EVALUATION OF PENICILLIN HYPERSENSITIVITY WITH PENICILLOYL POLYLYSINE AND PENICILLIN G

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One hundred patients with a positive history of penicillin reactions but requiring penicillin therapy were intradermally tested with penicilloyl polylysine (PPL) and penicillin G (PG). A total of 27 patients were found positive to either PPL or PG or both. There were more patients positive to PG than to PPL. All 73 skin test negative patients were safely administered full dosage of penicillin. Out of 4 patients with PPL positive but PG negative skin tests challenged with 10,000 units of penicillin, two reacted adversely. One developed grand mal epilepsy like seizure and the other generalised pruritus, urticaria and breathing difficulty. No patient positive to either PPL or PG should be administered penicillin.

Key words : Penicilloyl polylysine, Penicillin G, Hypersensitivity, Intradermal tests.

The question of penicillin hypersensitivity is frequently a major problem in the management of infectious diseases which can only be effectively treated with penicillin, especially when a significant population has been labelled allergic to penicillin.[1] The detection of penicillin allergy is important because of anaphylactic reactions which may occur because of penicillin administration in penicillin allergic patients. Although accurate figures for incidence of allergic reactions to penicillin are not available, the reported incidence varies from 1% to 10%.[2-4] Death from penicillin anaphylaxis is very uncommon, the range in various studies being 1.5 to 50 per 100,000 patient courses of treatment.[1,5,6] Rudolph and Price[6] reported a very low incidence of reactions, 0.66% and only one fatality in 94,655 of their STD patients treated with penicillin. For reasons of serious allergic reactions, physicians have long sought a reliable method of assessing allergic sensitivity to penicillin. Intracutaneous tests with penicilloyl polylysine (PPL) which contains the penicilloyl group as the major haptenic determinent and penicillin G containing minor determinants are both commonly used for detection of immediate type of allergy.[4,7-9] However, a positive test in vitro or in vivo does not necessarily imply an adverse reaction at subsequent administration of a penicillin derivative.[10] Nevertheless in a patient who had a definite history of anaphylaxis, maculo-papular rash or delayed urticaria or who shows a positive patch/scratch test, penicillin should be regarded as a drug strongly likely to produce an adverse reaction. One can be more sure with anaphylaxis, angioedema and urticaria indicating allergy, but maculo-papular rashes are more difficult to interpret especially in patients with glandular fever, cytomegalovirus infection and chronic lymphocytic leukemia.[3] Present study was devised to investigate the relationship of skin reactivity to penicillin hypersensitivity. Reagents used were penicillin G and penicilloyl polylysine (PPL) which prior studies have reliably utilised to predict majority of penicillin hypersensitivity reactions.[11]

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Materials and Methods

One hundred adult patients of either sex with a previous history of penicillin allergy, immediate or delayed in any form except anaphylaxis, or who had been earlier skin tested with penicillin and declared allergic, were taken for study. These patients needed penicillin for their existing

condition. Previous history of allergy after administration of drug or testing consisted of feeling of giddiness, nausea, vomiting, fainting, feeling of paraesthesias and itching. Feeling of swelling, heaviness, itching and discomfort was complained by many patients at the site of testing. We knowingly ignored the history of previous intradermal test positivity because the method of testing with penicillin is generally not standard.

Two preparations used for skin testing were, (1) penicilloyl polylysine (PPL) supplied by Kremers Urban Company, Milwaukee, Wis as Pre-pen in 1.0 ml ampoules, and (2) benzyl penicillin G (PG) supplied by Sarabhai Chemicals, Baroda as potassium penicillin G for injection.

Volar aspects of both the arms were used for testing, injecting 0.05 ml of the reagent with a 25 gauge needle. Dose of penicillin injected for testing was 100 units (2000 units/ml of penicillin G). The reactions were interpreted after 20 minutes. The wheals raised by the drug were outlined clearly by a fine ink line. Those reactions which produced a wheal twice or more than twice the previous size with erythema surrounding with or without pseudopodia were recorded as positive. Borderline reactions were not recorded because of their ambiguity. All necessary arrangements were made available in case an emergency arose due to penicillin testing. Those patients who were positive to both penicillin G or PPL were tested with buffered saline given in the same amount to check for false positivity. No patient positive for PG was challenged. Four patients from the PPL positive group were challenged with 10,000 units of penicillin G given intramuscularly.

Results

Except for mild local discomfort none of the patients experienced any serious side effects.

Seventy three patients were negative to both PPL and PG, 14 were positive to both, 9 patients were sensitive to PG only, and 4 were positive to PPL only. So there were more positive reactions to PG (23%) than to PPL (18%). The differences however are not significant. Of the four patients positive to PPL but not to PG and given a challenge with 10,000 units of penicillin, one developed grand mal epilepsy like seizure which lasted 1-2 minutes (subsequent follow up and EEG did not reveal any abnormality), and the other developed immediate generalised pruritus (especially on the palms and soles), urticaria, cough, breathing difficulty and hypotension.

All the 73 patients with negative skin tests were administered full therapeutic dose of penicillin. Two patients developed immediate type of allergic reactions consisting of nausea, vomiting, generalised pruritus and hypotension, and another patient developed urticaria after 4 weeks. All patients could be easily revived with subcutaneous adrenaline, intravenous hydrocortisone and intramuscular antihistamine. None of the other patients developed either early or late reaction.

Comments

Allergic reactions to penicillin comprise the major clinical problem of this otherwise remarkably safe drug. Allergy to penicillin gives rise to a wide variety of clinical syndromes.[3,12] Immediate reactions include anaphylaxis, angioedema, urticaria and some maculo-papular rashes. Late reactions have well-defined immunological basis such as serum sickness like reactions, hemolytic anemia, acute interstitial nephritis, and others less clearly immunological such as neutropenia and maculo-papular rash produced by ampicillin.

The clinical basis of penicillin allergy is complex and incompletely understood. Penicillins give rise to a number of different antigenic determinants either by metabolism in vivo or by breakdown in vitro.[3,13] Anaphylaxis usually occurs after parenteral route but has been reported after oral administration.[14] The

major antigenic determinant is the penicilloyl group and most and more serious reactions are due to this. Other breakdown products such as penicillamine and penicilloic acid also act as haptens and form the minor determinants. Despite the name, the minor determinants are of major clinical importance because of their association with IgE antibodies and the risk of anaphylactic and urticarial reactions. The PPL reagent (Pre-Pen) is more closely identified with major determinant in the penicilloyl nucleus and the PG with the minor determinant mixture. It is important to emphasize that no skin tests for penicillin allergy can predict the occurrence of other penicillin reactions including hemolytic anemias, serum sickness, drug fever, interstitial nephritis and exfoliative dermatitis. We now know that positive skin tests develop during a course of penicillin therapy which do not always imply the risk of reaction if the therapy is continued.

Negative skin tests are found in about 75% of patients having a history of previous penicillin reactivity, and some of them even with serious anaphylactic reactions and urticaria are able to tolerate penicillin.[15] Among the 328 history-positive and skin test negative patients given penicillin therapeutically, there were only 3 mild reactions and another 3.2% patients developed delayed maculo-papular rash.[15] More than 60% history-positive patients of bacterial endocarditis could also tolerate penicillin without allergic reactions.[16] In a study on 3000 patients Green et al[1] found only 19% patients to be positive to either PPL or PG with positive history of penicillin allergy compared to a positivity of 7% in their history-negative patients. We also observed 27% positivity to either PG or PPL in our history-positive patients.

Clinically, the situations which may require penicillin skin testing are clearly defined. (i) The most important is the assessment of risk in history positive patients. If there is a definite positive history of severe allergy than a scratch/patch test with penicillin should be performed and if positive intradermal test is not performed.

(ii) In all patients who are to receive penicillin if the cost benefit ratio permits, because the incidence of positive skin tests in history negative patients is quite low (2% to 4%). The cost factor especially for inclusion of PPL for testing should be considered. In the studies of Green and Rosenblum[11] and Green et al,[1] PPL gave more positive reactions as compared to PG. However, in our study more reactions were observed with PG than PPL even though the differences are not significant.

Intelligent use of tests should enable the practising physician to avoid the pitfalls. If tests are positive we can then balance the high risk of allergic reaction against the seriousness of the therapeutic problem considering that not every patient at risk of developing an adverse reaction to penicillin is detected by intracutaneous tests with PPL. A positive test to PPL and PG indicates the presence of IgE antibodies to penicillin or its major degradation product (penicilloyl) and an allergic reaction is likely if penicillin is administered. Whereas a negative test to both PPL and PG is a strong evidence that the IgE antibodies to penicillin are not present. Although a history of penicillin allergy may not be sufficient against usage of penicillin but a positive patch test to either PPL or PG is. From our experience of 2 severe reactions in 4 positive test patients we would tend to agree with the earlier observation against the use of penicillin in a patient who had adverse reaction to penicillin or with positive patch tests.[11] Penicillin study group of the American Academy of Allergy also revealed that allergic reaction to penicillin will occur in two third patients with positive skin tests as compared to 3% only in patients with negative skin tests.[1] Rudolph and Price[6] also observed

that patients with history of allergy reacted 20 times more than those who had negative history of penicillin allergy if the history was reliable. PG is supposed to detect sensitivity to minor determinant which is responsible for more serious allergic responses, and PPL the major determinant known to cause mostly milder form of reactions, so the combination of the two should give complete information about the current status of penicillin sensitivity. But from our experience of serious reaction in PPL positive but PG negative patients, we would like to conclude that, (i) penicillin should not be administered to patients positive either to PPL or PG or both, (ii) addition of PPL did not give significantly more information than PG alone, whereas it is supposed to pick up more penicillin allergic patients; (iii) thus, PPL testing can be omitted at enormous savings and not adding seriously to the increase in incidence if any, because of undetected allergic patients by PG alone.

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