

DERMATITIS FROM ALCOHOLS

With Special Reference to the Possible Importance of Impurities and Metabolites

S. Fregert, M.D., R. Håkanson, M.Sc.,** H. Rorsman, M.D.,* N. Tryding, M.D.,***
and P. Övrum, M.Sc.,**** Lund, Sweden*

CONTACT allergy to aliphatic alcohols appears to be uncommon. The case reports published by Sulzberger, Warshaw, and Herrmann,¹ Everall and Truter,² and Calnan and Sarkany³ deal with *higher* aliphatic alcohols such as hexadecanol and cis-9-octadecen-1-ol.† Only two instances of contact allergy to *lower* aliphatic alcohols, demonstrated by epicutaneous tests, have been described. Haxthausen⁴ examined a patient who gave a positive patch test reaction to methanol, ethanol, and 1-propanol but gave negative reactions to all the corresponding aldehydes and acids. Drevets and Seeböhm⁵ described a patient with contact allergy to methanol, ethanol, 2-propanol, 1-butanol, and 1-pentanol, but not to methanal, ethanal, methenoic acid, and 2-propanone.

When carrying out epicutaneous tests with ethanol as the solvent for certain substances we found one patient who developed allergic eczematous reactions to the solvent. We have since studied this patient for contact allergy to alcohols and aldehydes.

CASE REPORT

The patient was a 62-year-old housewife.

Heredity.—Inquiry into her familial history revealed nothing of interest.

Previous Illnesses.—For 6 years she had had ulcerative colitis for which she had undergone enterostomy.

Present Illness.—For the previous 12 years she had had a postthrombotic leg ulcer with periodic dermatitis. During an exacerbation of the dermatitis of the lower leg, epicutaneous tests were performed with the agents used for local treatment and routine test substances. The patient gave positive eczematous reactions to all test substances dissolved in ethanol. She also reacted positively to a patch test with ethanol.

In order to check that the reaction to the ethanol test really was due to the alcohol used and not to components of the test material, the patient was tested for allergy with alcohol in a cup made of glass according to the method of Blohm.⁶ On repeated epicutaneous tests, in which alcohol was not used as a solvent, the patient was found to be allergic to diethylstilbestrol, balsam of Peru, and Vioform (5-chloro-8-hydroxy-7-iodo-quinoline).

The urinary excretion of coproporphyrins and of uroporphyrins were normal.

Supported by a grant from the Alfred Österlund Foundation.

Received for publication April 8, 1963.

*Department of Dermatology, University of Lund, Lund, Sweden.

**Consultant chemist, Lund, Sweden.

***Department of Clinical Chemistry, University of Lund, Lund, Sweden.

****Department of Occupational Medicine, University of Lund, Lund, Sweden.

†Names approved by the International Union of Chemistry have been used.

TEST SUBSTANCES

The alcohols, aldehydes, carboxylic acids, ketones, and ethers used were all of commercially available types. In addition, tests were performed with vodka (Moskovskaya osobaya vodka, distilled and bottled in the USSR for v/o "Prodintorg," Moscow; 40 per cent ethanol).

TABLE I

COMPOUND	TEST REACTION	NO. OF EXTRA PEAKS IN GAS CHROMATOGRAM
I. Primary alcohols		
a. methanol, 10%*	+	1
ethanol commercial, 1%*	+	1
ethanol (vodka), 40%	+	0
ethanol, chromatographically prepared, 100%	+	0
ethanol, complex-formation of aldehydes, 2%	+	
1-propanol, 10%*	+	
1-butanol, 1%*	+	4
1-pentanol, 10%	+	11
1-hexanol, 10%	+	15
1-octanol, 10%	+	
1-nonanol, 10%	+	12
1-decanol, 100%*	-	6
b. 2-methyl-1-butanol, 10%	+	
3-methyl-1-butanol, 10%	+	
6-methyl-1-heptanol, 10%	+	
c. 3-amino-1-propanol, 100%	-	
d. 2-propen-1-ol, 10%	+	
e. 1, 2, 3-propanetriol, 100%	-	
f. α -hydroxytoluene, 1%	+	7
II. Secondary alcohols		
2-propanol, 100%	-	
2-butanol, 100%	-	
2-octanol, 100%	-	
III. Tertiary alcohols		
2-methyl-2-propanol, 100%	-	12
2-methyl-2-butanol, 100%	-	2
IV. Aldehydes		
a. methanal, 3%	-	
ethanal, 1%	+	4
ethanal (complex-formation) 2%	-	
propanal, 2%	-	
2-butanal, 2%	-	3
b. propenal, 0.5%	-	
2-butenal, 0.001%*	+	9
2-butenal (complex-formation) 0.1%	-	
2-ethyl-2-hexenal, 1%	-	5
c. benzenecarbonal, 2%	+	
2-hydroxy-benzenecarbonal, 1%	-	
3-phenylpropenal, 1%	+	
V. Ketones		
2-propanone, 100%	-	
2-butanone, 100%	-	
VI. Acids		
methanoic acid, 0.1%	-	
ethanoic acid, 1%	-	
VII. Ether		
diethylether, 100%	-	
VIII. Ester		
ethylacetate, 100%	-	

*Lowest eczematogenous concentration determined by titration.

GAS-LIQUID CHROMATOGRAPHY OF ALCOHOLS AND ALDEHYDES

Gas chromatography was done to ascertain the degree of purity of some commercially available alcohols and aldehydes and to secure a pure ethanol for test purposes.

For the *separation* procedures, a Pye argon chromatograph was used. The column material used was made of Perkin Elmer type K (20 per cent poly-1, 2-ethanediol 1,500 on Celite); column length was 1 meter. The temperatures were 50° and 100° C., respectively, for compounds with low and high boiling points. The gas flow was 25 ml. per minute. Samples of 0.0004 ml. were injected.

Extra peaks were obtained for all substances studied except vodka. Earlier gas chromatography of vodka has shown, in addition to ethanol, pentanols in a concentration of less than 25 parts per million.⁷ The number of extra peaks in the alcohols and aldehydes are given in Table I. Several peaks in alcohols corresponded to aldehydes.

For the *preparation* procedure of pure ethanol, a Perkin Elmer Vapor Fractometer, Model 116 E, provided with Termistor detector, was used. The column used was Perkin Elmer type W (20 per cent poly-1,2-ethanediol 1,500 on Teflon) and helium as carrier gas. The column length was 2 meters and the temperature was 75°C. The gas flow was 40 ml. per minute. A sample of 0.05 ml. of ethanol was injected. The compound corresponding to the main peak was trapped in a glass tube refrigerated in a Dewar flask containing liquid nitrogen. The tube was sealed by melting after argon was introduced.

COMPLEX-FORMATION OF ALDEHYDES

Anionic complexes were formed by adding 25 mg. of sodium hydrogen sulfite to 1 ml. of 2 per cent ethanol, 2 per cent ethanal, and 0.2 per cent 2-butanal in water solutions.⁸ Before testing, 100 mg. of an anion exchanger (Dowex 1-X8) was added to each of the solutions of the complexes formed.

INVESTIGATION OF SENSITIVITY

The tests were performed on various occasions within a total period of 18 months. At the beginning of a new series of tests the sensitivity to previously titrated allergens was checked. During one test period the patient reacted negatively to substances to which she had previously often reacted positively. When re-tested one month later the patient had recovered her sensitivity to the substances.

The various concentrations of the substances used for testing were based on experience gained when testing patients with dermatitis. Some of the substances could be titrated (Table I, footnote) and the concentration given is to be understood as the lowest concentration capable of producing any eczematous reaction. The test substances were applied for 48 hours and the results were read 3, 24, and 48 hours after removal of the test material. Classification of a test reaction as positive required the presence of erythema as well as infiltration and/or papules-vesicles.

Reactions to Alcohols.—Table I shows the alcohols with which the patient

was tested. Of the primary aliphatic unbranched alcohols the patient reacted positively to alcohols with up to nine carbon atoms (I, a). Testing with chromatographically pure ethanol (100 per cent) was done also according to the method of Blohm and this gave a positive reaction (I, a).

Testing with ethanol after complex-formation of possibly occurring aldehydes gave positive reaction (I, a).

The patient reacted positively to branched aliphatic primary alcohols and to corresponding unbranched alcohols (1, b). One amino substituted unbranched 1-propanol gave a negative reaction (1, c).

An unsaturated aliphatic unbranched alcohol with three carbon atoms gave a positive reaction (1, d).

The tri-valent alcohol, 1, 2, 3-propanetriol, gave a negative reaction (1, e).

An aromatic alcohol gave a positive reaction (1, f).

The patient reacted negatively to all the secondary alcohols used (II) as well as to the tertiary alcohols (III).

An intracutaneous test with 1 per cent ethanol proved negative.

Reactions to Aldehydes.—Table I shows the aldehydes for which the patient was tested. Of the lower aliphatic saturated aldehydes, the patient reacted positively to ethanal and negatively to methanal, propanal, and butanal (IV, a). Ethanal and 2-butanal after complex-formation gave negative reactions (IV, a).

Of the unsaturated aldehydes, 2-butenal gave positive reaction in low concentration (1:100,000) (IV, b).

Of the aromatic aldehydes, benzene carbonal and 3-phenyl propenal gave positive reactions (IV, c).

Reactions to Ketones, Acids, Ethers, and Esters.—Table I shows the compounds for which the patient was tested. All gave negative reactions.

DISCUSSION

Because of the tendency of primary aliphatic alcohols to form aldehydes, we realized from the very beginning that the patient's allergic reactions to alcohols need not be due to the alcohols themselves. Reactions to primary aliphatic alcohols and the absence of allergy to secondary and tertiary alcohols, the last two not being able to form aldehydes, might suggest that the eczematous reactions to primary alcohols were due to aldehydes which were present in or formed from the alcohol and which gave positive reactions. It should, however, be observed that methanal, which is a common allergen, failed to produce a positive reaction.

The negative reactions to aldehyde complexes show that the aldehydes per se, and not contaminants, were allergens.

The inability of sodium hydrogen sulphite to counteract allergenic properties of ethanols indicates that the positive test reactions were due to the ethanol per se and not to aldehydes.

The gas chromatograms show that contaminants are common in alcohols, except in vodka.

The positive reactions to gas chromatographically pure ethanol and vodka provide further support for the assumption that ethanol was the allergen.

However, it cannot be excluded that aldehydes may form from alcohol absorbed by *the skin* and in amounts large enough to produce an eczematous reaction. If aldehydes form below the epidermal barrier, they should presumably not be inactivated by application of sodium hydrogen sulphite, an assumption in accord with our findings. Even if there is no evidence for oxidation of ethanol in the skin,^{9, 10} this patient might have a metabolic error responsible for the abnormal reactions.

It would, of course, have been desirable to study more of the problems referred to but, because of the troublesome symptoms the patient has had from test reactions during the last 18 months, the investigation must be discontinued, at least for the time being.

SUMMARY

An eczematous contact dermatitis is described in a woman after application of low aliphatic primary alcohols, including methanol and ethanol. She reacted positively to ethanal but negatively to methanal. The corresponding acids gave negative reactions. Secondary and tertiary alcohols and ketones gave negative reactions.

Gas chromatography showed commercially available alcohols to contain contaminants, including aldehydes. However, even chromatographically pure ethanol produced dermatitis. Ethanol thus seems to possess allergenic properties in this patient but the possibility of a metabolite of ethanol, *i.e.*, ethanal, being the allergen responsible cannot be excluded.

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