

LOCAL ALLERGIC EDEMA INDUCED BY INJECTED PROCAINE

DIAGNOSTIC VALUE OF THE TWENTY-FOUR-HOUR INTRACUTANEOUS TEST

SHEPPARD SIEGAL, M.D.* NEW YORK, N. Y.

ALLERGY to procaine is uncommon. Its most frequent manifestation is contact dermatitis, occurring chiefly as an occupational disease among dentists.¹⁻³ Anaphylactic shock due to procaine is a rarity, perhaps best documented by Crip and Ribiero,⁴ and also noted in the course of repeated intravenous treatments with this drug.⁵ Others dispute these reactions and, indeed, appear to doubt that allergy to injected procaine occurs at all.^{6, 7}

The present report concerns three cases in which there was repeated reaction to procaine, characterized by definite, even marked, swelling of the cheek and face at the site of injection for dental anesthesia. In each instance a preliminary impression of infection or trauma as a cause of the edema had to be discarded. The suspicion of allergy was confirmed by the demonstration of a positive skin test reaction of the delayed twenty-four-hour type to intracutaneous procaine. This form of procaine allergy appears to be largely ignored in most current discussions of hypersensitivity to this compound. Thus, neither Crip and Ribiero, in their classification of procaine allergy,⁴ nor Sadove and associates,⁸ in their review of reactions to local anesthetics, take note of it. Gray and Geddes⁹ fail to refer to it in their extensive review of the local anesthetics. Rickles, however, has reported ten such cases, each with a positive skin test reaction of the twenty-four-hour type,¹⁰ and Mitchell described two more, also with similar positive delayed skin reactions on test.¹¹ Adler and Simon's¹² earlier case differed in that it reacted not only with edema but with vesiculation as well and presented positive patch and intracutaneous skin test reactions to procaine.

THREE CASES OF EDEMA DUE TO PROCAINE

Case 1.—Patient F. K., a 42-year-old housewife, was seen in May, 1952, because of marked edema of the face appearing two to four hours after minor dental work done under procaine anesthesia. The swelling occurred on two occasions, lasting six to eight days each time, and was accompanied by noticeable itching. There was no evidence of any generalized reaction to the injection. Three years earlier she had noticed a slight similar reaction to a local anesthetic. She gave a history of a brief period of urticaria many years before, proneness to wheezing after colds, and some intolerance to milk, which caused diarrhea. Family history was positive for allergy.

Intracutaneous tests were carried out with 2 per cent procaine in aqueous solution. The immediate reaction was negative, but the delayed test done with 0.1 ml. was positive at twenty-four hours. Similar tests with 1 per cent Monocaine and 2 per cent Xylocaine

*Associate Physician (Allergy), Lenox Hill Hospital; Associate Attending Physician (Allergy), Mt. Sinai Hospital.

Received for publication Feb. 10, 1958.

likewise gave negative immediate reactions. However, the delayed twenty-four-hour test was even more strongly positive to Monocaine, although negative to Xylocaine. To confirm further the significance of these positive responses, the three anesthetics were injected subcutaneously into the outer upper arms. Local edema was definitely visible twenty-four hours later at the procaine and Monocaine sites but not at the site of Xylocaine injection. These reactions reproduced the local swelling which had been the patient's chief complaint. The patient's dentist was advised that Xylocaine should be well tolerated. This proved correct, as subsequent procedures were performed under Xylocaine anesthesia without untoward incident.

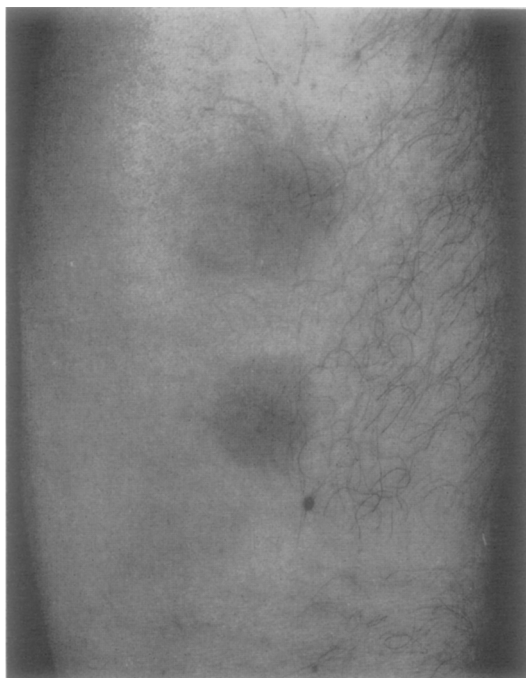


Fig. 1.—Case 2. Positive twenty-four-hour skin test reactions to procaine (upper) and Monocaine (lower) in patient with local allergic edema due to procaine.

Case 2.—M. G., a 26-year-old female schoolteacher, was seen in April, 1955, with a history of marked swelling over the jaw which occurred on three occasions after minor dental procedures under procaine anesthesia. The last time almost the entire left side of the face had been affected, with partial closure of the eye due to lid edema. Twice the reaction lasted for five days, and on the third occasion it took two weeks for the edema to subside. There was no itching but some local pain was present, aggravated by chewing and eating. There was no indication of any generalized reaction. She gave no history of atopy. Two years earlier, following penicillin injections, she had persistent generalized pruritus without eruption for several weeks. Family history revealed that the patient had a maternal aunt with severe asthma. Members of the immediate family were free of clinically apparent atopy.

Intracutaneous tests were carried out with 2 per cent procaine, 1.5 per cent Monocaine, 2 per cent Metycaine, 2 per cent Pontocaine, 2 per cent Unacaine, 1 per cent Lucaine, 1 per cent Cyclaine, and 2 per cent sodium sulfadiazine in aqueous solution. Several of these which were available without epinephrine could be read for the immediate reaction, and all were negative. At the twenty-four-hour reading procaine, Monocaine, and Unacaine

gave positive tests consisting of a circular area of erythema about 3.0 cm. in diameter with some central edema (Fig. 1). In this instance also, Xylocaine was recommended as a safe substitute for procaine and proved to be well tolerated in the course of subsequent dental procedures.

Because of the history of reaction to penicillin, this patient was also tested with crystalline penicillin G, 20,000 units per milliliter. The immediate test was negative by both scratch and intracutaneous methods. The test for the delayed reaction, after intracutaneous injection of 0.1 ml. of penicillin solution, proved positive at twenty-four hours, with an area of pink erythema 3.0 cm. in diameter and central edema. This induced lesion persisted longer than the reaction to procaine; it did not clear entirely within eight days. It was accompanied by more marked pruritus than the positive test lesions to the local anesthetics. Routine allergy tests with pollens and inhalants were negative.

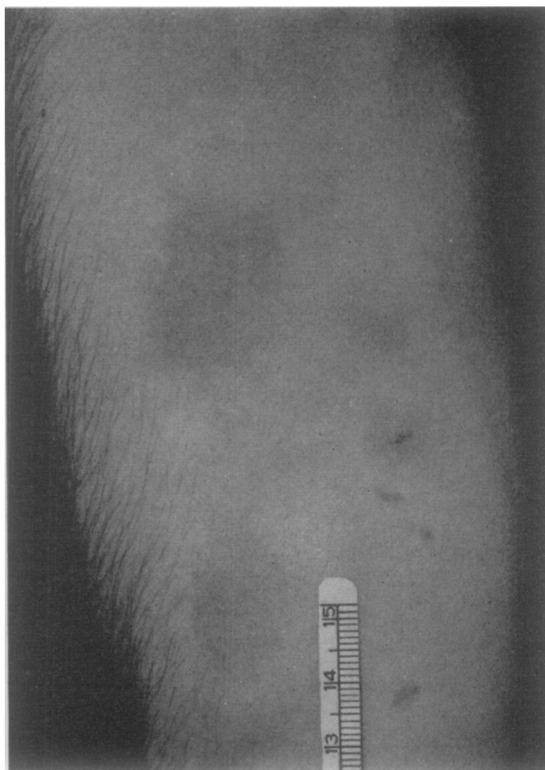


Fig. 2.—Case 3. Positive twenty-four-hour skin test reactions to procaine (left upper) and crystalline penicillin G (left lower) and slightly positive reaction to Monocaine (right). Negative test to Xylocaine (right lower). Case of local allergic edema due to procaine.

In November, 1957, two and one-half years after first observation, this patient was retested with procaine, Monocaine, and crystalline penicillin G solutions as she had been previously. Once again she reacted positively to all three but most strikingly to penicillin. Her allergy to these substances thus proved to be persistent. Two weeks after the retests, serum was tested for antibodies. No precipitation to either crystalline penicillin G or procaine could be demonstrated by either the gel diffusion technique or the ring method. Complement-fixation antibodies to these substances were also absent.

Case 3.—K. D., a 23-year-old female hospital worker seen in September, 1957, had noted in the preceding three months that three times she had developed swelling of the cheek on

the side of minor dental work done under procaine anesthesia. This began twelve to fourteen hours after treatment and lasted thirty-six to forty-eight hours. There was neither pain nor itching. Her reaction was thus less intense than that of the two other patients. Again there was no sign of general reaction. She had had procaine many times previously without ill effect. She was prone to an occasional single urticarial wheal, but there was no other personal history of allergy. Family history was negative for allergy. One year before she had received twice-daily injections of procaine penicillin for treatment of pneumonia, but there had been no evidence of any allergic reaction.

Intracutaneous tests were done with 2 per cent procaine. The immediate reaction was negative. The delayed test, after injection of 0.1 ml., was positive at twenty-four hours. The reaction at the test site began at four hours. It subsided after its peak at twenty-four hours, clearing almost completely by the end of forty-eight hours. It was characterized by a circular zone of bright pink erythema with central infiltration. A similar, though less intense, reaction to 1 per cent Monocaine was observed (Fig. 2). Negative tests were obtained with 2 per cent Xylocaine, 1 per cent Pontocaine, and 1 per cent Unacaine. This patient, too, was found able to tolerate Xylocaine anesthesia for subsequent dental procedures.

Because of the positive reaction to penicillin obtained in Case 2, skin tests with aqueous solution of crystalline penicillin G, 20,000 units per milliliter, were carried out. The immediate reaction was negative, but the delayed test reaction elicited with 0.1 ml. was definitely positive, presenting a circular zone of erythema, 2.0 cm. in diameter, with slight central edema.

Routine allergy tests with pollens, inhalants, and foods were negative throughout. This patient's serum was tested for antibodies in November, soon after retest had shown persistent positive skin test reactions to procaine and penicillin. No evidence of precipitins to procaine or to penicillin could be demonstrated by gel diffusion or ring techniques, nor were complement-fixing antibodies present. Passive transfer tests were negative to procaine and penicillin, observation being made for both immediate and delayed reactions.

CONTROL GROUP

Sixty-five adult ward patients, both men and women, were skin-tested with 2 per cent aqueous procaine solution. Twenty-five were tested intracutaneously for the immediate reaction, and all had negative reactions. All sixty-five were tested with 0.1 ml. intracutaneously for the twenty-four-hour test, and again all gave negative responses.

TWO CASES OF PENICILLIN ALLERGY WITH POSITIVE PROCAINE SKIN TESTS

Case 4.—M. B., a 24-year-old woman, had urticaria for seven months, occurring two months after treatment with procaine penicillin. When the patient was seen in May, 1955, skin tests with crystalline penicillin G, 30,000 units per milliliter, were negative on immediate reading, but the 24- to 48-hour reaction was positive. This showed a strongly positive reaction of erythema and central edema. Similar tests with 2 per cent aqueous procaine gave a negative immediate reaction and a milder but definitely positive twenty-four-hour skin test reaction (Fig. 3).

Case 5.—E. L., a 45-year-old man, first gave evidence of allergy to penicillin in 1953, when he reacted with marked erythema of the groins and buttocks twenty-four hours after a single penicillin injection for acute tonsillitis. He was skin-tested in 1954 with crystalline penicillin G, 10,000 units per milliliter, and gave a strongly positive delayed reaction, with erythema and edema; this reaction reached its height at forty-eight hours, but lasted with some eczematization for several days. A positive skin reaction to penicillin could be obtained with as little as 10 units per milliliter. The patient was not tested with procaine until January, 1958, when he was shown to have a negative immediate test but a positive delayed test reaction with definite erythema and edema, more than 2.0 cm. in diameter. This test lesion began to fade after forty-eight hours.

DISCUSSION

The phenomenon of local allergic edema due to injected procaine is not widely recognized. Although procaine has been in use for over half a century, reports of this type of allergic reaction have appeared only in recent years. It is possible that such reactions may be more frequent because of the widespread use of procaine penicillin since its introduction in 1948. In 1952 it was estimated that 75 per cent of the total production of penicillin was in the form of the procaine salt.¹³ This slowly absorbed depot preparation contains procaine in 12 per cent suspension and may be a more potent sensitizer than the usual procaine solution. This possibility is suggested by the concomitant presence of a positive penicillin skin test of the twenty-four-hour type in two of the foregoing cases of procaine edema. Of interest also are two instances in which patients with penicillin allergy, who gave positive skin test reactions to penicillin, were shown to have a positive twenty-four-hour skin test reaction to procaine as well.



Fig. 3.—Case 4. Positive twenty-four-hour skin test reactions to crystalline penicillin G (upper) and to procaine (lower). Reactions at left are at sites negative at the fifteen-minute reading, induced with 0.02 ml. Case of seven months of urticaria after procaine penicillin.

The association of penicillin and procaine allergy requires clarification. It may represent coincidence, a susceptible patient reacting to each allergen independently. Cross-sensitization between the two compounds appears unlikely in view of their quite different chemical configuration. The more complex penicillin molecule does not break down into elements related to procaine. Against cross-sensitization, too, are observations of contact allergy to procaine

from procaine penicillin without allergy to penicillin.^{14, 15} More complex explanations involving the possibility that penicillin allergy, with a positive skin test of the delayed type, may predispose to this form of procaine allergy are at present speculative.

In all three cases of procaine edema reported here, a positive skin test reaction was also elicited with Monocaine. Previous exposure to Monocaine may have occurred, for example, in Case 1 in which the skin test reaction to Monocaine was stronger than that to procaine. These two anesthetic compounds are chemically very similar, and both are esters of para-aminobenzoic acid. Included in the so-called procaine group of anesthetics are also Pontocaine, Butyn, Larocaine, and tutocaine. Cross-sensitization is considered more likely among members of this group on the basis of clinical observation,¹ in part confirmed by animal experiments.¹⁶

In Case 2 a positive skin test was found to Unacaine, a compound in which the amino group attached to the phenol ring is at the meta rather than the para position. This is in contrast with the observation by Rothman and colleagues that in contact dermatitis due to procaine, transfer of this amino group away from the para position is likely to be associated with loss of sensitivity.¹

Xylocaine is sufficiently distinct in chemical structure so that cross-sensitization is unlikely. Each of the three patients with procaine edema was found to tolerate Xylocaine without difficulty. As a widely accepted anesthetic agent in both dentistry and surgery, this drug is at present the most likely safe substitute in the presence of procaine allergy. This is in accord with Rickles' observations.¹⁰

With the establishment of local allergic edema due to procaine as a definite entity, the warning might be justified that within the closed space of the spinal canal even a transient allergic reaction might prove a significant hazard. Anesthetics other than procaine might therefore be considered safer for intraspinal use.

SUMMARY

1. Three cases of repeated edema at the site of procaine anesthesia for minor dental procedures are described.
2. Marked swelling of the cheek and face was noted several hours after injection and lasted for two to fourteen days. There was no evidence of general reaction or urticaria.
3. A positive twenty-four-hour skin test reaction of erythema and edema was induced by the intracutaneous injection of procaine and by injection of Monocaine as well. Immediate skin tests were negative.
4. Skin tests with Xylocaine were negative. This anesthetic proved a safe substitute for procaine.
5. A positive twenty-four-hour skin test reaction to crystalline penicillin G was also present in two cases. Two other patients with clinical allergy to

penicillin also proved skin test-positive to procaine. A possible etiological relationship of procaine penicillin treatment to this form of procaine allergy is discussed.

The author is indebted to Dr. Liselotte Graf for carrying out the complement-fixation tests and to Jerome S. Mittelman, D.D.S., for his interest in this problem.

REFERENCES

1. Rothman, S., Orlando, F. J., and Flesch, P.: Group Specificity of Epidermal Allergy to Procaine in Man, *J. Invest. Dermat.* **6**: 191, 1945.
2. Laden, E. L., and Wallace, D. A.: Contact Dermatitis due to Procaine, a Common Occupational Disease of Dentists, *J. Invest. Dermat.* **12**: 299, 1949.
3. Lane, C. G., and Luikart, R., Jr.: Dermatitis From Local Anesthetics, *J. A. M. A.* **146**: 717, 1951.
4. Criepp, L. H., and Ribiero, C. de C.: Allergy to Procaine Hydrochloride With Three Fatalities, *J. A. M. A.* **151**: 1185, 1953.
5. Schiff, L. F., and Schiff, L. I.: Anaphylactic Reaction to Intravenous Administration of Procaine, *Anesthesiology* **10**: 753, 1949.
6. Davis, H. S., and Boyce-Smith, R.: Allergy and Procaine, *J. A. M. A.* **152**: 477, 1953.
7. Ryan, E. A., and Shouldice, E. E.: Allergy and Procaine, *J. A. M. A.* **152**: 1554, 1953.
8. Sadove, M. S., Wyant, G. M., Gittelson, L. A., and Kretchmer, H. E.: Classification and Management of Reactions to Local Anesthetic Agents, *J. A. M. A.* **148**: 17, 1952.
9. Gray, T. C., and Geddes, E. C.: A Review of Local Anesthetics, *J. Pharm. & Pharmacol.* **6**: 89, 1954.
10. Rickles, N. H.: Procaine Allergy in Dental Patients: Diagnosis and Management, *Oral Surg., Oral Med., & Oral Path.* **6**: 375, 1953.
11. Mitchell, H. S.: Allergy to Local Anesthetic Agents, *J. Canad. Dent. A.* **19**: 127, 1953.
12. Adler, P., and Simon, M.: Contribution to the Problem of Allergy to Local Anesthetics, *Oral Surg., Oral Med. & Oral Path.* **2**: 1029, 1949.
13. The Dispensatory of the United States, ed. 25, Philadelphia, 1952, J. B. Lippincott Company, p. 1004.
14. Peck, S. M., and Feldman, F. F.: Contact Allergic Dermatitis due to Procaine Fraction of Procaine Penicillin, *J. Invest. Dermat.* **13**: 109, 1949.
15. Hitschman, O. B., Leider, M., and Baer, R.: Dermatitis due to Procaine Fraction of Procaine Penicillin, *J. Invest. Dermat.* **15**: 165, 1950.
16. Adler, P., Went, I., and Kesztoi, L.: Immunization Experiments With Procaine Azo-protein, *Oral Surg., Oral Med. & Oral Path.* **2**: 1140, 1949.