

Development of Sensitivity to Penicillinase Following Its Use in Penicillin Reaction

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PENICILLINASE, an enzyme derived from various bacterial sources, is a protein with a molecular weight of about 50,000. It acts by catalyzing the hydrolysis of the lactum ring of penicillin to penicilloic acid, a substance devoid of antibacterial activity. Initial studies^{2, 3, 7, 12} have suggested its value in treating penicillin sensitivity reactions. Our experience with a small group of patients, particularly with respect to their formation of antipenicillinase antibodies, is described below.

METHOD

Patients with penicillin reactions of the serum sickness type were given 800,000 units of penicillinase intramuscularly as soon as they were called to our attention. In addition, each was tested intradermally with the following mixtures: penicillin in saline 500 units per cubic centimeter, penicillinase in concentrations of 5,000 and 10,000 units per cubic centimeter, penicillin 500 units plus penicillinase 5,000 units per cubic centimeter, and penicillin 1,000 units plus penicillinase 10,000 units per cubic centimeter. The mixtures were allowed to interact for thirty minutes at room temperature prior to the test, and all testing material was less than twenty-four hours old. Where possible, these tests were performed before penicillinase administration and again two to three weeks later. Ten nonsensitive persons were similarly tested as controls.

RESULTS

Table I presents the clinical study of eight patients. Seven of these seemed to have penicillin reactions, and the eighth (patient M. F.) probably represented a case of chronic dermatitis with penicillin considered by the family physician to be a possible factor. All the reactions occurred within eleven days following the last dose of penicillin. Penicillinase was administered within two days thereafter in four patients, within four days in two more, nine days later in one, and fifteen months later in patient M. F. Of the seven patients with definite penicillin reactions, two (D. L. and F. H.)

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showed good to complete relief within twenty-four hours after penicillinase administration and required no further therapy, two more (R. C. and A. L.) had some improvement, and three (C. M., L. S., and S. H.) received no benefit. In none were second doses of penicillinase given. Two patients (A. L. and L. S.) had reactions consisting of chills and fever which appeared to be definitely related to the administration of penicillinase, and one (F. H.) had fever, the etiology of which was not clear, on the night of penicillinase administration.

TABLE I. CLINICAL DATA

PA-TIENT	PENICILLIN GIVEN	REACTION	ONSET OF REACTION P.C. LAST DOSE PENICILLIN	PENICILLINASE (800,000 U.) P.C. ONSET OF REACTION	RESULT	SIDE EFFECT
R. C.	Bicillin Feb. 15, 1958	Rash, arthralgia	11 days	1 day	Improved but still developed new erythematous areas	
C. M.	Duracillin Feb. 13, 15, 17, 18, 19, 1958	Urticaria, angioedema	10 days	2 days	Course unaltered; steroid needed	
D. L.	Duracillin 600,000 Feb. 26, 27, 28, 1958	Papular eruption, urticaria	5 days	2 days	Improved	
A. L.	Penicillin (Form K) 1,000,000 Feb. 2, 1958	Arthralgia, pruritus, urticaria	4 days	9 days	Better, but some new swelling next day	Chills and fever few hours later
F. H.	Procaine penicillin and streptomycin April 2, 1958	Urticaria	1 hour later	1½ hours	Cleared in 24 hours	Fever to 103° F. that night Etiology?
L. S.	Duracillin 600,000 Oct. 15, 17, 18, 1958	Urticaria, angioedema	7 days	3 days	No relief	Chills that night and following night
S. H.	Bicillin 1,200,000 July 31, 1958	Urticaria, angioedema	10 days	4 days	Increased angioedema; steroid given	
M. F.	Penicillin October, 1956	Dermatitis, nonallergic	11 days later	1½ years	No relief; Paise given diagnostically	

Table II presents data on the skin-test studies. Intradermal immediate wheal reactions were read in ten minutes and delayed reactions in twenty-four to forty-eight hours. It is noted that four patients (C. M., F. H., S. H., and M. F.) developed a positive immediate wheal reaction to penicillinase two weeks or more after therapy. In view of totally negative results in the control study, it seems reasonable to assume that in those patients (C. M.,

F. H., and M. F.) who had no tests prior to penicillinase therapy the positive reactions are valid evidence of injection-induced sensitivity. It is interesting to note that patients A. L. and S. H. showed positive reactions to penicillin, negative reactions to penicillinase, but still positive reactions to the mixture.

TABLE II. SKIN TEST RESULTS

TESTS A.C. AND P.C. PASE INJECTION	PATIENT							
	R. C.	C. M.	D. L.	A. L.	F. H.	L. S.	S. H.	M. F.
Penicillin 500 units per cubic centimeter								
A.C.								
Immediate*	Neg.					±	2+	
Delayed†	Neg.					Neg.	Neg.	
P.C.								
Immediate	Neg.	Neg.	Neg.	3+	1+	Neg.	2+	1+
Delayed	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	2 cm.	Neg.
Penicillinase 5,000 units per cubic centimeter								
A.C.								
Immediate	Neg.					Neg.	Neg.	
Delayed	Neg.					Neg.	1.5 cm.	
P.C.								
Immediate	Neg.	2+	±		2+	±	2+	3+
Delayed	Neg.	Neg.	Neg.		1 cm.	0.5 cm.	1.5 cm.	0
Penicillinase 10,000 units per cubic centimeter								
A.C.								
Immediate	Neg.					±	Neg.	
Delayed	Neg.					Neg.	2.5 cm.	
P.C.								
Immediate	Neg.	3+	±	Neg.	2+	±	2+	3+
Delayed	Neg.	Neg.	Neg.	Neg.	2.5 cm.	1.0 cm.	2 cm.	Neg.
Penicillin 500, penicillinase 5,000 units per cubic centimeter‡								
A.C.								
Immediate	Neg.					2+	1+	
Delayed	Neg.					Neg.	2 cm.	
P.C.								
Immediate	Neg.	2+	±	1+	1+	±	2+	Neg.
Delayed	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	2 cm.	Neg.
Penicillin 1,000, penicillinase 10,000 units per cubic centimeter‡								
A.C.								
Immediate	Neg.					2+	2+	
Delayed	Neg.					Neg.	0.5 cm.	
P.C.								
Immediate	Neg.	3+	±	3+	1+	2+	2+	2+
Delayed	Neg.	Neg.	Neg.	Neg.	1 cm.	Neg.	±	Neg.

*Immediate wheal tests were measured on size and shape of wheal.

†Delayed tests were measured in centimeters of induration.

‡Final concentration per cubic centimeter.

Of three patients who had pretreatment skin testing, one (S. H.) showed an initial positive delayed reaction to penicillinase while having a negative immediate wheal response, the significance of which cannot be definitely stated.

Ten normal patients, who were similarly tested, were all negative.

DISCUSSION

It has been proposed by various writers^{1-3, 7, 12} that penicillinase has a definite place in the therapy of penicillin reactions. Becker¹ demonstrated that penicillinase will lower circulating penicillin to nondetectable levels and will continue to do so for four to seven days after administration. The same results have been obtained in experimental animals by Sureau¹⁰ and Chen⁵ and their colleagues.

Penicillinase, being a protein, is antigenic in its own right. As such, it should have the ability to produce antibodies having properties of both the neutralizing and the anaphylactic types.

Boyer and associates⁴ demonstrated that pretreatment of guinea pigs with penicillinase appeared to stimulate "antipenicillinase" activity in the blood. In this study the animals were infected with a penicillin-sensitive organism and treated with penicillin, penicillin plus penicillinase premixed, penicillin and penicillinase given individually at separate sites, and penicillinase several days prior to the inoculation of bacteria. Inhibition of penicillin-protective effect on infection was demonstrable only where the penicillin and penicillinase were premixed. Survival of animals pretreated with penicillinase was greater than controls and this suggested the stimulation of antipenicillinase factors in the blood. Perlstein and Liebman⁸⁻⁹ produced antipenicillinase precipitins in rabbits. This serum inhibited the destructive effect of penicillin in vitro. Tacking¹¹ confirmed the above and, in addition, demonstrated that rabbits immunized with penicillinase, subsequently infected with a penicillin-sensitive organism and a penicillinase-producing *Staphylococcus aureus*, and then treated with penicillin showed a 35 per cent mortality, as compared to 100 per cent for nonpenicillinase-immunized animals. Likewise, nonpenicillin-treated but immunized animals all died. Tacking's results demonstrate the sparing effect of penicillin by the neutralization of the bacteria-produced penicillinase by the antipenicillinase antibodies resulting from the prior immunization with penicillinase.

Fisher and co-workers⁶ showed that all of thirty-six guinea pigs and nine rabbits developed sensitivity to penicillinase as demonstrated by circulating precipitins, agglutinins, passive cutaneous anaphylaxis, and positive skin tests.

In our limited human studies it appears that four out of eight patients developed positive skin sensitivity from a single injection of 800,000 units of penicillinase.

In theory, circulating penicillin in a sensitive host is the cause of the systemic allergic manifestation. By destroying the penicillin molecule, penicillinase theoretically inhibits further reaction. However, the demonstrated antigenicity of penicillinase in both human and animal experiments suggests caution in its use. The repeated injection of the drug under certain clinical conditions could result in serious anaphylactic reactions. Similarly, in addition to this potential hazard, the experimental demonstration of the development of antipenicillinase antibodies could well result in decreased effectiveness of

penicillinase activity. In some instances penicillinase fails to entirely destroy the antigenicity of penicillin in vitro (patients A. L. and S. H.) and this may occasionally explain therapeutic failure.

CONCLUSIONS

1. Penicillinase is an enzyme which causes the hydrolysis of penicillin to penicilloic acid. This material is devoid of antibacterial activity. The immunologic relationship of penicilloic acid to penicillin is not definitely known at this time.

2. Antibodies which inhibit penicillinase action have been reported experimentally.

3. Sensitizing antibodies are produced readily in animals and human beings. Repeated injections of penicillinase must be given with caution.

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