ANTIHISTAMINES IN TOPICAL PREPARATIONS

Antihistamines were introduced in France by Halpern in 1942 and in the United States at the end of World War II; they had been investigated extensively during the war for therapy of motion sickness. By the late 1940s, a mass of information on the structure activity relationship had accumulated and most major drug manufacturers had introduced antihistamines into the market for oral, parenteral, and topical administration. Topical use was efficacious in acute dermatitis because the local anesthetic activity of the drugs diminished pruritus.

The first reports of sensitization to the topical antihistamines, which began to appear in 1947, incriminated tripelennamine (Pyribenzamine), diphenhydramine (Benadryl), antazoline (Antistine), and pheniramine (Trimeton). In the ensuing 25 years, though thousands of instances of antihistamine contact dermatitis have occurred, many topical antihistamines remain on the market. The Committee is concerned about the use of topical antihistamines which are sold over the counter for use in such conditions as chickenpox and poison ivy. Table I lists most of the preparations currently available for topical use.

CLASSES OF ANTIHISTAMINES

The antihistamines are classified according to their chemical structure into five primary groups as shown in Table II. Each drug carries its own index of sensitization and other adverse effects when employed topically. The ethylenediamine derivatives include the following: antazoline phosphate (Antistine), promethazine hydrochloride (Phenergan*), and tripelennamine (Pyribenzamine). They are particularly active in inducing contact dermatitis and were responsible for the cases first reported. Ethylenediamine, because of its dibasic structure, is widely used in various organic syntheses for the preparation of dyes, inhibitors, rubber accelerators, fungicides, synthetic waxes, resins, insecticides, and asphalt-wetting agents. It is valuable for neutralizing the acidity of oils or controlling alkalinity. As ethylenediaminetetraacetic acid (EDTA), it is a ubiquitously used preservative in topical and systemic medications of all types. The induction of contact sensitivity to drugs of this class will result in a dermatitis on topical or oral readministration of agents of this class of antihistamines. The sensitized patient may also react to the oral or parenteral administration of aminophylline, which contains theophylline conjugated with ethylenediamine, as well as to contact with any of the many substances containing ethylenediamines.

The phenothiazines include drugs employed either as antihistamines or as psychotropic agents. Representative members of this group of compounds are given in Table II. Promethazine hydrochloride (Phenergan) is available as a topical prep-

* Phenergan is both an ethylenediamine and a phenothiazine derivative.

The statements presented herein do not preclude alternatives which may be more appropriate, taking into account local situations and all other relevant facts.

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Antihistamines are the worst topical offenders in the antihistamine group. Not only are they potent allergic contact sensitizers, but they may also evoke a photodermatic contact dermatitis. Photodermatitis, due to allergic contactants, is often characterized by persistence long after removal of the offending substance. Furthermore, since light of 360 nm wavelength and above is responsible, sunscreens and window glass offer no protection. This type of dermatitis can be debilitating for many years and may be activated by both incandescent and fluorescent light. Once topical sensitization to phenothiazines has occurred, systemic administration of any member of this class may elicit a severe dermatitis.

The ethanolamine compounds include diphenhydramine (Benadryl) and doxylamine succinate (Decapryn). While this group of substances has a lower sensitizing potential than the other two, the extensive use of topical diphenhydramine in the form of Caladryl Lotion or Ointment has resulted in frequent sensitization of children. Because the resulting dermatitis usually clears promptly on removal of the drug, cases are rarely reported.

Alkylamines and piperazine compounds capable of inducing a contact dermatitis include pheniramine (Trimetine), phenindamine (Theophorin), and pyrilamine (Neo-Antergan).

**COMMENT**

Recently, the National Academy of Sciences-National Research Council Drug Efficacy Study group evaluated a group of over the counter topical antihistamines. Based on their report, the Food and Drug Administration concluded that these drugs are ineffective for prophylaxis against dermatitis caused by poison ivy and other plants of the rhus genus. It further classified these drugs as “possibly effective” for other labeled indications for dermatologic use, placing the onus on the manufacturer to prove their efficacy. The American Medical Association has also recommended that topical antihistamines not be used because of their sensitizing potential.

The Committee on Drugs, on the basis of the foregoing evidence, urges pediatricians:

1. To discontinue the use of topical antihistamines.
thistamine preparations because their toxicity exceeds their limited benefit.

2. To discourage parents from purchasing over the counter topical antihistamines, especially Benadryl, Caladryl, Ziradryl, and Pyribenzamine for use in treating chickenpox, poison ivy, poison oak, and other types of dermatitis.

3. To keep in mind the frequency of contact dermatitis resulting from such agents in the evaluation of a dermatitis of unknown etiology. The Committee further urges that a warning about the sensitizing potential of these agents be placed on the label of these preparations.

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REFERENCES

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