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CONTACT SENSITIZATION TO CS, A RIOT CONTROL AGENT

Richard Levin, et al

Edgewood Arsenal
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The potential of the "tear gas" ortho-chlorobenzylidene malononitrile (CS) for causing allergic contact dermatitis in individuals exposed to high concentrations was investigated. Although CS has a high sensitizing potential under experimental conditions, there is evidence that a high risk of cutaneous sensitization would not exist under more realistic conditions. The cutaneous sensitivity is specific and lasts for at least 6 months, and sensitive individuals can be identified by appropriate patch testing. Patch testing highly sensitive individuals can augment the severity of the skin reactions in future exposures. Due to the extensive use of CS, the possibility of developing allergic

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contact dermatitis must be considered in exposed individuals.

SUMMARY

The potential of the "tear gas" ortho-chlorobenzylidene malononitrile (CS) for causing allergic contact dermatitis in individuals exposed to high concentrations was investigated. Although CS has a high sensitizing potential under experimental conditions, there is evidence that a high risk of cutaneous sensitization would not exist under more realistic conditions.

The cutaneous sensitivity is specific and lasts for at least 6 months, and sensitive individuals can be identified by appropriate patch testing. Patch testing highly sensitive individuals can augment the severity of the skin reactions in future exposures.

Due to the extensive use of CS, the possibility of developing allergic contact dermatitis must be considered in exposed individuals.

PREFACE

The work described in this report was authorized under Project 1W562606AD22, Medical Effects of Riot Control Agents. This work was started in January 1972 and completed in February 1973.

The volunteers in these tests are enlisted US Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

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CONTACT SENSITIZATION TO CS, A RIOT CONTROL AGENT

I. INTRODUCTION.

The lacrimator ortho-chlorobenzylidene malononitrile (CS) was first prepared by Corson and Stoughton[1] in 1928 and has been used in military operations and for riot control. One of the reasons it is replacing the well-known "tear gas" chloroacetophenone (CN) is its relative safety. CS is less toxic systemically and locally on the eyes and skin,[2-9] and CN is known to be a potent potential sensitizer of the skin in humans.[10,11] Recently, however, CS has been implicated as the cause of contact dermatitis in people working in manufacturing facilities who have been exposed to the agent.[12]

This study was undertaken to establish (1) whether CS can cause allergic contact dermatitis as well as primary irritation, (2) what the primary irritant response to various concentrations of CS is when an occlusive patch technique is used, (3) the appropriate concentration of CS for a 24-hour occlusive patch test, (4) what the potential for sensitization by patch testing is, and (5) whether there is a cross-reaction with CN or the metabolic products of CS and related compounds.

II. MATERIALS AND METHODS.

A. Subjects.

The volunteers in these tests are enlisted US Army personnel, ages 18 to 32. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25. Skin areas to be used were examined carefully to avoid applying patches to any irritated areas.

B. Primary Irritancy.

CS was dissolved in petrolatum by putting the mixture in a closed vial and heating it in a water bath until the petrolatum liquefied. Baseline testing was performed on 80 volunteers using 80 mg of 0.1% and 0.01% CS in petrolatum and petrolatum alone (control) applied to 154-sq mm occlusive patches* (0.0005 mg of CS and 0.00005 mg of CS/sq mm, respectively) and taped to the skin with Micropore Surgical tape.** Two patches of each concentration were applied to the upper back and were not removed for 24 hours. The responses at the test sites were evaluated 45 minutes after the patches were removed and then daily for at least 3 days.

Skin reactions were examined under a standard fluorescent light by one observer and graded 0 to 4 according to the following criteria:

0	No reaction
1	Minimally perceptible erythema
2	Macular confluent erythema

* Elastoplast coverlets: Duke Laboratories, South Norwalk, Connecticut.
** Minnesota Mining & Manufacturing Company, St. Paul, Minnesota.

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3 Erythema and induration

4 Vesicular or bullous reaction

The grade assigned to each test site was the maximum response that occurred during the period of observation. (All patch tests described subsequently were performed as described above with some modifications, which are mentioned.)

C. Sensitization.

To establish whether the concentrations of CS used to evaluate primary irritant capacity were in themselves sensitizing, the testing was repeated in the same volunteers on a different area of the upper back 2 weeks after the first patch tests. The baseline and repeat patches were the same size.

Baseline primary irritant response to 0.1% and 0.01% CS in petrolatum was established in another nine subjects as described above. Then skin sensitization to CS was induced in these subjects by exposing them the next day to a larger dose, 375 mg of 1% CS in petrolatum, on a 750-sq mm patch* (0.005 mg of CS/sq mm). If the reaction was grade 3 or 4, the patch was removed after 24 hours. If the reaction was grade 2 or less, the patch was not removed for 48 hours.

To enhance skin sensitization by repeated insult, 0.1% CS in petrolatum was applied to the same site 1 week later. Two weeks after the second insult, the smaller testing patches containing 0.1%, 0.01%, and 0.001% CS in petrolatum were applied to different areas of the upper back to establish whether sensitization had occurred.

D. Specificity of Reactions to CS.

To establish the specificity of the reactions to CS, the same nine subjects were patch tested (48 hours) with the following metabolic products of CS and structurally related compounds (1% in petrolatum): ortho-chlorobenzaldehyde, ortho-chlorobenzoic acid, parachlorobenzaldehyde, parachlorobenzoic acid, and metachlorobenzoic acid. Malononitrile was not tested because of the possible toxicity of its cyanide breakdown product.[13] The patches were applied 2 weeks after sensitization, at the same time the 0.001% to 0.1% CS was being tested.

E. Persistence of Sensitization.

Four of these nine subjects were available for reexamination 6 months after the sensitizing procedure. These men were then tested with 0.00001% to 0.1% CS in petrolatum to determine whether the cutaneous sensitivity to CS persisted. To establish whether the cutaneous sensitivity of these individuals had been increased by the 6-month retest, they were tested again 2 weeks later.

F. Cross Sensitivity.

Cross sensitivity to CS and CN was evaluated by patch testing the four volunteers

* Elastoplast coverlet: Duke Laboratories, South Norwalk, Connecticut.

sensitized to CS who returned after 6 months. They were tested with 0.1% CN in petrolatum, a concentration which had been found to be below the threshold of irritancy in 20 subjects.

Two other previously untested subjects were sensitized to CN by applying 0.5% CN in petrolatum for 24 hours. Evaluation for sensitization was performed 5 months later with both 0.1% CS and 0.1% CN.

III. RESULTS.

A. Primary Irritant Response.

The first exposure to 0.01% CS caused no primary irritant responses in 80 volunteers. Approximately 25% (19) of the 80 volunteers had a mild, primary irritation (grade 1 or 2) when tested with 0.1% CS. No responses were greater than grade 2.

B. Sensitization.

The results of reexposure to CS were no different from those of the first exposure in the 80 volunteers, which shows that these concentrations are not sensitizing.

During initial baseline testing in the second group, none of the nine subjects had a reaction to 0.01% CS. At the 0.1% CS concentration, two had a mild reaction (grades 1 and 2) and seven had no responses. At the time of the sensitizing dose and the repeated insult 1 week later, all subjects responded with induration or blisters. After sensitization, five of them had a mild to moderate reaction (grades 2 and 3) to 0.01% CS and eight had a moderate to severe reaction (grades 3 and 4) to 0.1% CS (table I). The one subject that did not become sensitized was black (the other eight were Caucasian).

C. Specificity of Reactions to CS.

The 48-hour tests with metabolites of CS and related compounds produced no response in any of the nine subjects.

D. Persistence of Sensitization.

Six months after sensitization, four of the original nine subjects were retested; sensitivity to CS persisted in all of them (table II). Unlike nonsensitized subjects, these four men, when again tested 2 weeks later, had a significant increase in sensitivity with erythematous to bullous reactions at concentrations that previously produced no response (table II). One subject responded to 0.0001% CS with a grade 4 reaction. He had a negative reaction to 0.00001% CS.

E. Cross Sensitivity.

At the time of the 6-month followup, the four CS-sensitized individuals did not respond to the subthreshold irritant concentration of 0.1% CN.

Table I. Effects of Sensitization to CS in Nine Subjects

Concentration of CS	Grade of reaction *																
	Before sensitization									Two weeks after completion of sensitization procedure **							
	Subject									Subject							
	A	B	C	D	E	F	G	H	I	A	B	C	D	E	F	G	H	I
%																	
0.001	No reaction									No reaction							
0.01	No reaction									0	3	0	2	0	3	2	0	3
0.1	0	1	0	0	0	0	0	0	2	4	4	4	4	0	4	4	3	3

* See text for description of grades of reactions.
** See text for sensitization procedure.

Table II. Persistence of Sensitization to CS for 6 Months

Time of testing	Concentration of CS	Grade of reaction*			
		Subject			
		A	B	C	H
	%				
Baseline	0.1	0	1	0	0
After sensitization	0.001	0	0	0	0
	0.01	0	3	2	0
	0.1	4	4	4	3
6-Month followup	0.0001	0	0	0	0
	0.001	0	0	0	2
	0.01	0	3	2	4
	0.1	1	4	4	4
2-Week retesting after 6-month followup	0.00001	0	0	0	0
	0.0001	0	0	4	0
	0.001	0	3	4	3
	0.01	0	3	4	—**
	0.1	3	—**	—**	—**

* See text for description of grades of reactions.

** As these subjects had a grade 4 reaction to these concentrations in the 6-month followup test, they were not retested at these concentrations.

The two volunteers who were sensitized to CN and retested with 0.1% CN 6 months later developed a grade 3 (induration) reaction extending 2 cm beyond the patch test site. When simultaneously tested with 0.1% CS for evaluation of cross sensitivity, the results were negative.

IV. DISCUSSION.

CS is a known primary skin irritant.[5,14] As early as 1960, presumptive allergic contact dermatitis had been attributed to this agent[15] but was not confirmed by patch tests. In 1969, apparent sensitization was reported in one volunteer during an experiment with CS under tropical climatic conditions.[16] Rothberg found that CS was a skin sensitizer in guinea pigs,[17] and this has recently been confirmed by Chung and Giles.[18] Shmunes and Taylor[12] have reported allergic CS contact dermatitis in industrial workers.

In a review of the cutaneous reactions to CS, Weigand[19] reported that the major factors related to developing CS dermatitis are: duration and frequency of exposure, heat and humidity, prolonged hydration, and possibly race.

The results of the present study suggest that a reaction of grade 1 or 2 to 0.1% CS is primary irritation; approximately 25% of the subjects in this study responded to this concentration of CS with primary irritation. The fact that a second exposure to 0.1% CS did not augment the response suggests that this dose is not sufficient to cause sensitization in nonsensitized individuals.

The studies in the sensitized subjects suggest that two criteria can be used to establish whether a person has been previously sensitized to CS: (1) any cutaneous reaction to a concentration of 0.01% CS or less and (2) a grade 3 or 4 response to 0.1% CS. Although these criteria appear to be well defined, the number of subjects studied is too small to draw absolute conclusions.

For practical purposes, a 24-hour occluded patch test of 0.1% CS will determine if the individual has allergic contact dermatitis to CS. A skin response of grade 1 or 2 may be due to primary irritation, whereas a reaction of grade 3 or 4 probably indicates sensitization. It must be remembered that this high concentration may augment future cutaneous reactions in previously sensitized individuals. Therefore, if a person's history makes him highly suspect of having been sensitized, it would be prudent to initiate patch testing with a concentration as low as 0.0001% CS, which produced a grade 4 reaction in one of our sensitized subjects. If this low concentration did not produce a response, the concentration would be increased until a reaction was produced but no higher than 0.1% CS. As previously noted, a grade 1 or 2 reaction to 0.1% CS may indicate only primary irritation and not sensitization.

Although the sensitization rate in this experiment is high, the probability of a comparable response in a military or riot control situation remains uncertain because the eye irritation would cause the people exposed to attempt to flee to an uncontaminated area before the CS was in contact with the skin for any length of time. Even in an industry where workers wearing protective masks are in contact with CS for long intervals, the dermatitis experienced is usually of the primary irritant type rather than allergic contact dermatitis.[12] Additional evidence that sensitization is unlikely in practical use is that many of the men who participated in the present

experiment had previously had extensive exposure to CS during field operations, but none had become sensitized. However, sensitization may be possible with a severe CS exposure of 1 hour or less under conditions of high humidity and temperature.[16]

The hypersensitivity reaction appears to be specific for the intact compound as there were no reactions to its metabolic products or to related compounds. CN did not cause a cross-reaction in our subjects.

As most of the subjects used in this study were Caucasians, no conclusion on the effect of skin color can be drawn.

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