

Editorials

Penicillin allergy: A public health perspective

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Soon after the widespread use of penicillin became common, it was recognized that allergy to this antibiotic was a significant side effect. Studies showed that administration of penicillin under certain conditions caused the universal production of antibodies in experimental animals¹ and likely in human subjects. Penicillin itself and degradation products of the antibiotic acted as haptens and provoked the formation of a variety of immunoglobulin classes, including IgG and IgM.^{2,3} When IgE was described as the atopic antibody, skin tests and in vitro tests to the major determinant penicilloyl, which was conjugated to polylysine, and the minor determinants, the degradation products of penicillin, were used to identify individuals who were subject to a type I reaction to the antibiotic.^{4,5} It is widely assumed that patients with a negative skin test response to either determinant and a negative in vitro test result can safely be given penicillin because they will not have a serious, immediate type I reaction,⁶ although not all investigators agree.⁷ There are no reliable or widespread tests for other types of penicillin allergies, such as serum sickness and rashes. Lurking in the background of studies of penicillin allergy is the problem of the vagueness of history.⁸ When taking a history, penicillin allergy is frequently reported to the physician on little basis, except, perhaps, that the patient was told of it when he or she was young. Rashes (both urticarial and otherwise), asthma, and even joint pain can be interpreted by the patient, family member, and, frequently, the physician as penicillin allergy when these signs are a manifestation of the disease for which penicillin was rightly or wrongly dispensed. Thus for the past 50-plus years, such questions as to the prevalence of penicillin allergy in patients who likely had a previous reaction have not been satisfactorily answered.

In summery, then, penicillin allergy is a morbid manifestation seen in a subset of patients subjected to

a potential toxin by a vector, the physician. Its natural history is, at the very least, unclear. Putting aside the immunologic mechanisms of this disease, it can be viewed as a public health issue, and it can be and has been studied by using the tools of epidemiology.

In an article in the current issue of *The Journal of Allergy and Clinical Immunology*, Apter et al⁹ attempted to answer a variety of outstanding questions concerning penicillin allergy by examining a large electronic database compiled from the reports of general practitioners in the United Kingdom.⁹ This database provided the investigators with the diagnoses of 3,375,162 outpatients coded by a medical practitioner. This study provides us with both the elements of the natural history of this epidemic and informs us of the approach that general practitioners in the United Kingdom take to it. Whether this approach is the same as that of physicians in the United States is currently unknown.

Because the aim of the study was to determine the risks of a repeated allergic reaction in patients who had such a reaction after being treated with penicillin, only those patients who received 2 doses of the drug were included in the core of the study. It was, however, indicated that only 0.18% of the original cohort had penicillin allergy, a number much lower than that usually quoted. The outcomes of the 3014 patients who experienced an allergic reaction and were re-treated were compared with the outcomes of the 2,014,943 patients who did not have an allergic reaction after the first administration and were then re-treated.

The advantages of the use of this kind of database are obvious. The diagnosis of the allergic reaction was made by a physician. It is hoped that this would remove at least some of the vagueness of the history of penicillin allergy frequently reported by patients and their families. On the other hand, the study is retrospective, and uniform criteria cannot be guaranteed. The physicians who generated the reporting used a series of codes. The authors used those codes covering many of the usual allergic manifestations, such as urticaria, anaphylaxis, and others, as a narrow definition of allergy. Broader definitions included asthma, which could be caused by the respiratory infection for which the patient might have been treated with penicillin, and eczema, which could be caused by other conditions or be a chronic disease present in the patient being treated. The third diagnosis in the broad definition is much more troubling: "unspecified adverse effect of a drug, medicinal and biologic substance." When it comes to penicillin, it would seem that except for diarrhea and fungal infections, most adverse effects would be allergic. Use of this code

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might well be the default reporting of many physicians who had to report the event but were not interested in looking up the other more specific codes. In fact, when the broader codes were used, the prevalence of the "penicillin event" after the first administration went from 0.18%, far less than that usually quoted, to 9%, far greater than that usually quoted. No doubt the prevalence is somewhere between these 2 extremes. The exclusion of asthma and eczema would appear to be justified. Whether the exclusion of the adverse event coding is appropriate is more problematic. Also, the large numbers increase clinically unimportant differences by investing them with statistical differences. Of the patients without life-threatening illnesses who demonstrated no allergic reaction on the first administration, 58.9% received a second prescription, as did 48.5% of those who did have such a reaction. These are statistically different, but so what? The second number should be close to zero. Fortunately, only 1.89% of the latter had an allergic reaction (narrow criteria), which is statistically different but of little clinical difference from the 0.17% of the former.

The data on anaphylaxis provided several surprises. The authors did not enumerate the allergic reactions of the initial 6212 patients with an initial allergic reaction because they were interested only in those patients who received a second dose. Sixteen patients who were given a diagnosis of anaphylaxis were given a second dose, likely by the same physician. Surprisingly (and thankfully), only one patient had a repeat anaphylactic episode, and this patient lived. Indeed, against conventional wisdom, not one patient in this study died.

This article will be quoted again and again, and I hope that the authors continue to mine this database. Should we and can we have similar databases concerning a variety of unanswered questions here in the United States? Although our diffuse health care system and privacy rights might

make it difficult, if we really want it, it can be done. In my clinic several weeks ago, 2 pharmaceutical representatives wanted to talk to me about their product. As a naive academician, I was surprised to learn that they knew that I routinely prescribed a rival product. If it is important to their economic interests to know one portion of our practice, the allergy-immunology community and indeed each specialty and subspecialty could learn much about the natural history and the diagnosis and treatment of disease by regularly collecting such data.

The Editors of The JACI are saddened to report that Dr Alan S. Josephson, whose many contributions to the Journal include this insightful editorial, passed away unexpectedly on January 30, 2004.

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