross-allergenicity, other medications, and other medical conditions beyond the allergen and subsequent histamine release. (10) Appropriate second-generation antihistamine selection often becomes quite patient-specific and intricate beyond the standard non-inferiority evidence-based histamine mitigation studies. (7,9,10)

KEYWORDS

Autoimmune, Antihistamines, Platelet Activation Factor, Rupatadine, Allergic Rhinitis, Urticaria

INTRODUCTION

Gell and Coombs classification of hypersensitivity reactions is commonly utilized to classify allergic disease. Gell and Coombs defined four types of hypersensitivity reactions. (11) Immediate, or IgE mediated is Type I. Type II is antibody dependent cytotoxicity. Type III is immune complex disease. Type IV is cell mediated. Type I and Type IV are often considered the main mechanisms behind the more common allergic disease presentations. Type I reactions include allergic rhinitis, food allergy, and anaphylaxis. Type IV reactions are allergic contact dermatitis, and severe delayed drug allergy. (11) Type I reactions are the most common types of allergic reactions, with Allergic Rhino-conjunctivitis being the most common, affecting up to 25% of the general population. (11,12)

There are multiple hierarchical tiered levels of treatment of allergic conditions such as allergic rhino-conjunctivitis. Primary prevention and the first line approach is allergen avoidance, where the patient is advised to avoid the allergenic trigger. (13) Second line options would be the use of an antihistamine medications. (14) Third line therapies may involve augmentation strategies, such as combination of antihistamine and steroids (usually topical, via nasal spray), and for patients with significant eye symptoms, topical drops may also be prescribed. (15) Fourth line therapies would be immunotherapy, which could be either in an injectable or tablet formulations. (16)

Type I hypersensitivity reactions requires an allergen (antigen) that binds to an IgE molecule that is bound to the mast cell. (9,11) A mast cell is a type of immunological cell found in the skin, airway, and the GI tract predominately, but also in small number in the blood. (9,17) The binding of the antigen to two or more receptors on the mast cell, is called cross-linking, where the mast cell is activated and degranulates, releasing a variety of mediators.(9,18) Histamine is one of the major mediators. By blocking histamine, you can prevent the downstream effects of histamine, thereby minimizing the symptoms that a patient can experience. (9) The process of mast cell activation/degranulation is complex and involves many more mediates. (9,17,19)

Another common condition where antihistamines are the foundational treatment would be urticarial. (20) Urticaria can be divided into acute (symptoms for <6 weeks) or chronic (symptoms most days for > 6 weeks). (21) Acute causes of urticaria are most commonly secondary to viral infections but can also include food or drug allergy. (22) Chronic urticaria however, is often idiopathic. (23) Treatment would be high dose antihistamine, defined as 4 times the recommended dose. If symptoms are not controlled, then guidelines suggest using omalizumab. (24)

Role Of Histamine And Other Mediators In Allergies

Once mast cells have been activated and release histamine, histamine will activate one of the histamine subtype receptors in a lock and key format, resulting in dilation of blood vessels that allow enhanced blood flow and permeability. (25)

Other products of mast cell degranulation are platelet activation factor (PAF), cytokines, leukotrienes, and serotonin. (9,26) These mediators are responsible for inflammation, heart rate changes, smooth muscle lung changes, and vasodilation with increased blood vessel permeability and tissue edema. (27) The body's reaction to degranulation from allergen exposure also may result in abdominal pain, gastrointestinal tract motility changes as well as diarrhea. (27) PAF is responsible for much of the inflammatory and vascular responses, platelet aggregation/ degranulation and life-threatening anaphylaxis. (28,29)

Canadian prescription second-generation antihistamines include bilastine (Blexten®), cetirizine (Reactine®) and rupatadine (Rupall®). (30) Common medical conditions treated with antihistamines include conditions identified in Table 1. Antihistamines control allergic, seasonal and perennial, chronic spontaneous or contact symptoms such as nasal or skin reactions by decreasing histamine, which is a component of our body's reaction against triggers, irritants or allergens. Antihistamines have also been used in the treatment of: vertigo, bronchitis, nausea and/or vomiting. (31,32,33)

Table 1: Common Conditions treated with antihistamines (31,32,33)
Allergic rhinitis
Asthma
Pruritus and related diseases
Allergic conjunctivitis
Allergic dermatological reaction(s)
Sinusitis
Urticaria
Chronic spontaneous urticaria
Angioedema
Atopic dermatitis

Antihistamine Selection

Windaus and Vogt first identified the chemical synthesis of histamine in 1907 and its actions described three years later, being isolated from ergots and putrefactive bacteria in 1910. (34) Pharmacologist Daniel Bovet in 1937 identified molecules resulting in antihistamine effects, resulting in the first "selective" antihistamine being synthesized in 1942 (35). By 1947, the antihistamine dimenhydrinate was used beyond the allergic cascade, in order to control nausea and vomiting. This work led to an awarding of the Nobel Prize in 1957, which speaks to the impact this class of molecules have on reduction of morbidity, mortality and suffering. (36) As histamine is a G-protein coupled receptor that is located in the heart, central nervous system (CNS), immune cells, adrenal medulla and gastrointestinal smooth muscle, it may be expected that "overspill" effects of antihistamines present across conditions. (37,38) These effects may be beneficial (histamine or PAF antagonism) or undesirable (anticholinergic cascade activation) and depend on the individual molecule. (9,27) Antihistamines become one of the cornerstones of therapy, and have been widely available in Canada since the 1950s. (Figure 1)

Further undesirable effects of older, first-generation antihistamines (e.g. diphenhydramine, hydroxyzine) have significant (cardiac) and more common side effects including sedation, impairment with altered cognitive function, sleep impairment, dry mouth, dizziness, and orthostatic hypotension. (39) Cognitive changes are linked to impaired functionality in activities requiring alertness, including accidents. (39)

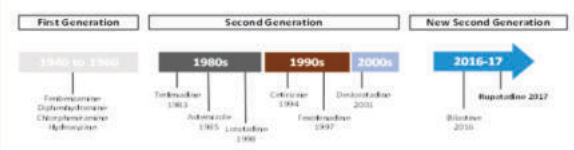

Figure 1: Antihistamine History In Canada (40)

There are many antihistamine options available in Canada that are over the counter and on prescription. As with any medication, every antihistamine should have a positive effect on mitigating symptoms, resulting in improved functionality.(41) As the clinical trials for antihistamines are setup to study noninferiority.(8) This make choosing an antihistamine superficially easy as you know that whatever antihistamine you chose should result in symptom improvement. (31,32,33) However, symptom improvement alone is not the only factor that is important to patients. For example, side effects from treatment, safety and cost are three important patient identified factors in addition to efficacy. (42)

Other factors to consider when choosing an antihistamine would be its mechanism of action. (9, 27) Type I reactions/allergies are more than histamine-mediated processes and resultant histamine treatments. (11) Our natural defense/chemotactic mediator response to triggers also release/activate: inflammatory mediators, PAF antagonism, mast cells, basophils, eosinophils, cytokines, interleukins, tissue necrosis factor (TNF) and other damaging by products, which have their own downstream physiological impacts. If an antihistamine has other mechanisms of action besides histamine blockade, then that may be beneficial. (9,27)

Premises of medical and pharmaceutical care delineate the best therapeutic option. A validated mnemonic that helps clinicians optimize medication selection and dose based on symptom presentation TAIDCC; representing therapeutics, accuracy/allergies, interactions, duplications, compliance and cost assessments. The use of this systemic approach supports evidence-informed medicine, remove biases and ensures an equal delivery of clinical services for any patient. It also allows for more fluidity in dose selection and adjustments through the course of treatment. (7,43) TAIDCC involves asking ourselves set questions regarding patient-specific demographics, clinical presentation, goals of care and evidence-based care to produce an evidence-informed therapeutic intervention. There are six categories in a TAIDCC review: therapeutics, allergies, interactions, duplications, compliance/concordance and cost. (43)

THERAPEUTICS

Patient-Specific Factors

Quality of Life data helps determine the desired effect of the therapeutic intervention. (44) Identification of the patient's goals of treatment can help strategize therapy and doses using pharmacokinetic and pharmacodynamic factors. (43,44) Patient confounders and factors used in clinical optimization of antihistamine selection are multifactorial and include age, symptoms and severity (intermittent or persistent) and the presence of cardiac, hepatic or renal impairment allows for safety in medication selection. (45) Other factors that may not always be considered include concomitant disease, pregnancy, and familial history of atopic or autoimmune diseases where the immune cascade or mast cell activation influence treatment selection. (27,45,46) The pattern of symptom occurrence and trigger identification is also another consideration—some patients report an inadequate control of bothersome symptoms, while others experience symptoms of allergic rhinitis that occur in the morning and gradually improve by midday.(46) This may also have unintended negative downstream effects on sleep, and subsequently functionality, mood and behaviour. (47,48) Patients with chronic urticaria often need to have above the recommended dose of antihistamine for symptom control. This can result in increased side effects from the medication. (39) Many factors are considered in medication selection for allergic rhinitis and urticaria. A 2017 paper by Recto et al identified the ten most significant factors in antihistamine selection, with patients' goals of pharmacotherapy being a medication that is effective, safe, well tolerated and easy to take are listed amongst the most important. (49)

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamics help determine dose ranges and predict concentrations at the receptors, which delineate the clinical response of the patient. As all patients are unique, there may become a "spectrum of activity" where genetics, past allergen exposure, other medications, disease severity, physiological state, concurrent conditions, age, gender, diet (fat absorption/distribution), and environment factors play a role in response/efficacy. (50,51,52)

More rapid onset of action, efficacy and better adverse effects (safety) profiles are three of the primary drivers that positively influence patients' selection. (32,49) Ease of use using once or twice daily dosing is often preferred compared to more complex, usually historical, dosing regimens. Older (Figure 1) antihistamines demonstrated unpleasant adverse effects including sedation and anticholinergic properties. (53) The newest prescription antihistamines (bilastine and rupatadine) in Canada have a side effect profile comparable to placebo at standard prescribed doses. (54,55)

In short, pharmacokinetics are multi-faceted processing bodily systems that include absorption, distribution, metabolism, and excretion. Medication levels are increased or decreased, with subsequent alterations in efficacy through a variety of intestinal and hepatic pathways that include the p-glycoprotein transport protein and the cytochrome P-450 (CYP) enzymes. (56,57) There are a number of exogenous and internal factors that can decrease or increase medication absorption, metabolism or excretion pathways including dietary fat, gastric pH and presence of food. (58)

When medications are absorbed through the gastrointestinal tract, they are often metabolized by a variety of enzymes. There are two types of interactions: pharmacokinetic and pharmacodynamic. CYP 1, 2 and 3 there are more than 50 subclasses of these enzymes. (59) The majority of medications are metabolized through the CYP 3A4 system, which is a very common metabolizing system. In fact, within. CYP 3A4 is the most prolific of medication metabolism, metabolizing approximately 60 percent of all pharmaceuticals. (59,60) The liver is responsible for metabolizing CYP medication substrates, as it contains the largest number of CYP enzymes, and is one of the best studied metabolic or transport systems. Of the 23 pathways, CYP1, CYP 2, and CYP3 are the primary enzymatic pathways that metabolize medications. (59,60) There are isozymes that exist within each larger family.(59) CYP system metabolism does not preclude an agent to be used in selection, but rather is part of the clinical picture of indication, efficacy, patient response, other medications, genetics and other factors. (61) A medication that is impacted and metabolized by CYP is called a substrate and is changed, usually to an inactive form by these isozymes. Some medications may also cause drug interactions by altering the levels and activity (inhibition or induction) of a particular CYP enzyme. Inhibitors of the CYP system will result in an active molecule to increase in concentration and inducers of the CYP system will cause decreases in target medication concentration. (61) Multiple substrates may be combined together, with minimal effects (usually less than 20% variation) on resultant concentrations. (62) An example of combined substrates in a commercially available product, would be Caduet ™ , which is amlodipine and atorvastatin, both CYP3A4 substrates, which combined in the same tablet. This is possible in part

through the large capacity of these hepatic metabolizing enzymes. (62,63)

These normal metabolic pathways are responsible for metabolizing the majority of known medications to their next states, which may be active or inactive. Interactions may result in higher or lower medication levels, resulting in the potential for a lack of efficacy or increase levels of side effects due to heightened levels. (61) Some medications are not metabolized (or modified) by the body, yet their concentration is dependent on a body transport system. A common body transport mechanisms that increases or decreases medication (substrate) levels by efflux transport is called p-glycoprotein (PgP). (56)

PgP is extensively located within the intestine endothelium and bile ducts and is an important protein that also is known as the multidrug resistance protein 1 (MDR1). PgP removes drugs and toxins that are ingested in a pump-like fashion, with medications being pumped out of blood back into the intestine or into the bile ducts from the liver, where the medications are excreted unchanged. PgP also acts as a "detoxifier" and "barrier" at the brain and placenta especially, preventing medication crossing the blood brain barrier into capillaries and removing medications in the proximal tubule of the kidney into urine. (64,65) Active transport of the substrate by PgP thus ultimately regulates medication distribution, bioavailability, medication levels and ultimately the therapeutic response and/or side effects that a patient experiences. (64,65,66)

As with the CYP system, PgP is associated with inducers and inhibitors that respectively decrease or increase substrate levels. (67) Unlike CYP, PgP activity may be altered in multiple medical conditions, including some cancers, inflammatory bowel disease, ulcerative colitis and Alzheimer's disease. (68,69,70) Substrates of PgP are vulnerable to changes in their pharmacokinetic profile secondary to drug interactions from disease states, inhibitors and inducers. The number of medications that are PgP substrates is very comparable, and there is a substantial overlap with CYP 3A4, with Church et al identifying a link between PgP and CYP3A4 working synergistically to remove medications from the body. (71,72,73)

Various reviews theorize that both CYP3A enzyme and PgP transporters both have a large role to play in oral drug bioavailability and elimination of numerous drugs. This is not unusual, as both CYP3A4 and PgP work together in the first-pass phenomenon of medication absorption and metabolism. (71,72,73)

Bilastine is a substrate of P-glycoprotein. P-glycoprotein is responsible for metabolizing/controlling the removal of bilastine from the system. From a drug-interaction perspective, agents that inhibit P-glycoprotein activity would result in higher bilastine levels, whereas inducers of this transport mechanism may result in sub therapeutic bilastine levels. Both bilastine and cetirizine are excreted mainly unchanged in feces and urine. (54,74)

The parent drug and any resultant metabolites are then excreted through primarily through the urine, feces, and sweat. These pharmacokinetic alterations in the molecule and their resultant levels equate to the positive physiological responses that we see, as well as downstream effects. (51,52) Pharmacodynamics is in part the effects of the medication on the body. (52) Some molecules, including bilastine note in their monograph that states: "Plasma levels of bilastine can be increased by inhibitors of P-glycoprotein; the concomitant use of these drugs with bilastine is not recommended. Drugs that inhibit P-glycoprotein include, but are not limited to certain azole antifungal, macrolide antibiotics, and HIV protease inhibitors". (54) No specific drug interaction or efficacy studies have been completed on bilastine's Canadian oral-dissolvable or liquid formulations as of June 2022 based on the most recently accessed Health Canada monograph, although pharmacodynamic effects from food are reported. (54)

Pharmacodynamics is the study of what the medication does from a biochemical and physiological perspective. This includes the agonist, stabilization or antagonism of receptors and biochemical markers and their downstream effects. Within this assessment falls the clinical therapeutic window. (75) Undesirable effects of a medication include overspill or impact on receptors beyond what has been targeted. (76) An excellent example in antihistamines is the anticholinergic effects seen due their blockade of the transmitter acetylcholine. Of the prescription antihistamines in Canada, cetirizine has the highest incidence of dose dependent anticholinergic effects, with bilastine and rupatadine having the least. (54,55,77)

Anticholinergic effects may present as: dry mouth, blurred vision, constipation, weight gain, falls risk, airway drying and agitated delirium; this is a clinical concern and consideration for a variety of patient populations. These may include the frail, elderly, patients with mental health or substance abuse histories or are already on medications with a high anticholinergic load. (78,79)

Table 2: Pharmacokinetics And Pharmacodynamics Of Current Canadian Prescription Antihistamines (54,55,57,80-82)

	Cetirizine	Bilastine	Rupatadine
Time for Maximum concentration	1 h1	1.5 h	0.5-1 h
Prodrug	No (Molecule already active)	No (Molecule already active)	No (Molecule already active)
Metabolism	Excreted unchanged-Renal (70%); Faeces (10%)	P-Glycoprotein Substrate	CYP 3A4 Substrate
Active Metabolites	No	No	Yes (Desloratadine, 6-hydroxy-desloratadine)
Drug interactions (Pharmacokinetic)	Low potential	Low/Moderate Inhibitors and inducers of intestinal P-glycoprotein Grapefruit juice decreases plasma levels 30%	Low/Moderate Inhibitors and inducers of hepatic 3A4 Grapefruit juice increases plasma levels 3 fold
Drug Interactions (Pharmacodynamic)	High (sedation, anticholinergic)	Low	Low
Interaction with food	No	YES. Up to 46% reduction in CMax depending on formulation when taken with moderate to high fat meal	No
Elimination rate	T 1/2= 6.5-10 h 1	T1/2=14.5 h (renal)	T1/2= 6+27 hrs (rupatadine plus active metabolite)

Accuracy

The therapeutic window of safety is the dosage range that exists between sub-therapeutic and toxic. Toxicity may be defined in this setting as intolerable or potentially life threatening adverse effects, or simply above the upper window where the molecule has been assessed. Multi-dose supra-therapeutic dose studies appear to have identified the therapeutic window for rupatadine and bilastine to be 100mg per day. (54,55) This corresponds to a ten-fold safety margin for rupatadine and 5-fold for bilastine, based on standard doses. The therapeutic window for rupatadine and bilastine is presented in Figures 2 and 3. Cetirizine doses are associated with clinically significant sedation and anticholinergic effects, which may limit use at doses of 20mg or greater. (83) Given the narrower therapeutic window before marked adverse effects occur such anticholinergic effects and sedation, cetirizine is not included in Figure 1. The therapeutic window can help address a common question regarding the safety of combining cardiac medications or medications that can cause QTc with antihistamines. Bilastine and rupatadine have been studied up to 100mg per day with no resultant QTc prolongation. (54,55,72,80,82,84)

Higher doses up to four times usual dose have recently been included in urticaria treatment guidelines for bilastine and rupatadine, taking advantage of their safety margin and dose-response curves. (85)

As expected, different clinical presentations and patient exposure requires the ability to have a range of doses available. As with all

medications after launch, there have been studies addressing use of doses that may be higher or lower than identified with initial registration trials. Guidelines emerge from exposure to "real-world" prescribing and clinical presentation. Limitations include adverse effects, safety and tolerability. (85)

Table 3: Prescribed Doses Of Prescription Antihistamines In Canada (54,55,57,80-82)

	Usual Adult Dose	Urticaria Guideline Dosing Range	Pediatric Dose
Bilastine	20mg	20-80mg	10mg* Children and infants up to 4 years of age and/or under 16kg: Use is not recommended
Cetirizine	20mg	20mg	Age 6-11year: 5 to 10 mg once a day. Age 4 to 6: 2.5 mg once or twice a day. Max 5mg daily Children and infants up to 2 years of age: Use is not recommended
Rupatadine	10mg	10-40mg	Children 10 to 25kg: 2.5 mg once daily Children over 25kg: 5 mg once daily Children and infants up to 2 years of age: Use is not recommended

* For urticaria

Sub-therapeutic doses produce an ineffective clinical response, but it is important to note that the molecule may still have a "low-grade" activity and action on the target receptors. There is debate with conflicting evidence that not only does repeated sub-therapeutic doses not relieve patient symptoms, but may contribute to resistance to the molecule through receptor downregulation or sensitization of histamine receptors. The root etiology of the allergen, especially if viral, may play a role in resistance. (86,87)

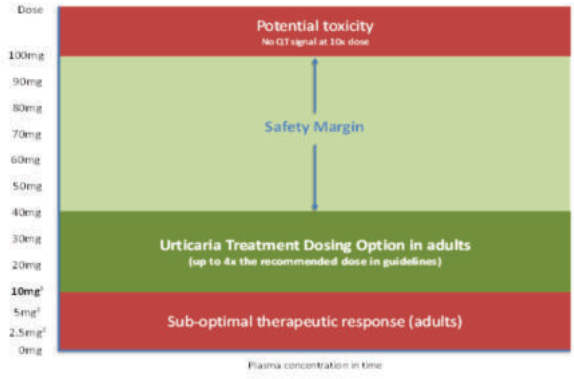

Figure 2 Therapeutic Window for Rupatadine (55,73,80,81)

Figure 3 Therapeutic Window for Bilastine (54,71,82)

Interactions Affecting Therapeutic Window

Multiple medication metabolizing and processing systems extend beyond the CYP system. These medication-processing pathways are called transport systems. Transport systems that affect absorption and elimination of medications may also result in sub or super-therapeutic (toxicity) levels of a medication. Transport systems are involved in penetrating placental and blood brain barriers. An example of one of these efflux transport systems is called P-glycoprotein (PgP) which is most predominant in the small intestine. (64-67,89) Examples of PgP substrates include digoxin, dabigatran and bilastine. There are approximately 300 PgP inhibitors listed in Drug Bank, medications which cause the substrates to increase in level by decreasing their removal from the body across the cytosol. (82) Inducers of PgP increase removal of substrates into the intestine, thus resulting in lower substrate levels. Carbamazepine and phenytoin are two examples of inducers. (82,89)

Food is a confounder in the medication selection rubric that is often overlooked. However, this is a critical confounder and food is has a similar impact medication on levels, and subsequent therapeutic success or failure of pharmacotherapy. The question of fed vs fasting and fat vs not fat meals should be as rigorously reviewed as other parameters that affect medication level (metabolism, elimination and excretion). (58) Questions that present include time of day, type and volume of food and lipophilic and hydrophilic profiles of the medications. (89,90) Interestingly, food and especially high fat food may decrease absorption, resulting in lower medication levels, requiring patients to take their dose an empty stomach, which may negatively affect concordance. (90) An example would be the minimum 25% reduction in bilastine levels when the tablet is taken with food and a 33% reduction when taken with a high fat breakfast. (54,82) (These numbers increase to a reduction in bilastine maximum concentration levels of 46% and 36% for the orodispersible and oral solution products respectively, which may result in subtherapeutic response and potential therapeutic failure. (54) Another example may be loratadine, where an empty stomach increases medication levels by over 50 percent. As there is a wide dosing range for loratadine, at standard doses this would not be expected to have any negative clinical consequences, especially as there is an active metabolite, desloratadine. (91,92)

Beverages also fit into the food thought process. Hydration status, sugars, juices, flavonoids all may impact medication levels. (93,94,95) Grapefruit juice is the "gold standard" that identified downstream effects on increasing medication levels. Most CYP 3A4 substrates are increased in concentration by a factor of 2 to 5 fold. (96) This reinforces the need for understanding the therapeutic window and dosing appropriately. Grapefruit juice is also high in flavonoids, which is an inducer of the not just the CYP3A4, but also inhibits PgP absorption, resulting in lower levels of PgP substrate medications by 25 percent with some antihistamines. (81,97) These flavonoids are also present in other mainly abundant in fruits and vegetables, plus in some herbal supplements, being plant-derived. There is conflicting literature on whether flavonoids are inhibitors or inducers of PgP, which may be as a result of the interplay between CYP and PgP, resulting in medication specific changes in levels versus expected. (98, 71-73)

Duplications

Duplication occur when the patient receives multiple concurrent antihistamines in order to control a complex clinical symptom presentation. Guidelines indicate the desired goal aligns with monotherapy, using a single antihistamine while optimizing the dose to treat symptoms. Considering the manner of clinical presentations for many dermatologic and autoimmune, it is no surprise that duplications and medication "combination cocktails" occur. (99,100) The gold standard is monotherapy, while being aware of the downstream effects of the allergic reaction, such as occurs with mast cell degranulation. There becomes a release of a variety of cytokines, interleukins, serotonin, tissue necrosis factor (TNF) and other cytotoxic mediators. (9,18,19,27)

Introducing treatment later from the time of initial presentation may take days to weeks to mitigate the mast cell and histamine cascade, and is linked to polypharmacy. In the interim, there may be negative impact on the patient's quality of life, as the full complexity of the immune cascade may not be effectively managed. (9,27,101) Bilastine, desloratadine and rupatadine all have high to very high affinity for the H1 histamine receptor and may be considered "potent" antihistamines, in addition to cetirizine. This is an excellent example of why a clinician

cannot merely compare against registration trials. These agents have been found to be non-inferior at set endpoints that align with the H1 receptor. (102) However, the other three histamine receptors (H2, H3, H4) nor the mast cell inflammatory cascade (interleukins, TNF, PAF) are not effectively addressed in a short term "non-inferiority" trial. (9,27,103,104) This real world experience may explain some of the "therapeutic failures" or marked dosing ranges that may be required to achieve symptom relief. Inflammatory cascade understanding and building into clinical decision making links to discoveries and emerging data with the PAF antagonists and the H4 antagonists. (105,106) Rupatadine alone has demonstrated efficacy against the mast cell degranulation clinical presentation. (105)

Using an antihistamine where only histamine is being controlled, other by-products of the mast cell degranulation still remain unchecked that may cause negative physiological effects and distress for the patient. (9,19,26,27) The most common classes of medications that are added to antihistamine therapy depend on the underlying condition, and are often added where the full complexity of the clinical picture is not treated with one agent. Even in over the counter product line extensions, we see decongestants, anti-inflammatories, cough suppressants and antipyretics mixed with antihistamines. (107-109) Addition of an over the counter nasal steroid in Canada may not necessarily be indicated and presents its own drug interaction and side effect profile. (110) Other common classes of medications that are observed in the literature include corticosteroids, immune modulating agents, biologicals, leukotriene-inhibitors and more, each which have their own set of unique interactions and adverse effects. (110-112)

CONCLUSION

From a prescribing and safety perspective, second-generation antihistamines are in general are a very well studied and safe class of medications. As there are multiple molecules within this therapeutic category, identifying which agent to use may be a challenge. There are a number of factors that determine selection of an antihistamine that go beyond antihistamine non-inferiority. The goal is to provide the right medication to the right patient at the right dose with a high degree of efficacy and a minimum of adverse effects, or need for duplication. Primary drivers for positive adherence are efficacy, safety, tolerability, impact on lifestyle (side effects) and cost. Evidence-informed treatment assessments should extend beyond simple non-inferiority histamine blockade, addressing other parts of the allergic cascade such as mast cell activation, interleukins or platelet activation factor. Addressing root cause analysis in medication selection based on clinical picture is essential. Medication absorption, distribution, metabolism and excretion all factor into obtaining the right dose for patient care. Selection of a medication with a wide therapeutic window helps mitigate risk-benefit concerns, while at the same time allowing for more aggressive dosing strategies that have recently emerged in the field of allergy medicine. Selecting an antihistamine that is safe, effective, has a minimum of adverse effects and addresses the "cascade gestalt" may be considered to be best practice to mitigate patient antihistamine-related disorders.

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