CROSS SENSITIZATION FROM PARA-AMINOBENZOATE IN SUNBURN PREVENTIVES

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Evansville is the fourth largest city in Indiana and has a population of 130,000. In this relatively small urban center 2 patients have been seen during the past year with severe complications from the use of local anesthetics.† They were known to be sensitive to para-aminobenzoate in sunburn lotions. The first patient experienced an explosive dermatitis after she applied a remedy containing benzocaine to a patch of Rhus dermatitis on the left wrist. She spent a week in the hospital and was away from work for a month. In the second patient a bullous lesion developed with sloughing and ulcer formation at the site of procaine infiltration for the removal of a small fibroma. Fortunately, the fibroma was on the thigh instead of the eyelid or face. Patch tests showed hypersensitivity to para-aminobenzoate and various local anesthetics.

REPORT OF CASES

Case 1. A single, white woman, aged 22 years, was seen in June 1949 because of an eruption of five days’ duration. The face, neck and extremities were the most severely involved. An erythro-edematous dermatitis topped with vesicles and bullae was present; it was sharply demarcated and corresponded to the areas of skin receiving the greatest exposure to sunlight. She brought with her a partly used bottle of sun lotion that she had used the preceding afternoon to prevent sunburn while at the beach. Only two hours were spent in the sun. The dermatitis appeared the same evening. The edematous reaction had closed her eyelids, and her parents who were concerned about sight insisted on hospitalization. Customary and routine examinations were normal.

The past history was reviewed especially for drugs. The tonsils were removed in 1945 under local anesthesia. Sulfathiazole was prescribed as a prophylaxis. In 1949 she was again exposed to sulfathiazole with codeine because of a sore throat. No rash appeared. She could not recall the use of a sulfonamide on the skin. She had a severe sunburn in 1946, but no time was lost from work. There had been attacks of Rhus dermatitis in 1946, 1947 and 1948. The dermatitis was treated with “shots” reinforced by penicillin injections. The brand of the latter was not known. Topically, for sunburn and Rhus dermatitis, she had used phenol, benzoic acid, salicylic acid, camphor and tannic acid. The attack of Rhus dermatitis in 1948 took six weeks to heal. This aroused suspicion that sensitization to certain therapeutic chemicals might

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† Dr. Elmer Gross, in Wilmington, Delaware, saw 23 cases in one summer of dermatitis venenata from sunburn preventives.
have developed at that time. She had never used eye, nasal or gargle medications. Aspirin was taken occasionally.

Patch tests in 1949 disclosed sensitivity to para-aminobenzoic acid. The short incubation period to the sun lotion—roughly six hours—is evidence that she was already sensitive to para-aminobenzoic acid. In June 1951 an incapacitating dermatitis again developed. Several days earlier she had noticed a rash on the left wrist. This was self-diagnosed as poison ivy. A tube of soothing cream was purchased to treat the rash. Within hours the rash worsened and further application over areas of spreading was followed by a generalized dermatitis. The cream contained 5 per cent benzocaine. Patch tests were positive to the cream and a 1 per cent alcoholic solution of benzocaine.

Case 2. A white girl, aged 13 years, was seen the end of March 1947 for a pustular, weeping dermatitis of the hands and knees with lymphangitis and adenopathy involving the left upper extremity. The eruption appeared first on the left ring finger early in February. She was indefinite about the onset, but recalled a severe chapping episode about the same time (1). Exposures to soap, cosmetics and lotion continued, and soon the dermatitis had spread to the third and second left fingers. At that stage a different type of treatment was tried. Calgisic® was used on the left fourth finger, sulfathiazole ointment on the left third and a yellow ointment on the left second to determine which salve should be used. To assure success, sulfathiazole was taken by mouth. As the eruption worsened treatment was changed to penicillin injections. Eruptions then appeared suddenly on the right hand and knees. Six weeks of care and management led to a normal skin. The parent refused patch tests with substances used previously for treatment.

The history revealed no previous use of local anesthetics. The severity of the dermatitis suggested a benzocaine sensitivity at this time. Sulfonamide and penicillin sensitization also were considered. The brand of penicillin was not known.

Late in September 1948 a number of vesicles appeared on the toes. The feet were soaked in lysol solution. An eruption promptly appeared on the hands. This attack proved to be mild; the patient was well in less than four weeks. The hand dermatitis recurred in March 1950 during a severe cold spell. The eruption was recalcitrant, and the advice of a consultant was obtained. Warm weather in May was associated with rapid healing (1). Almost two years passed without further skin trouble. In March 1952 she was seen for a generalized dermatitis which was most severe where pink rayon panties apposed the skin. Pityriasis rosea was considered in the differential diagnosis and, in addition, the dye was suspected. She was well in less than three weeks. During the evening of June 16, 1952, the fifth attack of dermatitis developed on the face, neck, back and extremities. The same afternoon she had been at the beach, and to prevent sunburn had applied a sunburn lotion. The eruption involuted in about ten days. A patch test with the lotion produced a 4 plus reaction. For several years she was aware that a fibroma on the left thigh occasionally became irritated. It was removed the end of September 1952. The pedicle measured about 1 mm. in diameter. The base was infiltrated with 2 per cent procaine solution, and the lesion was removed by electrodesiccation. The next day the site of anesthesia showed a bullous lesion; weeping and eventual slough occurred of an area about 1 cm. in diameter. Sensitization to procaine was suspected (table 1, fig. 1).
### TABLE 1
**Tests for Cross Sensitization**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Aminobenzoic acid 5% solution</td>
<td>4 plus</td>
<td>4 plus</td>
</tr>
<tr>
<td>Butyn 2% solution</td>
<td>4 plus</td>
<td>4 plus</td>
</tr>
<tr>
<td>Benzocaine 1% solution</td>
<td>4 plus</td>
<td>4 plus flare</td>
</tr>
<tr>
<td>Procaine 2% solution</td>
<td>4 plus</td>
<td>4 plus</td>
</tr>
<tr>
<td>Surfacaine® 0.5% cream</td>
<td>1 plus</td>
<td>1 plus</td>
</tr>
<tr>
<td>Thipental 2% solution</td>
<td>neg.</td>
<td>neg.</td>
</tr>
</tbody>
</table>

**Structure**

- p-Aminobenzoic acid: ![Structure](image)
- Butyn: ![Structure](image)
- Benzocaine: ![Structure](image)
- Procaine: ![Structure](image)
- Surfacaine®: ![Structure](image)
- Thipental: ![Structure](image)
Unfortunately, it is impossible in these cases to detect the initial sensitizing substance. The greatest suspicion can be directed to therapeutic agents. Each patient had had recurrent attacks of dermatitis. A similar history is often obtained in dermatologic patients. This should alert us to look not only for avenues of cross sensitization, but also for chemicals that had previously sensitized. Both patients had been subjected to sulfonamide therapy. Sulzberger, Kanof and Baer (2) reported cross sensitization between sulfathiazole, sulfadiazine, sulfanilic acid, sulfaguanidine, para-aminobenzoic acid and procaine following a dermatitis from sulfanilamide. The studies of Phillips (3) revealed that in a group of subjects hypersensitive to sulfonamide drugs, the incidence of sensitization to procaine was 16 per cent. It was known in case 1 that sensitization to para-aminobenzoate had existed since June 1949 and to benzocaine since June 1950. Patch tests three and two years later indicated no lessening of sensitivity. This patient might have used benzocaine for attacks of Rhus dermatitis, but there was no known exposure to para-aminobenzoic acid, butesin and surfacaine®, indicating probable cross sensitization. On therapeutic use or patch tests, or both, all the substances reacted in less than twenty-four hours. Pre-existing sensitization was definitely present. Case 2 had a known contact with benzocaine, but no known exposure to para-aminobenzoic acid, butesin, procaine and surfacaine®. On therapeutic use or patch tests, or both, with these chemicals, reactions were obtained in less than twenty-four hours. Pre-existing sensitization was definitely present either from past exposures or cross sensitization. It is difficult to prove cross sensitization in these cases. An objection previously raised by Rostenberg and Kanof (4), "lack of knowledge on the part of investigators concerning other related sensitizing substances to which the patient may have been simultaneously

![Fig. 1. Patch test reactions to (1) procaine (flare reactions); (2) para-aminobenzoic acid; (3) butyn; (4) procaine; (5) surfacaine, and (6) thiopental (negative). The sensitivity to benzocaine was discovered by patch test an an earlier date.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931681/)
"exposed," is apparently substantiated by the history in these cases. Previous attacks of dermatitis had exposed them to a wide range of chemicals. All chemicals believed to have cross sensitized, produced reactions in less than twenty-four hours, an indication of existing sensitizations to the particular structures.

Meltzer and Baer (5) in 1948 reported a case in which sensitization to benzocaine was discovered in 1939. At later dates a dermatitis developed when a sulfonamide drug was taken and an eruption occurred after applying a sunburn preventive containing para-amino-benzoic acid was applied. Patch tests disclosed that the patient was sensitive to several local anesthetics, sulfanilamide, paraphenyldiamine and aniline, and weaker reactions to certain azodyes and picric acid were noted. In 1948 Baer (6) reviewed the literature on cross sensitization in allergic eczematous dermatitis. The chemical groups producing cross sensitization among local anesthetics were classified on the basis of various reports. Cross sensitizations occurred between certain local anesthetics and paraphenylenediamine and between sulfonamide drugs. The phenomenon also occurs between nitrobenzene and aniline and among paraphenylenediamine and azodyes.

**INCIDENCE OF PATCH TEST REACTIONS TO LOCAL ANESTHETICS AND ORGANOMERCU RiALS**

The sensitizing properties of organomercurials have been well established (7, 8, 9, 10). Five years ago it was an everyday experience to see dermatologic lesions well soaked with red antiseptics. Today they are seen much less frequently. Physicians have avoided them, but laymen still believe in them. The fate of the organomercurials apparently will set the pattern for the local anesthetics. Overtreatment dermatitis from cutaneous application of the latter is sufficiently common that reporting its occurrence is not deemed worth while. They produce such severe sensitization complications that hospitalization of the patients is often necessary. These chemicals can be purchased by anyone. They are advertised extensively and claims of relief and cure are fantastic.

In 1946 a review of 106 remedies for athlete's foot disclosed that five of them contained benzocaine (8). In 1948 a survey of 114 remedies for poison ivy revealed that 16 of them contained various local anesthetics (9). Lane and Luikart (11) found 81 preparations of local anesthetics for topical use in 1951. I could add several dozen more to this list. Butesin piperate, benzocaine and nupercaine hydrochloride were declared in 1948 to be unsafe for self-therapy (9). In 1951 Lane and Luikart (11) advised that a word of caution about the possibility of sensitization should be issued in all advertising that concerns local anesthetics, but the advice was not heeded concerning organomercurials (7). Pillsbury (12) commented that if an antipruritic agent has sensitizing properties, its effect on itching unquestionably is
greater than that of many bland ointment bases, and such convincing
evidence is not available in many compounds in common use. Al-
though the local anesthetics are declared to relieve itching, as sensi-
tizers they produce as severe itching as I have encountered.

In 1948, intradermal tests with a solution of 1 per cent procaine
were performed on 6 patients who were sensitive to benzocaine after
the local and systemic signs of sensitization had subsided. The tests
were done on the flexor surface of the forearm. In 4 cases a flare
response of the entire flexor surface of the arm appeared. In the
remaining 2 cases, flare reactions 4 cm. in diameter were observed.
At the point of injection, a ring erythema persisted for several days
and the area involuted by pustulation. The duration of the sensitivity
to benzocaine is not known, but it is possible that the wide use of this
chemical on the skin can predispose to violent systemic reactions when
procaine is used as a local anesthetic agent. Recently, a physician told
me of sudden death of his patient after procaine was instilled into the
nasal mucous membrane for a resection.

The literature on local anesthetic dermatitis had a humble be-
ginning. An occasional case was reported. Today, it is no less un-
usual than Rhus dermatitis. A good example is surfacaine®. This
local anesthetic was introduced in this locality in 1948. It was placed
in the hands of those who would be most likely to use it on the skin.
In 1949 the first case was seen; it produced a generalized, incapacit-
ing dermatitis. The local anesthetics producing reactions are shown
in table 2. Today, one or 2 cases are seen every month. The tendency

<table>
<thead>
<tr>
<th>Substance</th>
<th>Structure</th>
<th>Case W. S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfacaine® 0.5%</td>
<td><img src="image" alt="Structure" /></td>
<td>4 plus</td>
</tr>
<tr>
<td>Nupercaine 1%</td>
<td><img src="image" alt="Structure" /></td>
<td>neg.</td>
</tr>
<tr>
<td>Substance</td>
<td>Structure</td>
<td>Case W. S.</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Procaine 2% solution</td>
<td><img src="image1" alt="Structure" /></td>
<td>neg.</td>
</tr>
<tr>
<td>Benzocaine 2% solution</td>
<td><img src="image2" alt="Structure" /></td>
<td>neg.</td>
</tr>
<tr>
<td>Pontocaine 2% solution</td>
<td><img src="image3" alt="Structure" /></td>
<td>4 plus</td>
</tr>
<tr>
<td>Butyn 2% solution</td>
<td><img src="image4" alt="Structure" /></td>
<td>neg.</td>
</tr>
<tr>
<td>Metycaine 0.5% ointment</td>
<td><img src="image5" alt="Structure" /></td>
<td>4 plus</td>
</tr>
<tr>
<td>p-Aminobenzoic acid 5% solution</td>
<td><img src="image6" alt="Structure" /></td>
<td>neg.</td>
</tr>
</tbody>
</table>
exists to regard topical sensitizing drugs in terms of their incidence of sensitizing reactions. An incidence of 1 or 2 per cent is not serious, but over 5 per cent is cause for concern. These figures have little true meaning. If a given topical drug can produce a characteristic sensitization pattern in a given case, more cases will occur and the incidence of sensitization will follow closely its extent of use.

**SUMMARY**

Local anesthetics can be classed as essential drugs for many minor and major surgical procedures. In addition, they are essential drugs for numerous and important diagnostic procedures—to mention but one, obtaining biopsy specimens. There is abundant evidence that with the use of local anesthetic skin remedies as antipruritic chemicals, and particularly when they are allowed to saturate injured skin (8), exquisite degrees of allergic eczematous sensitization may occur. There is further evidence that when sensitization develops to one agent, for instance benzocaine, cross sensitization to procaine also develops. The chief apprehension over the widespread use of para-aminobenzoate in sunburn preventives is that it can be the primary sensitizing allergen with the result that the person so sensitized will experience sequelae when exposed to local anesthetic agents. It would seem that before a large quantity of procaine is instilled locally, local anesthetic sensitivity should be ruled out, especially if the history disclosed previous use of local anesthetics for dermatitis.

**REFERENCES**

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15. Rostenberg, A., Jr., and Sulzberger, M. B.: Some Results of Patch Tests; Compilation and Discussion of Cutaneous Reactions to About 500 Different Substances, as Elicited by Over 10,000 Tests in Approximately 1,000 Patients, Arch. Dermat. & Syph. 35: 433 (March) 1937.