ALLERGEN Focus

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Focus on N.A.C.D.G. Allergen: Mixed Diakyl Thioureas

BY BRYAN ANDERSON, M.D.

In 1997 the Food and Drug Administration granted an indication for the use of the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) test Panels 1.1 and 2.1 as a valuable, first-line screening tool in the diagnosis of allergic contact dermatitis. Many dermatologists utilize this standard tool in their practice and refer to contact dermatitis referral centers when the T.R.U.E test fails to identify a relevant allergen. Specifically, the T.R.U.E. test screens for 46 distinct allergens and the Balsam of Peru mixture. The test is thought to adequately identify an allergen in approximately 24.5% of patients with allergic contact dermatitis.[1] This being said, many relevant allergens are not detected by use of this screening tool alone and, for this reason, "Allergen Focus" has been expanded to cover the notorious Allergens of the Year and North American Contact Dermatitis Group's (NACDG) Standard Allergens.

"Allergen Focus" is a column designed to concentrate on common allergens and is intended to answer some of the most frequent questions relating to their origin and most common uses. This month, we focus on the NACDG allergen mixed diakyl thiourea, an agent that is commonly used in synthetic rubber products such as Neoprene, the material used to manufacture divers' wetsuits.

CONTACT DERMATIDES

The contact dermatides include, irritant contact dermatitis, contact urticaria, and allergic contact dermatitis. ***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 would be latex protein 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.[2,3]

Allergic Contact dermatitis (ACD) is an important disease with high impact both in terms of patient morbidity and economics. Allergic contact dermatitis 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 Daltons. On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated which includes cytokines, i.e. interleukin 2 [IL-2] and interferon gamma [IFN-γ], T cells and Langerhans cells. This complex interaction leads to the clinical picture of ACD.

CLINICAL ILLUSTRATION

An athletic young female presented to the Hershey Medical Center Department of Dermatology in Hershey, PA, with an 8-month history of eyelid dermatitis. She was seen by a community dermatologist who diagnosed her with an allergic contact dermatitis. Treatment with topical tacrolimus was minimally

effective. The community dermatologist performed the T.R.U.E. test, which was entirely negative. She was referred to our clinic for more extensive patch testing.

Of note, she was an avid swimmer and wore swim goggles during her daily swims.

HISTORY OF DIVING: THE EARLY YEARS

The first piece of diving equipment that humans used dates back to 100 A.D. when divers used a hollow reed as a type of snorkel. Then, about 1,200 years later reports of Persian divers indicated that they used underwater goggles.[4] Diving bells were the next invention. Initially made of wood and limited in their ability to carry oxygen, diving bells restricted divers in the amount of time they could stay under water. It was not until a reliable air pump was invented that divers could now stay underwater for considerably longer times. Initially, the divers had a copper helmet connected to a watertight leather suit. An air hose was connected to the mask, and air was pumped to the diver.

Over the years, more inventors perfected the technology until attaining the technology of modern-day SCUBA (self-contained underwater breathing apparatus), which enables divers to remain submerged for prolonged periods of time. The famous marine scientist Jacques Cousteau was instrumental in bringing the technology to the masses. He is considered the father of modern scuba diving. Recreational divers across the globe have Mr. Cousteau to thank for bringing this technology to the public.

THE HISTORY OF NEOPRENE AND THIOUREAS

Neoprene (polychloroprene) was invented in the 1930s by scientists working for the Dupont Corporation.[5] Neoprene was originally called Duprene, but this name was later changed to Neoprene. Neoprene is not one single rubber compound but instead is the name given to a large family of synthetic rubber compounds that are made from the polymerization of chloroprene. Chloroprene (2-chlorobutidiene) is a liquid used for the production of Neoprene and was also developed by Dupont scientist. Neoprene is produced when chloroprene is cross-linked through a process known as vulcanization. This process is dependent on various additives, accelerators, anti-oxidants and sulfur. These polymerization techniques account for the varying types of Neoprene available, and they play a major role in the properties of the final Neoprene compound that results from the process and exhibits wonderful elastic and cushioning properties.

THIOUREAS ARE WIDELY USED IN THE PRODUCTION OF SYNTHETIC RUBBER — PARTICULARLY NEOPRENE, THE WELL-KNOWN COMPONENT OF WETSUITS.

Photos courtesy of James Marks, MD

Other important properties that have made Neoprene one of the world's most commonly used synthetic rubber products include its corrosion resistance, cushioning properties, thermal insulation, noise insulation, oxygen and ozone resistance, and resistance to oils, solvents and abrasion.[5]

Car industry uses. Interestingly, it is one of the most common synthetic rubber compounds in the car manufacturing industry, where full advantage is taken of its oil and solvent resistance and it is utilized in automobile hoses, fan belts and gaskets.

Orthopedic applications. Neoprene has been also been used in the chemical, textile and orthopedic brace industries.[6]

Diving gear uses. One of its more interesting and well-recognized applications has been in the diving industry. Divers taking advantage of its cushioning and insulating properties have used neoprene wetsuits for years. Another added advantage to wearing a wetsuit is sun protection. Neoprene wetsuits come in a myriad of colors, thickness and styles (shirts/pants/full body). The thicker wetsuits are better at insulating the body from cold exposure. Wetsuits are made from foam Neoprene, which has small air spaces in it that enhance its insulating properties.

As a generalization, as a diver descends deeper into water, the temperature becomes colder, so it is important to protect against the cold. Wetsuits (or drysuits) made of Neoprene, which is a good insulator, perform this task well. However, it is important for divers to know that as they descend the Neoprene wetsuit will compress and lose some of its insulating properties. This will cause a loss of body heat from the diver and decrease the time they are able to stay underwater.[7]

THIOUREA USE IN PRODUCTS

Thioureas are widely used in the production of synthetic rubber (particularly Neoprene) as well as a fixative agent

TABLE 1

EXAMPLES OF THIOUREA DERIVATIVES[6]

- Ethylenethiourea
- Dimethylthiourea
- Diethylthiourea
- Dibutylthiourea
- Diphenylthiourea
- Ethylbutylthiourea
- Dibutylthiourea
- N,N-Diethylurea

TABLE 2

COMPONENTS OF MIXED DIAKYL THIOUREAS

- Diethylthiourea
- Dibutylthiourea

(Available from Chemotechnique Diagnostics)

TABLE 3

COMMON SOURCES OF EXPOSURE TO THIOUREAS[4,6,10-12]

- Photocopy Paper
- Wet Suits
- Neoprene Containing Orthopedic Braces
- Rubber Products — Rubber Gloves, Shoe Insoles
- Commercial Detergents
- Paint and Glue Removers
- Plastics
- Metal Anti-corrosive Agents
- Clothing Elastic
- Photographic Fixing Agents

in photography and diazo copying paper. In addition to these sources of exposure, thiourea allergic contact dermatitis has been caused by swim goggles, medical devices (knee braces, splints, continuous positive airway pressure masks), keyboard wrist supports, weather stripping, athletic shoe insoles, rubber gloves, and paint remover.[8]

You should consider thioureas as potential allergens in any patient for whom you believe rubber to be the cause of their allergic contact dermatitis.[8,9] (**See Table 3**).

ALLERGY TO MIXED DIAKYL THIOUREAS

It is important to note that neoprene itself has very rarely caused ACD. It is much more likely that a patient with a suspected contact dermatitis to a neoprene product is actually more likely allergic to one of the additives in the vulcanization/polymerization process. These include but are not limited to the thiourea accelerators and antioxidants. It is important to note that the thiourea accelerators are the most common agents found responsible. This is the reason that the mixed diakyl thioureas patch test product is used and when is positive is often an indicator of neoprene allergy. A negative test to the mixed diakyl thiourea does not however exclude an allergy to the neoprene product, or another of the thiourea family of chemicals.[9]

For this reason if someone has a suspected thiourea allergy it may be wise to **patch test the patient to a panel of specific thioureas**. This is because of the variety of ways neoprene is manufactured (which **includes a variety of additives being used**). Because of this, it can be difficult to determine which of the additives were used in a particular neoprene product. Furthermore, companies may be unwilling to give up such information or which is more likely the case, **their products are made overseas and no one can say with certainty the production method that was used**. Occasionally, this can present a challenge when thoroughly assessing patients who have Neoprene-induced ACD.

TESTING FOR MIXED DIAKYL THIOUREAS

The mixed diakyl thioureas can be tested in 1% petrolatum and are included in the North American Contact Dermatitis Society 2007 standard tray of 65 allergens. It is available from Chemotechnique Diagnostics. Of note: Only a portion of patients will be identified by patch testing with the mixed diakyl thioureas, which contain only two thioureas (diethylthiourea and dibutylthiourea). If you suspect a thiourea allergy, it may be wise to patch test the patient to the other available thioureas, in addition to a swatch of the suspected product. Again it is important to note that these chemicals are not found on the commercially available T.R.U.E. test screening tool.

THE VALUE OF THIS PATIENT CASE

Extensive patch testing on this patient demonstrated a positive reaction to mixed diakyl thioureas in 1% petrolatum (the rubber accelerator used in the production of Neoprene). Neoprene was found to be the component of her swim goggles that came in direct contact with her eyelids. She was seen in follow-up 10 weeks after she discontinued using the Neoprene containing goggles, and her eyelid dermatitis had completely resolved.

This case illustrates the importance of an appropriate patch-test history and patch testing with the appropriate antigens. Once an allergen is identified, patient education and handouts for continued avoidance is the mainstay of therapy for allergic contact dermatitis. ■

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Dedication: This column is dedicated to James G. Marks Jr., Dr. Anderson's mentor and an avid scuba diver.

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