

**Chapter 36: Medications**

**Antihistamine**

An antihistamine acts as a competitive antagonist by occupying the "receptor site" on the effector cells. It does not prevent the release of histamine nor does it destroy the histamine. The basic formula for an antihistamine is:



There are many derivatives sharing the same pharmacologic action and side effects. In general, an antihistamine blocks the histamine effect on smooth muscles of the gastrointestinal tract and respiratory tract, inhibits the histamine vasoconstricting effect of major vessels and vasodilating effect of venules and arterioles. It also inhibits the increase in capillary permeability caused by histamine. Antihistamine has no effect on gastric secretion secondary to histamine stimulation. Since it acts by competitive inhibition and has no direct effects on the smooth muscles of the vasculature or the bronchial muscles, it has little therapeutic benefit in anaphylactic shock. Antihistamine also has no pharmacologic effect on other autacoids, and hence it is not used in the treatment of bronchial asthma.

Antihistamine can cause either CNS depression or stimulation depending on the dose and the individual (Table 36-1). Depressive symptoms include somnolence, lassitude, and fatigue. The aminolakyl ethers (i.e. diphenhydramine) are particularly prone to giving this side effect. CNS stimulative symptoms may include restlessness, nervousness, insomnia, and focal seizures in patients with previous cerebral lesions.

**Table 36-1. Effects of Antihistamines**

Derivatives	Trade Names	Effect
Ethanolamines (diphenhydramine)	Benadryl Dramamine	4 + sedative effects 4 + atropine-like effects
Ethylendiamines (pyrilamine)	Pyribenzamine	2 + sedative effects 4 + GI symptoms
Alkylamines (chlorpheniramine)	Chlor-trimeton Dimetane	1 + sedative effects 2 + stimulation effects
Piperazines (chlorcyclizine)	Cyclizine HCl Marezine HCl Meclizine HCl Bonine HCl	2 + sedative effects
Phenothiazines (promethazine)	Phenergan	4 + control motion sickness.

Antihistamines also suppresses motion sickness. The diphenhydramine, promethazine, and piperazine derivatives are particularly effective in this regard. Promethazine and pyrillamine have mild local anaesthetic effects.

All antihistamines produce atropine-like activity giving rise to dry mouth, possible micturition problems, and impotence. It is possible to experience blurred vision, diplopia, euphoria, elevated blood pressure, anorexia, constipation or diarrhea, and epigastric distress from antihistamines. Antihistamines seldom cause allergic reactions although when used topically they may produce urticaria. Leukopenia and agranulocytosis have been reported. Piperazine compounds (i.e. cyclizine, chlorcyclizine, meclizine) have demonstrated teratogenic effects in experimental animals, and hence should be avoided during pregnancy. Antihistamine is usually contraindicated in patients taking MAO inhibitors.

When antihistamine is taken orally, the onset of action is about 15-30 minutes lasting 3-6 hours. It is metabolized mainly in the liver.

Acute poisoning, particularly in children, can be lethal. Patients may experience CNS stimulatory symptoms to include convulsions, ataxia, athetosis, and hallucinations. They then may elapse into coma and cardiorespiratory arrest in 2-18 hours. Treatment of antihistamine poisoning is supportive.

Commercial preparations have combined antihistamine with decongestive medications (i.e. phenylephrine hydrochloride). Sometimes preparations contain stimulants such as caffeine to counteract the depressive effects.

Drixoral: contains dexbrompheniramine maleate and d-iso-ephedrine sulfate

Dimetapp: contains brompheniramine (Dimetane) and vasoconstrictors (phenylephrine hydrochloride and phenylpropanolamine)

Actifed: contains Actidil (triprolidine HCl) and Sudafed (pseudoephedrine HCl)

Ornade: contains Teldrin (chlorpheniramine maleate), phenylpropanolamine, and isopropamide iodide (drying agent)

Ornex: contains no antihistamine. It has acetaminophen, salicylamide, caffeine, phenylpropanolamine.

(Other can be found in the PDR.)

### **Anticholinergic Drugs**

This group of drugs is considered by some to be the best established agents for the prevention of motion sickness. The mechanism of action is blocking of acetylcholine from its receptor sites. This action produces both peripheral and central effects such as blocking of the parasympathetic system, depression of smooth muscle activity, and depression of cerebral and medullary centers. Experiments with DFP (diisopropyl fluorophosphate, a potent anticholinesterase) provide evidence to suggest that the vestibular receptors are cholinergic.

Drugs in this category include scopolamine (Hyoscine), atropine, and the synthetic agents: amphetamine (Amphenadrine), cycrimine, and trihexyphenidyl. The most effective one is scopolamine. Scopolamine has fewer side effects than atropine and the synthetic belladonna drugs. A dose of 0.6 mg of scopolamine appears to be best for suppression of motion sickness with minimal side effects. The side effects are:

1. Dry mouth.
2. Increase in pulse rate.
3. Drowsiness.
4. Headache.
5. Stomach awareness.
6. Nightmares.
7. Blurred vision.
8. Vertigo.

The addition of 10 mg of d-amphetamine to 0.6 mg of Hyoscine may decrease the side effect of drowsiness. The onset of therapeutic action is approximately 1 hour after the medication is given, the duration of action is approximately 4 hours.

### **Phenothiazines**

This group includes prochlorperazine (Compazine), chlorpromazine (Thorazine), promethazine (Phenergan), perphenazine (Trilafon), trifluoperazine (Stelazine), and promazine (Sparine). Phenergan is the best in this group for controlling motion sickness. It also can be classified as an antihistamine. It is also a hypnotic which means its side effect is drowsiness. The duration of action of phenergan is about 6 hours. An amphetamine can be added to combat the drowsiness.

### **Vasoconstrictors**

#### **Epinephrine**

1. It stimulates the sympathetic nervous system.
2. It increases tone and vasoconstriction as evidenced by marked pallor and shrinkage of the mucous membrane.
3. It is vagolytic and antagonistic toward the parasympathetic nervous system.
4. It is a bronchial dilator.
5. Its onset of action is only a few minutes after subcutaneous injection. Its action lasts 1 hour.

#### **Dosages:**

- 0.05-0.1 mL infants
- 0.15-0.25 mL up to 8 years old
- 0.3-0.5 mL older children and adults
- 6. It is irritating to the nasal mucosa. Phenylephrine (Neo-Synephrine) and ephedrine are less irritating.
- 7. It cannot be given orally.

## **Ephedrine**

1. It stimulates the peripheral sympathetic system and the CNS. It thus produces insomnia, palpitation, and nervousness.
2. It can depress the heart giving rise to extrasystoles.
3. It may cause urinary retention.
4. It can be given orally.

## **Neo-Synephrine (Phenylephrine)**

Phenylephrine is a synthetic ephedrine.

## **Isuprel (Isoproterenol)**

1. It does not have the excitatory and pressor effects of epinephrine.
2. It can be given sublingually, orally, and it can be inhaled.
3. Overdosage can cause bronchial spasm instead of bronchial dilation.

## **Topical Vasoconstrictors**

These agents include:

Propylhexedrine (Benzedrex)  
Naphazoline (Privine)  
Oxymetazoline (Afrin)  
Tetrahydrozoline (Tyzine)  
Xylometazoline (Otrivine).

## **Steroids**

1. The adrenal cortex secretes:
  - a. Glucocorticoids, i.e. hydrocortisone.
  - b. Mineralocorticoids, i.e. aldosterone.
- 1) Glucocorticoids have the following properties:
  - a) Increase gluconeogenesis.
  - b) Decrease the sensitivity of tissue to the action of insulin.
  - c) Increase protein catabolism.
  - d) Increase diuresis of water.
  - e) Delay wound healing.

- f) Retard growth centers.
- g) Inhibit formation of fibroblasts and tissue vascularization.
- h) Alter the union of antibody and antigen.
- i) Increase the plasma level of the oxidase enzyme which degrades histamine.
- j) Suppress the secretion of ACTH from the anterior pituitary gland.

2) Mineralocorticoids have no anti-inflammatory properties and cause Na retention and K secretion: i.e. Aldosterone.

2. Clinically, it is better to administer glucocorticoids than ACTH because the patient may be allergic to the ACTH extract, and further ACTH depresses pituitary function.

3. When indicated, the use of corticosteroids should not replace the use of epinephrine since corticosteroids are not effective till 60-120 minutes after administration even when given intravenously.

4. Normal daily secretion of glucocorticoids is 20 mg of cortisone a day or 5 mg prednisone a day.

Table 36-2 lists some commonly used steroids, their trade names, and properties.

**Table 36-2. Commonly Used Steroids**

Generic Name Trade Name	Relative Dosage Anti-inflammatory	Cushingoid or Gluconeogenic Properties	Na <sup>+</sup> #
Hydrocortisone Solu-Cortex Cpd F	20 mg 1	1	1
Cortisone Cpd E	25 mg 0.8	1	1
Prednisone	5 mg 3-5	5	0.8
Prednisolone Delta-Cortef	5 mg 3-5	5	0.8
Triamcinolone Aristocort Kenacort	4 mg 20	20	0
Dexamethasone	0.75	20	0

Decadron	20-30		
Methylprednisone	4 mg	10	0
Medrol	10		
Solu-Medrol			
Betamethasone	0.6 mg	20	0
	25		

### **Antibiotics**

1. Competitive Antagonist: i.e. sulfonamide is a structural analogue of para-aminobenzoic acid (PABA) and PABA is needed for folic acid synthesis in the bacteria.

2. Inhibition of Cell Wall Synthesis: i.e. penicillin, cephalothin (Keflin), bacitracin, vancomycin, novobiocin, cycloserine.

3. Inhibition of Cell Membrane Function: i.e. polymyxin (colistin) on gram-negative organisms, polyenes on fungi.

4. Inhibition of Protein Synthesis: i.e. chloramphenicol, tetracycline, streptomycin, and erythromycin.

5. Inhibition of Nucleic Acid Synthesis: i.e. actinomycins and griseofulvin.

- |    |                   |                                                                                                           |
|----|-------------------|-----------------------------------------------------------------------------------------------------------|
| 6. | Sulfonamides:     | Bacteriostatic.                                                                                           |
|    | Penicillin:       | Bactericidal in high concentrations and bacteriostatic in low concentrations.                             |
|    | Cephalosporin:    | Bactericidal.                                                                                             |
|    | Streptomycin:     | Bactericidal.                                                                                             |
|    | Tetracycline:     | Bacteriostatic and rickettsiostatic.                                                                      |
|    | Chloramphenicol:  | Bacteriostatic.                                                                                           |
|    | Bacitracin:       | Bactericidal (when used systemically, it is toxic to the kidney causing tubular and glomerular necrosis). |
|    | Neomycin:         | Bactericidal.                                                                                             |
|    | Kanamycin:        | Bactericidal.                                                                                             |
|    | Polymyxin B/E:    | Bactericidal (colistin).                                                                                  |
|    | Vancomycin:       | Bactericidal.                                                                                             |
|    | Erythromycin:     | Bacteriostatic or bactericidal.                                                                           |
|    | Lincomycin:       | Bacteriostatic or bactericidal.                                                                           |
|    | Cleocin (clinda): | Bacteriostatic or bactericidal.                                                                           |

7. Sulfa drugs and hemophilic streptococcal infections can give rise to secondary anemia.

8. Phenylalanine helps to combat the agranulocytosis encountered in patients receiving chloramphenicol (Chloromycetin).

9. Tetracycline potentiates the hypoglycemic effects of oral hypoglycemic agents.

10. Probenecid (Benemid) inhibits the tubular secretion of penicillin thus increasing the plasma levels.

11. Lincomycin (Lincocin) may cause severe diarrhea with blood and mucus in the stool. Fatal colitis may ensue. The same applies to clindamycin (Cleocin).

12. Chloromycetin may cause aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia. There are reports of aplastic anemia that terminated in leukemia following administration of chloromycetin. Blood dyscrasias have been reported following short- and long-term therapy.

### **Ototoxicity**

#### **Salicylates**

Salicylates cause a reversible hearing loss and tinnitus. It has been postulated that salicylates exert an uncoupling action on oxidative phosphorylation. They inhibit various transaminases and dehydrogenases. In humans, discontinuation of high doses of the drug will cause the salicylate level to fall as the drug is excreted and the hearing reverts to normal within 24-72 hours. No histologic changes have been demonstrated. To cause toxicity, 6-8 g/day have to be taken. Salicylates are rapidly metabolized in tissues and approximately 50% is eliminated in 24 hours. Within 48-72 hours all salicylates will have been excreted in the urine.

Salicylate serum levels of 20 mg% or higher will cause hearing loss. The higher the serum level (up to 50 mg%) of salicylate, the greater the hearing loss.

Aspirin is found in the following medications: Percodan, Fiorinal, Coricidin, Trigesic, Norgesic, Talwin Compound, and Equagesic.

#### **Dihydrostreptomycin**

Dihydrostreptomycin can cause severe and erratic hearing loss even as long as 2 months after the medication has been stopped. The hearing loss is unpredictable and not dose related. Since this drug has no advantage over streptomycin sulfate, it never should be used. In the United States, it has been taken off the market.

#### **Streptomycin**

Streptomycin sulfate causes vertigo before the onset to tinnitus and hearing loss. Its affinity for the vestibular over the auditory system has been capitalized on to treat intractable bilateral Ménière's disease. For this purpose an average dosage of 2 g/day is given until no caloric response is obtained upon stimulation with ice water.

The vestibular toxic effect of streptomycin sulfate is dose related. 1 g q. d. for 10 days does not give vestibular symptoms. However, 2 g q. d. for 14 days has been reported to give vestibular symptoms in 60-70% of the patients.

Fifty to sixty percent of streptomycin sulfate is excreted by the kidneys in the first 24 hours. The larger the dose the faster the excretion by a normal kidney. Hence, any renal impairment will build up the serum level very quickly. A very small amount is secreted by the liver to be excreted through the gastrointestinal tract.

Peak plasma level is detectable within 1 or 2 hours after IM injection and diminishes by about 50% in 5 hours. The antibiotic can be detected in the plasma for at least 8-12 hours after administration. Recommended doses for children are 15-30 mg/kg/day.

Histologic findings following ototoxicity due to streptomycin are:

- a. Minimal scattered loss of outer hair cells in the upper basal turn of the cochlea. Normal supporting cells.
- b. Severe damage to the sensory epithelium of the cristae of all canals. Severe hair cell loss and flattening of the sensory epithelium of the cristae and saccule. The utricular macula is involved but least so in the vestibular end organs.
- c. Stereocilia in the canal ampullae are swollen and are twice their normal diameter.

### **Kanamycin**

Kanamycin may not be as ototoxic as neomycin. However, in patients with poor renal function, its administration has to be justified and the minimal necessary dosage used. In adults with good renal function, 15 mg/kg/day will cause mild or no hearing loss.

Kanamycin is poorly absorbed orally. Inframuscular administration of 1 g yields a peak plasma level of 20-35 microg/mL in about 1 hour. In 12 hours, the level falls to 1.2 microg/mL. Fifty to eighty percent of this drug is excreted by the kidney in 24 hours. In patients with normal kidney function, repeated injections of kanamycin should not lead to accumulation of the drug. Kanamycin is also nephrotoxic.

Histologic findings following ototoxicity due to kanamycin are:

- a. Destruction of inner and outer hair cells. The latter are believed to be destroyed first. A more severe hair cell degeneration is found in the basal turn, the apical turn being less involved.
- b. The supporting cells usually are not altered. Hence, neural degeneration is insignificant.
- c. Normal semicircular canal cristae and maculae of the utricle and saccule.



## **Neomycin**

Neomycin is not absorbed well topically or orally. Therefore, using neomycin orally to sterilize the bowel carries little risk of ototoxicity. However, repeated use of neomycin over inflamed gastrointestinal mucosa has caused irreversible deafness.

Five to eight grams given parenterally over 4-6 days have caused tinnitus and irreversible hearing loss. A 1 g parenteral dose will give a plasma level of 20 microg/mL for 6-8 hours. Neomycin is secreted by the kidneys. Hence, when renal disease is present, neomycin should be withheld because of its potential for nephrotoxicity.

Neomycin, dihydrostreptomycin, and kanamycin are eliminated more slowly from the inner ear than from the rest of the body, resulting in delayed ototoxicity. Hearing loss as a result of neomycin ototoxicity may occur as late as 1-2 weeks after the drug is stopped. The following histologic findings have been noted in neomycin ototoxicity:

- a. Destruction of inner and outer hair cells, the outer ones being slightly less involved. Apical and basal turns are both involved, the basal turn being more so than the apical turn.
- b. Some destruction of pillar cells is present with some atrophy of the stria vascularis.
- c. A minimal loss of Deiters' cells and Hensen's cells.
- d. Maculae and cristae remain normal.

## **Ethacrynic Acid**

This diuretic has been demonstrated to cause destruction of the intermediate layer of the stria vascularis and outer hair cells of the organ of Corti, most severe in the basal turn. The hearing loss can be transient or permanent. The transient hearing loss could be secondary to its effect on the respiratory enzyme (succinodehydrogenase and adenosine triphosphatase) in the organ of Corti and stria vascularis. It apparently decreases the sodium content of the endolymph. The symptoms include hearing loss, tinnitus, and vertigo.

## **Quinine**

Quinine is readily absorbed when taken orally. Ninety-five percent of the drug is metabolized in the liver so no untoward effects are feared in the event of renal disease. Most of the drug is excreted in 24 hours. The usual dosage is 0.3-0.6 g q.i.d. The ototoxic effects of quinine are hearing loss and tinnitus, both of which are reversible. The ingestion of quinine in therapeutic doses may not give rise to hearing loss in the mother, but may affect the fetus, giving rise to severe bilateral sensorineural hearing loss. Histologically, the external hair cells and stria vascularis have been noted to be atrophied. The brain stem vestibular and cochlear nuclei have been noted to be normal. Taking chloroquine in pregnancy is similarly hazardous to fetus.

### **Gentamicin**

Gentamicin affects the vestibular nuclei rather than the auditory system. If used at serum levels of 10-12 microg/mL, it does not cause any ototoxicity. The recommended dosage is 1 mg/kg/day. In patients with renal damage, this dose should be adjusted.

### **Nitrogen Mustard**

Nitrogen mustard causes destruction of hair cells giving rise to sensory hearing loss.

### **Tobramycin**

Tobramycin has ototoxic effects similar to kanamycin. The hearing loss consists of a high-frequency hearing loss that produces a steeply sloping audiogram. The vestibular symptoms are less common.

### **Cisplatin**

Cisplatin may give rise to high-tone hearing loss. Temporal bone studies reveal a loss of outer hair cells of the basal turns.

### **Misonidazole**

Misonidazole is a new potent antitumor agent that selectively increases the effect of ionizing radiation on poorly oxygenated tumor cells. It can cause sensorineural hearing loss of cochlear origin.

Other ototoxic drugs include: polymyxin B, colistin, viomycin, vancomycin, ristocetin, arsenicals, oils of Chenopodium, chloroform, iodoform, alkaloids (strychnine, opiates, pilocarpine, scopolamine), and tetanus antitoxin.

### **Neurologic Medications**

1. Sodium diphenylhydantoin (Dilantin): It stabilizes seizure activities and prevents the spread of seizure activities.
2. Carisoprodol (Soma) is a muscle relaxant. It acts by blocking the interneuronal activity in the descending reticular formation and spinal cord.
3. Ergotamine tartarate (Sansert) selectively constricts cerebral vessels thus relieving the headache from cerebral vascular dilation.
4. Carbamazepine (Tegretol) is used for genuine trigeminal neuralgia. Death from aplastic anemia (agranulocytosis, thrombocytopenia, leukopenia) has been reported. Its mechanism of action is unclear.

## **Chemotherapeutic Agents**

### **Folate Antagonist (Methotrexate)**

1. Inhibits DNA synthesis.
2. Binds and inhibits dihydrofolate reductase.
3. Single most effective drug against squamous cell cancer in the head and neck.
4. Major toxicity: bone marrow (reversible), gastrointestinal tract, and kidneys (in patients with impaired function).

### **Antibiotics**

1. Doxorubicin (Adriamycin).
  - a. Interferes with both DNA and RNA synthesis.
  - b. Binds to DNA.
  - c. Major toxicity: cardiovascular.
2. Bleomycin.
  - a. Inhibits DNA synthesis.
  - b. Binds to DNA and causes splits in strands of DNA.
  - c. Major toxicity: pulmonary.

### **Pyrimidine Analogues (5-fluorouracil)**

1. Blocks DNA synthesis.
2. Inhibits thymidylate synthetase.
3. Major toxicity: bone marrow, gastrointestinal tract, oral mucosa.

### **Alkylating**

1. Mustard drugs.
  - a. Nitrogen mustard, melphalan, chlorambucil, cyclophosphamide.
  - b. Interfere with mitosis and cell division.

c. Their metabolism stimulates the formation of a highly reactive carbonium ion which most frequently alkylates the purine.

d. Major toxicity: lymphotoxicity, gastrointestinal irritation, alopecia, cystitis.

2. Nonmustard alkylating drugs.

a. Nitroureas (CCNUY, methyl CCNU), thiotepa, BCN4, and dicarbazine.

b. Inhibit DNA, RNA, and protein synthesis.

c. Major toxicity: myelosuppression, gastrointestinal.

### **Cisplatin**

a. Inorganic metallic salt.

b. Mode of action unknown.

c. Major toxicity: bone marrow, kidney, gastrointestinal, cochlear.