ALLERGEN Focus

TRUE Test Allergen #11:

Ethylenediamine Dihydrochloride

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The thin-layer rapid-use epicutaneous (T.R.U.E.) test is a valuable first-line screening tool used by many dermatologists and allergists. Although the test focuses on common allergens, frequent questions have arisen from colleagues and patients as to where a specific allergen is derived or what products patients should avoid. With this in mind, this column was developed to provide educational information about the T.R.U.E. test allergens.

This month, the column explores T.R.U.E. test allergen #11: ethylenediamine dihydrochloride. Many antihistamines are derived from ethylenediamine, and this agent can still be found in many topical preparations today.

We will delve into the history of ethylenediamine and discuss its origins. It is linked to the advent of the discovery of histamines and the coining of the term "anaphylaxis".

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THE CONTACT DERMATITIDES

Allergic contact dermatitis (ACD) is an important disease with high impact both in terms of patient morbidity and economics. ACD represents a T helper cell Type 1 (Th1) dependent delayed-type (Type IV) hypersensitivity reaction. The instigating exogenous antigens are primarily small lipophilic chemicals (haptens) with a molecular weight less than 500 Da. On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated, which leads to the clinical picture of ACD

Irritant contact dermatitis, the most common form, accounts for approximately 80% of environmental-occupational based dermatoses.

Contact urticaria (wheal and flare reaction) represents an IgE and mast cell-mediated immediate-type hypersensitivity reaction that can lead to anaphylaxis, the foremost example of this being latex hypersensitivity. While this is beyond the scope of this section, we acknowledge this form of hypersensitivity due to the severity of the potential reactions and direct the reader to key sources.[1,2]

ACD affects more than 70 million Americans each year and has a high impact both in terms of patient morbidity and economics. The primary focus of this section is to highlight the educational component of this important inflammatory disorder.

CLINICAL ILLUSTRATION

A patient presented with a history of a contact dermatitis following the use of generic nystatin cream for intertrigo. Notably, his dermatitis worsened when he was treated with topical triamcinolone and hydroxyzine.

HISTORY OF HISTAMINE AND ROLE IN ALLERGY

In the late nineteenth century, during a scientific expedition, Charles Richet, a

physiologist from the University of Paris, along with Paul Portier, a French zoologist, and Prince Albert I of Monaco, decided to investigate which element from Portuguese man o' war jellyfish caused severe urticaria on contact with the species. Their mission was to develop an antiserum for divers and swimmers who may get stung by the jellyfish.[3]

Upon returning to France, to Richet and Portier's remiss they quickly ran out of their jellyfish extract, so as ingenuity would have it, the two scientists went on to complete their experiments using locally available sea anemone instead. While they did not identify the element, Richet happened on an important discovery; that with subsequent doses of the nontoxic extracts, he was able to induce serious — often lethal — reactions. He named this reaction *anaphylaxis* (c. 1902) to emphasize its direct contrast to prophylaxis or disease prevention.[4]

Around this same time, serum sickness was first described in patients treated with anti-toxin (horse serum) for diphtheria by Austrians,Von Pirquet and Schick (c. 1905). Furthermore, they also noted that some patients developed severe or fatal reactions with subsequent injections of the antitoxin.

Von Pirquet and Schick suggested that it was the first inoculation, in fact, that made the body hypersensitive to the second injection. They then concluded that serum sickness was the human equivalent of the anaphylaxis previously induced in laboratory animals. To mark their monumental observation, they coined this unusual phenomenon "allergy" from the Greek *allos* (meaning altered) and *ergon* (meaning reaction).[5]

The race had now begun to identify the causal element behind the "allergy" phenomenon that had so evaded Richet and Portier. Albeit an an incidental discovery, Adolf Windaus, a German organic chemist, inadvertently discovered the novel amino acid histidine, while attempting to convert carbohydrates into amino acids. Subsequently, Windaus partnered with W. Vogt of the University of Freiburg, and together they synthesized *histamine* (ß-imidazolylethylamine) through the decarboxylation of histidine.

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They were not alone in their discovery, as unbeknownst to either paired scientists, Sir Henry Dale and George Barger while studying the *Claviceps purpurea* (ergot), a parasitic fungus that infects rye, had serendipitously found that decomposition of the stored mold resulted in the release of two novel chemicals: *histamine* and acetylcholine.[4] That being said, these scientists did not know the functions of their discovered chemical. It was not long before physiologists were able to establish the ability of histamine to induce visceral changes mimicking anaphylaxis (i.e. bronchiolar/arterial constriction and cardiac contraction) in a wide range of animals.[6,7]

In 1927, scientists from the University of Toronto, Charles H. Best and his collaborators (including Sir Henry Dale) isolated histamine from ox liver and lung sections to demonstrate that it was a native component in animals. Further experiments showed that histamine, in fact, was released in the lungs during an anaphylactic reaction by comparing lung histamine concentrations before and after the reaction.

The complex immunology behind anaphylaxis took more than 50 years to discern. And, by the 1970s, anaphylaxis in humans was classified as IgE-mediated Type I hypersensitivity reaction mediated by basophils and mast cells, which in turn released histamine.

Indeed, the final confirmation of the lead role of histamine came when increased histamine was detected in the bloodstream following shock.[8] This important link between histamine and systemic shock spawned an entire pharmaceutical industry dedicated to counteracting the potentially lethal effects, namely the antihistamines.[9,10]

ADVENT OF THE ANTIHISTAMINE

Einhorn and Rotlauf chemically formulated thymoxyethyldiethylamine in 1911. It would become the chemical basis of the first antihistamines, but it would take more than 20 years for scientists to use these chemicals to inhibit histamine's actions.

While working at the Pasteur Institute in Paris, Ernest Fourneau and Daniel Bovet discovered that certain ethers countered histamine's actions.

Among these phenolic ethers, 2-isopropyl-5-methylphnoxy-*ethyldiethylamine* was the most clinically efficacious.[4] Four years later, in 1937, Bovet and his graduate student, Anne-Marie Staub, demonstrated that thymoxyethyldiethylamine, a.k.a. F929, effectively

TABLE 1

PRODUCTS CONTAINING ETHYLENEDIAMINE OR POTENTIAL CROSS-REACTANTS

ANTI-ASTHMA	AMINOPHYLLINE (2:1 FORMULATION OF THEOPHYLLINE AND ETHYLENEDIAMINE)
ANTIHISTAMINES	PIPERAZINES [HYDROXYZINE (ATARAX, VISTARIL), CETIRIZINE (ZYRTEC), CYCLIZINE (MAREZINE)]; TRIPELENNAMINE HYDROCHLORIDE (PYRIBENZAMINE); PYRILAMINE (RYNA 12 S); MEPYRAMINE (ANTISAN CREAM)
ANTI-NAUSEA	MECLIZINE (BONINE, ANTIVERT); PHENOTHIAZINE (PHENERGAN)
FIRST-AID	TINCTURE OF MERTHIOLATE
SUNSCREENS	SHADE UVA/UVB SUNBLOCK SPF 15, 25, AND 30

HISTAMINE BLOCKERS WERE MASS MARKETED IN THE 1950s AS NOVELTY DRUGS FOR SYMPTOMATIC RELIEF OF ALLERGIES, COMMON COLDS, RHINITIS, URTICARIA, AND PRURITUS.[15] THE MOST COMMON ADVERSE EFFECTS OF EARLY HISTAMINE BLOCKERS WERE SEDATION, DIZZINESS, AND XEROSTOMIA; HOWEVER, DERMATITIS WAS ALSO REPORTED.[16-18]

prevented anaphylaxis in guinea pigs that had been exposed to lethal amounts of histamine.

Although a myriad of subsequent antihistaminic compounds would be later developed, it is important to note that structurally they were nearly all based on the *ethylenediamine* derivates of Bovet's F929. Furthermore, while toxicities of these early antihistamines limited their clinical utility, Bovet notably received the Nobel Prize in 1957 to commemorate his life's work in this important area.[4]

HISTORY OF ETHYLENEDIAMINE

Research biologist and physician Bernard N. Halpern was the first to discover an antihistamine with a clinical safety profile warranting its utility in humans, Antergan (phenbenzamine; N_1N-dimethyl-N_1-benzyl-N-phenyl-*ethylenediamine*, c.1942).

Halpern later formulated another antihistamine, pyrilamine (mepyramine, Neo-Antergan, c. 1944), which was also derived from ethylenediamine and can still be found in topical preparations.[11]

Due to clinical efficacy and low side effect profiles, ethylenediamine derivatives came to dominate the market, especially with the advent of highly successful Pyribenzamine (tripelennamine), Thenfadil (WIN 2848; Winthrop-Stearns, Inc.), Phenergan (Wyeth) and Resistab (Bristol-Myers Co.).[12]

These histamine blockers were mass marketed in the 1950s as novelty drugs for symptomatic relief of allergies, common colds, rhinitis, urticaria, and pruritus.[13] The most common adverse side effects of early histamine blockers were sedation, dizziness, and xerostomia; however, dermatitis was also reported.[14-16]

ALLERGY TO ETHYLENEDIAMINE

The first case of a cutaneous allergy to ethylenediamine dihydrochloride (EED) was reported by Tas and Weissberg in 1958. They described a 52-year-old pharmacist who developed vesicles and papules on the exposed areas of his skin. He was known to prepare nearly 600 aminophylline suppositories each week.[17,18]

Six months after changing pharmacy employment venues (where he did not prepare the suppositories), his dermatitis cleared. Re-exposure upon returning to work at the original pharmacy led to a severe recall of his dermatitis.

The patient was later patch tested to aminophylline and its active component theophylline. A strong positive reaction was noted to aminophylline, with a negative reaction to the theophylline component. By deduction, ethylenediamine, the inactive component, was implicated as the offending allergen.

Besides being used as a counter ion to theophylline in aminophylline for increased solubility, ethylenediamine was also widely used in creams. For example, Mycolog (also called Tri-Adcortyl in the United Kingdom, Kenacomb in Australia, and Assocort in Italy) was prescribed for a wide range of Dermatitides.

The original formulation contained a combination of triamcinolone acetonide, neomycin, gramicidin, nystatin, and the stabilizer ethylenediamine, without which the nystatin and neomycin were not chemically compatible in an aqueous base preparation.[19,20] Importantly, frequent sensitizations to the ethylenediamine component led to the reformulation of the cream devoid of ethylenediamine, a.k.a. Mycolog II.

It is important to note, however, that ethylenediamine can still be found in generic preparations of triamcinolone acetonide/nystatin/gramicidin creams — but not in their ointment counterparts.

POTENTIAL CROSS-REACTIONS

There are a number of notable products that either can contain ethylenediamine or potentially cross-react with it including antihistamines, anti-nausea medications, and first-aid products (**See Table 1**).

Although some controversy exists, and despite the name similarity, ethylenediamine does not seem to appear to cross-react with ethylenediamine tetra-acetic acid (EDTA). One hundred patients with known EED sensitivity were tested to EDTA, and not one was found to react to EDTA.[21]

That being said, other amines may interact and so should be avoided in an allergic patient. These other amides include diethylenetriamine and triethylenetetramine.[22] And, patients should be alerted to the synonyms of ethylenediamine **(See Table 2)**.

UNSUSPECTING EXPOSURES

The chemical composition of ethylenediamine also led to its inclusion in insecticides, herbicides, and industrial applications (e.g. solvents, lubricants, corrosion retardants, and resin adhesive).

TABLE 2

SYNONYMS FOR ETHYLENEDIAMINE

1,2-Ethanediamine Dihydrochloride
1,2-Diaminoethane Dihydrochloride
Chlorethamine

TABLE 3

EXAMPLES OF ETHYLENEDIAMINE-FREE DRUGS

ANTI-ASTHMA	THEOPHYLLINE, DYPHYLLINE, ETHANOLAMINE ANTIHISTAMINES
ANTIHISTAMINE	DIPHENHYDRAMINE (BENADRYL), CYPROHEPTADINE HYDROCHLORIDE (PERIACTIN), FEXOFENADINE (ALLEGRA), LORATADINE (CLARITIN)
ANTI-NAUSEA	DIPHENHYDRAMINE (BENADRYL)
TOPICAL CREAMS	DOXEPIN (ZONALON), NYSTATIN, TRIAMCINOLONE ACETONIDE (MYCOLOG II)

TABLE 4

PRODUCTS CONTAINING ETHYLENEDIAMINE

PRODUCT TYPE	EXAMPLE
INSECTICIDES	MICROBICIDE 288, SANITROL MICROBICIDE, BUSAN 882, MICROFAC 300
HERBICIDES	KOMEEN AQUATIC HERBICIDE
ANIMAL FEED	LICK YOUR CHOPS CAT FOOD, MERRICK DOG FOOD

Furthermore, while most adhesive sensitivities are associated with the rubber or colophony components, case reports have implicated the chemical N, N'-disalicylidene-1, 2-diaminopropane, which notably is hydrolyzed to a derivative of ethylenediamine. Thus, in predisposed, sensitized patients adhesives may exacerbate a dermatitis associated with an ACD to ethylenediamine.[23]

TESTING FOR EED SENSITIVITY

Patch testing for ethylenediamine allergy can be accomplished with the T.R.U.E. test (site # 11). While the T.R.U.E test recognizes only a fraction of the great number of possible allergens that can cause ACD, it is a valuable screening tool that can be utilized by general dermatologists and allergists everywhere.

VALUE OF THIS PATIENT CASE

Our patient with allergy to ethylenediamine underscores the importance of appropriate patch testing and subsequent patient education. The patient discontinued his hydroxyzine pills and dramatically improved. Furthermore, he was educated on the utilization of products derived from or containing *ethylenediamine* **(See Tables 3 and 4)**. ■

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