

ANAPHYLACTIC SHOCK FOLLOWING PENICILLIN THERAPY IN BRONCHIAL ASTHMA

ALEXANDER STERLING, M.D.,* PHILADELPHIA, PA.

A GREAT deal has been written about the morbidity and mortality following injections of penicillin.^{1, 2} Penicillin reactions may be local or generalized; may produce pruritus, urticaria, exfoliative dermatitis, angioneurotic edema, or anaphylactic shock which occurs immediately, while the urticaria and angioneurotic edema may be delayed for a week or longer.

We will discuss here the surprise alarm reactions (anaphylactic shock), the possibility of which many forget unless they have had the personal experience of witnessing a patient near death within minutes after an injection.

It is doubtful if anaphylactic shock to penicillin, whether crystalline, potassium, aqueous, procaine, etc., ever occurs at the first injection. Sensitization may take place from previous oral use, or when repeated injections have to be given daily for prolonged periods. We will assume that sensitivity to procaine or other vehicles has been eliminated. Daily injections of 300,000 units of penicillin given for one or two weeks are commonly used in chronic respiratory infection. We use this treatment freely in asthmatic bronchitis when the patients have accompanying mucopurulent expectoration, no matter what the original specific factor.³ Frequently we have used it for two-week periods, three or four times during the winter months with excellent results. The physician should never hesitate to use it when indicated.

Considering the amount of penicillin used, anaphylactic shock reactions are extremely uncommon. But because of the severity when they do occur, we have found certain precautions necessary.

In checking the medical literature⁵⁻¹⁰ we found only one article in which signs and symptoms have been pointed out to the physician which he could use to guide him against the possible occurrence of anaphylactic shock. Quoting from Waldbott's article in the *Journal of the American Medical Association* (1949)⁶: "It was noted that this patient had severe urticaria, some aggravation of asthma, joint pains and slight fever . . . about one week after the last administration of penicillin. This had not been identified at the time as serum sickness from penicillin, but in all probability presented the outward signs of the development of sensitization to penicillin."

All nine of our patients who had shock reactions (three of them almost fatal) noticed some symptoms after the one or two preceding injections of penicillin but did not consider them severe enough to mention.

It is our suggestion to note carefully reactions after the previous injection of penicillin. If any one or all of the five cardinal symptoms appear, in ad-

Received for publication June 17, 1953.

*Chief, Department of Allergy, Eastern Division, Albert Einstein Medical Center.

dition to aggravation of existing chest condition, we can be forewarned of anaphylactic shock and refuse further parenteral penicillin therapy. We can be guided by the following symptoms:

1. Syncope, mild to severe, at the time of injection, or a feeling of faintness recurring periodically for the following three to four hours.
2. Sensation of burning or heat throughout the body, especially in the throat, palms of hands, soles of feet (similar to reaction after intravenous calcium).
3. Local or generalized pruritus *never before present* may occur in various parts of the body, beginning within a few hours after the injection.
4. Choking sensation in the throat, with increasing cough, dyspnea, and wheezing.
5. Severe paroxysmal pain varying in location, such as precordial, epigastric, or diaphragmatic.

The number of injections needed to sensitize an individual varied considerably in our nine cases:

- One was sensitized after 12 injections
- Two were sensitized after 18 injections
- Four were sensitized after 26 injections
- Two were sensitized after 54 injections

Penicillin G or procaine penicillin was used for all. Intervals between penicillin series varied from two weeks to six months. None of our reactions occurred at a first injection of any series.

(a) An effort was made to skin test patients suspected of penicillin sensitivity before giving injections, but it proved an unreliable guide. We had ten patients who gave false-positive skin tests, that is, the skin test was positive but there was no reaction after injection. We have not observed negative skin tests which have been followed by reactions to subsequent injections.

(b) The occurrence of angioneurotic edema of the uvula after using penicillin powder by inhalation is not a contraindication to using penicillin by intramuscular injection. Three of our patients who had such reactions after penicillin inhalation later received intramuscular penicillin with full therapeutic benefit and no shock reaction.

(c) When we found that existing dermatitis in patients with dermatophytosis and varicosities of the legs were much more pronounced after penicillin injection, we hesitated at first to use it again. However, subsequent injections in these individuals produced no other reaction except the previously mentioned local discomfort.

None of these three tests were conclusive guides to penicillin sensitivity and we had to rely on our five cardinal symptoms.

Since then all patients were instructed to wait in the office fifteen minutes after each injection and to report any untoward signs or symptoms occurring

immediately following the last injection. Fifteen patients who experienced one or more of the suggested symptoms were refused further injections of penicillin. A trial injection was made in three suspicious cases to determine whether we were justified in withholding the penicillin injections and, to our regret, we caused three anaphylactic shock reactions. One patient, who did not believe his reaction was due to penicillin, insisted on another trial. He had as severe a reaction within two minutes after receiving 30,000 units as he had the week before after 300,000 units of penicillin.

In the emergency of a shock reaction the greatest immediate aid is obtained with small doses, 2 to 3 minims (0.12 to 0.2 ml.), of epinephrine solution (1:1,000), given intradermally every two minutes until the patient is out of danger, usually fifteen or twenty minutes, or beyond help. In many of the fatal shock reactions to penicillin reported to date,⁸⁻⁹ aminophylline or antihistaminics were used. Epinephrine directly in the heart muscle has been used when the patient was almost moribund. Remember that large doses of epinephrine are sometimes dangerous in themselves.¹¹ In one instance death followed after an injection of penicillin was given at home by a member of the family, where epinephrine or other emergency treatment was not available. This episode should serve as warning to make sure that penicillin trays at home, office, or at hospital always have a sterile syringe and epinephrine ready for emergency use.

Pharmaceutical firms have recently placed on the market injectable penicillin maintaining high blood level concentrations lasting two weeks. Should sensitivity occur the constant presence of penicillin in the blood might cause repeated attacks of anaphylactic shock (although we have never seen it) and we do not suggest its use in allergic individuals. Penicillin-O-Potassium in tablet and by injection has been recommended for patients sensitive to penicillin G, but we feared to use it after experiencing near fatal shock reactions with penicillin G. Desensitization may be attempted if absolutely necessary, but we usually switch to a different antibiotic.

The following case reports will illustrate our experience.

CASE 1.—W. M. was a 56-year-old fruit and produce store worker. He called at the office July 31, 1947, complaining of severe attacks of bronchial asthma for one year, which began after a cold and rhinitis for several months. He had a past history of three attacks of pleurisy with effusion, the last attack thirty-three years previously. Otherwise he had been well.

While under our care he had an x-ray of the chest, electrocardiogram, complete blood count, complete blood chemistry, and all were within normal limits. He was tested for inhalants, foods, pollen, bacteria, house dust, and molds, and was positive to ragweed pollen, a number of inhalants, molds, bacteria, and house dust. Appropriate extracts and their dilutions were made and treatment started. Asthmatic attacks were kept under control. However, he was subject to acute colds which were complicated by purulent bronchitis and asthma. It was then necessary to give him injections of penicillin for eight days before he recovered from his asthmatic bronchitis. During the first winter, two courses of penicillin injections, consisting of 8 each, were given. He was perfectly well the following summer and during a Florida visit from December to March. When he returned he had a severe attack of bronchitis followed by asthma. Daily injections of penicillin were given for eight days, with improvement.

After this he was well for six weeks, then caught another cold and again penicillin injections were begun. This time, within two minutes after the second injection (the twenty-sixth of the sum total of penicillin injections received), he was seized with a terrific anaphylactic shock. It was with difficulty that he was placed on the table with head and chest raised. He felt a burning sensation in his face and hands; the palms of hands, face, and neck turned red. He complained of terrific pains in his chest and over the precordium, and had a weak, imperceptible pulse. He pleaded for help in his extreme distress of wheezing, coughing, and orthopnea. Immediately 2 minims (0.12 ml.) of epinephrine (1:1,000) were administered intradermally and repeated every two minutes for four doses before he began to show signs of relief. The acute anaphylactic shock lasted twenty minutes.

He and his family were informed of his sensitivity to penicillin and advised never to have any further injections. Since then he has improved with desensitization treatment. Colds and asthma attacks are much less frequent and are controlled with aureomycin and other measures.

CASE 2.—A. M., aged 59, was married thirty-three years, and had 3 children. He worked in a leather tannery; he called at the office in February, 1948, complaining of bronchial asthma for six years. This began in the winter of 1942 after frequent colds, worse in winter and somewhat better in summer.

For the last six winters he had suffered from frequent colds, which were followed by severe attacks of dyspnea, wheezing, coughing, and purulent expectoration, occasionally tinged with blood. There was bilateral nasal obstruction, sneezing, and rhinitis (watery discharge) in the morning.

Physical examination showed him to be very undernourished, with large inflamed tonsils, pharyngitis, marked emphysema, numerous moist and dry râles scattered throughout his chest. There was moderate anemia; otherwise the blood was normal. Urine was normal, also the electrocardiogram.

Intradermal tests with inhalants, foods, pollens, bacteria, house dust, and molds showed little or no reactions.

Frequent colds, lasting one to two weeks, with or without fever, brought on several recurring attacks of bronchial asthma. These recurring infections, four to five times a year, were best controlled by daily injections of penicillin for periods of seven to ten days.

The first winter under our care he had 30 injections of penicillin; the second winter, he had two courses of penicillin. During the sixth course, started four weeks after the last previous series, within two minutes of the fourth injection he had a severe anaphylactic shock. (This was the sixty-fourth injection of the sum total of the penicillin received.) Burning and itching sensations occurred over all the body; his face and hands turned red; his lips became blue; he suffered severe chest pains, most pronounced in the precordial area. Wheezing, dyspnea, and orthopnea were very marked, and the pulse was imperceptible.

Injections of epinephrine (1:1,000), 2 minims (0.12 ml.) were immediately started, and repeated every two minutes. In all he had 10 minims (0.6 ml.) of epinephrine (1:1,000). It was twenty-four minutes before he quieted down. He was told his reaction was due to penicillin and he should never have any more. He insisted upon being given another trial injection because he felt convinced penicillin was a great factor in his recovery every time he had respiratory infection. One week later he received 30,000 units. Instantly he suffered the same type of anaphylactic shock experienced one week before. He was finally convinced of the danger of further injections of penicillin. Since then we have used aureomycin or other antibiotics to combat his upper respiratory infection.

CASE 3.—I. M., a white, single man, aged 49 years, a newspaper reporter for twenty years, called at the office in June, 1946, complaining of bronchial asthma and bilateral persistent nasal obstruction of two years' duration. He had irregular uncontrollable attacks of coughing, wheezing, dyspnea, and orthopnea. At times he had six or eight attacks of asthma in twenty-four hours. At other times he would be free from asthma for several weeks.

He was subject to colds in the spring (May) and the fall (October), but worse in the winter months. The nasal obstruction did not respond to any local treatment, to antihistaminics, or to three electrocauterizations.

On physical examination, his chest revealed dry and moist râles and wheezing. The patient did not have any knowledge of environmental contacts which might be in some way responsible for his respiratory difficulties.

We tested him with inhalants, foods, pollen, dust, molds, and antigens of bacteria responsible for upper respiratory infections. He did not show any typical immediate allergic skin reactions but delayed inflammatory local reactions to bacterial proteins and house dust. Clinically he was highly sensitive to insecticides, printer's ink, glue, and sizing material.

He had electrocauterization of his nasal turbinates in 1946 and 1947 by a nose and throat specialist. This was followed in 1950 by sclerosing (Silnosal) treatment of the turbinates with no improvement. In October, 1951, he had a polypectomy. Several months later he had another sclerosing treatment of the turbinates.

Courses of daily injections of penicillin (300,000 units) were given. After 6 or 8 injections he would make a satisfactory recovery and remain well from two to four weeks.

In April, 1951, he had a recurrence of his respiratory infection. Eight weeks had elapsed since the previous series of penicillin injections. Another course of penicillin, the seventh to date, was begun. After the third injection, which was approximately the fifty-fourth penicillin injection, he sustained a severe anaphylactic shock. It was difficult to place him on the table. He had itching all over the body, the face and hands turned red, lips blue. He was weak, with an imperceptible pulse, severe chest and precordial pains, dyspnea, and orthopnea. Intradermal injections of 2 minims (0.12 ml.) of epinephrine (1:1,000) were started immediately, and given every two minutes. In all, he had 10 minims (0.6 ml.) of epinephrine. It was twenty-four minutes before he recovered from shock. Since then we have used other antibiotics to combat his respiratory infections. The importance of avoiding all contact with fresh newspapers, magazines, and other lithographic material was explained to him. He was compelled to give up his reporter's position. He managed to obtain other employment as a secretary and public relations manager in a private fraternal organization. Since this change, for the last year and a half, he made almost a complete recovery.

SUMMARY

Although anaphylactic shock following penicillin injections in bronchial asthmatics is not common, we must be alert for it because of its severity when it does occur. Signs and symptoms that can forewarn of shock reactions have been discussed, emergency treatment outlined, and three illustrative cases presented.

REFERENCES

1. Goldman, Jack S.: Penicillin Reactions, *Memphis M. J.* **26**: 100, 1951.
2. O'Donovan, W. J., and Klorfajn, I.: Sensitivity to Penicillin, *Lancet* **2**: 444, 1946.
3. Sterling, Alexander, Fishman, Aaron E., and Sharps, Frank: Massive Dose of Penicillin in Chronic Asthmatics, *Am. Pract.* **2**: 570, 1948.
4. Sterling, Alexander: The Importance of Pre-Operative Local Treatment in Nose and Throat Surgery, *Arch. Pediat.* **65**: 377-380, 1948.
5. Thomson, W. O.: Sudden Death Following an Injection of Penicillin, *Brit. M. J.* **2**: 70, 1952.
6. Waldbott, George L.: Anaphylactic Death From Penicillin, *J. A. M. A.* **139**: 526, 1949.
7. Higgins, George A., and Rothchild, Thomas P. E.: Fatal Anaphylactic Shock From Procaine Penicillin, *New England J. Med.* **247**: 644, 1952.
8. Pratt-Thomas, H. R., and Waring, J. I.: Fatal Delayed Anaphylactic Shock After Penicillin, *J. A. M. A.* **131**: 1384, 1946.
9. Burleson, R. J.: Anaphylactoid Shock Due to Penicillin, *J. A. M. A.* **142**: 562, 1950.
10. Everett, Reginald: Anaphylactic Reactions From Local Use of Penicillin, *J. A. M. A.* **146**: 1314, 1951.
11. Sterling, Alexander: Dangers Attending the Clinical Use of Epinephrine in Bronchial Asthma, *M. Clin. North America* **24**: 1851, 1940.