

Contact dermatitis due to 2,2'-azobis(2-amidinopropane) dihydrochloride: an outbreak in production workers

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2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH) is an azo compound which has been used as a radical chain initiator. The purpose of this study was to confirm contact sensitivity to AAPH in individuals who were engaged in the production of AAPH, and presented with prolonged eczematous eruptions mainly on exposed areas. Patch testing was carried out with AAPH (1 and 5% aq.) on 8 patients and 6 healthy volunteers who had never been exposed to this chemical. All patients showed a strong positive patch test reaction to this agent, while all control subjects showed negative results. Because this chemical has recently been used for studies on the oxidation of biological materials, not only production workers in the chemical industry but also medical researchers should avoid prolonged exposure to this agent.

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2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH) (Fig. 1) is a water-soluble radical chain initiator, which has been used not only in the chemical industry but also in the field of experimental medicine and biochemistry. In 1994, workers who were engaged in the production of AAPH in a chemical plant complained of itchy eczematous eruptions, mainly on exposed areas such as the hands and forearms. As a result of patch tests in these patients and control subjects, AAPH was confirmed to be the causative agent of this outbreak of contact dermatitis. As far as we are aware, this is the 1st report of contact allergy to AAPH, except for an unpublished document.

Case Reports

8 male production workers in a chemical plant, aged 43–51 years, visited our department with their manager in August 1994 because of itchy eruptions on their hands and other locations, lasting for a few months. The chemical plant had started to produce AAPH in March of that year and all patients had been assigned to the final production process of the agent (Fig. 2). These pa-

tients stated that the eruption developed 1–4 weeks after having begun this work. None of them had any history of hand eczema or atopic dermatitis. The manufacturer had already stopped the production of AAPH because of fear of a possible link between AAPH and an increase in the number of patients with a similar type of dermatitis. According to the manager, all 14 members in this section, including the patients, had complained of itchy eruptions, of whom 6 workers had already recovered after cessation of production. All production workers in the plant were obliged to wear rubber gloves whilst working, but measures to protect them from exposure to chemical dust, other than the use of ventilation fans, had not been taken.

On physical examination, scaly erythema and many papulovesicles were present on the fingers and palms of all patients. Fissures and small eroded lesions were noted on the distal parts of the fingers of some patients. Most patients also presented with confluent red papules or erythematous plaques, varying in size, on the face, neck, forearms, back, or lower legs. The following laboratory tests were performed: CBC and differential cell count, automated blood chemistry analysis,

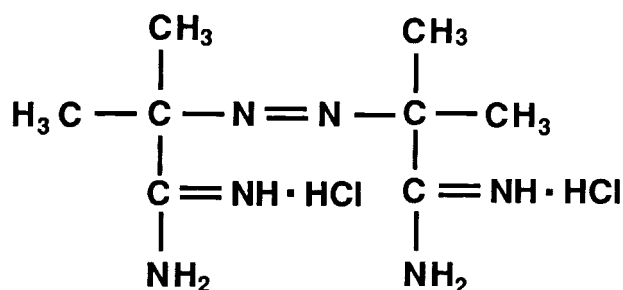


Fig. 1. Structure of 2,2'-azobis(2-amidinopropane) dihydrochloride.

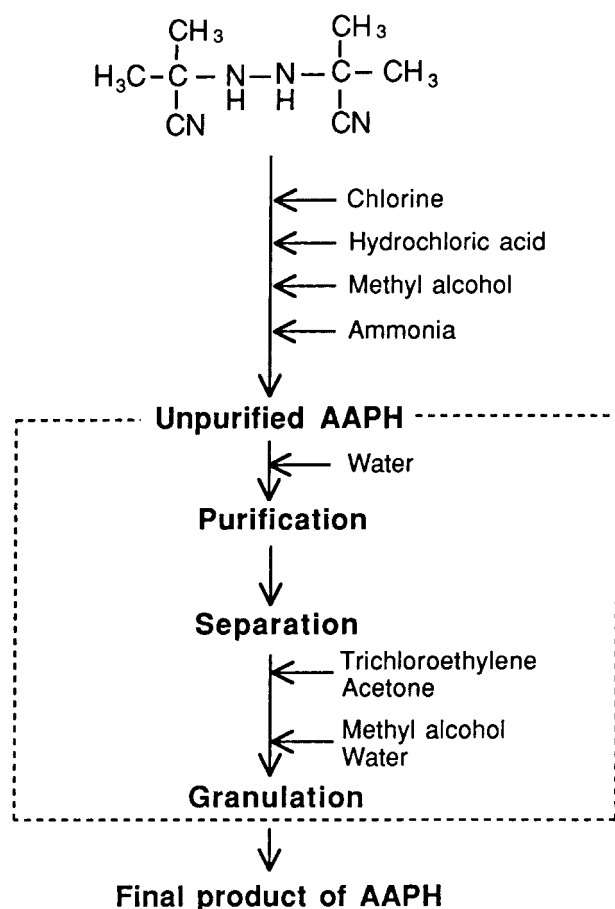


Fig. 2. Flowchart of AAPH production; the portion surrounded by dotted lines indicates the section in which all patients worked.

IgE RIST and RAST for various allergens, erythrocyte sedimentation rate, and urinalysis. 1 patient showed elevation in the levels of GOT, GTP, and γ -GTP. However, the data for this patient were similar to those that had been obtained 1 year earlier, before production of AAPH had been started. Mild elevation of IgE RAST values for house dust were noted in 2 patients, although RIST values were within normal limits in all pa-

tients. None of the patients showed abnormal findings on chest X-rays. A biopsy specimen from a papulovesicle from the palm of 1 patient revealed a spongiotic vesicle with exocytosis in the epidermis and a mild, perivascular lymphocytic infiltrate in the upper dermis. No relationship could be seen between the vesicle and intraepidermal eccrine ducts.

Patch tests were carried out with materials as follows: AAPH 1% and 5% aq.; tetramethylthiuram disulfide (TMTD) 1% pet.; formaldehyde 5% aq.; urushiol 0.01% pet.; nickel sulfate 5% aq.; mercuric chloride 0.05% aq.; cobalt chloride 2% aq.; potassium dichromate 0.5% aq.; and paraphenyldiamine (PPD) 2% pet.. Patch tests for AAPH were also performed on 6 healthy volunteers who had never been exposed to this chemical. All materials, except AAPH, were from the standard patch test series (Torii Pharmaceutical Company, Tokyo, Japan), allergens that had previously been reported to show relatively high rates of positive reaction in patients in this part of Japan with contact dermatitis, atopic dermatitis, and dyshidrotic eczema (1). The Miniplaster® (Torii Pharmaceutical Company), with which new allergens such as hydroxycitronellal were discovered in the 1970s (2), was used as the patch testing device to reduce the distress to the patients caused by the expected strong reactions. The severity of positive allergic reactions is usually less with this classical type of vinyl plaster than with the now standard patch testing device, Finn Chambers®, owing to its smaller size and lesser degree of occlusion. Patches remained on the back for 2 days and were read at 2, 3, 7, and 14 days using ICDRG scores. All patients showed positive reactions to both 1% and 5% AAPH at 2 and 3 days, while all control subjects showed negative results. No flare-up reaction was found at the test sites in all control subjects at 7 and 14 days. The results of patch tests at 3 days are summarized in Table 1.

The diagnosis of allergic contact dermatitis due to AAPH was made for all patients. The company discontinued the manufacture of AAPH, and the workplace was carefully cleaned with plenty of water. All working clothes, gloves, and rubber boots used by the production workers were discarded. All patients were treated with topical corticosteroids and oral antihistamines. On follow-up, it was found that, although the severity of the lesions was far milder, most patients still suffered occasional recurrences of hand dermatitis during the following 1–2 years. In 1 patient, dark brown, 1–2 mm diameter, sparse hyperpigmented macules developed on the palms after the eczematous lesions disappeared.

Table 1. Results of patch tests at 3 days

Patient no.		1	2	3	4	5	6	7	8	9-14 (control) 37-56
Age		46	51	44	43	46	44	49	49	
AAPH	1% aq.	++	+	++	++	++	+	++	++	all -
AAPH	5% aq.	++	++	++	++	++	++	++	++	all -
TMTD	1% pet.	-	-	-	-	-	-	-	-	
formaldehyde	5% aq.	-	-	?+	-	-	-	-	-	
urushiol	0.01% pet.	-	-	+	+	++	++	++	+	
NiSO ₄	5% aq.	+	-	+	++	-	-	-	-	NT
HgCl ₂	0.05% aq.	+	-	-	-	-	-	-	-	
CoCl ₂	2% aq.	+	-	++	+	-	-	-	-	
K ₂ Cr ₂ O ₇	0.5% aq.	+	-	?+	-	-	-	+	-	
PPD	2% pet.	-	-	-	-	-	-	-	+	

Discussion

AAPH is an azo-compound that was first registered in 1950 (3) and has been used as a polymerization initiator for acrylamide and acrylic acid in the chemical industry. This agent generates carbon-centered free radicals in an aqueous environment at a known and constant rate, which react with oxygen and are converted to peroxy radicals. This reaction does not require the addition of potentially interfering cofactors and transition metals (4, 5). Because of the potential of using these beneficial characteristics to study the reaction of biological components with free radicals, AAPH has been utilized for biochemical studies concerning lipid peroxidation (6, 7), oxidative damage of cells and tissues (5, 8), and evaluation of various antioxidants (9, 10) since the mid 1980s.

AAPH was synthesized by the process shown in Fig.2 in this chemical plant. All patients were engaged in the final production process of this chemical, and none of the workers who were exposed to either the raw materials or the intermediates formed during the chemical's synthesis complained of dermatitis similar to that seen in our patients. All patients showed strong positive reactions to AAPH on patch testing, and their dermatitis improved after the production of AAPH was discontinued. According to the manufacturer, the final product was highly purified and the concentrations of contaminants, if any, were considered to be quite low. Therefore, it is most likely that AAPH itself was the causative agent of the contact dermatitis in these patients, although allergy to other materials used in the production process or possible contaminants in the final products cannot be strictly ruled out. From our investigations in this plant, contamination of protective rubber gloves, during scraping-out of products from the tanks for purification, was suspected as being causative of this occupational contact dermatitis. The reactions to AAPH were negative in all control subjects, in-

dicating that this chemical probably acted as an allergen rather than as an irritant. This was also supported by the clinical observation that most patients suffered occasional eruptions for as long as 1-2 years after production of AAPH had been discontinued. The recurrence of skin lesions may be due, at least in part, to contact with AAPH remaining in very small amounts in the workplace despite several rounds of cleaning.

Concerning the results of patch testing for materials other than AAPH, many patients showed positive reactions to urushiol, nickel, and cobalt. It is not surprising that 6 out of 8 patients were allergic to urushiol, because there are numerous *urushi* plants in the woods and forests in this part of Japan, and the rate of positive reaction to urushiol in standard patch testing is reported to be about 80% for patients with dermatitis in this region (1). There were no *urushi* plants in the factory yard, however, and Japanese lacquer made from *urushi* had not been used in this plant. The reason why so many patients showed a positive response to metal allergens such as nickel is unclear. Some of the positive or weakly positive reactions in case nos. 1 and 3 may be due to the "excited skin syndrome", as both patients showed positive responses to many allergens. Metal-containing chemicals were not used in the synthesis of AAPH. However, as all patients had been engaged in the production of various chemicals before the manufacturer started to produce AAPH, they might have been sensitized to these allergens through their previous work.

Although oxidative damage to certain organs or tissues due to AAPH has been reported in some experimental animal studies (8, 11), we could not find any reports on allergic reactions to AAPH in the MEDLINE or TOXLINE databases. However, we found a record of an outbreak of contact dermatitis which was probably due to AAPH in a chemical plant in England, similar to the current report, in the documents of the US. Environmental

Protection Agency (12). According to this record, patch tests for AAPH were positive in 5 of 6 patients with dermatitis and the results of a guinea pig maximization study revealed that AAPH was considered to be a strong skin sensitizer in guinea pigs. The manufacturer in the present report also carried out guinea pig maximization tests and obtained similar results.

We conclude that the outbreak of dermatitis in this plant is due to contact allergy to AAPH. This chemical has recently been used by the researchers involved in medical studies of free radical oxidation. Therefore, not only production workers in the chemical industry but also these researchers should take care to avoid prolonged exposure to this agent.

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