CUTANEOUS SENSITIVITY TO MONOGLYCEROL PARA-AMINOBENZOATE

Cross Sensitization and Bilateral Eczematization

Report of a Second Case

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PARA-AMINOBENZOIC acid, hereinafter referred to as PABA, and its metallic salts are used in the treatment of such diseases as lupus erythematosus, dermatomyositis, the rickettsial diseases, dermatitis herpetiformis, scrub and murine typhus fevers, rheumatic fever, leukemia and vitiligo. Many of the local anesthetics such as procaine, monocaine, pontocaine and butyn are derivatives of PABA as well as certain of the so-called skin analgesics including benzocaine and butesin.

Rothman and Rubin[1] recently discussed the sunburn preventive effect of PABA, incorporated in ointment bases and lotions. As a result of this preventative action, certain of the alkyl and alcoholic agents derived from PABA are the principal constituents of commercial lotions. We know of two such preparations, one of which contains monoglycerol para-aminobenzoate and the other propylene glycol para-aminobenzoate. There is evidence that internal organs, the liver and hematopoietic system, may become sensitized to PABA. Systematic reactions and eczematous contact-type dermatitis are well known phenomena produced by local anesthetics and skin analgesics. Dyes, such as the azo variety, paraphenylenediamine, and aniline frequently sensitize the skin as do the sulfonamides. These two groups of compounds are closely related to PABA and its derivatives in molecular structure because of the common aminobenzene nucleus ($H_2N\ C_6H_5$) and the often structurally allied side chains. The similarity in molecular structure may be said to be the basis for cross sensitization.

Clinically, this cross sensitization has been extensively studied in contact dermatitis. Sulzberger et al[2] observed positive reactions to patch tests with PABA in persons who showed cross reactions among the sulfonamides. Fascinating studies of cross sensitivity in dermatitis caused by local anesthetics (PABA derivatives) which extended even to anesthetics not structurally related, have been reported by Rothman et al,[3] Goodman,[4] Strauss,[5] James[6] Laden and Wallace,[7] Laden and Rubin[8] and others. A thought provoking study was made by Baer et al[9] who suggested that in cross sensitization between azo dyes incorporated in foods and paraphenylenediamine (a constituent of hair and clothing dyes), cross-eczematous dermatitis is possible. Lever's and Luikart's[10] patient who evidenced positive reactions to patch tests with dyes, local anesthetics (PABA derivatives), PABA and its alkyl ester derivatives

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(surface anesthetics), also had an eczematous dermatitis medicamentosa caused by PABA.

Meltzer and Baer[11] first reported eczematous dermatitis caused by monoglycerol para-aminobenzoate in a patient who had applied a commercial sunburn preventive. They found a wide range of cross sensitivity to para-aminobenzoic acid, its local anesthetic and skin analgesic derivatives, sulfonamides, and structurally related dyes, as well as other anesthetics and chemicals not thus related. We report herein a second case of sensitization to monoglycerol para-aminobenzoate in which cross sensitivity was demonstrated to the alkyl ester derivatives (butesin, benzocaine), paraphenylenediamine and aniline, but with an additional observation that the eczematous dermatitis was reproduced in the patient by ingestion of para-aminobenzoic acid.

Case Report

A white woman aged 40, housewife and part time cashier, was admitted to the Cleveland Clinic December 21, 1948. She complained of an itching eruption readily identified as lichen ruber planus, and which followed a "sunburn." The patient also presented a localized area of eczematoid dermatitis on the left foot of 2 months' duration which had occurred on the same site 7 years previously. A year prior to admittance, she had experienced an attack of acute urticaria which had developed at the end of 4 days' administration of a sulfonamide, probably sulfadiazine.

The lichen planus has been persistent with the exception of a remission of about 2 months' duration. During the remission the patient applied a sunburn preventative to her husband's skin and within 4 hours she developed itching, and within 24 hours, an acute vesicular and edematous dermatitis appeared on the hands, and patches on the forearms, arms, face and neck. At this time, it became known that the same lotion had been applied to her skin when she acquired the "sunburn" in July, 1948. The dermatitis rapidly subsided following treatment with soothing wet dressings and lotions. Three months later, she took a 100 mg. dose of para-aminobenzoic acid followed the next day by an erythema with itching on the hands and forearms. The dorsa of the hands were slightly swollen but there was no vesiculation. The reaction subsided during the next 3 or 4 days.

The manufacturer obligingly supplied the various ingredients of the suntan lotion in suitable form for patch tests. Other significant chemicals also were applied to the patient's skin as patch tests in standard concentrations. The patches were removed at the end of 48 hours and observed again at the end of 72 hours. The results are recorded in Table 1. For the sake of brevity, test number 1 which is recorded as negative, represents the negative results of 6 patch tests with combinations of the various ingredients of the lotion.

Comment

The sunburn experienced by our patient may have been the trigger mechanism for the development of lichen planus. Not infrequently a history of chronic nervous exhaustion, mental strain or shock, or trauma precedes the onset.

For some years the patient had been under the strain of two jobs and symptoms of an anxiety state were manifest; hence the subsequent development of lichen planus was not considered unusual.

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Table 1

COMPARISON OF RESULTS OF PATCH TESTS WITH INGREDIENTS OF A SUNBURN PREVENTIVE LOTION AND STRUCTURALLY RELATED AND NONRELATED COMPOUNDS

Chemicals Tested	Meltzer's and Baer's[11] Patient	Our Patient
1. Various ingredients of sunburn preventive lotion other than monoglycerol PAB*	0	0
2. Monoglycerol PAB*	4+	4+
3. PABA	4+	4+
4. Benzocaine	4+	4+
5. Butesin	4+	-----
6. Butyn	-----	4+
7. Procaine	4+	0
8. Pontocaine	0	0
9. Sulfaquanidine	3+	0
10. Sulfanilamide	3+	0
11. Sulfadiazine	1+	0
12. Sulfathiazole	-----	0
13. Aniline	4+	2+
14. Paraphenylendiamine	4+	3+
15. Azo dye "A"	2+	-----
16. Azo dye "B"	0	-----
17. Nupercaine	1+	0
18. Saccharin	2+	0
19. Picric acid	3+	0
20. Metycaine	-----	0
21. Stovaine	0	-----
22. Paranitrobenzoic acid	0	0
23. Phenol	0	0
24. 3 5 Dinitrobenzoic acid	0	-----
25. Anthranilic acid	0	-----
26. Apothesine	0	-----
27. Methyl anthranilate	0	-----
28. Alypin	0	-----
29. Paranitrobenzaldehyde	-----	0

*Supplied by the manufacturer.

Of considerable interest was the sensitization to monoglycerol PAB and the demonstration of cross sensitivity to related chemicals. Our case may be compared to that of Meltzer and Baer which showed a much wider range of cross sensitization (table 1). Among factors influencing sensitization in eczematous dermatitis are the capacity of a chemical compound to sensitize, frequency of exposure, unilateral or bilateral transepidermal penetration, and the physical conditions at the skin surface. It is not known what possible decomposition products form a breakdown of a chemical, or what chemical protein conjugates (hapten linkage), producing an eczematous dermatitis, are formed

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on or within the epidermis. Explanations for cross sensitivity have been based on analysis of the molecular structural relationships between primary and secondary allergens e.g. the nucleus, substituted radicals in the nuclei, and/or the whole or portions of the side chains. Experiments utilizing the patch test with compounds closely approximating the various parts of the molecule of the primary eczematizing chemical have partially substantiated this hypothesis. Baer[12] assumes that the sensitized cell may be unable to differentiate between a primary allergen, and/or its conversion products or the secondary allergen. However, this hardly explains the limited range of cross sensitization even among members of a homologous group of compounds as well as the broader spectrum of cross sensitivity including apparent heterologous chemicals.

The immunochemical theory of complementariness for the precipitin reaction discussed by Pauling, Campbell and Pressman[13] may conceivably account for cross sensitization by the interaction of the hapten-protein group formed from sensitizing compounds in the epidermis and the cellular proteins (antibodies?). The haptenic groups assume molecular spatial relationships which provide certain corresponding surface areas for the forces such as Van der Wool's attraction, hydrogen bond formation, and interaction of electrically charged groups to attract. The complementary antibody polypeptid chains then fold into a stable configuration in the presence of the antigen, and the reaction takes place. Thus for every antigen (allergen) a specific complementary antibody is present.

We may postulate that a sensitizing compound on entering the skin may form one or more different haptenic groups or, assuming a breakdown of the chemical in the body or epidermis, the products may form one or more hapten-protein groups. Formation of cellular antibodies may result to only a few or perhaps to many of the groups. In a person having had multiple or polyvalent episodes of eczematous dermatitis to different chemicals, the number of haptenic groups and corresponding antibodies may be greatly multiplied. Conversely, one episode of eczematous dermatitis to only one compound may result in the formation of a relatively few antigens. Applying the complementariness theory, a smaller or larger number of the antibody polypeptid chains within the cell may fold into a spatial configuration stable in the presence of the haptenic groups. We believe that the immunochemical theory of complementariness may explain why Meltzer's and Baer's patient who had several episodes of contact type eczematous dermatitis to different chemicals showed cross reactions to 14 compounds and our patient, having a single outbreak of eczematous dermatitis to but one chemical, evidenced positive reaction to only 6 closely related compounds.

In the cases studied by the authors herein referred to, 85 chemicals were applied by the patch test technic. The majority of the patients were physicians and dentists who handled local anesthetics. In Table 2 we have collected those chemicals producing positive reactions into groups and in the order of frequency of administration. If one wishes to determine the trend of cross sensitivity in a patient who is sensitive to a probable local anesthetic, one may selec-

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Table 2

FREQUENCY OF POSITIVE PATCH TESTS IN 22 PATIENTS PRESENTING CROSS SENSITIZATION REACTIONS

Name	Molecular Formula	Number of Patients with Positive Reactions
I. Local anesthetics. Esters of PABA with a tertiary amine in the side chain		
Procaine	$H_2N \cdot C_6H_4 \cdot CO_2 \cdot C_2H_4 \cdot N : (C_2H_5)_2$	18
Monocaine	$H_2N \cdot C_6H_4 \cdot CO_2 \cdot C_2H_4 \cdot NH \cdot CH_2 \cdot CH : (CH_3)_2$	10
Larocaine	$H_2N \cdot C_6H_4 \cdot CO_2 \cdot C(CH_2)_2 \cdot CH_2 \cdot N : (C_2H_5)_2$	10
Tutocaine	$H_2N \cdot C_6H_4 \cdot CO_2 \cdot CH(CH_3) \cdot CH(CH_3) \cdot CH_2 \cdot N : (CH_3)_2$	9
Butyn	$H_2N \cdot C_6H_4 \cdot C_3H_6 \cdot N : (C_4H_9)_2$	8
Pontocaine	$C_4H_9 : N \cdot C_6H_4 \cdot CO_2 \cdot C_2H_4 \cdot N : (CH_3)_2$	5
Procaine borat	$H_2N \cdot C_6H_4 \cdot CO_2 \cdot C_2H_4 \cdot N : (5\ HBO_2)\ (C_2H_5)_2$	3
II. Surface anesthetics. Alkyl esters of PABA and substituted compounds		
Benzocaine	$H_2N \cdot C_6H_4 \cdot CO_2 \cdot C_2\ H_5$	6
Butesin	$H_2N \cdot C_6H_4 \cdot CO_2 \cdot C_4H_9$	4
Orthoform	$H_2N \cdot C_6H_3(OH) \cdot CO_2 \cdot CH_3$	1
Neo-orthoform	$OH \cdot C_6H_3(NH_2) \cdot CO_2 \cdot CH_3$	1
III. Sunburn preventives, PABA, alkyl esters of PABA and metallic salts of PABA		
PABA	$H_2N \cdot C_6H_4 \cdot CO\ OH$	7
Sodium PAB	$H_2N \cdot C_6H_4 \cdot C\ O\ O\ Na$	2
Monoglycerol para-aminobenzoate	$H_2N \cdot C_6H_4 \cdot CO_2 \cdot CH_2 \cdot C\ H\ O\ H \cdot CH_2O\ H$	2
IV. Chemotherapeutic agents. Sulfanilic acid derivatives structurally related to PABA		
Sulfadiazine	$H_2N \cdot C_6H_4 \cdot SO_2 \cdot N : C_4N_2H_3$	5
Sulfanilamide	$H_2N \cdot C_6H_4 \cdot SO_2 \cdot N\ H_2$	4
Sulfaquanidine	$H_2N \cdot C_6H_4 \cdot SO_2N : C : (NH_2)_2$	3
Sulfathiazole	$H_2N \cdot C_6H \cdot SO_2 \cdot N\ H \cdot S \cdot N \cdot C_3H_2$	2
V. Dyes		
Aniline	$H_2N \cdot C_6H_4$	4
Paraphenylene-diamine	$H_2N \cdot C_6H_4 \cdot NH_2$	4
Azo dye "A"	$CH_3CO \cdot HN \cdot C_6H_4N : N \cdot C_6H_3OH\ Cl$	1
Methyl orange	$(CH_3)_2N \cdot C_6H_4N : N \cdot C_6H_4SO_2OH$	1
VI. Miscellaneous. Includes local anesthetics and compounds that may or may not be structurally related to PABA		
Para-aminophenol	$H_2N \cdot C_6H_4OH$	3
Apothesine	$C_6H_5 \cdot CH : CH \cdot CO_2 \cdot C_3H_6 \cdot N : (C_2H_5)_2$	2
Alypin	$C_6H_5CO_2 \cdot C : [\cdot CH \cdot N(CH_3)_2]\ [\cdot CH_2 \cdot N(CH_3)_2]\ C_2H_5$	1

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one or more chemicals from the several groups for preliminary patch tests. On the other hand we agree with Sulzberger and Baer[14] that the important motive, from the patient's standpoint, is to determine the chemicals which may be considered "safe" as determined by negative patch tests. In the patient sensitive to a local anesthetic, positive patch tests would more likely be obtained with chemicals of the same group than with other chemicals. Conversely, negative reactions are more frequently obtained with local anesthetics or other chemicals not listed in the groups in Table 2.

An eczematous reaction was reproduced in one of Lever's and Luikart's patients, and in our own, by ingestion of small amounts of PABA. It is recognized that some chemicals may, by transepidermal penetration either from within or without the body or both, cause an eczematous dermatitis. Baer, Leider and Mayer[9] have indicated the possible dangers of cross sensitization reactions between dyes in foods and dyes in clothing or those having come in contact otherwise with the skin. Cross sensitization induced by para-aminobenzoic acid, (presumably a factor in the vitamin B complex) and/or its derivatives, and structurally related compounds by virtue of their wide use in medication, in foods, and in contactants may be a potential factor in eczematoid dermatitis of unknown origin.

Summary

A second case of cutaneous sensitivity to monoglycerol para-aminobenzoate, an ingredient of a proprietary sunburn preventative, is reported. The dermatitis was reproduced by ingestion of para-aminobenzoic acid. Cross sensitivity to PABA, certain of its alkyl derivatives, and structurally related dyes was demonstrated. The immunochemical theory of complementariness between allergen and cellular antibodies in the epidermis is discussed in relation to cross sensitization in the skin. A compilation of chemicals is arranged in groups and in order of frequency in producing positive reactions from which structurally related chemicals may be selected for a rapid survey by the patch test technic in order to determine the trend of cross sensitization.

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