

PENICILLINASE IN THE TREATMENT OF ALLERGIC REACTIONS TO PENICILLIN

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PENICILLINASE, the protein enzyme discovered in 1940, by Abraham and Chain,¹ was suggested as a possible approach to the treatment of penicillin reactions by Becker² in 1956. He reported that penicillinase administered intramuscularly in guinea pigs and human beings reduced the levels of previously administered penicillin to zero within one hour. Following a single dose of penicillinase, no circulating penicillin could be detected for periods of four to seven days, despite the continued injection of penicillin twice a day. Chen and co-workers,³ studying the effects of penicillinase in rabbits, reported that it is rapidly absorbed, reaches its maximum activity about one hour after intramuscular injection, and is slowly metabolized, remaining active for a prolonged period. A dose of 5,000 units of penicillinase was found to inactivate 100,000 units of either crystalline or procaine penicillin G. While these workers failed to anaphylactically sensitize a small number of guinea pigs, Fisher and associates,⁴ in a much more extensive immunologic study, demonstrated that penicillinase is a very strong antigen. They found that all guinea pigs and rabbits in their series became sensitive to penicillinase when given repeated injections alone or in combination with human albumin. Freund's adjuvant potentiated this sensitizing activity of penicillinase.

A purified form of penicillinase was used by a number of clinical investigators, who reported favorably on its effectiveness in controlling the manifestations of penicillin allergy.⁵⁻⁷ In view of the allergist's great interest in the problem of penicillin sensitivity, a clinical study was undertaken by the Committee on Drugs of the American Academy of Allergy approximately one year ago.⁸ During this time a total of fifty case reports of patients treated with penicillinase have been submitted by the following members of the Committee: Clarence Bernstein, Orlando, Florida; Theodore B. Bernstein, Evanston, Illinois; Joseph Besser, Philadelphia, Pennsylvania; Earl B. Brown, New York, New York; Monroe Coleman, Stamford, Connecticut; Seymour B. Crepea, Madison, Wisconsin; Alex S. Friedlaender, Detroit, Michigan; Sidney Friedlaender, Detroit, Michigan; Frank T. Joyce, Denver, Colorado; Lloyd D. Mayer, Lexington, Kentucky; Gustavus A. Peters, Rochester, Minnesota; Isadore Pitesky, Long Beach, California; Samuel E. Rynes, Philadelphia, Pennsylvania; Aaron D. Spielman, New York, New York; and Paul VanArsdel, Jr., Seattle, Washington.

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MATERIALS AND METHODS

Pencillinase* was supplied in the form of 800,000 unit ampules of a lyophilized powder to be dissolved in 2 c.c. of sterile distilled water at the time of use. The recommended dose was 800,000 units intramuscularly, repeated in three days if necessary. The manufacturer's brochure, however, mentioned that the solution might be given intravenously if the urgency of the situation warranted.

Each investigator was advised to use penicillinase in any case which, in his judgment, was one of penicillin allergy. Special forms were prepared for the accumulation of the desired information in a uniform manner, and a report on every patient treated was submitted for analysis. Each of the clinicians involved in this study was intimately concerned with the treatment of allergic reactions and well aware of the vagaries of allergic symptomatology and therapy, the possibilities of spontaneous recovery, and the difficulties of accurately relating the symptom complex under consideration to a particular antigen (in this case, penicillin). In some instances, the investigator was the first physician to render treatment; in others, he was called in consultation because of his special interest in such cases and usually because the patient was not progressing satisfactorily. Because of the diverse manifestations of penicillin allergy and the variation from patient to patient, each case report was carefully studied and placed into a generally accepted classification. The fifty case reports submitted may be categorized as follows:

<i>Type</i>	<i>Number of cases</i>
Serum sickness type	19
Acute urticarial eruptions	13
Acute nonurticarial eruptions	4
Chronic urticarial eruptions	9
Acute anaphylactic reactions	5
Total	50

CLINICAL OBSERVATIONS

In attempting a fair evaluation of the effects of penicillinase in the cases submitted, it appears desirable to consider separately the various types of reaction involved and the possible influence of penicillinase on their course.

Reactions of Serum Sickness Type.—Nineteen patients manifested symptoms of urticaria, fever, and joint involvement from three to fourteen days after the administration of penicillin. Treatment with penicillinase was instituted from one to thirty days after the onset of symptoms.

In eleven cases complete clearing of symptoms occurred in ten to ninety-six hours after the use of penicillinase. Lasting improvement occurred in six instances after a single injection. Two improved temporarily after one

*Penicillinase (Neutrapen brand) used in this study was generously supplied by B. M. Lanman, M.D., and William T. Strauss, M.D., SchenLabs Pharmaceuticals, Inc., New York, New York.

injection with subsequent recurrence but cleared permanently after a second injection. Three cases showed improvement only after a second injection had been given.

In two of those who improved penicillinase was the only treatment given. In two others improvement occurred only after penicillinase was added to existing treatment. In the remaining seven cases penicillinase was used concomitantly with other measures, such as steroids, ACTH, and antihistaminics.

Eight patients failed to improve in direct relationship to penicillinase administration which was given from one to nine days after onset of symptoms. Five of these received only one injection; two were given two injections; and one received three injections without favorable response. One of these patients had also received a local anesthetic, a blood transfusion, and iodides, in addition to penicillin, before the development of the serum sickness type of reaction.

Acute Urticarial Eruptions.—Thirteen patients developed acute urticarial eruptions within minutes to five days after penicillin administration. Ten were given penicillinase within the first twenty-four hours; three received such treatment two to six days later.

In seven patients the symptoms cleared completely within one to seventy-two hours after a single injection of penicillinase. All of these patients received epinephrine injections and antihistaminics in addition to penicillinase. However, in three cases symptoms had been present for two to six days and cleared permanently only after penicillinase was added to treatment. In one other case, clearing of urticaria began in one hour after administration of penicillinase but recurred several hours later. No additional injections of penicillinase were given in this case.

Five patients in this category failed to improve after penicillinase, although each received an injection within twenty-four hours following onset of symptoms. Four of these received only one dose of penicillinase, while one was given a second dose without apparent benefit.

Acute Nonurticarial Eruptions.—Four patients developed morbilliform, erythematous, or "erythema multiforme type" eruptions within twenty-four hours of penicillin administration. Penicillinase was given from four to eight days after onset. The eruption in one case cleared permanently one hour after penicillinase, whereas previous treatment with antihistaminics had failed to benefit. In three other patients intensive use of steroids or ACTH and antihistaminics accompanied the administration of penicillinase. Complete clearing of the eruption was reported in two to four days in these three cases.

Chronic Urticarial Eruptions.—Nine patients had recurrent urticaria and angioneurotic edema, which had its inception in relation to penicillin administration, of one to twelve months' duration. One patient cleared permanently within a short time following a single injection of penicillinase. Another patient cleared temporarily after a single dose but improved and remained well only after a second dose had been given. In two patients

temporary improvement lasting up to two weeks was observed after two injections of penicillinase. In one of these, penicillinase was not repeated when symptoms recurred. In the other, a repetition of the same treatment failed to benefit. Still another patient was reported slightly improved after penicillinase, but complete clearing was not evident.

Four patients in this category failed to achieve any discernible benefit from penicillinase administration. Each had received two doses of penicillinase at the recommended intervals.

Acute Anaphylactic Reactions.—Four patients who experienced reactions of the anaphylactic type, consisting of shock, bronchoconstriction, and angioedema, within one hour following penicillin administration received penicillinase. Other measures for the treatment of shock and bronchoconstriction were administered in each instance.

In one patient penicillinase was given after thirty-six hours of intensive steroid and antihistaminic therapy had failed to control angioedema. Some improvement was noted shortly after the first injection of penicillinase, with further improvement and subsequent clearing after a second dose three days later.

Three patients received penicillinase immediately following the onset of their reaction in addition to other emergency measures. In two of these, complete recovery ensued. In the third case, severe urticaria was still present at the end of twenty-four hours and was treated and controlled with steroids. A second injection of penicillinase was not given.

SIDE EFFECTS

Pain at the site of injection was reported in the majority of cases. In addition, the occurrence of local swelling and tenderness, sometimes very severe, for several days afterward was reported in twenty-two patients. The occurrence of an acute febrile reaction within a short time following the administration of penicillinase was noted in thirteen patients. In several instances this was quite alarming to the attending physician, and a second dose of penicillinase which otherwise would have been given was deemed inadvisable.

COMMENT

It would be most difficult, if not foolish, to attribute each instance of improvement noted in the aforementioned series to the use of penicillinase. In many cases other potent therapeutic agents were used concomitantly. Even in those cases where penicillinase was used alone, it is difficult to be absolutely certain. Any clinician familiar with the variable course of allergic reactions, especially those related to penicillin hypersensitivity, realizes that a much greater experience with penicillinase is necessary before its exact value can be properly assessed. One investigator in this study treated every other penicillin reaction encountered in his institution with penicillinase. Three cases treated with penicillinase showed improvement within

a few days of its administration. In two other similar patients with reactions of the serum sickness type who did not receive the enzyme, one improved spontaneously forty-eight hours after onset, and in another symptoms which had persisted for three weeks subsided four days after hospitalization without specific treatment.⁹ Indeed, others have reported good response in such cases even after placebo treatment.⁵

One cannot help being impressed, however, by the rapid improvement which occurred following the administration of penicillinase in some reactions of the serum sickness type and urticarial eruptions. While most of the acute reactions treated are self-limited, the rapidity of clearing which occurred in some instances shortly after the enzyme was used is sufficiently striking to suggest that it was of definite therapeutic benefit. A permanent improvement in chronic urticarial eruptions, if it occurs, would seem equally impressive, especially when other treatment measures have failed to influence the course of such symptoms.

From the experimental work with penicillinase, there is little reason to believe that it has a place in the treatment of the acute anaphylactic type of reaction. While it is possible that it may be useful in controlling the later symptoms of this sensitivity reaction, it cannot take the place of the emergency lifesaving measures necessary to overcome shock and relieve bronchospasm. A more rapid effect in neutralizing circulating penicillin might be achieved by giving penicillinase intravenously, but the foreign protein type of reaction so frequently encountered with intramuscular administration would make this route seem ill-advised. In the present series, one patient did receive penicillinase intravenously, with a subsequent shaking chill and a frightening febrile reaction.

In considering those who failed to improve following the use of penicillinase, a number of explanations must be considered. First of all, there is the possibility that the sensitivity reaction was due to something other than penicillin. It was noted in more than one patient in this series who failed to benefit that other drugs were used at the same time as penicillin. This line of reasoning might be carried much farther by saying that if a patient fails to respond to penicillinase, the cause of his difficulty is either not due to penicillin allergy or there are new or continued contacts with penicillin antigen from less obvious sources.

Next, in the case of treatment failure, there is also the possibility that the patient failed to receive enough penicillinase to neutralize the residual penicillin. It was noted in a number of cases in the present study that substantial and prolonged improvement did not occur until a second injection of penicillinase was given. It would therefore seem reasonable that a second dose should be administered if the patient fails to respond favorably to the first, before it is concluded that penicillinase is ineffective.

In view of the relative ease of sensitization to penicillinase in animals reported by Fisher and co-workers,⁴ the possible effects of readministration of penicillinase to human beings must be given serious consideration. While

presumably a patient who experiences a penicillin reaction would in the future not be given penicillin and therefore would not require penicillinase again, there are sufficient possibilities that penicillin might be given inadvertently or encountered in some overt form, making it desirable to administer the enzyme again in treatment. The possibility of anaphylactic or other allergic reactions to penicillinase itself could then pose a real problem. This type of occurrence could become even more frequent if the recommendation that penicillinase be given prophylactically to any patient with a history of penicillin allergy who is to be given a vaccine, such as polio or adenovirus vaccine, known to contain penicillin were to be followed. Until such time as the sensitizing potential of penicillinase in human beings is further investigated and ascertained, the advisability of routine administration of this protein enzyme in such cases is open to question. One investigator who submitted cases for this report tested three patients with penicillinase before and two weeks after its administration. All gave a negative cutaneous response before treatment, while two weeks afterward the skin test reaction to the enzyme became strongly positive. Three other patients who were tested after receiving penicillinase also reacted strongly, while three control patients were negative.¹⁰

Since the conclusion of this clinical study, we have learned that a highly purified form of penicillinase has been developed which may have less local and systemic effect, and possibly lower antigenicity.¹¹

SUMMARY

A purified form of penicillinase was used in treatment of fifty cases of sensitivity reactions related to the administration of penicillin. Rapid improvement following intramuscular administration was observed in some cases of reactions of the serum sickness type, acute urticarial and nonurticarial eruptions, and chronic urticaria. A number of similar cases failed to improve with the same treatment. Two injections of 800,000 units each at three-day intervals appeared more effective than a single dose. Its mode of action is such that it does not appear to have a place in the treatment of immediate anaphylactic reaction. Local pain and swelling and systemic febrile reactions were commonly encountered after intramuscular injections of the enzyme. Intravenous use is not advised. The antigenicity of penicillinase is such that the possibility of sensitization from repeated administration must be considered in its use.

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Erratum

In the article entitled "A Quantitative Study on the In Vitro Release of Histamine From Leukocytes of Atopic Persons" by VanArsdel, Middleton, Sherman, and Buchwald, which appeared in the September, 1958, issue of the JOURNAL, the concentrations reported in the seventh and eighth lines of the second paragraph on page 435 should be corrected to read as follows:

1.6×10^{-9} , 1.2×10^{-11} , and 1.4×10^{-8} .