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Antihistimine poisoning in children

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ANTIHISTAMINE POISONING IN CHILDREN

During recent years we have witnessed the development of an increasing number of antihistaminic agents, whose role in the therapy of allergic diseases has now become established. An avid public has been eagerly supplied by various manufacturers until at present the consumption of these agents is enormous. In 1951 there were 37 pharmaceutical firms which have taken 19 antihistamines, created 102 trade names and distributed them in 123 different forms.[1] For the list of proprietary antihistaminic preparations see end of article.

Fortunately, the antihistaminic compounds have proved to be relatively nontoxic in the usual doses, though they frequently give rise to bothersome side effects. With larger doses, however, such as have frequently occurred in children by accidental poisoning, there have been several cases of acute toxicity and death. The purpose of this report is an attempt at formulation of a plan for the emergency treatment of acute poisoning by antihistamines in children. A series of 19 cases of fatal intoxication and 11 cases of non-fatal intoxication will be presented. Also the pharmacology and toxic effects of the antihistaminics will be discussed.

HISTORICAL

In 1911 Dale and Laidlaw noted the similarities between the effects of histamine and anaphylaxis in the guinea pig.[2,3] This

started the search for drugs to neutralize or prevent the effects of histamine, in the hope that allergy symptoms could thus be prevented. Many drugs, such as epinephrine, atropine, papaverine and other sympathomimetic substances, antagonize the action of histamine through their antagonistic effect on the tissues involved. They are, however, relatively non-specific for histamine mediated conditions. They frequently effect only one or a few phases of the allergic reaction.

The first real progress in the antihistaminic field began with the Fourneau-Bovet phenolic ether compounds in 1933, followed by the ethylene-diamines of Staub in 1939. In 1942 Antergan, an ethylene-diamine which was the first clinical compound, was described by Halpern. In 1945 Benadryl, then Pyribenzamine were introduced in this country by Loew and by Mayer. Since then many antihistamine compounds have been made available.

CHEMISTRY AND PHARMACOLOGY

Loew[2] has defined antihistaminic agents as "drugs which are capable of diminishing or preventing several of the pharmacological effects of histamine and which do so by a mechanism other than the production of pharmacologic responses diametrically opposed to those produced by histamine. True antihistaminic agents are able to antagonize histamine without eliciting pharmacologic responses, or if responses are elicited, they do not appear to be of the type or degree which suggest an important

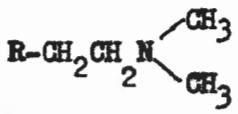
causal relationship to the histamine antagonism".

The rationale for the use of the antihistaminic agents rests on two theories: (1)that symptoms of anaphylactic shock are due, in part at least, to a liberation of histamine, and (2)that allergic disease in man is the counterpart of anaphylaxis.

In animal tests and in clinical experience, it has been found that the antihistaminics do not counteract all of the pharmacological properties of histamine. This may be due to a number of reasons.[4] The antihistamine drugs may act through adsorption or other combination with histamine receptors, thus directly blocking off the histamine. This would explain the action, in some cases, of the antihistaminic moderating histamine activity to a greater extent when introduced into the tissues before the histamine, than when applied simultaneously or afterward. Under other circumstances, the reverse may be true. Histamine evidently has a number of receptors, presumably many of them different from each other. Therefore, if the antihistaminic drugs act by virtue of the similarity of its structure to histamine, as there is some evidence that it does, a consideration of the stereochemical relationship would lead to a possible explanation as to why some antihistamine compounds vary in both type and degree of activity. Spatial relationships may permit ready combination with some of the histamine receptors and little or none with others. The relatively high (240 and up) molecular weight of the more effective histamine antagonists would seem to bear this out.

The size and shape of the groups at the ends of the key grouping quite possibly determine the degree of blocking of the histamine as well as the ability of the antihistamine molecule to replace the histamine already in contact with its receptors.

Seyler[5] has prepared a table correlating the chemical structure, antihistamine activity, drowsiness and toxicity of the antihistamine compounds. Most of the antihistamines have in their composition or decomposition, this general formula:

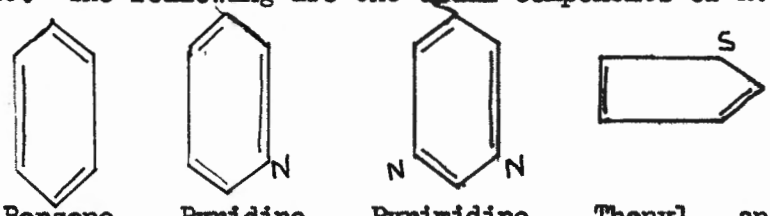


Antihistamine Compounds
Some Basic Pharmocological Principles

Antihistamine Activity	Drowsiness	Toxicity	Ring Compound Linkage and Variant
2+	3+	3+	$R\text{-}O\text{-}CH_2CH_2N(CH_3)_2$ Blocks Histamine Tissue Reaction
3+	2+	2+	$R\text{-}N\text{-}CH_2CH_2N(CH_3)_2$
1+	1+	1+	$R\text{-}CH_2\text{-}CH_2CH_2N(CH_3)_2$ Side Chain Common to Many Histamines

O-linkage: increases drowsiness and toxicity more than antihistamine activity. Examples are Benadryl, Decapryn, Hydryllin.
N-linkage: increases antihistamine activity more than drowsiness and toxicity. Examples are Pyribenzamine, Neo-Antergan, Neohetramine.
CH_2-linkage: decreases antihistamine activity, drowsiness, and toxicity. Examples are Trimeton, Chlortrimeton.

R in the general formula for antihistamines is any large slightly basic radical representing about 75% of the molecular weight. The following are the usual components of R:



Benzene Pyridine Pyrimidine Thenyl and various polycyclic ring compounds in arbitrary combinations modify side effects and antihistamine activity.

Other effects of these drugs besides blocking histamine are:

1) They are good sedatives.
2) Most of them are local anesthetics.
3) They have definite anticholinergic effects.
4) They may potentiate epinephrine by neutralizing histamine.
5) They also have quinidine-like, anti-hyaluronidase and spasmolytic effects.

There are many other pharmacologic properties of the antihistamines, which have limited clinical application. The better known effects, not yet mentioned, are:

1. They neutralize the following effects of histamine (a) Aerosol bronchoconstriction, (b) Spasm of guinea pig ileum, (c) Whealing of the skin, (d) Depressor action on arterial blood pressure, (e) Oxytocic action, (f) Increase in capillary permeability.

2. They protect against (a) Active and passive anaphylaxis, (b) Specific contraction of the uterus of sensitized guinea pigs, (c) Experimental anaphylactic uveitis, (d) Experimental allergic nephritis. Large doses are required for most of these effects.
3. They prevent experimental orthostatic albuminuria in rabbits. 4. They may produce hyperglycemia. 5. They may inhibit oxidation of glucose and pyruvates in brain homogenates.
6. They inhibit, partially, the Schwartzmann phenomenon and the lesions of experimental chemical contact dermatitis.

They do not prevent: (a) Histamine production of gastric HCL, (b) Experimental meningoencephalitis, (c) Reversed anaphylactic reactions of the guinea pig to anti-guinea-pig- rabbit serum, (d) Arthus and tuberculin reactions.

The antihistamine drugs have demonstrated great supportive value, but inasmuch as the basic mechanism responsible for allergic symptomatology is unaffected, they offer little in the way of curative benefit in allergic diseases.[6] The most satisfactory results are achieved in hay fever and acute urticaria, in relieving pruritis and excessive nasal and lachrymal secretions. The excessive itching in chickenpox is often ameliorated, although these drugs offer little or no lasting benefit in eczema.

ABSORPTION, FATE AND EXCRETION

Comparatively few investigations have been made to secure information relating to the absorption, fate and excretion of antihistamines. In general, it can be safely stated that intestinal absorption is rapid, since with all antihistamines subjective and objective improvement has been reported to occur within 20 to 45 minutes after oral administration. It is also obvious that destruction, inactivation or excretion must be quite rapid since therapeutic effects can be maintained only if doses are repeated, usually every three, four or six hours. The principle site of detoxification particularly for benadryl and pyribenzamine, lies in the liver[6]. Approximately 10% of these substances are excreted in the urine in a conjugated form and a small amount in a free state[7]. The distribution of the antihistamine in tissues is widespread, having been recovered not only from the blood but also the cerebrospinal fluid after oral administration[8]. Maximal concentration is usually found in the lung, but the brain, liver, kidney, spleen, and muscle also share in deposition and contain large amounts[9].

TOXICITY[4,10]

The toxic effects in animals vary greatly from those seen in man and there has so far been no predictable correlation between the effects in the experimental animal and in human beings. In any case, the effects are multiple and the good results seen may as often be due, as for instance, to sedation in Benadryl, as to

stimulation as seen in Neohetramine, as well as to other effects not directly related to those antihistaminic in nature. Without exception, all of the histaminalytic drugs cause side reactions. No regularity of pattern response is known, although millions of doses have been administered. A drug, which causes severe side reactions in one patient, may be taken by another with no ill effects. Another drug, of supposedly lower toxicity, may cause unbelievably severe untoward reactions in a susceptible individual. In some patients, such reactions may be caused by two drugs of dissimilar origin, while in others, another drug of similar but not identical chemical structure can be taken with impunity.

The antihistaminic agents are inconsistent in their action, in that a drug may be effective at one time for a patient and not for a second administration, although the patient's condition may appear to be the same. Ineffectiveness is also capricious. In occasional patients, prolonged administration of a drug which causes side reactions may lessen them, while in others, each successive dose brings on more severe side reactions until the patient is completely intolerant of even the smallest dose. There is no predictable method of deciding whether the patient will benefit from any one drug, although it is usually the rule to administer the drug which is either known to have the smallest percentage of side reactions, or the greatest degree of efficacy.

TABLE I - ACUTE TOXICITY OF ANTIHISTAMINIC-AGENTS IN THE HUMAN

I NERVOUS SYSTEM

A. Central

1. Stimulation
   - Insomnia
   - Nervousness
   - Vagal stimulation
   - Tachycardia and hypertension
   - Muscular twitchings
   - Hyperreflexia
   - Tremor
   - Convulsions

2. Depression
   - Drowsiness
   - Somnolence
   - Narcolepsy
   - Weakness
   - Ataxia
   - Delirium
   - Coma

3. Neuropsychiatric
   - Nightmares
   - Impaired judgment
   - Delusions
   - Hallucinations
   - Mental depressions
   - Reduced mental efficiency
   - Confusion
   - Toxic psychosis

4. Miscellaneous
   - Dizziness
   - Headache
   - Syncope
   - Fever
   - Hyperthermia
   - Cerebral edema
   - Electroencephalographic changes

B. Peripheral
   - Toxic neuritis
   - Parasthesias
   - Paralysis
   - Areflexia

C. Special sense organs

1. Ears
   - Tinnitis
   - Vertigo
   - Labyrinithitis

2. Eyes
   - Dilated pupils
   - Blurring of vision

II. GASTROINTESTINAL SYSTEM

- Anorexia, nausea and vomiting
- Heartburn
- Cardiospasm
- Diarrhea
- Constipation

III. CARDIOVASCULAR SYSTEM

- Hypotension
- Vasovagal phenomena
- Syncope
- Shocklike state
- Palpitation
- Tachycardia
- Hypertension
- Cerebral edema
- Electrocardiographic changes

IV. RESPIRATORY SYSTEM

- Asthma

V. GENITOURINARY SYSTEM

- Irritative symptoms
- Spasmogenic retention
- Upper nephron nephrosis

VI. SKIN AND MUCOUS MEMBRANES

- Dry mouth
- Dermatitis
- Urticaria

VII. HEMATOLOGICAL SYSTEM

- Neutropenia
- Agranulocytosis
- Hemolytic anemia

The commoner side reactions to these drugs are drowsiness, sleepiness, dizziness, headache, insomnia, nervousness, nausea, vomiting, constipation, diarrhea and dryness of the mouth. These side reactions are usually easily controlled by reducing the dosage, discontinuing the drug, or resorting to a different antihistaminic. Different agents may possess these side effects to varying degrees; the incidence of side reactions ranges from 10 to 63% or more in patients using various preparations.

In table I, the more acute reactions to the antihistaminic drugs are listed. They are roughly grouped into seven systems. Neuropsychiatric manifestations are the most frequent. The most severe reactions occur with higher doses. However, a severe toxic reaction does not depend on dosage, and the question of the patient's idiosyncrasy to one of the drugs is important.

Both stimulation and depression of the nervous systems can occur as pointed out by Loew.[2] Children are more susceptible to the convulsive effects of these drugs. The clinical pattern in the small child resembles that seen with atropine poisoning.[52] There is diffuse central nervous system involvement with cerebral and cerebellar stimulation and depression. Convulsions are of the intermittent tonic-clonic type and are exceedingly refractory to treatment. Hallucinations, excitement, ataxia, athetoses, and incoordination give further evidence of central

nervous system stimulation. In a few patients, muscular tremors and athetoid movements may herald a convulsion. Fixed dilated pupils, flushed facies, and hyperthermia are not uncommon findings. Terminally, deepening coma and cardio-respiratory failure occur. Death has resulted from 2 to 26 hours after poisoning. Should the patient survive the immediate critical phase, renal and hepatic failure may be superimposed. Gastrointestinal complaints are not prominent. This is unfortunate, for immediate vomiting after ingestion of the drug would abort the poisoning.

Autopsy findings in the fatalities reported have revealed evidences of an acute stress reaction with anoxic changes consisting of cerebral edema, pulmonary edema, passive congestion of viscera and cloudy swelling of viscera. The resemblance to heat stroke has been commented upon by several authors.[47]

The majority of laboratory animals, particularly the mouse and rat, when given a lethal dose of an antihistamine, manifest symptoms identical to those in the child. Convulsive or post-convulsive depressant deaths are characteristic in these animals.

The exact mechanism of intoxication with the antihistamines is unknown. The pharmacologic explanation of antihistamine intoxication has several possibilities: (1)that this substance blocks, depletes or inactivates the histamine in the tissues

which would therefore be indirect proof that histamine has a physiologic function; (2) that it may also antagonize and inhibit acetylcholine and thereby disturb the functioning integrity of the nervous system; (3) that it may cause untoward effects through its other known pharmacologic activities, namely, sympatholytic, sympathomimetic, anesthetic and antihyaluronidase properties; (4) that intoxication results from an intrinsic property apart from those functions already given but common to various drugs; and lastly from a combination of these actions.

If one assumes that the poisoning is due to histamine deprivation or antagonism, the injection of a histamine or a substance with histamine activity should constitute a true antidote and be specific. Although benadryl will relieve fatal bronchoconstriction in most experimental animals, antidotal therapy with histamine has not been satisfactory in man. Duerfeldt [50] administered 3 mg. of histamine to a 15 kilo child who had taken 50 to 60 mg. per kilo of benadryl. This drug could not control the frequent convulsions of the patient, and aggravated the already belabored respiratory distress by inducing an asthmatic state. Guinea pigs are not completely protected against the toxic effects of histamine, even though the antihistamine will relieve the induced bronchoconstriction. It was also shown that convulsions caused in mice by 45 mg./kg. of Neoantergan were decreased by 26-35 mg./kg. of histamine and abolished by 52-105 mg./kg. but

the animals given the higher doses died within 6-48 hours.[11] Another reason for not using histamine as an antagonist is the fact that it causes dilatation and increased permeability of blood vessels--a picture closely resembling clinical shock. This could aggravate the condition.

There is clinical and experimental evidence that the antihistaminic drugs will inhibit acetylcholine. This action would be comparable to atropine, and would explain many of the central nervous system manifestations. One author has given neostigmine to a young adult with severe trimeton intoxication.[30] The results were equivocal and evidence of diffuse cortical stimulations persisted, despite apparently adequate dosage. Furthermore the clinical pattern of antihistamine poisoning does not suggest that the sympatholytic, sympathomimetic, anesthetic, or antihyaluronidase activity of these agents are responsible for the toxicity.

Several studies have supported the hypothesis that these drugs act directly on nervous tissue. It has been shown that the brain will store considerable amounts of antihistaminic drugs after administration. After these are fed to rats and rabbits over a prolonged period (three months), sections from the brains showed ganglion cell destruction.[12] It is interesting to note that the pulmonary arteries revealed medial hyperplasia and hyalinosis. More recently, in an effort to elucidate the mechanism of the hypnotic and convulsive effects of Pyribenzamine, in vitro studies showed selective inhibition of mouse brain

homogenates.[13,14] The oxidation of cytochrome oxidase and the succinic oxidase systems were unaffected. Methylene blue was able to overcome the block interposed by Pyribenzamine. This suggested to these investigators that the toxic action occurred between the pyridene nucleotides and cytochrome system. The inhibition is similar to that observed with the barbiturates, and may account for the known synergistic effects of these drugs upon the antihistamines when the latter is given in toxic doses to man, the rat, and monkey.[15] The authors of the experimental work just described did not believe that the convulsant properties of Pyribenzamine could be related to the inhibition of tissue glucose oxidation and respiration. However, they did state that the hypnotic and anesthetic action of the antihistamine might be accounted for by this phenomenon.

Preliminary experiments were carried out to study the action of methylene blue on mice poisoned with a lethal dose of benadryl. No evidence was given by these in vivo studies that methylene blue could be used as a specific antidote for this type of antihistamine poisoning. Thirty mice were used in the study. Benadryl was administered as a lethal dose in varying amounts, from 50-200 mg. per kilo of body weight, depending upon the route of administration, intravenously or intraabdominally. Methylene blue was injected either intraabdominally or intravenously prior to or after administration of the antihistamine. In another ex-

periment, the methylene blue was mixed with the benadryl in a test tube and after 15 minutes given to the animals, in the amount of 500 mg. per kilo of body weight.[47]

Other workers have attempted to correlate the hypnotic and narcotic action of these drugs with ascorbic acid synthesis and secretion. It is known that this vitamin increases tissue resistance to the various nerve depressants and toxic agents. Large doses of the antihistaminic drugs led to an increased ascorbic acid secretion in the experimental animal. No conclusions could be made, since one drug (Thephorin), producing stimulation rather than somnolence, yielded a similar result.[16]

Clinical support has also been given to the possible action of these drugs upon the central nervous system by Churchill and Gammon.[17] The effect of Benadryl and Pyribenzamine on a group of epileptics was studied. It was concluded that these drugs could directly influence the electrical activity of brain tissue. This was manifested not only by electroencephalographic changes but also by a change in the clinical state of the patient. In one patient focal convulsions resulted after ingestion of the antihistamine.

It is of interest that Seevers,[10] working with a barbiturate (Thiopental Sodium) in an attempt to antidote antihistamine intoxication in monkeys, was able by cautious titration to control convulsions. He concluded that although a short-acting

barbiturate would control convulsions, death would usually follow from deepening coma. Other clinical and laboratory studies support his observations.

UNUSUAL TOXIC EFFECTS

Several cases of agranulocytosis have been reported. One case in a girl, 13, who developed agranulocytosis after taking Neo-Antergan for three weeks, is described by Clement and Godlewski.[18] Blanton and Owens[19] reported the occurrence of a similar blood change in a man, 74, who had been taking Pyribenzamine for a period of eight weeks. Another case due to Pyribenzamine was reported by Cahan and co-workers and they mentioned a similar incident reported by their colleagues.[20] Still another case was cited in a report of the Council on Pharmacy and Chemistry of the American Medical Association,[21] and two more have been reported.[22,23] Drake[24] described a case of agranulocytosis in a man, 81 years old, who took Diatrin in daily doses of 150 mg. for 20 days. The total white cell count dropped to 1,000, with almost complete absence of granulocytes. The bone marrow counts also showed granulocytic depression. Three cases of hemolytic anemia, reported by Crumbley,[25] were diagnosed 10, 14 and two months, respectively, following frequent, average doses of an antihistamine. In two cases Benadryl was taken and in the third, Pyribenzamine. In all three, the blood picture returned rapidly to normal after discontinuing use of the drug.

Other reactions that are serious enough to be classified as side effects are urinary obstruction, ocular changes, and dermatoses. Pyribenzamine and Thenylene have been reported to cause urinary obstruction probably due to their spasmogenic effect on the vesical sphincter.[26] Discontinuance of both drugs produced alleviation of the symptoms.

Ocular effects that have been noted are refractive changes corneal edema, and permanent vitreous opacities.[27] The permanent vitreous opacities and a case in which a heminopsia[28] persisted after a reaction to Thenylene are the only permanent effects of any kind from antihistamine toxicity that can be found in the literature.

Barksdale and Ellis[29] reported that the antihistamines used locally have very little effect on pruritus ani, atopic dermatitis, urticaria and poison ivy. On the contrary they found that they sometimes produce vesicular lesions. They concluded that because of such allergic reactions these drugs are contraindicated for topical use.

DOSAGE

The doses of the antihistamines vary strikingly depending on the individual drug and individual taking it. The differences in individual compounds are predicated both on the degree of effectiveness and limitations due to toxicity.

Despite the claim of many manufacturers that their compound is the most potent or the least toxic, generally speaking, these two phases neutralize each other. Usually the most potent drugs are also more toxic; thus, although milligram potency may be greater, the higher toxicity will as a rule prevent the use of a dose as large as that of a less toxic drug. An extremely potent antihistamine with a very low toxicity, resulting in a very high potency/toxicity index, has not yet been presented. The average adult dose, depending on which drug is used varies from 4 to 100 or 200 milligrams. Feinberg[3] recommends the following general rule for dosage in children. Those over 12 or 14 years of age are given adult doses. Children over 5 and up to 10 or 12 years are given 50% of the adult dose and those from 2 to 5, 33%. In infants 2 years or under doses vary from 5 to 25% of the adult dose.

COMMENT ON CASES REVIEWED

There were several different antihistamine drugs responsible for acute intoxication and death. Benadryl (Diphenhydramine hydrochloride) and Anthisan (Mepyramine maleate), a British drug, were the most common offenders probably because they were two of the earlier antihistamines manufactured for public consumption. Most of the children died from massive doses of the antihistamines, although two childred died from 100 and 200 mg. respectively. The amount of drug causing death ranged from 100 mg. to 1500 mg. Those

children who developed signs of toxicity but recovered ingested from 100 to 850 mg. of antihistamine with the average amount being slightly less than that causing death. All cases except one showed signs of central nervous system stimulation such as hyper-exciteability and convulsions. The one child was lethargic and had hypoactive feflexes. In most of the children signs of depression followed the period of stimulation.

The majority of those children recovering from excessive ingestion were completely symptom free in 24 hours. In a few cases, however, the symptoms slowly disappeared in a period of 5 to 6 days. One child, age three, reverted to baby talk after other signs of toxicity had disappeared. This gradually was replaced after three weeks. None of the cases of excessive ingestion showed permanent sequelae. The critical period with intoxication involves the first 24 hours after ingestion. If the child survives this period, he has a very good chance of recovery. The pulmonary and cerebral edema probably result from anoxia which causes increased capillary permeability. The anoxia is secondary to respiratory depression and an inadequate circulation. The respiratory depression appears to be central in origin.

TABLE II

FATALITIES FROM ANTIHISTAMINE POISONING [10,31-44]

AGE Yr.	DRUG & DOSE (mgm)	CLINICAL COURSE & TREATMENT	AUTOPSY FINDINGS
1/2	Benadryl (Diphenhydramine Hydrochloride) (? mgm)	Convulsions in 1 hour Died in 2 hours	
1	Neo-Antergan 320-400 (Pyranisamine Maleate)	Vomiting, Hypotension, Cyanosis, Convulsions and Coma. Death a few hours after ingestion.	Cloudy swelling of viscera, cerebral edema. Diffuse vasculitis.
1 1/12	Anthisan (Mepyramine maleate) Maximum of 200	In 10 minutes became unconscious and twitched. Became cyanotic. Some vomiting. Twitching until death 6½ hrs. after ingestion.	Pulmonary edema. Cerebral congestion Small hem. in right lung; congestion in middle third of stomach.
1 1/6	Anthisan (Mepyramine maleate) About 300	Vomited in 3-4 hours. Convulsions in about 5 hours. Signs of Bronchopneumonia. Death in 12 hours.	
1 1/4	Anthisan (Mepyramine maleate) Maximum of 600	Vomiting and convulsions a short time after ingestion. Died on same day.	Acute Emphysema Congestion
1 1/4	Antergan 1500	Convulsions and coma. Death 6 hours after ingestion	
1 1/4	Anthisan (Mepyramine maleate) About 600	In about 2½ hours became unconscious, muscular twitchings, profuse catarrhal discharge. Convulsions probably; Death 3 hours after ingestion	Passive cong. of lungs Intra-alveolar hem. Edema of lungs; cloudy swelling of liver; cong. of spleen.

TABLE II CONT'D

AGE Yr.	DRUG & DOSE (mgm)	CLINICAL COURSE & TREATMENT	AUTOPSY FINDINGS
1 1/3	Thenylene (Methapyrilene Hydrochloride) 100	Projectile vomiting in 2 hrs. followed by listlessness, convulsions, intermittent unconsciousness and hyperpyrexia of 107.2°. Severe nitrogen retention. Death 15 hours after ingestion. Treated with Chloral Hydrate, Ether, Oxygen, 5% dextrose; Venesection.	Cerebral edema. Upper nephron nephrosis. Cloudy swelling of pancreas and liver. Edema of lungs with intra-alveolar hemorrhage
1 1/2	Antallergan 800	Cyanosis, convulsions. Death 4 1/2 hr. after ingestion.	Pulmonary Edema
1 3/4	Anthisan (Mepyramine maleate) 600	Unconscious 2 hr. after ing. Profuse catarrhal discharge. Epileptiform convulsions. Death 2 3/4 hr. after ingestion. Treated with gastric lavage and oxygen.	
1 5/6	Dimenhydrinate 700 (?)	Died in convulsions and coma 4 1/2 hr. after ingestion.	
1 11/12	Antergan "10" tablets	Died 6 hr. after ingestion.	
2	Pyramisamine Hydrochloride 1400	Died in convulsions 4 hr. after ingestion.	
2	Anthisan (Mepyramine maleate) 1100	Convulsions 2 hr. after ing. Death 5 hr. after ingestion with cyanosis, unconsciousness and convulsions. Rx.- Phenobaritol gr. 0.75 I.M. and ether failed to halt convulsions. Gastric lavage also performed.	Congestion of brain and kidney; lung edema with petechial hemorrhage.
2	Desentol (Large Dose)	Died in epileptic fits 2 hr. after ingestion.	

TABLE II CONT'D

AGE Yr.	DRUG & DOSE (mgm)	CLINICAL COURSE & TREATMENT	AUTOPSY FINDINGS
2	Benadryl (Diphenhydramine hydrochloride) 474	Lethargy and shallow resp. in 30 min. followed by cyanosis and convulsions. In 2 hr. developed high fever, Cheyne-Stokes breathing. Pupils dilated and fixed. Fever of 104.4 F in spite of cool sponges and flushes. Expired 13 hrs. after ing. with shallow resp. and irregular pulse. Alpha-lobelin and epinephrine had no effect. Rx.- Gastric lavage (had to be stopped because of cyanosis) Vinyl ether controlled conv. temporarily but cyanosis developed. Oxygen increased convulsions. Caffeine Na Benz. gr. 2 1/2 hypo. and Na Phenobarbitol had no effect. 5% Dextrose by clysis; 100 mg. Na Pentothal I.V. caused some relaxation.	Epicardial petechial hemorrhages; lung edema and congestion; cerebral edema; passive congestion of liver and kidneys.
2 7/12	Benadryl (Diphenhydramine hydrochloride) (?)	In 2 1/2 hr. began to roll eyes and wave arms. Developed convulsions and cyanosis. Death 4 hr. after ingestion. Rx.- Gastric lavage and oxygen.	Cloudy swelling of liver; Congestion of spleen; Hemorrhagic areas in lungs.

Below is the description of a recent case of death from antihistamine poisoning.

PI: This 3 year old white female entered hospital at 4:00 p.m. via the rescue squad in a generalized convulsive seizure. The patient had been well until 1:45 p.m. the day of admission when she vomited once and complained of pain behind the ears. She was put to bed, found at 2:15 p.m. in a convulsive seizure (generalized). She was immediately taken to the office of the attending physician in partial decerebrate attitude.

TABLE II CONT'D

At the office the patient continued to convulse, developed laryngeal spasm, apnea, cyanosis. She was given artificial respiration and adrenalin until the rescue squad arrived. Patient given oxygen by rescue squad and brought to the hospital. That evening the parents discovered 10-15 candy-coated antihistamine tablets containing Antazoline and Tripelennamine had been removed from a bottle to which the patient had access. They estimated that it must have happened around noon that day.

PX: Well developed, well nourished white female in spasmodic generalized tonic seizures alternating with bizzare flailing and athetoid movements of the body and all extremeties. Pupils were widely dilated, eyes roving. Laryngeal strider was marked. Color was dusky. She required frequent suctioning of mucous and saliva from the airway and was given oxygen by mask continually. Heart rate was rapid, lungs clear.

Lab: 8/24/53, CSF: clear, 1 wbc, 75.5 mgm% sugar; protein 20 mgm%, culture negative. Blood sugar: 236 mgm%.
CBC: 2800 wbc, 65 segs, 10 staff, 21 lymphs, 4 juveniles, 5.05 rbc, 13 gm hemoglobin. Sed rate, 10 mm.
8/25/53, Blood calcium 11.4 mgm%, blood potassium 5.3 mgm%.
X-ray, 8/24, diffuse bilateral pulmonary edema.

Course: Patient was given continuous oxygen and 40 cc. of glucose 35% in 1/3 normal saline I.V. on admission. In the first hour the patient received 2½ gr. Na. luminal with no effect on the convulsive seizures. Six c.c. paraldehyde was given rectally which quieted the child.

The patient was given 10% Glucose in ½ strength lactate ringers, 10 drops per minute IV steady drip. 50 cc. of glucose 35% in 1/3 normal saline was given by push IV every 4-6 hours. The patient was supported with repeated aqueous adrenal extract IV and received penicillin, streptomycin, vitamin K. In the evening of admission, moist rales were heard over both lung fields and x-ray showed pulmonary edema. Lungs were clear the following a.m.

TABLE II CONT'D

Temperature three hours after admission was 104.4, resp. 42. Heart rate varied between 120-140. Temp. was gradually reduced to 100.8; the following morning, it rose again to 102.4. The patient sobbed and moaned incohorently much of the night and the following morning but never became aware or responsive. Blood pressure was maintained at 110/120/70/99, in the leg; 80/50 in the arm. By noon of the day following admission, heart rate dropped to 80-100. At 2:00 p.m. the patient suddenly stiffened in generalized tonic contracture. Respirations became more labored, color more cyanotic. Breathing suddenly ceased. Chest respirator and stimulants were administered to no avail. Patient pronounced dead at 2:30 p.m.

TABLE III

10,45-51

NONFATAL EXCESSIVE INGESTION OF ANTIHISTAMINIC DRUGS

Case 1.
1 and 1/6 yr. old child swallowed 4 to 5 times the normal daily dose of Pyribenzamine (Tripelennamine hydrochloride). Two hours after ingestion vomiting, convulsions, disturbances of the equilibrium, slow pupil reaction, strabismus and tachycardia were present. Gastric lavage and cardiotonics were used. Five to six hours after ingestion, abundant sweating appeared. Symptoms slowly disappeared in 5 days.

Case 2.
1 and 1/2 yr. old boy, wt. 22 lb., swallowed 150 to 250 mg. of Benadryl (Diphenhydramine hydrochloride). Restlessness, cyanosis and convulsions 1/2 hr. after ingestion. Pupils dilated, non-reactive to light, bilateral nystagmus. Treatment was gastric lavage with instillation of 6 cc. Magnesium Sulfate, 10 cc. Elixir of Phenobarbitol, and 75 mg. Sodium Amytal I.V. Patient recovered in 24 hours.

Case 3.
1 and 1/2 yr. old girl swallowed 200 to 300 mg. of Benadryl (Diphenhydramine hydrochloride). Six hours after ingestion was admitted to hospital with jerky movements of head and extremities. Also showed incoordination. Pt. fell asleep in 14 hr. Recovered in 24 hr. Caffeine was given hypodermically during the sleep period.

Case 4.
1 and 2/3 yr. old boy swallowed 800 mg. of Thenylene (Methapyrilene hydrochloride). One hour after ingestion child was drowsy. Given milk and castor oil. In a few minutes began convulsing, appeared markedly cyanotic, and was unconscious. Pupils fixed and dilated. Neck stiff; marked tachycardia. Chest clear and abdomen soft. Blood count and Ua. normal.

Rx. 1. Gastric lavage
2. Oxygen and 21/2% glucose per clysis.
3. 1/2 gr. Na Phenobarbitol by hypo. and soapsuds enema two hours after ingestion.
4. At 3 hours, 1/4 gr. Phenobarbitol by hypo. Convulsions continued.
5. At four hours, mixture of Na Bromide gr. 10 and Chloral Hydrate gr. 5 given per rectum. Convulsions decreased and respirations became slower.

TABLE III CONT'D

6. At five hours 1/2 ampule of Caffeine Na Benzoate given by hypo because of slow respirations.

Child was completely recovered in 24 hours.

Case 5.
2 year old girl swallowed 100 mg. of Tripelennamine. Vomited few hours after ingestion. Became weak and unable to stand, even with support; would continually fall to right side. Unsustained coarse horizontal nystagmus, pupils dilated, and reacted sluggishly to light. Deep tendon reflexes were hypoactive. CBC normal. Ua. showed strong positive reaction to acetone. Cerebrospinal fluid exam was normal. Child given several injections of Caffeine Na Benzoate over 24 to 36 hr. period for lethargy without appreciable effect. After the second day child gradually improved. By sixth day child completely recovered.

Case 6.
2 and 1/2 year old girl swallowed 850 mg. of Diphenhydramine hydrochloride. About 1 and 1/2 hr. after ingestion child was drowsy and listless. Became disoriented and walked with a staggering, awkward gait. Began having generalized clonic convulsions. Gastric lavage 5 hours after ingestion. Then treated with fluids I.V., Na Phenobarbitol subcut. (160 mg. over 6 to 8 hr.) and oxygen. There were recurrent generalized convulsions for 8 hr. Face flushed, pupils dilated and nearly fixed. Between seizures, child cried out and talked in a rambling manner. Also showed hyperextension of trunk and involuntary movements of extremities. Normal the following day.

Case 7.
2 and 1/2 yr. old girl swallowed about 500 mg. of Diphenhydramine hydrochloride. One hour after ingestion the child became disoriented and ataxic. Gastric lavage at this time. Developed hallucinations, muscular twitchings, hyperreflexia and intermittent tremors. Na Phenobarb. gr. 2 1/2 given by hypo over a period of 3 hours. Pupils dilated and fixed. Pulse of 165. Temp. rectally of 99.8 F. B.P. of 76/48. Three hours after ingestion child fell into restless sleep which lasted for five hours. Dextrose sol. given parenterally. Thirty hours after ingestion child was talkative but normal otherwise and gradually improved.

Case 8.
2 and 2/3 year old child swallowed 450 mg. of Diphenhydramine hydrochloride. Some time after ingestion a state of excitation was observed. Phenobarbitol given and baby well next day.

TABLE III CONT'D

Case 9.

3 year old girl, wt. 30 lb., swallowed 700 to 800 mg. of Benadryl (Diphenhydramine hydrochloride). Became hypomaniac, had dilated pupils, muscular twitchings and generalized convulsions which alternated with periods of depression. Respiratory collapse recurred several times and required artificial respiration. Histamine, 3 mg. I.M. increased the excitement and caused asthmatic breathing, necessitating adrenaline. Convulsions eventually controlled with 30 cc. of 50% ether in olive oil rectally. The following day she seemed quite well except for ataxia, drowsiness and slight fever. Ataxia disappeared in 4 days. She reverted to baby talk shortly after leaving hospital but this gradually was replaced after 3 weeks. No sequelae.

Case 10.

3 and 1/2 year old boy, wt. 33 lb., swallowed 100 mg. for 2 days and 200 mg. on 3rd day of Diphenhydramine hydrochloride. He developed epileptiform movements. Complete recovery after withdrawal of drug.

Case 11.

4 year old boy, wt. 36 lb., swallowed 175 mg. of Diphenpyridamine. Flushing of skin and fever of 102 F. in 3 hours. Became irrational, delirious, and disoriented. Pupils dilated. Fluids forced. 10 drops of Phenobarbitol elixir every 4 hour for nervous symptoms. Voided 18 hours after ingestion and was much improved. Recovery complete the next day.

TREATMENT

A therapeutic regimen for antihistamine poisoning should begin with a word about prophylaxis.[52] Parents should be informed as to the hazards of these agents and the nature of possible toxic symptoms. They should be stopped with the onset of minor side effects. The dosage should always be adjusted to the patient's medical needs rather than be rigidly fixed. These drugs should be prescribed in small amounts so as to limit their availability to the child and adult when no longer needed. The attractiveness of the medication as well as the pleasant taste of the elixir of syrup may act as a lure and hence should be stored in a safe place.

Since no specific antidote has been found for antihistamine poisoning, treatment must be symptomatic.[53,54,59] If antihistamine poisoning is suspected the drug should be removed from the gastrointestinal tract as soon as possible. The latent period before toxic manifestations has been reported to be as short as 10 minutes. A few cases were reported where the child had been seen by a physician after ingestion of the drug and since the child was asymptomatic he was dismissed without treatment. A few hours later the patients suddenly developed convulsions and died.

GASTRIC LAVAGE

Emetics are not recommended due to the danger of aspiration. The procedure of choice is gastric lavage. Use a large tube. A Levin tube is not sufficient, for the flow is too slow. A stomach pump or a large Crump tube is satisfactory but an enema tube may be used if neither is available. It is desirable to have the patient lying on his left side with head hanging over the edge of the bed with the face down. This precaution may prevent aspiration in the event of reflex vomiting with the passage of the tube. Make sure that the tube is in the stomach and then wash the stomach with any readily available material such as tap water which may be poured down through the funnel a pint at a time. The patient is then swung on his back, sloshing the water around in the stomach, and the fluid is then removed by siponing or with the pump. This procedure may be repeated at least six times or continued until the return is clear.[55] In a few cases the gastric lavage had to be discontinued because of severe convulsions and cyanosis. One physician had difficulty aspirating because the lavage tube was too small and continually became plugged up with food particles. It is well to have a bronchoscope available during this procedure in case of aspiration of foreign material into the airways.

If no equipment is available for lavage, milk or eggs can be given as diluting agents, hence slowing the rate of absorption

of the drug. The universal antidote consisting of the following may be given:

1. Pulverized Charcoal (burnt toast) 2 parts
2. Tannic Acid (strong tea) 1 part
3. Magnesium hydroxide (milk of magnesia) 1 part

CONVULSIONS

Many of these children are not seen until they develop convulsions. The convulsions from antihistamines agents are notoriously resistant to treatment. A few children survived convulsant reactions with little or no treatment. Others with mild seizures have been treated successfully with small doses of sedatives and hypnotics. Secobartial (Seconal) and Phenobarbital have been used effectively. Magnesium sulfate, oral administration of phenobarbitol and intravenous infections of amobarbital proved efficacious in saving one infant with severe convulsions. Duerfeldt employed dihydromorphinone (dilaudid) with partial success but finally resorted to the rectal administration of ether to gain control. Snyderman utilized phenobarbital, sodium bromide and chloral hydrate in the successful treatment of a 20 month old infant with convulsions from Methapyriline. It appears that with very large doses of antihistamines the mere control of convulsions is not effective in preventing death, which often occurs from deepening coma despite the administration of stimulants. In a

2 year old child suffering from convulsions, coma and cyanosis as a result of diphenhydramine ingestion, Davis and Hunt found that thiopental produced relaxation, with return of pupils to normal, without any real improvement in the patient's condition. It has been shown that pretreatment of rats with barbiturates will prevent convulsions from diphenhydramine, but will not alter the subsequent mortality rate of toxic doses of that drug. The use of barbiturates to control the convulsions is not advised because:

1. They are respiratory depressants.
2. Winter[15] has demonstrated that several antihistamines prolong the depression caused by barbiturates in animals.

Narcotics should also not be used because of the attendant respiratory depression. The convulsions are best controlled with ether. This may either be given by rectal instillation with oil ($\frac{1}{2}$ to 1 cc. per kilo of a 50% solution) or by mask. In a few cases the convulsions failed to cease even after the use of ether. One report stated that the child developed cyanosis when the convulsions were controlled by ether. In such a case an initial dose of 4 to 5 cc. of paraldehyde rectally should be tried and the patient be given oxygen by mask. Convulsions were controlled in a few cases with Chloral Hydrate.

RESPIRATION [56]

In the treatment of any poisoning it is essential to keep the air passages free, so that the patient can inhale and exhale freely. The children poisoned with antihistamines frequently developed respiratory depression and cyanosis. The mouth and nostrils should be cleansed and the patient placed in the prone position to facilitate drainage of fluid from the respiratory passages. The head should be extended and turned to one side. In this position the tongue and jaw fall forward from the posterior pharynx. If a free airway is not obtained by these means the tongue should be grasped and pulled forward. A pharyngeal airway may be inserted to keep the base of the tongue away from the hypopharynx. A No. 3 is suitable for children and a No. 1 for infants. Should the masseter muscles be in spasm, obstruction to the airway may be relieved by passage of a large bore rubber catheter through one of the nares to the hypopharynx.

Artificial respiration should be started by one of the accepted methods; no time may be wasted. Drinker [57] says there is only a 25 per cent chance for recovery if 5 minutes have elapsed between the cessation of breathing and the institution of competent artificial respiration. If 12 minutes have elapsed, there is practically no chance of recovery. Wyngaarden and Seevers produced death in the Macacus rhesus monkeys by injecting anti-

histamines subcutaneously in 5 to 10 per cent solutions. Early death resulted from convulsions or, if these were survived, from postconvulsive respiratory depression. In all cases of death the heart was noted to beat some minutes after respiration had ceased.[10]

Oxygen, to combat the acute asphyxial emergencies, is desirable but is not essential and no time should be lost in the treatment by waiting for it. The patient should be removed when possible to a hospital or emergency center where artificial respiration can, if necessary, be continued by mechanical means. Artificial respiration must continue as long as there is evidence of cardiac activity, determined preferably by means of the electrocardiogram. It may be stopped when spontaneous respiration is resumed.

Pulmonary edema is a frequent complication in antihistamine poisoning. The use of ethyl alcohol in the oxygen humidifying apparatus reduces frothing of the sputum and so improves ventilation. Ethanol 95% may be used in the humidifier for a nasal catheter; 30 to 40% ethanol for the mask.

It should be pointed out that in pulmonary edema the heart has to be watched very carefully because it has to perform an increased amount of work on account of the increased resistance in the small cycle and the greater viscosity of the blood under

unfavorable conditions, namely, lack of oxygen resulting from the inadequate oxygenation of the blood in the lungs. The administration of saline or glucose solution is contraindicated because it will not decrease the visosity of the blood, but may increase the pulmonary edema, and thus may contribute to the fatal outcome. Following recovery from the acute effects the patient should be watched closely for some time because late pneumonia may develop.

COMA or STUPOR [53]

Following convulsions the patients usually develop coma or stupor. Nikethamide U.S.P. (Coramine) and Metrazol are contraindicated in the treatment of antihistamine depression because their stimulant doses are rather close to their convulsant doses. Drugs of choice are Amphetamine sulfate, 5-10 mg. I.M. or I.V., and repeated at frequent intervals depending upon the response and age of the patient. Caution should be used since convulsions may be precipitated with overdosage. Another stimulant is Caffeine U.S.P. Caffeine may be given intramuscularly in large doses of 10 mg. of the caffeine sodium benzoate preparation per kg. of body weight. These doses may be repeated every 30 or 60 minutes until distinct signs of improved respiration appear. Caffeine seldom causes secondary depression.

CARDIOVASCULAR STIMULANTS [53]

Digitalis was not used in any of the cases as a cardiac stimulant. In cases of severe toxicity, most of these patients are in a shocklike state. Digitalis, ephedrine, and epinephrine are contraindicated in cases of shock. The circulation can only be restored to normal if an adequate blood volume is maintained over a period of time sufficient to relieve tissue anoxia and allow restoration of capillary tone.

OLIGURIA and ANURIA [53]

Renal shut-down has occurred in a few cases of antihistamine poisoning. In one case the patient had anuria for less then 24 hours probably because of the spasmogenic effect of the antihistamines. Another died in 15 hours with uremia. The general treatment suggested is divided into three stages: (a) the treatment of the immediate emergency; (b) the treatment of the period of oliguria and anuria; and (c) the treatment of the period of diuresis and convalescence. The patient should be placed on a regimen of restricted fluid intake with daily intake and output recorded. Careful control of fluid during the oliguric phase in order to avoid pulmonary edema is recommended. In the third or diuretic phase, dehydration and negative electrolyte balance may occur suddenly. The fluid and electrolyte requirements of a patient should be carefully followed and satisfied at all times.

The guiding therapeutic principle during the period of oliguria and anuria is to prolong the patient's life long enough for tubular regeneration to occur and for diuresis to develop.

HYPERTHERMIA [59]

Hyperthermia has been mentioned as occurring occasionally with antihistaminic poisoning. It is important to recognize that in and of itself hyperthermia may kill the patient. Measures used to reduce the fever should include water and alcohol sponging. If these are not successful the colonic instillation of cool water must be instituted. Should these measures fail, final resort must be made to ice packs, the patient being wrapped in wet sheets.

SHOCK [53,54,59]

The general principles which govern the treatment of shock in antihistamine poisoning do not differ from those in shock resulting from other causes. Untreated shock will eventually enter a stage of irreversibility from which recovery is impossible. Death occurs from a variety of causes such as escape of plasma, renal failure, pulmonary edema, myocardial insufficiency or respiratory failure. In no type of shock is there depletion of only one of the elements of the circulating blood alone. To restore the circulating blood volume, plasma and blood transfusions are desirable. These should be administered cautiously however, due to danger of overloading the heart. It is difficult to evaluate

the effect of hypertonic glucose solutions. These solutions produce only a transient dehydrating effects. Saline and glucose solutions should be given with care or possibly not at all in the early stages of poisoning due to the danger of pulmonary edema. Therapy will require repeated revision according to the response of the patient.

SUMMARY

The public has consumed tremendous quantities of antihistamine drugs since the first clinical compound was marketed in 1942. Numerous cases of toxicity and death have resulted from this drug. Side reactions with therapeutic doses of the drug have ranged from 10 to more than 63%. The side reactions most frequent are neuropsychiatric and can usually be controlled by reducing the dosage, discontinuing the drug, or resorting to a different compound. Most cases of poisoning with antihistamines in children result from accidental ingestion of large doses, although relatively small doses have caused death.

Both stimulation and depression of the central nervous system can occur. Children are more susceptible to the convulsant action of the antihistamines. The exact mechanism of intoxication with antihistamines is unknown. Usually the first sign of poisoning in a child is hyperexciteability followed by convulsions. The child then goes into coma with respiratory depression and cyanosis. Death usually results from deepening coma and cardiorespiratory collapse.

In those children who recover, no sequelae of a permanent nature have been observed. Antopsy findings showed anoxic changes with pulmonary and cerebral edema being most prominent.

Numerous attempts to find a specific antidote for antihistamine poisoning have been made but so far none have been successful. The treatment is entirely symptomatic. Therapy is as follows:

1. Gastric lavage as soon as possible.
2. Convulsions are best controlled with ether. Paraldehyde or Chloral Hydrate may also be tried.
3. For coma and respiratory depression, the treatment is artificial respiration, oxygen, amphetamine sulfate, caffeine, or ephedrine sulfate.
4. If hyperthermia develops, active measures to reduce the fever should be instituted.
5. The patient should be watched constantly, preferably by a physician. The critical period is usually the first 24 hours.

CONCLUSIONS

Several cases of toxicity and death in children have resulted from antihistamine drugs. Usually the toxicity is due to accidental ingestion of large doses of the drug.

Most of the cases reviewed developed convulsions followed by coma with respiratory depression and cyanosis. Autopsy findings showed anoxic changes with pulmonary and cerebral edema being most prominent. No permanent sequelae were observed in those children who recovered.

The dosage of these drugs should be carefully controlled. Agranulocytosis, hemolytic anemia, dermatoses are but a few of the toxic effects resulting from prolonged administration. Parents should be warned about the signs of toxicity and be instructed to discontinue the drug if any appear.

Treatment of acute antihistaminic intoxication is entirely symptomatic. The first 24 hours is the most critical time and patient should be watched closely during this period.

PROPRIETARY ANTIHISTAMINIC PREPARATIONS

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Antistine (Antazoline hydrochloride)	Ciba	Antistine	Tablet	100 mg.
		Antistine	Ophthalmic solution	0.5%
		Antistine-Privine	Nasal solution	0.5% plus 0.025% Privine HCL
Benadryl (Diphenhydramine hydrochloride)	Parke, Davis	Kapseals Benadryl	Capsule	50 mg.
		Benadryl	Capsule	25 mg.
		Benadryl Emplets	Enteric-coated tablet	50 mg.
		Steri-vial Benadryl	Injectable	10 mg./ml.
		Elixir Benadryl	Liquid	10 mg./4 ml., 14% alcohol
		Benadryl Cream	Ointment	2%
		Benylin Expectorant	Liquid	each oz.= 80mg. plus 12 gr. ammonium chloride plus 5 gr. sodium citrate plus 2 gr. chloroform plus 1/10 gr. menthol, 5% alcohol
		Caladryl *	Lotion	1% in calamine
	G.D. Searle	Hydryllin	Tablet	25 mg. plus 100 mg. aminophylline
		Hydryllin with Racephedrine	Tablet	25 mg. plus 100 mg. aminophylline plus 25 mg. racephedrine HCL
		Hydryllin Compound	Liquid	4 ml. = 6.25 mg. plus 25 mg. aminophylline plus 15 mg. potassium iodide plus 8 mg. chloroform plus 2.8 Gm. sugar, 2.5% alcohol
		Hydryllin Elixir	Liquid	4 ml. = 12.5 mg. plus 50 mg. aminophylline, 19% alcohol

Drugs with * do not require prescription.

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Benadryl cont'd (Diphenhydramine 8-chlorotheophyllinate; Dimenhydrinate		Dramamine	Tablet	50 mg.
		Dramamine	Liquid	4 ml.-12.5 mg., 5% alcohol
Chlorcyclizine hydrochloride	Abbott	Di-Paralene	Tablet	25 and 50 mg.
	Burroughs Wellcome	Perazil	Tablet	50 mg.
Chlorothen citrate	George A. Breon	Fernoxydyne	Tablet	25 mg. plus 320 mg. acetohenetidin plus 32 mg. caffeine
	Lederle	Tagathen	Tablet	25 mg.
	Whittier	Chlorothen	Tablet	25 mg.
		Caubren Compound	Tablet	25 mg. plus 320 mg. acetophenetidin plus 32 mg. caffeine
Chlor-Trimeton (Chlorprophenpyridamine maleate)	Schering	Chlor-Trimeton	Tablet	4 mg.
		Coricidin	Tablet	2 mg. plus 3½gr. aspirin plus 2½ gr. acetophenetidin plus ½ gr. caffeine
Decapryn (Doxylamine succinate)	Wm. S. Merrell	Decapryn	Tablet	12.5 and 25 mg.
		Decapryn	Liquid	5 ml. = 6.25 mg.
		Decapryn with APC	Tablet	6 mg. plus 230 mg. aspirin plus 150 mg. acetophenetidin plus 30 mg. caffeine
		Decapryn Compound	Liquid	5 mgl. = 6 mg. plus 300 mg. sodium salicylate plus 15 mg. caffeine
		Decapryn Minergic	Injectable	5 mg./ml.
		Mercodol with Decapryn	Liquid	30 ml. - 36 mg. plus 10 mg. dihydrocodeinone bitartrate plus 100 mg. methylethylamino-phenylpanol HCL (Nethamine plus 1.2 Gm. sodium citrate

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Decapryn (cont'd) (Doxylamine succinate)		Nethaprin	Liquid(also Capsule)	5 ml. = 6 mg. plus 25 mg. methylethylamino-phenyl-propanol HCL (Nethamine) plus 60 mg. theophylline aminoisobutanol
Diatrin (N,N-dimethyl-N'-phenyl-N'-(2-thienylmethyl)-ethylenediamine monohydrochloride)	Wm. R.	Diatrin	Tablet	50 mg.
Dramamine (see Banadryl)				
Histadyl (Thenylpyramine hydrochloride)	Abbott	Thenylene	Tablet	25,50 and 100 mg.
		Thenylfred	Tablet	50 mg. plus 25 mg. ephedrine HCL
		Thenylene & Desoxyn	Tablet	50 mg. plus 2.5 mg. desoxyephedrine HCL
		Thenylene Cream	Ointment	2%
		Thenylene-APC	Capsule	25 mg. plus 230 mg. aspirin plus 150 mg. acetophenetidin plus 30 mg. caffeine
	Blue Line Chemical	Methapyrilene hydrochloride	Tablet	50 mg.
	Chilcott(Maltine Co.)	Pentryl	Tablet	50 mg. plus 16 mg. ephedrine HCL plus 16 mg. pentobarbital sodium
		Pentryl	Enteric-coated tablet	50 mg. plus 16 mg. ephedrine HCL plus 16 mg. pentobarbital sodium
	Cole Chemical	Histafed	Capsule	25 mg. plus 8 mg. ephedrine HCL plus 10 mg. ascorbic acid

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Histadyl	Eli Lilly	Pulvules Histadyl	Capsule	25, 50 and 100 mg.
		Histadyl	Injectable	20 mg./ml.
		Cream * Histadyl	Ointment	2%
		Cream * Histadyl-Surfacaine *	Ointment	2% plus 0.5% surfacaine (cyclomethycaine)
		Enseals Histadyl	Enteric-coated tablet	50 mg.
		Histadyl	Ophthalmic ointment	0.5%
		Pulvules Histadyl-ASA Compound	Tablet	25 mg. plus 3½ gr. aspirin plus 2½ gr. acetophenetidin plus ½ gr. caffeine
		Pulvules Histadyl-Ephedrine HCL	Tablet	25 mg. plus 8 mg. ephedrine HCL; 50 mg. plus 16 mg. ephedrine HCL
		Solution Histadyl	Liquid	0.5%
		Histadyl	Liquid	4 mg./ml.
		Histadyl Compound-Ephedrine and Codeine	Liquid	each oz.= 80 mg. plus 1 gr. codeine plus ½ gr. ephedrine
		Histadyl-Surfacaine	Lotion	2% plus .5% Surfacaine (cyclomethycaine)
		Hista-Clop-ane Pulvules	Capsule	25 mg. plus 12.5 mg. cyclo-pentamine
	Flint, Eaton	Pyrathyn	Capsule	50 mg.
		Capathyn	Tablet	20 mg. plus 230 mg. aspirin plus 150 mg. acetophenetidin plus 30 mg. caffeine
		Pyracol	Liquid	each oz. - 160 mg. plus 778 mg. ammonium chloride plus 648 mg. citric acid plus 130 mg. chloroform plus 6 mg. menthol.

Drugs with * do not require prescription

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Histadyl (cont'd)	Mc Neil	Methozylene	Tablet	50 mg. plus 2.5 mg. racemic desoxyephedrine HCL 25 mg. plus 7.5 mg. extract belladonna plus 1.25 racemic desoxyephedrine HCL
	S.E. Massengill	Semikon	Tablet	50 mg.
		Semikon	Enteric-coated tablet	
		Dasikon	Capsule	25 mg. plus 30 mg. caffeine plus 200 mg. aspirin plus 120 mg. acetophenetidin plus 0.06 mg. atropine sulfate
Histadyl		Sedacof Expectorant	Liquid	5 ml. = 15 mg. plus 200 mg. sodium citrate plus 100 mg. ammonium chloride plus 10 mg. ephedrine HCL plus 1 mg. antimony potassium tartrate plus aromotics qs.
	Pitman-Moore	Cohistine	Tablet	25 mg. plus 225 mg. aspirin plus 160 mg. acetophenetidin plus 1 mg. dextroamphetamine sulfate
	Sharp & Dohme	Proketal Compound	Capsule	25 mg. plus 230 mg. aspirin plus 150 mg. acetophenetidin plus 30 mg. caffeine
		Proketal Compound with Codeine	Capsule	25 mg. plus 230 mg. aspirin plus 150 mg. acetophenetidin plus 30 mg. caffeine plus 15 mg. codeine phosphate
	Smith, Kline & French	Nuclon	Capsule	37.5 mg. thenylpyramine fumarate (- 25 mg. of the HCL) plus 1.25 mg. dextroamphetamine sulate plus 2½ gr. aspirin

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Histadyl (cont'd)	Asthmanefrin Company	AhistoA	Tablet	25 mg.
	Grove Laboratories	Antomine	Tablet	25 mg. plus acetophenitidin 1 7/8 gr. plus caffeine plus Quinine H 6r 3/8 gr.
Neo-Antergan (Pyranisamine maleate)	Buffington's	Paraminyl Maleate	Tablet	50 mg.
		Dolopar	Tablet	32 mg. plus 225 mg. aspirin plus 162 mg. acetophenetidin plus 15 mg. caffeine plus 1 minum tinct gelsemium
	Otis Clapp	Pyranisamine Maleate	Tablet	25 mg.
	Columbus	Pyramal	Tablet	50 mg.
		Pyrasal	Tablet	25 mg. plus 325 mg. aspirin plus 16 mg. caffeine
	Direct Sales	Pyranisamine Maleate	Tablet	25 and 50 mg.
	Merck	Neo-Antergan	Tablet	25 and 50 mg.
	Premo	Pyranisamine Maleate	Tablet	50 mg.
		Neo-Cafotan	Tablet	1/4 gr. plus 1/2 gr. caffeine plus 2 1/2 gr. acetophenetidin plus 3 1/2 gr. aspirin
	Professional Drug Service	Neomine	Tablet	25 mg.
		Acetomine	Tablet	25 mg. plus 3 1/2 gr. aspirin plus 2 1/2 gr. acetophenetidin plus 1/2 gr. caffeine

Drugs with * do not require prescription

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Neo-Antergan (cont'd) (Pyranisamine maleate)	Rexall	Pyranisamine Maleate *	Tablet	25 and 50 mg.
		Monhiston with APC*	Tablet	25 mg. plus 2 1/2 gr. acetophenetidin plus 3 1/2 gr. aspirin plus 1/2 gr. caffeine
	William H. Rorer	Thylogen	Tablet	25 and 50 mg.
Neo-Antergan	Smith-Dorsey	Pyranisamine Maleate	Tablet	50 mg.
		PPA Capsule	Capsule	25 mg. plus 1 gr. acetophenetisin plus 5 gr. aspirin
		Pye Capsule	Capsule	50 mg. plus 10 mg. ephedrine sulfate
		Antopic Cream	Ointment	5% plus calamine plus zinc oxide plus benzocaine
	R.J. Strasenburgh	Renstamine	Tablet	25 mg. plus 2.5 mg. amphetamine phosphate
		Renstamine	Liquid	5 ml. = 10 mg. plus 1 mg. amphetamine phosphate
	Van Pelt & Brown	Pyra-Maleate	Tablet	25 and 50 mg.
	Vitamix	Dexa-pyramine	Capsule	25 mg. plus 2 mg. dextro-amphetamine HCL plus 2 1/2 gr. aspirin plus 1/4 gr. caffeine plus 2 1/2 gr. acetophenetidin
		Dexa-pyramine	Injectable	each ml. = 25 mg. plus 2 mg. dextro-amphetamine HCL plus 0.3% phenol plus dist. water qs.
	Walker Vitamin	Histacin	Capsule	20 mg. plus 180 mg. aspirin plus 120 mg. acetophenetidin plus 60 mg. caffeine plus 30 mg. ascorbic acid.

Drugs with * do not require prescription

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Neo-Antergan (cont'd) Pyranisamine 8-bromtheophyllinate; Pyrabrom	E.L. Patch	Glybrom	Tablet	50 mg.
	Anahist Company	Anahist*	Tablet	25 mg.
		Anahist nasal spray	Liquid	1%
		Histo-Plus	Ointment	25 mg. plus Aspirin 2.5 gr. plus Phenocetin 2.5 gr. plus Caffeine 0.5 gr.
Neohetramine (Thonzylamine hydrochloride)	Wyeth	Neohetra-* mine	Tablet	25, 50 and 100 mg.
		Neohetra-* mine	Liquid	6/25/ mg/ml.
		Neohetra-* mine Cream	Ointment	2%
Pyribenzamine (Tripelennamine hydrochloride)	Ciba	Pyribenza-mine	Tablet	50 mg.
		Pyribenza-mine	Enteric-coated	50 mg.
		Pyribenza-mine Elixir	Liquid	7.5 mg. (citrate)/ ml.
		Pyribenza-mine Ointment*	Ointment	2% (Petrolatum base)
		Pyribenza-mine Cream	Ointment	2% (water-washable base)
		Pyribenza-mine Ephedrine	Tablet	25 mg. plus 12 mg. ephedrine sulfate
		Pyribenza-mine Expector-and with Ephedrine	Liquid	each 4 ml. - 30 mg.(citrate plus 10 mg. ephedrine sulfate plus 80 mg. ammonium chloride

Drugs with " do not require prescription

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Pyribenzamine (Tripelennamine hydrochloride)	Ciba	Pyribenzamine	Nasal Solution	0.5%
		Pyribenzamine	Injectable	25 mg./ml.
		Pyribenzamine	Nebulizer	0.5%
		Pyrrolazote	Tablet	50 mg.
Pyrrolazote	Upjohn	Pyrrolazote	Liquid	each ml. - 2.5 mg. plus 10% alcohol plus tolu balsam, glycerin and aromatics
Pyrrolazote		Pyrrolazote	Laminated Tablet	50 mg. (enteric-coated 25 mg. core)
		Pyrroxate	Capsule	12.5 mg. plus 25 mg. Orthoxine plus 2 1/2 gr. acetophenetidin plus 3 1/2 gr. aspirin plus 1/2 gr. caffeine
Tagathen (see Chlorothen)				
Thenfadil (N,N-dimethyl-N'-(3-thenyl)-N'-(2-pyridyl) ethylenediamine hydrochloride)	Winthrop-Stearns	Neo-Synephrine Thenfadil	Nasal Solution	0.1% plus 0.25% Neo-Synephrine
Thenylene (see Histadyl)				
(Methapyrilene hydrochloride)				
Thephorin (Phenindamine tartrate)	Hoffmann-La Roche	Thephorin	Tablet	25 mg.
		Thephorin	Liquid	10 mg./4 ml.
		Thephorin	Ointment	5% in carbowax base
		Thephorin	Lotion	5%
		Thephorin-AC*	Tablet	10 mg. plus 160 mg.aspirin plus 160 mg. acetophenetidin plus 15 mg. caffeine

Drugs with * do not require prescription

PROPRIETARY ANTIHISTAMINIC PREPARATIONS CONT'D

ANTIHISTAMINE	PHARMACEUTICAL COMPANY	TRADE NAME	DISPENSED AS	INGREDIENTS
Thephorin (Phenindamine tartrate	Hoffmann-La Roche	Thephorin Expectorant	Liquid	4 mg. = 10 mg. plus 4 mg. codeine phosphate plus 4 mg. papaverine hydrochloride plus 50 mg. ammonium chloride plus 0.016 ml. chloroform
		Thephorin	Injectable	12.5 mg./ml.
Trimeton (Prophenpyridamine)	Organon	Cehistra	Effervescent Tablet	10 mg. (maleate) plus 100 mg. ascorbic acid plus 320 mg. aspirin plus 1,820 mg. sodium bicarbonate, calcium hydroxide, citric acid
	Schering	Trimeton	Tablet	25 mg.
		Trimeton Maleate Elixir	Liquid	4 ml. - 7.5 mg., 7% alcohol
		Trimeton Maleate Cream	Ointment	3%
Thenylpyramine HCL	Miles Laboratories	Tabcin	Tablet	25 mg. plus caffeine 30 mg. plus na Salicylate 200 mg. plus Acetophenetidin 150 mg.
1-phenyl-1-(2-pyridyl)-3 dimethylamino propane maleate	Union Pharmaceutical Co.	Inhiston APC	Tablet	10 mg. plus aspirin 3.5 gr. plus caffeine 0.5 gr. plus Acetophenetidin 1.5 gr.

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