BILASTINE: A Drug Review

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***Abstract*—An effective and highly specific H1-antihistamine, bilastine is licenced to treat allergic urticaria and rhinoconjunctivitis. The information that is currently known on the use of bilastine in the treatment of allergic diseases in various age groups, including school-age children and adolescents, younger and older people, is included in this page. Adults and adolescents over the age of 12 get oral bilastine at a dose of 20 mg once day, while children between the ages of 6 and 12 receive oral bilastine at a dose of 10 mg once daily. Clinical studies have shown that it is effective at reducing wheals and itching in urticaria patients as well as nasal and ocular symptoms in people with allergic rhinitis. It acts quickly and effectively for a long time. Bilastine's potential for drug-drug interactions is constrained because it does not undergo considerable metabolism and does not interact with the CYP450 system. In individuals with renal or hepatic impairment, as well as in the elderly, there are no dose changes necessary. Bilastine is often well tolerated, even when given in dosages that are beyond the recommended amount. It has very little sedative effects and neither anticholinergic nor cardiotoxic effects, nor does it penetrate the central nervous system. It has been demonstrated to enhance life quality as it relates to health. From school-age children to senior patients, bilastine is a useful alternative for the treatment of individuals with allergic rhinoconjunctivitis or urticaria.**

***Index Terms* - Allergic rhinitis, antihistamines, bilastine, urticaria**

I. INTRODUCTION

In many affluent nations, diseases like urticaria and allergic rhinoconjunctivitis are becoming more common. Estimates indicate that allergic rhinoconjunctivitis[1] affects 10–40% of the world's population. Similar rates of urticaria are seen, with a lifetime incidence of about 20%. Although plausible causes have been presented by two different researchers, the reasons for the rising occurrence of allergy disorders remain mainly unexplained.[2]

The "hygiene hypothesis" is the first and contends that decreased exposure to allergens during childhood increases the likelihood of allergies. The "pollution theory," on the other hand, asserts that air pollution increases the likelihood of acquiring allergy disorders[3]. Due to fatigue, headaches, irritability, and the inability to focus, these disorders can have a major negative influence on a patient's quality of life.[4]

The effects of these symptoms may eventually affect academic and professional performance. Given the high frequency of allergic rhinoconjunctivitis[5] in particular, the costs to society can be quite significant, with estimates indicating that indirect costs due to lost productivity are more than those expended for providing treatment to this patient group. As a result, the development of successful therapies should not only relieve symptoms and enhance patients' quality of life, but also enhance personal performance, decrease the need for medical attention, and boost productivity. Potentially huge advantages for society as a whole, overcrowded healthcare systems, and resources.[6]

In the literature, the part played by histamine in allergic disorders is extensively characterised. In a nutshell, immunoglobulin E (IgE) antibodies are recognised at the surface of mast cells and, upon exposure to the correct antigen following an allergic stimulus, cause mast cell degranulation, which results in the release of histamine. Histamine works by activating a number of receptors, including the H1-, H2-, H3-, and H4- receptors. Histamine's biological effects on allergic responses are influenced by activity at H1-receptors and include smooth muscle contraction, bronchospasm, increased endothelial permeability, and activation of cough receptors and sensory neurons. Therefore, therapies that inhibit histamine's activities at H1-receptors (antihistamines) are essential for the management of illnesses including allergic rhinoconjunctivitis and urticaria.[7]

H1-receptor antagonists have been suggested as the first-line therapy for allergic rhinoconjunctivitis and urticaria in several national and international clinical recommendations. The ability of first-generation antihistamines to block H1-receptors and successfully manage allergy symptoms was what gave them their name. However, they were commonly linked to negative outcomes, particularly sedation. Due to this, second-generation H1-antihistamines were created. These medications were created to be less lipophilic in order to minimise transfer across the blood–brain barrier[8] and prevent the production of sedative effects. Although the ultimate objective was to increase the therapeutic index, several second-generation H1-receptor antagonists have been linked to undesirable side effects, including weight gain, drug-drug interactions, and, most concerningly, possibly fatal outcomes.[9]

Bilastine is a brand-new, non-sedating histamine H1-receptor antagonist created to treat allergic urticaria and rhinoconjunctivitis[10]. The purpose of this study is to assess the preliminary scientific data on the clinical efficacy and safety of bilastine and to examine the current literature concerning its pharmacological characteristics.[11]

Proper name: Bilastine

Chemical name: 2-[4-(2-(4-(1-(2-ethoxyethyl)-1H-benzimidazol-2-yl) piperidin-1-yl)ethyl)phenyl]-2-

methylpropionic

acidor

p-[2-[4-[1-(2-ethoxyethyl)-2-benzimidazolyl]piperidino]ethyl]-α-methylhydratropic acid

Molecular formula: $C_{28}H_{37}N_3O_3$

Molecular mass: 463.61 g/mol

Structural formula:

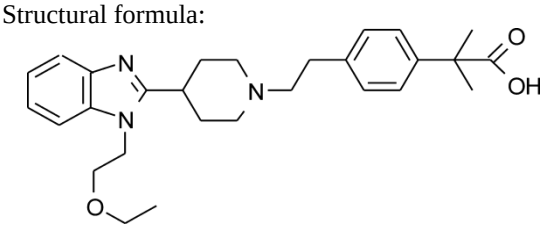

Figure 1 Chemical structure of bilastine.[12]

Bilastine, F-96221-BM1, 2(2-[4-(2-(4-(1-(2- ethoxyethyl) bencimidazole-2-yl) piperidine-1-yl) ethyl) phe- nyl]-2-methylpropanoic acid)

Physicochemical properties:Physical Form: White, crystalline powderSolubility:

pKa Value: 4.15 □ 0.06, when determined by ultraviolet spectrophotometry and 4.18 by HPLC.

Hygroscopicity: Bilastine is not hygroscopic tested under ambient temperature (25.1 ± 0.1 °C) and relative humidity (85 % RH) conditions.[12]

Practically insoluble	Acetonitrile
Very slightly soluble	water, buffer pH=6, buffer pH=4.5, buffer pH=8, acetone and isopropyl alcohol, glycerin
Slightly soluble	NaOH 0.01N, ethanol, methanol and dimethylsulfoxide (DMSO), 1,2-propylene glycol
Sparingly soluble	dimethylformamide (DMF), 0.1N hydrochloric acid (HCl) and buffer pH=3.5
Freely soluble	chloroform, HCl 1N and NaOH 1N

CLINICAL USE AND INDICATIONS

Rhinitis Allergic to Season

For the symptomatic treatment of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older, bilastine is recommended.[13]

Urticaria Spontaneous and Chronic

Bilastine is prescribed for people 18 years of age and older to alleviate the symptoms of chronic spontaneous urticaria (CSU), such as itching and hives.[14]

Geriatrics (patients older than 65):

In individuals older than 65, no dose modifications are required.[15]

Pediatrics (under 12 years old):

Bilastine has not been shown to be safe or effective in children under the age of 12.[16]

CONTRAINDICATIONS

Patients who have: hypersensitivity to bilastine or to any other element in the formulation or component of

the container should not take BILESTINE. For a detailed list of the components and elements (see Dosage Forms, Composition and Packaging).[17]
A history of torsade de pointes or qt prolongation, including congenital long qt syndromes (see warnings and precautions, drug interactions, action and clinical pharmacology).[18]

PRECAUTIONS AND WARNINGS

QTC interval lengthening has been linked to BILASTIN (see action and clinical pharmacology, cardiac electrophysiology). Torsade de pointes risk is thought to be increased by medications that lengthen the QT/QTC interval. A polymorphic ventricular tachyarrhythmia is torsade de pointes. Generally speaking, the amount of QT/QTc prolongation a medicine causes raises the risk of torsade de pointes. Torsade de pointes symptoms might include dizziness, palpitations, syncope, or convulsions, or they can be asymptomatic. Torsade de pointes can develop into ventricular fibrillation and rapid cardiac death if it is left untreated.[19]
Patients having a history of qtc prolongation and/or torsade de pointes, including those with congenital long qt syndromes, should not use BILASTINE .[20]

Hepatic
Subjects with hepatic impairment have not been examined for hepatic BILASTINE. Hepatic impairment is not anticipated to elevate systemic exposure over the safety limit because bilastine is not metabolised and renal clearance is the primary route of elimination.[21]

Renal:
Bilastine co-administration with P- glycoprotein inhibitors, such as ketoconazole, erythromycin, cyclosporine, ritonavir, or diltiazem, may raise plasma levels of bilastine and hence increase the risk of negative effects in persons with moderate or severe renal impairment. Bilastine and P-glycoprotein inhibitor co-administration is to be avoided in patients with moderate to severe renal impairment.[22]

ADVERSE REACTIONS

Overview of Adverse Drug Reactions
Bilastine was used at dosages ranging from 10 to 40 mg throughout treatment periods of 2 to 4 weeks in 10 Phase 2 and 3 trials on 2186 patients with allergic rhinitis or chronic spontaneous urticaria (CSU), which examined the drug's clinical safety. Bilastine 20 mg was administered to 931 participants in double-blind Phase 3 investigations, and the most frequent treatment-emergent adverse events were central nervous system-related.
system (headache, wooziness, and sleepiness) and the digestive system (abdominal pain upper). In clinical research, treatment-emergent cardiovascular side effects were uncommon or infrequent (bundle branch block right sinus arrhythmia, sinus bradycardia and ventricular extrasystoles, abnormal ECG findings).
513 people with allergic rhinitis participated in a one-year open-label safety trial using BILASTINE. Headache, influenza, and nasopharyngitis were the most typical adverse events observed in this open-label research.[23]

Adverse drug reactions in clinical trials
Clinical trials are done under extremely tight guidelines, thus the adverse reaction rates shown there may not be representative of those seen in real-world settings. As a result, they shouldn't be compared to those seen in clinical trials for other drugs. Information from clinical trials about adverse drug reactions is helpful for identifying adverse events that are caused by drugs and for estimating rates.
Treatment-emergent adverse events with BILASTINE at the indicated dose of 20 mg per day were comparable to those treated with a placebo. Dizziness, headaches, and somnolence were the most frequently reported associated adverse events.[24]

- Abnormalities of the lymphatic and blood systems: *Anaemia*
- Cardiac conditions include right bundle branch block, sinus bradycardia, sinus arrhythmia, and ventricular extrasystoles.
- Electrocardiogram (ECG) examinations: abnormal ST-T segment, abnormal T wave, abnormal T wave inversion, abnormal QT prolongation, abnormal electrocardiogram, abnormal QRS axis.
- Disorders of the ear and labyrinth: vertigo, tinnitus, and motion sickness
- eye conditions: eye pain
- gastrointestinal disorders: nausea, stomach discomfort, dry mouth, eructation, dysgeusia,

dyspepsia, constipation, diarrhoea, vomiting, and vomiting with blood in the stool

- Conditions at the administration site and general problems include asthenia, discomfort in the chest, weariness, jitteriness, pain, and pyrexia.
- Infestations and diseases: pharyngitis and oral herpes
- Studies: Gamma-glutamyltransferase increased, weight reduced, weight rose, blood bilirubin increased, blood cholesterol increased, blood triglycerides increased, and alanine aminotransferase increased.
- problems of metabolism and nutrition: increased appetite
- Disorders of the musculoskeletal system and connective tissue: myalgia, weakened muscles, and back discomfort
- Disorders of the nervous system: Hypersomnia and attention disturbance Psychiatric disorders: nightmares, anxiety, and insomnia Diseases of the breast and the reproductive system: delayed menstruation
- Disorders of the respiratory, thoracic, and mediastinum Dyspnea, epistaxis, nasal pain, dry nose, and throat irritability
- Open-label, long-term research
- The adverse event profile in the controlled 2-4 week Phase 2 and 3 clinical investigations showed a comparable profile to that shown in the long term follow up study (1 year) with 513 individuals (see Adverse Reactions Overview).
- adverse drug reactions after marketing
- The safety profile shown after the product's launch is similar with that seen in carefully monitored clinical studies.
- When bilastine is used together with other drugs that have the potential to cause QT prolongation, a case of torsade de pointes has been documented.
- diseases of the skin and subcutaneous tissues: urticaria, pruritus, common rash, and dermatitis acneiform[25-27]

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