ORIGINAL ARTICLE

Penicilloyl-Polylysine Stability and Clinical Use Over Time

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Abstract

Background: The major penicillin skin test reagent, penicilloyl-polylysine, has not been commercially available since October 2004. The minimal concentration of penicilloyl-polylysine necessary for safe penicillin skin testing has not been determined.

Methods: Penicillin skin testing was performed on 596 individuals between October 2004 and October 2006 using out-of-date commercially produced penicilloyl-polylysine as part of a complete panel of reagents. The concentration of active penicilloyl-polylysine was measured. Outcomes were compared with those for 921 individuals tested between October 2002 and September 2004 using in-date commercially produced penicilloyl-polylysine.

Results: There was no significant difference in the fraction of patients who had positive skin test results using indate (5.1%) versus out-of-date (4.7%) penicilloyl-polylysine . There were four mild but no serious adverse reactions in the patients tested with the outdated reagent who were then challenged with oral penicillin class antibiotics.

Conclusion: Penicillin skin testing can be safely done using penicilloyl-polylysine down to a concentration of 4.29×10^{-5} M.

Penicillin skin testing using a complete panel of reagents is useful for evaluating individuals with a history of adverse reaction to penicillin-class antibiotics. The minimal concentration of penicilloyl-polylysine necessary for safe penicillin skin testing has not been determined.

Penicilloyl-polylysine, also known as benzylpenicilloyl-polylysine and commercially known as Pre-Pen (HollisterStier, Spokane, WA), was available as an FDA-approved penicillin skin test material in the US and other parts of the world from July 1974 to September 2000 and again from November 2001 to September 2004. There have been large studies dating back to the 1960s using benzylpenicilloyl-polylysine as a safe and effective reagent to evaluate penicillin allergy and commercial versions of this material have been reported on since the 1970s.[1–3] The current lack of a commercial source for penicilloyl-polylysine has almost completely stopped penicillin allergy skin testing.

We have had an active penicillin allergy skin testing program at the Kaiser Permanente (KP) San Diego Medical Center since the mid-1990s. We typically test 300 to 500 individuals per year. Because of a lack of a commercial source of penicilloyl-polylysine and the availability of outdated Pre-Pen, we studied the clinical use of outdated Pre-Pen in patients with a history of penicillin allergy.

The United States Pharmacopoeia defines benzylpenicilloyl-polylysine injection as having a molar concentration of the benzylpenicilloyl moiety ($C_{16}H_{19}N_2O_5S$) of not less than 5.4×10^{-5} M and not more than 7.0×10^{-5} M as determined by mercuric chloride titration.[4] Data are sparse on the clinical use of penicilloyl-polylysine at concentrations lower than 6.0×10^{-5} M, the nominal concentration of commercial Pre-Pen.

Methods

This project was reviewed and approved by the Southern California KP Health Care Program Institutional Review Board.

Between October 2004 and October 2006, we penicillin skin tested 596 individuals, using outdated Pre-Pen as the only major determinant reagent as part of a complete panel of penicillin skin test reagents, including penicilloate, penilloate, penicillin, and amoxicillin, as previously described.[5] Most of the tested individuals were referred to the Allergy Department for routine penicillin skin testing in advance of need.

Several of the individuals tested

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had syphilis. If the penicillin skin test results were negative, the patients with syphilis were given a 500-mg oral penicillin challenge and observed for one hour before being given their first intramuscular injection of sustained-release penicillin. They were also observed for 30 minutes after the penicillin injection. There were no adverse events noted in the individuals treated for syphilis.

All of the other individuals with negative skin test results were given a 250-mg oral amoxicillin challenge and were observed for one hour.

The concentration of penicilloyl-polylysine over the duration of the study was determined by mercuric chloride titration.[4]

Table 1. Patient demographics and skin test outcomes

Study group	October 2002–September 2004	October 2004–October 2006
Number	921	596
Female (%)	648 (70.4)	385 (64.6)
Age (years ± SD)	56.2 ± 59.9	54.2 ± 63.7
Time since reaction (years ± SD)	25.6 ± 18.7	25.2 ± 20.0
Skin test results positive (%)	47 (5.1)	28 (4.7)
Testing reactions (in study subjects with positive results; in study subjects with negative results)	3 (1; 2)	6 (4; 2)
Challenge reactions (within one hour; delayed)	Not done	4 (2; 2)

SD = Standard deviation

Table 2. Pre-Pen concentration after expiration

Date of assay	Months after expiration[a]	Concentration[b]	Percentage of original concentration[c]
January 31, 2005	4	4.88×10^{-5} M	81.3
February 15, 2006	17	4.68×10^{-5} M	78.0
October 4, 2006	25	4.29×10^{-5} M	71.5

[a]Pre-Pen lot number 91101 from HollisterStier expired in September 2004.
[b]Benzylpenicilloyl moiety concentration measured by penamaldate assay (mercuric chloride titration).
[c]Benzylpenicilloyl concentration labeled as 6×10^{-5} M.

Results

The skin test results in the 596 individuals tested with the outdated Pre-Pen were compared with the results of skin tests done on the 921 individuals tested between October 2002 and September 2004 with non-outdated Pre-Pen as a part of a complete panel of penicillin skin-testing reagents. Of the 921 pre-September 2004 study subjects, 46 had been previously reported on in a study of skin testing in pregnant women with group B strep colonization[6] and 120 were reported on in a study of penicillin skin testing in hospitalized patients.[7]

Table 1 shows the demographic characteristics of the study populations and the skin test results and adverse reactions associated with penicillin skin testing and penicillin-class antibiotic challenge in individuals with negative penicillin skin test results. Three of the reactions associated with the skin test itself occurring in skin test positive individuals were treated with epinephrine and antihistamines; one in an individual with positive results was treated with just antihistamines; one in an individual with positive results was just observed; and the four reactions occurring in individuals with negative results were just observed. A tryptase sample was obtained in one individual having a reaction to the skin test who was treated with epinephrine; the results were negative. Two of the oral-challenge reactions were itch without rash within one hour of dosing, and those study subjects were just observed; one was a delayed-onset rash at 24 hours, and that study subject was also just observed; and the final reaction was a delayed-onset rash at 24 hours, and that study subject was treated with oral antihistamine.

Table 2 shows the decline in the concentration of the benzylpenicilloyl moiety in the Pre-Pen during the two years of the study.

Conclusion

Penicillin skin testing can be safely performed using penicilloyl-polylysine at a concentration down to 4.29×10^{-5} M. We currently are using self-produced penicilloyl-polylysine at a concentration of 6.0×10^{-5} M as a part of a complete panel of reagents and giving an amoxicillin 250-mg or penicillin 500-mg oral challenge to all negative individuals. ❖

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