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Review Article

Allergic Rhinitis: Therapeutic Agents against the Disease and Analytical Methods for their Quantification in Biological Fluids

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Abstract

Allergic rhinitis (AR) is a common debilitating disorder that can adversely affect the quality of life, productivity and is characterized by nose itching, nasal blockage/congestion, rhinorrhea, and sneezing. Inflammatory mediators namely histamine, leukotrienes, platelet-activating factor, and prostaglandins account for its symptoms. *In vitro* and *in vivo* tests are utilized for the diagnosis. Management of allergic rhinitis mostly involved use of pharmacological active agents such as anticholinergics, antihistamines, antileukotrienes, corticosteroids, and immunotherapy. Alternative therapies, namely avoidance of allergen, acupuncture, herbal preparations, probiotics and nasal irrigation with isotonic saline have also been employed to alleviate the symptoms.

In this article we try to provide comprehensive information on the disorder namely the symptoms, diagnosis, therapeutic treatment options, structural features of the active agents as well as a number of analytical methods that have been utilized to assay these active agents in biological fluids. The methodology involved the use of pertinent articles obtained from the literature through library journals and internet search. The results show that under-diagnosis and/or inadequate treatment, could increase the risk of asthma or other comorbid conditions. Adverse effects limit the use of first-generation oral antihistamines (brompheniramine, chlorpheniramine, clemastine, diphenhydramine, and hydroxyzine) when compare with second generation of oral antihistamines (desloratadine, fexofenadine, levocetirizine, and loratadine). Of these antihistamines, fexofenadine seems to be most beneficial and non-sedating, even at doses higher than the recommended doses. Hyphenated chromatographic methods are the most utilized analytical technique in the determination of these therapeutic agents in biological fluids.

***Keywords**: Allergic Rhinitis; Pharmacological Active Agents; Assay Methods; Biological Fluids*

Introduction

Allergic rhinitis is one of different subtypes (clinical phenotypes) of rhinitis consisting of an immunoglobin E (IgE) mediated hypersensitivity response (type 1) to a variety of inhaled environmental allergens [1,2]. Other subtypes may include non-allergic, non-infectious rhinitis and infectious rhinitis [3]. Rhinitis itself presents a pattern of symptoms arising from nasal inflammation and/or dysfunction of the nasal mucosa. It is considered to be a pathologic condition with considerable financial burden, and represents a risk factor to disorders such as asthma, behavioral changes, learning disabilities, psychological impairment, and sinusitis [4,5].

Allergic rhinitis is characterized by itching of the nose, nasal blockage/congestion, anterior or posterior rhinorrhea, and sneezing [6]. The characterization is based on (i) duration of symptom (intermittent, persistent); (ii) severity (mild, moderate and severe). A cascade of immunological and biochemical events account for clinical expression of the disease. Such events occur when allergens inhaled are superimposed to nasal mucous followed by diffusion into nasal tissues. Allergens are proteins that can come from airborne particles of animal dander, dust mites, insect feces, molds and pollens.

The mechanism of immunological and biochemical events involves activation of CD^{4+} T lymphocytes when antigenic peptides produced from antigens (by antigen-presenting cells) migrate to lymph nodes to present the peptides to CD^{4+} T lymphocytes (T cells). This is followed by activation of the production of specific cytokines which cause the synthesis of IgE antibodies from B-cells. The IgE antibodies on binding to receptors on the surface of dendritic cells, B-lymphocytes, monocytes macrophages, basophils and mast cells induce the cellular allergic reaction, and activation of several signaling cascades. Finally, this is followed by granule exocytosis and release of preformed or newly created inflammatory mediators namely histamine, leukotrienes, platelet-activating factor, and prostaglandins etc. [7-9]. These inflammatory molecules account for the symptoms of the disorder [10].

The symptoms can be early phase symptoms provoked by the binding of histamine on the H_1-receptor receptors. The late phase symptoms arise from infiltration of nasal mucosa by basophils, eosinophils, mast cells, mononuclear cells, and neutrophils [11]. Eosinophil's predominant in the late phase symptoms is activated by cysteinyl leukotrienes and cationic proteins, eosinophil peroxidase, and proinflammatory mediators [5].

The diagnosis involves *in vitro* tests-skin prick test, immunoassay capture test (immunoCAP test) and *in vivo* tests-radioallergosorbent test (FAST test), multiple antigen simultaneous test (MAST test), radioallergosorbent test (RAST test). Of all the tests for allergic rhinitis, skin prick test (percutaneous skin test) is the most common diagnostic test. The test detects the immediate allergic response brought about by the release of mast cell or basophil IgE-specific mediators. The allergic response creates the classic wheal-and-flare reaction within fifteen minutes of which a wheal ≥3 mm diameter is considered a positive result [12-14].

The management of allergic rhinitis is achieved through pharmacological and non-pharmacological procedures. The pharmacological procedure using therapeutic agents should be based on the patient's age and severity of symptoms [15]. On the basis of severity of symptoms pharmacological strategies for the treatment of allergic rhinitis would be use of (i) second-generation oral or intranasal antihistamines for mild intermittent symptoms (ii) intranasal corticosteroids alone as first-line of treatment for mild to moderate persistent symptoms. However, when congestion, rhinorrhea and persistent nasal ocular symptoms are implicated, decongestants, anticholinergics and oral or intranasal antihistamines are used respectively (iii) intranasal corticosteroids plus (a) oral or intranasal antihistamines (b) oral leukotriene receptor antagonists (c) intranasal cromolyn for severe persistent symptoms (iv) immunotherapy, (v) alternative therapy namely avoidance of allergen, acupuncture, herbal preparations, probiotics and nasal irrigation with isotonic saline [16-18].

On the basis of age, utilized clinical active agents with the starting age in parentheses include: (a) intranasal corticosteroids- beclomethasone (6 yr.), budesonide (6 yr.), ciclesonide (6 yr.), flunisolide (6 yr.), fluticasone furoate (2 yr.), fluticasone propionate (12 yr.), mometasone (2 yr.) and triamcinolone (12 yr.), (b) intranasal antihistamines- azelastine (5 yr.), and olopatadine (6 yr.), (c) intranasal anticholinergics- ipratropium (6 yr.), (d) intranasal cromolyn- cromolyn sodium (2 yr.), (e) oral antihistamines- cetirizine (6 months), desloratadine (six months), fexofenadine (6 months), levocetirizine (12 yr.), and loratadine (2 yr.), and (f) leukotriene receptor antagonists- montelukast (6 months).

Intranasal corticosteroids are the mainstay of treatment of allergic rhinitis. These active agents act by inhibiting the release of cytokines, decreasing the influx of inflammatory cells, and thus leading to reduction in inflammation of the nasal mucosa [19]. Their onset of action

is about 30 minutes with maximum effectiveness occurring two to four weeks after administration. The most commonly adverse effects are burning, epistaxis (nosebleeds), headache, nasal dryness, stinging, and throat irritation. Potential systemic adverse effects, such as suppression of the hypothalamic-pituitary axis could also occur.

Intranasal antihistamines are utilized as first or second-line therapy for allergic rhinitis [20]. They act by blocking smooth muscle constriction, mucus secretion, vascular permeability, and sensory nerve stimulation elicited by histamine. Antihistamines bind peripheral H_1-receptor selectively or non-selectively [21]. Onset of action is about 15 minutes and lasts up to 4 hours. Adverse effects include bitter aftertaste, epistaxis, headache, nasal irritation, and sedation. Their adverse effects and cost limit their use when compare with second generation of oral antihistamines (desloratadine, fexofenadine, levocetirizine, and loratadine), while their decreased effectiveness also limit their utilization when compared with intranasal corticosteroids.

Oral antihistamines consist of first and second-generations active agents. The first-generation oral antihistamines include brompheniramine, chlorpheniramine, clemastine, and diphenhydramine. Their onset of action is within 15 to 30 minutes. They cause more adverse effects than the second-generations. Such substantial adverse effects include constipation, dry mouth, dry eyes, fatigue, impaired mental status, sedation, tachycardia, and urinary retention [22]. These adverse effects are as result of nonselective binding to other receptor types leading to impaired driving, increase in automobile collisions, poor school performance, and work injuries [22,23].

Decongestants-oral and topical active agents improve nasal congestion associated with allergic rhinitis. They stimulate adrenergic receptors in the nasal mucosa to cause vasoconstriction, resulting in decreased nasal swelling (inflammation) and decreased congestion [24]. Typical examples are oxymetazoline, phenylephrine, pseudoephedrine etc. Adverse effects associated with oral decongestants are elevated blood pressure, dizziness, headache, insomnia, tachycardia, and urinary retention. Rebound congestion (rhinitis medicamentosa) may occur after several days of using intranasal (topical) decongestants. To avoid medicamentosa, administration should not be more than 3 - 5 days. Other common adverse effects for intranasal decongestants include nasal dryness, sneezing.

Intra-anticholinergics (ipratropium nasal spray) relief excessive rhinorrhea and are not systemically absorbed. However, post-marketing experience suggests that there may be some systemic absorption. Cautious use is advised for patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction, particularly if another anticholinergic is co-administered. Local adverse effects may include nosebleeds, nasal and oral dryness. Common adverse effects are nasal dryness, epistaxis, and headache.

Intranasal cromolyn (nasal mast cell stabilizers) act by inhibiting the degranulation of mast cells. They are commonly administered prophylactically, prior to triggering of an allergic reaction. Systemic absorption is minimal. Likely, adverse effects are nasal irritation, sneezing, and unpleasant taste.

Leukotriene receptor antagonists act by reducing inflammation. They are second or third-line oral therapy. Potential adverse effects are headache and upper respiratory tract infection.

A number of analytical methods have been utilized to determine therapeutic agents in biological fluids. Such methods include capillary electrophoresis, electrochemical, immunological, spectroscopic and chromatographic methods. Chromatographic methods are mostly used either as hyphenated or non-hyphenated systems. Hyphenation is an on-line combination of a chromatographic technique and one or more spectroscopic detection techniques.

Biological fluids are very important to life and provide assistance in maintaining body homeostasis. Biological fluids very often used are blood (whole blood, serum or plasma), urine, cerebrospinal fluid (CSF) and saliva. Others that could be used are amniotic fluid, synovial fluid, pleural fluid, peritoneal fluid and pericardial fluid [25,26].

Discussion

Out of the pharmacological classes of active agents listed in the present work, not more two from each class will be selected to examine their determinations in biological fluids. These active substances include are discussed below.

Beclomethasone (Beconase): Beclomethasone is chemically defined as (8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*S*,17*R*)-9-chloro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-3-one. It has a molecular formula $C_{22}H_{29}ClO_5$ and molecular weight of 408.9 g/mol respectively. The derivative is dipropionate ester, and molecular weight of 521.04 g/mol. The chemical structure is given in figure 1.

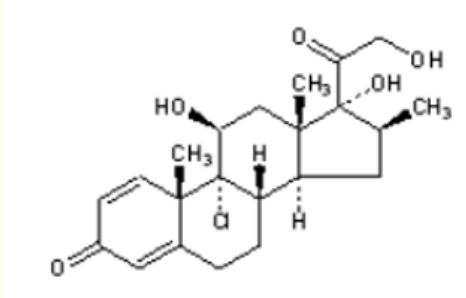

Figure 1*: Warts in the back.*

Beclomethasone has been determined in:

(a) Human plasma:

(i) Girault., *et al*. 1991, [27] - by hyphenated liquid chromatographic system (LC/MS).

(ii) Dirk., *et al*. 1998, [28] - by hyphenated liquid chromatographic system (LC/MS-MS).

(b) Human urine:

(i) Mazzarino., *et al*. 2008, [29] - by hyphenated liquid chromatographic system (LC/MS).

(ii) Andersen., *et al*. 2008, [30] - by hyphenated liquid chromatographic system (LC/MS-MS).

Triamcinolone (Nasacort): Chemically defined as (8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,16*R*,17*S*)-9-fluoro-11,16,17-trihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-3-one. It has a molecular formula of $C_{21}H_{27}FO_6$ and molecular weight of 394.4 g/mol respectively. The derivative is acetonide ether and molecular weight of 434.5 g/mol. Anti-allergic and anti-inflammatory drug. The chemical structure is given in figure 2.

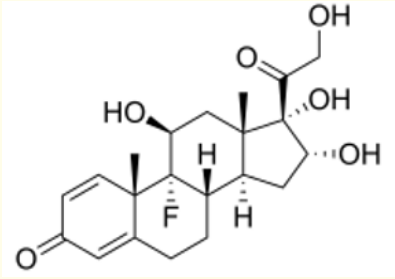

Figure 2: *Chemical structure of triamcinolone.*

Triamcinolone has been determined in:

(a) Human plasma:

(i) Cesar., *et al*. 2011, [31] - by hyphenated liquid chromatographic system (LC/MS-MS).

(ii) Muralidharan., *et al*. 2016, [32] - by non-hyphenated liquid chromatographic system (HPLC).

(iii) Ponec., *et al*. 1977, [33] - by radioimmunoassay (RIA).

(b) Human serum:

(i) Hammam E 2007, [34] - by adsorptive cathodic stripping voltammetry.

(c) Human urine:

(i) Amendola., *et al*. 2003, [35] - by hyphenated gas chromatographic system (GC-MS).

(d) Human bronchoalveolar lavage fluid:

(i) Hubbard., *et al*. 2001, [36] - by hyphenated gas chromatographic system (GC-MS).

Cetirizine (Zyrtec): A human metabolite of hydroxyzine (piperazine H_1-receptor antagonist) is chemically defined as 2-(2-(4-(4-chlorophenyl) phenylmethyl) piperazin-1-yl) ethoxy) acetic acid. It has a molecular formula of $C_{21}H_{25}ClN_2O_3$ and molecular weight of 388.9 g/mol respectively. The derivative is dihydrochloride salt and molecular weight of 451.9 g/mol. Second-generation histamine H_1-receptor antagonist. The chemical structure is given in figure 3.

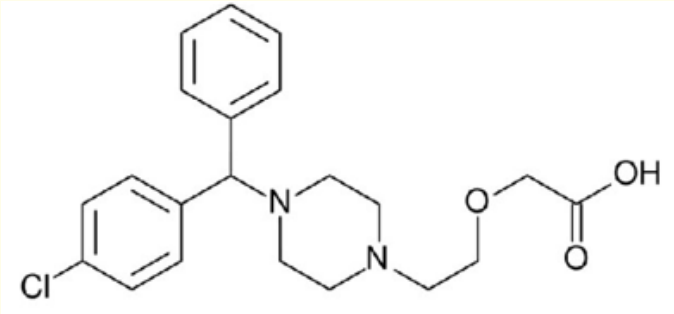

Figure 3: *Chemical structure of cetirizine.*

Cetirizine has been determined in:

(a) Human plasma:

(i) Erikson., *et al*. 2002, [37] - by hyphenated liquid chromatographic system (LC/MS-MS).

(ii) Al-Swayeh., *et al*. 2013, [38] - by non-hyphenated liquid chromatographic system (HPLC).

(iii) Pandya KK., *et al*. 2007, [39] - by high-performance thin-layer chromatographic system (HPTLC).

(iv) Kowalski and Plenis 2007, [40]- by non-hyphenated liquid chromatographic system (HPLC) and capillary electrophoresis (CE) methods.

(v) Bakes., *et al*. 1988, [41] - by non-hyphenated gas chromatographic system (GC).

(b) Human serum:

(i) Zaater., *et al*. 2000, [42] - by non-hyphenated liquid chromatographic system (HPLC).

(c) Human urine:

(i) Choi., *et al*. 2000 [43] - by non-hyphenated liquid chromatographic system (HPLC).

(ii) Roussel and Lefebvre 1991, [44] - by non-hyphenated liquid chromatographic system (HPLC).

(iii) Dharuman., *et al*. 2011, [45] - by non-hyphenated liquid chromatographic system (HPLC).

Loratadine (Claritin): Chemically defined as Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) piperidine-1-carboxylate. It has a molecular formula of $C_{22}H_{23}ClN_2O_2$ and molecular weight of 382.88 g/mol respectively. It is a second-generation H_1 histamine antagonist. The chemical structure is given in figure 4.

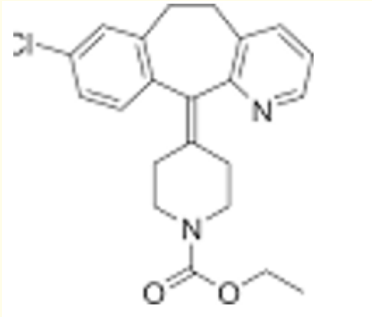

Figure 4: *Chemical structure of loratadine.*

Loratadine has been determined in:

(a) Human plasma:

(i) Nagwa., *et al*. 2014, [46] - by hyphenated liquid chromatographic system (LC/MS-MS).

(ii) Vlase., *et al*. 2007, [47] - by hyphenated liquid chromatographic system (LC/MS).

(iii) Sebaiy and Ziedan 2019, [48] - by non-hyphenated liquid chromatographic system (HPLC).

(iv) Jhonson., *et al*. 1994, [49] - by non-hyphenated gas chromatographic system (GC).

(v) Seyed., *et al*. 2016, [50]- by ultraviolet-visble spectrophotometric and multivariate calibration method.

(b) Human serum:

(i) Nawab., *et al*. 2014, [51]- by non-hyphenated liquid chromatographic system (HPLC).

(ii) Kanthiah and Kannappan 2017, [52] - by non-hyphenated liquid chromatographic system (HPLC).

(iii) Martens 1995, [53] - by hyphenated gas chromatographic system (GC/MS).

(c) Human urine:

(i) Kanthiah and Kannappan 2017, [52] - by non-hyphenated liquid chromatographic system (HPLC).

(ii) Belal., *et al*. 2016, [54]- by non-hyphenated liquid chromatographic system (HPLC).

Azelastine (Astelin): Chemically defined as 4-(4-chlorobenzyl)-2-[(4RS)-1-methylhexahydro-1H-azepin-4-yl] phthalazin-1(2H)-one. It has a molecular formula of $C_{22}H_{24}ClN_3O$ and molecular weight of 381.9 g/mol respectively. The derivative is hydrochloride salt and molecular weight of 418.4 g/mol. Acts as histamine H_1-receptor antagonist. The chemical structure is given in figure 5.

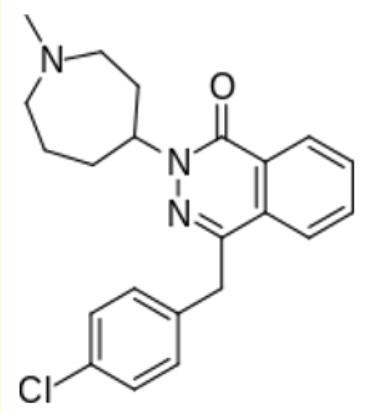

Figure 5: *Chemical structure of azelastine.*

Azelastine has been determined in:

(a) Human plasma:

(i) Pivonaka., *et al*. 1987, [55] - by non-hyphenated liquid chromatographic system (HPLC).

(ii) Mano., *et al*. 1994, [56] - by hyphenated liquid chromatographic system (LC/MS).

(iii) Zha and Shum 2012, [57] - by hyphenated liquid chromatographic system (LC/MS-MS).

(iv) Park., *et al*. 2010, [58] - by hyphenated liquid chromatographic system (LC/MS-MS).

(v) Elghobashy., *et al*. 2013, [59] - by electrochemical method.

Olopatadine (Patanase): Olopatadine is chemically defined as (11Z)-11-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid. It has a molecular formula of $C_{21}H_{23}NO_3$ and molecular weight of 337.37 g/mol respectively. The derivative is hydrochloride salt and molecular weight of 373.87 g/mol. Dual acting histamine H_1-receptor antagonist and mast cell stabilizer. The chemical structure is given in figure 6.

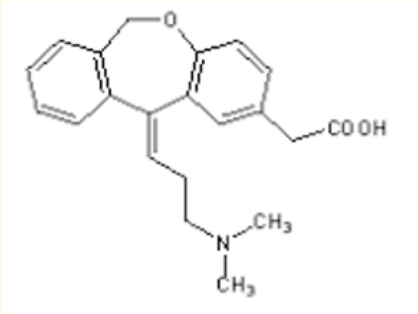

Figure 6: *Chemical structure of olopatadine.*

Olopatadine has been determined in:

(a) Human plasma:

(i) Zhu., *et al*. 2011, [60] - by hyphenated liquid chromatographic system (LC/MS-MS).

(ii) Fujita., *et al*. 1999, [61] - by hyphenated liquid chromatographic system (LC/MS-MS).

(iii) Koichiro., *et al*. 2006, [62] - by hyphenated liquid chromatographic system (LC/MS-MS).

Ipratropium (Atrovent): Ipratropium is chemically defined as [(1*S*,5*R*)-8-methyl-8-propan-2-yl-8-azoniabicyclo[3.2.1]octan-3-yl] 3-hydroxy-2-phenylpropanoate. It has a molecular formula of $C_{20}H_{30}NO_3^{\pm}$ and molecular weight of 332.5 g/mol respectively. The derivative is bromide salt and molecular weight of 412.37 g/mol. It is an antagonist of the muscarinic acetylcholine receptor. The chemical structure is given in figure 7.

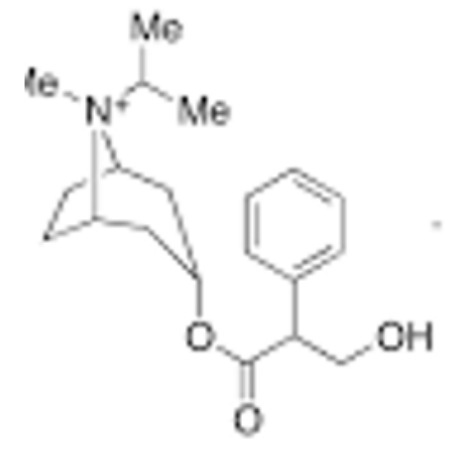

Figure 7: *Chemical structure of ipratropium.*

Ipratropium has been determined in:

(a) Human plasma:

(i) Ensinger., *et al*. 1987, [63] - by radioreceptor assay using [H] N-methyl-scopolamine as a radioligand.

(ii) Ensing., *et al*. 1988, [64] - by radioreceptor assay using [H] N-methyl-scopolamine as a radioligand.

(iii) MacGregor., *et al*. 1992, [65] - by radioreceptor assay using [H] N-methyl-scopolamine as a radioligand.

(iv) Wood., *et al*. 1995, [66] - by radioreceptor assay using [H] N-methyl-scopolamine as a radioligand.

(v) Zhang., *et al*. 2023, [67] - by hyphenated liquid chromatographic system (LC-MS).

(b) Human urine:

(i) Ensing., *et al*. 1988, [64]-by radioreceptor assay using [H] N-methyl-scopolamine as a radioligand.

(ii) MacGregor., *et al*. 1992, [65]-by radioreceptor assay using [H] N-methyl-scopolamine as a radioligand.

(iii) Wood., *et al*. 1995, [66]-by radioreceptor assay using [H] N-methyl-scopolamine as a radioligand.

Montelukast (Singulair): Montelukast is chemically defined as 1-[[[(1R)-1-[3-[(1E)- 2-(7-chloro-2-quinolyl) ethenyl] phenyl]-3-[2-(1-hydroxy1methylethyl) phenyl] propyl] thio] methyl] cyclopropane acetate. It has a molecular formula of $C_{35}H_{36}ClNO_3S$ and molecular weight of 586.2 g/mol respectively. The derivative is sodium salt and molecular weight of 609.2 g/mol. It is a selective leukotriene receptor antagonist. The chemical structure is given in figure 8.

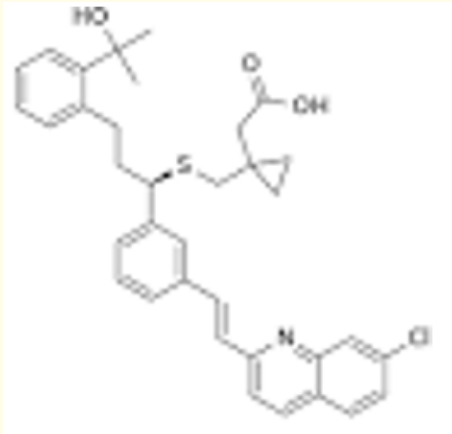

Figure 8: *Chemical structure of montelukast.*

Montelukast has been determined in:

(a) Human plasma:

(i) Bharathi., *et al*. 2009, [68] - by hyphenated liquid chromatographic system (LC-MS).

(ii) Challa., *et al*. 2010, [69] - by hyphenated liquid chromatographic system (LC-MS/MS).

(iii) Ahmed and Atia 2013, [70] - by non-hyphenated liquid chromatographic system (HPLC).

(iv) Alsarra., *et al*. 2005, [71] - by voltammetric method.

(v) Shimaa., *et al*. 2023, [72] - by densitometry and spectrophotometric methods.

(b) Human serum:

(i) Arayne., *et al*. 1998, [73] - by spectrophotometric method.

In general, it is important to emphasize that not all the analytical methods utilized to quantify these therapeutic agents in biological fluids have been discussed.

Conclusion

Allergic rhinitis is a common debilitating disorder that can adversely affect the quality of life. Inflammatory mediators namely histamine, leukotrienes, platelet-activating factor, and prostaglandins are responsible for the symptoms experienced with allergic rhinitis. Of all the therapeutic agents used against allergic rhinitis, intranasal corticosteroids are the mainstay of treatment. Finally, hyphenated or non-hyphenated chromatographic methods have been observed to be the analytical techniques of choice in the determination of therapeutic agents against allergic rhinitis in biological fluids.

Bibliography

1. Sin B and Togias A. "Pathophysiology of allergic and nonallergic rhinitis". *Proceedings American Thoracic Society* 8 (2011): 106-114.

2. Scadding G., *et al*. "Rhinology future trends": 2017 EUFORE A debate on allergic rhinitis". *Rhinology* 57 (2019): 49-56.

3. Papadopoulos NG and Guibas GV. "Rhinitis subtypes, endotypes, and definitions". *Immunology Allergy Clinical N. America* 36 (2016): 215-233.

4. Settipane RA and Charnock DR. "Epidemiology of rhinitis: allergic and nonallergic". *Clinical Allergy Immunology* 19 (2007): 23-34.

5. Papadopoulos NG., *et al*. "Phenotypes and endotypes of rhinitis and their impact on management A PRACTALL report". *Allergy* 70 (2015): 474-494.

6. Bousquet J., *et al*. "Unmet needs in severe chronic upper airway disease". (*SCUAD) Journal Allergy Clinical Immunology* 124 (2009): 428-433.

7. Bugeon L and Dallman M. "Costimulation of T cells". *American Journal Respiratory Critical Care Medicine* 162 (2000): S164-S168.

8. Henry AJ., *et al*. "Participation of the N-terminal region of Cε3 in the binding of human IgE to its high-affinity receptor FcεRI". *Biochemistry* 36 (1997): 15568-15578.

9. Liu YJ. "IPC: Professional type 1 interferon-producing cells and plasmacytoid dendritic cells precursors". *Annual Review Immunology* 23 (2005): 275-306.

10. Gelfand EW. "Inflammatory mediators in allergic rhinitis". *Journal Allergy Clinical Immunology* 114 (2004): 135-138.

11. Orban N., *et al*. "Allergic and non-allergic rhinitis". In: Adkinson N, Bochner B, Busse W, et al., editions. Middleton's Allergy: Principles and Practice. 7th edition. New York: Mosby (2008).

12. Quillen DM and Feller DB. "Diagnosing rhinitis: allergic vs nonallergic". *American Family Physician* 73 (2006): 1583-1590.

13. Kwon SH and Cho YS. "Comparison of allergic skin prick test and fast system in patients with allergic rhinitis". *Journal Rhinology* 7 (2000): 105-108.

14. Wallace DV., *et al*. "The diagnosis and management of rhinitis: an updated practice parameter". *Journal Allergy Clinical Immunology* 122.2 (2008): S1-84.

15. Sur DK and Scandale S. "Treatment of allergic rhinitis". *American Family Physician* 81.12 (2010): 1440-1446.

16. Pullerits T., *et al*. "Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis". *Journal Allergy Clinical Immunology* 109 (2002): 949-955.

17. Karatzanis A., *et al*. "Contemporary use of corticosteroids in rhinology". *Current Allergy Asthma Repiratory* 17 (2017): 1-6.

18. Talbot AR., *et al*. "Mucociliary clearance and buffered hypertonic saline solution". *Laryngoscope* 107 (1997): 500-503.

19. Yanez A and Rodrigo GJ. "Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with metaanalysis". *Annual Allergy Asthma Immunology* 89.5 (2002): 479-484.

20. Kaliner MA., *et al*. "The efficacy of nasal antihistamines in the treatment of allergic rhinitis". *Annual Allergy Asthma Immunology* 106.2 (2011): S6-S11.

21. Hoyte FC and Katial RK. "Antihistamine therapy in allergic rhinitis". *Immunology Allergy Clinical North American* 31.3 (2011): 509-543.

22. Vuurman EF., *et al*. "Seasonal allergic rhinitis and antihistamine effects on children's learning". *Annual Allergy* 71.2 (1993): 121-126.

23. Szeinbach SL., *et al*. "The impact of allergic rhinitis on work productivity". *Primary Care Respiratory Journal* 16.2 (2007): 98-105.

24. Kushnir NM. "The role of decongestants, cromolyn, guaifenesin, saline washes, capsaicin, leukotriene antagonists, and other treatments on rhinitis". *Immunology Allergy Clinical North American* 31.3 (2011): 601-617.

25. McGeown MG. "The fluid compartments of the body". In: Clinical Management of Electrolyte Disorders. Developments in Critical Care Medicine and Anaesthesiology, Springer, Dordrecht 2 (1983).

26. Dave Armbruster Kelley Cooper. "Abbott Diagnostics Clinical Chemistry". Learning Guide: Introduction to Clinical Chemistry" (2020): 5-13.

27. Girault J., *et al*. "Simultaneous determination of beclomethasone, beclomethasone monopropionate and beclomethasone, dipropionate in biological fluids using a particle beam interface for combining liquid chromatography with negative-ion chemical ionization mass spectrometry". *Journal Chromatography* 564 (1991): 43-53.

28. Dirk C., *et al*. "LC/MS-MS method for the determination of Beclomethasone Dipropionate and Beclomethasone-17- monoproprionate in human plasma". *Analyst* 123 (1998): 2409-2414.

29. Mazzarino M., *et al*. "A screening method for the detection of synthetic glucocorticosteroids in human urine by liquid chromatography-mass spectrometry based on class-characteristic fragmentation pathways". *Analytical Bioanalytical Chemistry* 390 (2008): 1389-1402.

30. Andersen JH., *et al*. "Optimization of solid phase extraction clean up and validation of quantitative determination of corticosteroids in urine by liquid chromatography-tandem mass spectrometry". *Analytica Chimica Acta* 617 (2008): 216-224.

31. César IC., *et al*. "Determination of triamcinolone in human plasma by a sensitive HPLC-ESI-MS/MS method: application for a pharmacokinetic study using nasal spray formulation". *Journal Mass Specrometry* (2011).

32. Muralidharan S. "Development and validation of a new RP-HPLC method for the analysis of triamcinolone in human plasma". *Turk Journal Pharmaceutical Science* 13.1 (2016): 9-16.

33. Ponec M., *et al*. "Plasma levels of triamcinolone acetonide as determined by radioimmunoassay after topical application". *Archives of Dermatological Research* 259 (1977): 63-70.

34. Hamman E. "Determination of triamcinolone acetonide in pharmaceutical formulation and human serum by adsorptive cathodic stripping voltammetry". *Chemical Analysis* 52 (2007): 43.

35. Amendola L., *et al*. "Determination of endogenous and synthetic glucocorticoids in human urine by gas chromatography-mass spectrometry following microwave-assisted derivatization". *Analytica Chimica Acta* 489 (2003): 233.

36. Hubbard WC., *et al*. "Measurement of low picomolar levels of triamcinolone acetonide in human bronchoalveolar lavage fluid by gas chromatography-electron-capture negative-ion mass spectrometry". *Analytical Biochemistry* 290.1 (2001): 28.

37. Erikson H. "Determination of cetirizine in human plasma by liquid chromatography-tandem mass spectrometry". *Chromatographia* 55 (2002): S145-S149.

38. Al-Swayeh R. "A validated reversed phase HPLC assay for the determination of cetirizine in human plasma". *Indian Journal Analytical Chemistry* 12.2 (2013): 56-61.

39. Pandya KK., *et al*. "High-performance thin layer chromatography for the determination of cetirizine in human plasma and its use in pharmacokinetic studies". *Journal Pharmacy Pharmacology* 48 (1996): 510-513.

40. Kowalski P and Plenis A. "Comparison of HPLC and CE methods for the determination of cetirizine dihydrochloride in human plasma samples". *Biomedical Chromatography* 21 (2007): 903-911.

41. Bakes E., *et al*. "Gas chromatographic method for the determination of cetirizine in plasma". *Journal Chromatography* 430 (1988): 149-155.

42. Zaater MF., *et al*. "RP-LC method for the determination of cetirizine in serum". *Journal Pharmaceutical and Biomedical Analysis* 22 (2000): 739-744.

43. Choi SO., *et al*. "Enantioselective determination of cetirizine in human urine by HPLC". *Archives of Pharmaceutical Research* 23 (2000): 178-181.

44. Roussel MT and Lefebvre RA. "Determination of cetirizine in human urine by high-performance liquid chromatography". *Journal Chromatography* 565 (1991): 504-510.

45. Dharuman J., *et al*. "High performance liquid chromatographic method for the determination of cetirizine and ambroxol in human plasma and urine-A boxcar approach". *Analytical Technology Biomedical Life Science* 879.25(2011):2624-2631.

46. Nagwa AS., *et al*. "Determination of loratadine in human plasma by liquid chromatography tandem mass spectrometry (lc/ms/ms) and its pharmacokinetic application". *International Journal Pharmaceutical Science Research* 1(2014): 102-108.

47. Vlase L., *et al*. "Determination of loratadine and its active metabolite in human plasma by high-performance liquid chromatography with mass spectrometry detection". *Journal Pharmaceutical and Biomedical Analysis* 44.3 (2007): 652-657.

48. Mahmoud M., *et al*. "Developing a high-performance liquid chromatography method for simultaneous determination of loratadine and its metabolite desloratadine in human plasma". *Current Drug Metabolism* 20.13(2019): 1053-1059.

49. Jhonson R., *et al*. "Sensitive gas liquid chromatographic method for the determination of loratadine and its major active metabolite, descarboethoxy loratadine, in human plasma using a nitrogen-phosphorus detector". *Journal Chromatography B* 657(1994): 125-131.

50. Seyed KHD., *et al*. "UV-vis spectrophotometry and multivariate calibration method for simultaneous determination of theophylline, montelukast and loratadine in tablet preparations and spiked human plasma". *International Journal Pharmaceutical Research* 15.3 (2016): 379-391.

51. Sher N., *et al*. "Simultaneous determination of antihistamine antiallergic drugs, cetirizine, domperidone, chlorphenamine maleate, loratadine, meclizine and buclizine in pharmaceutical formulations, human serum and pharmacokinetics application". *Analytical Methods* 8 (2014).

52. Kanthiah S and Kannappan VD. "Optimal mixture design optimization of an HPLC method for simultaneous determination of commonly used antihistaminic parent molecules and their active metabolites in human serum and urine". *Biomedical Chromatography* 31.8 (2017): e3932.

53. Martens J. "Determination of loratadine and pheniramine from human serum by gas chromatography-mass spectrometry". *Journal Chromatography B: Biomedical Sciences Applications* 673.2 (1995): 183-188.

54. Belal F., *et al*. "Rapid micellar HPLC analysis of loratadine and its major metabolite desloratadine in nano-concentration range using monolithic column and fluorometric detection: application to pharmaceuticals and biological fluids". *Chemistry Central Journal* 10 (2016): 79.

55. Pivonka J., *et al*. "Determination of azelastine and desmethylazelastine in human plasma by high-performance liquid chromatography". *Journal Chromatography* 420 (1987): 89.

56. Mano N., *et al*. "Resolution of 4-(4-chlorobenzyl)-2-(hexahydro-1-methyl-1Hazepin-4yl)-1(2H)-phthalazinone enantiomers in plasma with frit-FAB LC-MS using a conalbumin column". *Journal Pharmaceutical Biomedical Analysis* 12 (1994): 557.

57. Zha W and Shum L. "Simultaneous determination of azelastine and its major metabolite desmethylazelastine in human plasma using high performance liquid chromatography-tandem mass spectrometry". *Journal Chromatography B* 906 (2012): 69-74.

58. Park YS., *et al*. "Determination of azelastine in human plasma by validated liquid chromatography coupled to tandom mass spectrometry (LC-ESI/MS/MS) for the clinical studies". *International Journal Biomedical Science* 6 (2010): 120-127.

59. Elghobashy M., *et al*. "Application of membrane selective electrodes for the determination of azelastine hydrochloride in the presence of its alkaline degradant in eye drops and plasma". *Analytical Bioanalytical Electrochemistry* 5 (2013): 325-340.

60. Zhu P., *et al*. "A rapid and sensitive liquid chromatography tandem mass spectrometry method for determination of olopatadine concentration in human plasma". *Journal Analytical Toxicology* 35 (2011): 113-118.

61. Fujita K., *et al*. "Determination of olopatadine, a new antiallergic agent, and its metabolites in human plasma by high-performance liquid chromatography with electrospray ionization tandem mass spectrometry". *Journal Chromatography B: Biomedical Science Applications* 731 (1999): 345-352.

62. Koichiro F., *et al*. "Determination of some antiallergic drugs in human plasma by direct-injection high-performance liquid chromatography-tandem mass spectrometry". *Forensic Toxicology* 24 (2006): 8-16.

63. Wahl ED and Brantl V. "Radioreceptor assay for determination of the antimuscarinic drug ipratropium bromide in man". *European Journal Clinical Pharmacology* 33 (1987): 459-462.

64. Ensing K., *et al*. "Radioreceptor assays of ipratropium bromide in plasma and urine". *Journal Pharmaceutical Biomedical Analysis* 6 (1988): 433-439.

65. MacGregor TR., *et al*. "Evaluation of the systemic absorption and excretion of intranasal ipratropium bromide in healthy volunteers". *Journal Allergy Clinical Immunology* 89 (1992): 182.

66. Wood CC., *et al*. "Product characteristics and pharmacokinetics of intranasal ipratropium bromide". *Journal Allergy Clinical Immunology* 92 (1995): 1111-1116.

67. Zhang J., *et al*. "Bioequivalence study of ipratropium bromide inhalation aerosol using PBPK modeling". *Frontiers in Medicine (Lausanne)* 10 (2023): 1056318.

68. Bharathi DV. "Quantification of montelukast, selective cysteinyl leukotriene receptor (CysLT1) antagonist in human plasma by liquid-chromatography-mass spectrometry-validation and its application to human pharmacokinetic study". *Biomedical Chromatography* 23 (2009): 804-810.

69. Challa BR., *et al*. "Method development and validation of montelukast in human plasma by HPLC coupled with ESI-MS/MS: Application to a bioequivalence study". *Scientia Pharmaceutica* 78.3 (2010): 411-422.

70. Ahmed S and Atia NN. "Simultaneous determination of montelukast as sparing therapy with some inhaled corticosteroids in plasma of asthmatic patients" *Journal Pharmaceutical Biomedical Analysis* 74 (2013): 250-256.

71. Alsarra I., *et al*. "Voltammetric determination of montelukast sodium in dosage forms and human plasma". *II Farmaco* 60 (2005): 563-567.

72. Shimaa A., *et al*. "Simultaneous determination of montelukast sodium and loratadine by eco-friendly densitometry and spectrophotometric methods". *Journal of Chromatographic Science* (2023): 1-11.

73. Arayne MS., *et al*. "Spectrophotometric method for quantitative determination of montelukast in bulk, pharmaceutical formulations and human serum". *Journal Analytical Chemistry* 64 (2009): 690-695.

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