Penicilloyl-Polylysine Stability and Clinical Use Over Time

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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. 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 Because of a lack of a commercial source of penicilloyl-polylysine and the availability of outdated Pre-Pen, we studied the clinical use of outdated Pre-Pen in patients with a history of penicillin allergy.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 $5.4 \times 10^{-5}$ M and not more than $7.0 \times 10^{-5}$ M as determined by mercuric chloride titration. Data are sparse on the clinical use of penicilloyl-polylysine at concentrations lower than $6.0 \times 10^{-5}$ 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Between October 2004 and October 2006, we penicillin skin tested 596 individuals, using outdated Pre-Pen as the only major determinant reagent as part of a complete panel of penicillin skin test reagents, including penicilloate, penilloate, penicillin, and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. 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...
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

### 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 colonization6 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 $4.29 \times 10^{-5}$ M. We currently are using self-produced penicilloyl-polylysine at a concentration of $6.0 \times 10^{-5}$ 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.8

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### References