Allergy and Immunology Review Corner: Chapter 87 of Middleton’s Allergy Principles and Practice, 7th Edition, edited by N. Franklin Adkinson, et al.

Chapter 87: Histamine and H-1 Anti-Histamines

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1. Which of the following chemical properties contributes to the ability of first generation H1-antihistamines to cross the blood brain barrier?
   A. Recognition by the P-glycoprotein efflux pump.
   B. Lipophilicity, as a result of multiple aromatic or heterocyclic rings and alkyl substituents
   C. High molecular weight
   D. Negative electrostatic charge
   E. A core ethanolamine group, imparting a resemblance to dopamine

2. H1-antihistamines decrease the size of the wheal and/or flare by which mechanisms?
   A. Inhibiting histamine synthesis in mast cells.
   B. Increasing leakage of plasma protein.
   C. Blocking the histamine-induced axon reflex.
   D. Increasing post-capillary venule permeability
   E. Both A and C.

3. Which of the following effects of cetirizine is well documented in clinical trials?
   A. Prevention of acute urticaria.
   B. Shortened duration of symptoms in rhinovirus infection due to decreased expression of ICAM-1.
   C. Improvement in tympanic membrane compliance in acute otitis media.
   D. A significant decrease in exercise-induced bronchospasm.
   E. Decreased size of and symptoms due to nasal polyps.

4. Which of these host factors is associated with an increased risk of cardiac toxicity via QTc prolongation from H1-antihistamines?
   A. Hypermagnesemia
   B. Male sex
   C. Large body mass
   D. Concomitant use of cytochrome P450 inhibitors
   E. Both A and C

5. Which of these antihistamines should be dose-adjusted in patients with renal impairment?
   A. Doxepin
   B. Hydroxyzine
   C. Fexofenadine
   D. Loratadine
E. Diphenhydramine

6. Which of the following represents a clinically significant drug interaction with fexofenadine?
   A. P-glycoprotein inducer such as rifampin
   B. P-glycoprotein inhibitor such as erythromycin
   C. Liver impairment
   D. Administration within 15 minutes of aluminum/magnesium containing antacids
   E. There are no significant drug interactions with fexofenadine

7. Which of the following antihistamines is pregnancy FDA Category B?
   A. Desloratadine
   B. Fexofenadine
   C. Cetirizine
   D. Hydroxyzine
   E. Azelastine

8. Which of the following histamine receptors (HR) triggers histamine-mediated eosinophil and mast cell chemotaxis?
   A. HR1
   B. HR2
   C. HR3
   D. HR4
   E. All of the above

9. Which of the following best describes the mechanism of action of anti-histamines?
   A. Irreversible antagonist
   B. Inverse agonist
   C. Indirect antagonist
   D. Partial agonist/antagonist
   E. Stimulation of L-histidine decarboxylase activity

10. Which of the following receptors potentially mediate adverse effects of first generation H1 antihistamines?
    A. Muscarinic receptors
    B. α-adrenergic receptors
    C. Beta receptors
    D. Norepinephrine receptors
    E. Both A + B

Answers
1. B, page 1525
   "The presence of multiple aromatic or heterocyclic rings and alkyl substituents in first-generation H1-antihistamines results in lipophilicity. This, along with other properties such as relatively low molecular weight, positive electrostatic charge, and for some H1-
antihistamines, lack of recognition by the P-glycoprotein efflux pump, enhances their ability to cross the blood–brain barrier.”

2. C, pages 1528 and 1534
“H1-antihistamines decrease the size of the wheal directly by acting on endothelial cells to decrease post-capillary venule permeability and leakage of plasma protein, and they decrease the size of the flare indirectly by blocking the histamine-induced axon reflex.” (page 1528). All H1-antihistamines likely have some mast cell-stabilizing activity (page 1534).

3. A, page 1535-1536
“Recently in two different large, randomized, double-masked, placebo-controlled studies in young atopic children in which the efficacy of the H1-antihistamines in acute urticaria was a planned secondary outcome, cetirizine or levocetirizine were found to be significantly more effective than placebo in preventing and treating hives.”

No beneficial effect of H1-antihistamines on nasal polyps has been documented in randomized, controlled trials.

Although H1-antihistamines, usually in combination with a decongestant, are often prescribed for children with acute otitis media or otitis media with effusion, placebo-controlled, double-masked studies involving repeated objective assessments of tympanic membrane compliance do not support this practice.

In studies in volunteers inoculated with rhinoviruses, some first-generation H1-antihistamines such as chlorpheniramine and clemastine have been reported to reduce symptoms during colds, due in part to their antimuscarinic, anticholinergic actions. In this model, loratadine, desloratadine, and other second-generation H1-antihistamines have not been effective, although in vitro, these medications decrease expression of ICAM-1, a cellular receptor for major group rhinoviruses, on cultured bronchial epithelial cells.

4. D, page 1542
Host variables play a role in the development of cardiac toxicity from H1-antihistamines and other medications. Individuals with increased vulnerability include females (sex differences in specific cardiac ion densities), individuals with small body mass (large mg/kg dose), and those with hepatic or renal dysfunction (drug accumulation in cardiac tissue). Also at increased risk are those with pre-existing organic heart disease such as myocardial ischemia or cardiomyopathy; cardiac arrhythmias such as congenital or acquired long QT syndrome or bradycardia; or metabolic abnormalities such as hypokalemia, hypocalcemia, or hypomagnesemia. Other individuals at increased risk include those ingesting medications, herbal formulations, or dietary substances that inhibit drug elimination by the cytochrome P450 system and potentially lead to drug accumulation.

5. C, pages 1531-2
Table 87.4 shows dose adjustment may be required for patients with renal impairment who are taking cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine or rupatadine.
6. D, page 1525
Administration within 15 minutes of aluminum/magnesium containing antacids. Bioavailability of fexofenadine is dependent on P-glycoprotein transporters. P-glycoprotein inducers and inhibitors have the potential to decrease and increase fexofenadine absorption respectively, but are thought to be of little clinical significance secondary to fexofenadine’s favorable therapeutic index. Fexofenadine needs to be dose adjusted in renal not hepatic impairment. Aluminum/magnesium containing antacids bind to fexofenadine leading to a decrease in plasma concentrations and concurrent administration should be avoided.

7. C, page 1543 and respective package inserts. Azelastine, epinastine, deesloratadine, fexofenadine and olopatadine are pregnancy category C. Certirizine, emedastine, levocetirizine and loratadine are category B.

8. D, page 1522
Activation of HR induces enhanced migration of eosinophils towards eotaxin and eotaxin-2. It also induces chemotaxis of mast cells. Mast cells from HR3 deleted mice migrated in response to histamine, while mast cells from the HR4 deleted mice did not. Thus chemotaxis of eosinophils and mast cells via histamine is triggered mainly through HR4. Combination H1 and H4 antihistamines is new potential new therapeutic option currently being investigated.

9. B, page 1518 and Fig 87.3.
The histamine H1 receptor is equilibrium with the inactive and active state. An inverse agonist has preferential activity for the inactive state, stabilized the receptor in this conformation and causes a shift in the equilibrium toward the inactive state. All H1-antihistamine described to date function as inverse agonist.

10. E, page 1543 and Fig. 87.10.
First generation H1 antihistamines potentially cause adverse effects, not only through H1 receptors in the central nervous system (CNS), but also through the muscarinic, α-adrenergic, and serotonin receptors and cardiac ion channels.


Chapter 88: Pharmacology of Glucocorticoids

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1. Approximately what percentage of circulating cortisol is bound to plasma proteins?
   A. 10%
   B. 20%
   C. 50%
2. Which of the following has the lowest relative binding to transcortin, a corticosteroid binding globulin?
   A. Prednisolone
   B. Dexamethasone
   C. Hydrocortisone
   D. Methylprednisolone

3. Which if the following medications can prolong the half-life of methylprednisolone?
   A. Barbiturates
   B. Diphenylhydantoin
   C. Ephedrine
   D. Troleandomycin

4. Long-term treatment with glucocorticoids causes most significant atrophy of which organ?
   A. Anterior pituitary
   B. Posterior pituitary
   C. Hypothalamus
   D. Adrenals

5. Which of the following has the highest mineralocorticoid activity?
   A. Betamethasone
   B. Dexamethasone
   C. Hydrocortisone
   D. Triamcinolone

6. In the presence of ACTH in the adrenal cortex, cholesterol is converted through a pregnenolone intermediate to progesterone, which is sequentially hydroxylated to form hydrocortisone, the parent molecule for glucocorticoids. Hydrocortisone consists of a:
   A. 2-ring structure
   B. 3-ring structure
   C. 4-ring structure
   D. 5-ring structure

7. Factors that influence local and systemic activity of inhaled glucocorticoids include:
   A. The delivery device/method, which when used with spacers/aerochambers can increase the oral deposition by up to 90%.
   B. Oral bioavailability of the drug, in which high oral bioavailability is preferred when treating severe asthma.
   C. Volume of distribution, in which inhaled steroids saturate mucosal glucocorticoid receptors due to high affinity for the receptor.
   D. Plasma clearance/terminal half-life, in which little variability is seen between the inhaled steroids.
8. The molecular basis for glucocorticoid actions include:
A. Binding of free glucocorticoid to glucocorticoid receptors in the cytoplasm.
B. Binding of transcortin-bound glucocorticoid to glucocorticoid receptors on the cell-surface.
C. Binding of free glucocorticoid to glucocorticoid receptors in the nucleus.
D. Binding of free glucocorticoid to glucocorticoid receptors on the cell-surface and tyrosine kinase activation.

9. Numbers of which of the following cell types are not altered by acute steroid administration?
A. Basophils
B. Eosinophils
C. CD4 T cells
D. Natural Killer cells

10. Combining steroids and long-acting β agonists into a single inhaler:
A. Decreases adherence /compliance.
B. Facilitates the efficacy the both drugs.
C. Complements the anti-asthmatic effects of steroids and the bronchoconstriction from β2 agonists
D. Inhibits the efficacy of steroids.

Answers
1. D, page 1550
More than 90% of circulating cortisol is bound to plasma proteins.

2. B, page 1550
Relative binding of common glucocorticoids to transcortin is prednisolone = hydrocortisone > methylprednisolone (3%) > dexamethasone (0.1%).

3. D, page 1552
Troleandomycin interferes with liver mixed-function oxidases and can prolong the half-life of methylprednisolone. Barbiturates, diphenylhydantoin, ephedrine and agents of occupational exposure can induce liver mixed-function oxidases and shorten the half-life of steroids by increasing their rate of metabolism.

4. A, page 1550
Chronic elevations in glucocorticoids can produce a more long lasting inhibition of ACTH secretion that can result in atrophy of the anterior pituitary and have serious consequences after sudden withdrawal from treatment.

5. C, page 1552 (Table 88.1)
Hydrocortisone has some mineralocorticoid activity. Betamethasone, dexamethasone, and triamcinolone do not.

6. C, page 1550
Hydrocortisone consists of a 4-ring 21-carbon structure. There are numerous structural elements on each ring important for anti-inflammatory actions.

7. C, pages 1553-1554 (Figure 88.5)
Inhaled steroids have high affinity compared to oral glucocorticoids and after inhalation, local concentrations are high enough to saturate mucosal receptors. When inhaled corticosteroids are delivered with spacers/aerochambers, the oral deposition decreases by up to 90%. Because a large proportion of drug can be swallowed, it is advantageous that inhaled steroids have a low oral bioavailability. There is significant variability in clearance between the inhaled steroids with a <2 hour half-life for budesonide and >5 hour half-life for mometasone.

8. A, page 1555 (Figure 88.6)
Free steroid diffuses across the plasma membrane and becomes associated with the glucocorticoid receptor in the cytoplasm. After heat shock proteins dissociate and the receptor is phosphorylated, the glucocorticoid plus glucocorticoid receptor complex translocates to the nucleus where it binds glucocorticoid response elements and either represses or activates gene expression.

9. D, page 1558
Basophil, eosinophil, and CD4 T cell numbers fall in response to acute steroid treatment, while NK cell numbers are not influenced.

10. B, page 1558
Combining steroids and long β agonists into a single inhaler facilitates the efficacy of both drugs and increases adherence/compliance. It complements the anti-asthmatic effects of steroids with the smooth muscle relaxation and bronchodilation of β2 agonists.