

Case report

Could a routine skin test to penicillin lead to fatal anaphylaxis?

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Introduction

Penicillin has been the most widely administered antibiotic, and the frequency of associated allergic reactions ranges from 0.7% to 10% [1-4]. Systemic allergic reactions secondary to IgE antibody-mediated hypersensitivity (anaphylaxis) occur in 0.01% of penicillin administrations. Allergic reactions to such β -lactam antibiotics account for 2% of cases of anaphylactic reaction [3,4]. In the past, penicillin has caused about one fatal anaphylactic reaction per day in the United States of America [3,4]. Similar fatal reactions to penicillin have also been reported in other countries [5-7].

When clinically indicated, skin testing with standard penicillin components has been widely accepted as a screening technique for the detection of IgE hypersensitivity [8,9]. Testing includes the major determinant of benzylpenicillin (benzylpenicilloyl) and a minor determinant mixture of benzylpenicillin [10]. Such a test is positive in approximately one-sixth of those patients reporting an allergy to penicillin [11]. The predictive value of a properly conducted negative skin test in preventing major allergic reactions to penicillin is > 90% 95% [6,7,9,11]. The risk of systemic anaphylaxis in patients with a suspected

penicillin allergy who have a negative skin test to penicillin is very low (< 2%), which is similar to normal individuals [6,7,9,11].

Unfortunately, skin testing with allergenic extracts is not totally free from side-effects, especially if the extracts are not properly prepared or if the test is performed on highly sensitive individuals. Testing using two techniques, the scratch or prick skin test (PST) and the intradermal skin test (IST), can be associated with a low rate of systemic allergic reactions, usually < 0.5% of tested patients [12-17]. So, although skin tests appear to be relatively safe in the prediction of systemic reactions to penicillin, catastrophic outcomes cannot be avoided. Here we report a case of anaphylactic reaction with a fatal outcome after an intradermal penicillin skin test. Current views on the management and prevention of such reactions are discussed.

Case report

The data of this case report were obtained by interviewing the doctor and the nurse separately. A 36-year-old female presented walking on 12 November 1997 to a dispensary in Saudi Arabia. She complained of pain and tenderness of the left foot, which she had felt for 4 days. The problem started

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3 days after a minor abrasion. Systemic review revealed only a low-grade fever with no other associated symptoms. There was no significant past history of medical or surgical illness. The patient had no past history of allergy to penicillin or other drugs. There was no personal or family history of any allergic disorder. She worked as a housemaid and did not smoke.

On physical examination the patient was not in any distress. Vital signs showed a pulse rate of 90 beats/minute, blood pressure of 130/80 mmHg, respiratory rate of 16 breaths/minute and a temperature of 37.9 °C. There was an area of erythema, swelling and hotness extending from her big toe up to half of the distal dorsum of her left foot. The rest of her physical examination was normal. No laboratory tests were performed.

The preliminary diagnosis of the attending practitioner was left foot cellulitis. The attending nurse was instructed to administer penicillin-G 600 000 IU intramuscularly to the patient after performing a skin test. The skin test extract was prepared by diluting 0.5 mL penicillin-G with 0.5 mL normal saline (0.9% sodium chloride) in a 1 mL plastic syringe. After cleaning the patient's left forearm with propyl alcohol, 0.2 mL of the mixture was injected intradermally after ensuring that there was no blood back-flow in the syringe.

Apart from the usual discomfort at the injection site, the patient was sitting comfortably on a couch. Three minutes later she complained to the nurse of itching and increasing discomfort at the injection site and feeling unwell. A few minutes later she complained of chest tightness. The nurse reassured the patient and left immediately to call the doctor who was examining another patient. Five minutes later the doctor arrived and found the patient lying on the

couch, very drowsy, and she rapidly lost consciousness. On examination, she was in respiratory distress with a weak and thready pulse of 140 beats/minute. There was no skin rash, and no other systemic abnormalities were noted. Several attempts to insert an intravenous cannula to initiate fluid therapy failed. Soon the patient was unresponsive and pulseless, with an unrecordable blood pressure. Basic life support was initiated with cardiopulmonary resuscitation with cardiac massage and manual ventilation. Further attempts to find a peripheral venous axis for medication failed. The patient was transferred after 20 minutes to a hospital where she was found to be asystole. More attempts of advanced resuscitation, including intravenous adrenaline, atropine, bicarbonate and crystalloid fluids, were not successful and the patient was subsequently declared dead.

This case was presented for discussion at the grand round of the Medical Department of King Abdul Aziz University Hospital. Differential diagnoses were discussed, including sudden arrhythmias, septic shock and other types of shock. Based on the available evidence, it was felt that the most likely diagnosis was severe anaphylactic reaction secondary to the penicillin skin test with a tragic fatal outcome.

Permission for publication was obtained from the director of the dispensary where the case occurred, primarily because of the scientific value of this medical problem. The patient's nationality and the city name were kept anonymous for confidentiality and for ethical reasons.

Discussion

Traditionally, skin testing with penicillin dilutions has been widely used as a screening

technique for the detection of IgE hypersensitivity to penicillin. This case report documents a severe anaphylactic reaction following a routine intradermal skin test with penicillin, which tragically had a fatal outcome. On reviewing the literature, only a few incidents of fatal anaphylactic reactions to penicillin skin test have been documented in the past, more with IST than PST [18,19]. Fatalities to other allergens have also been reported, particularly with IST with venom or chymopapain extracts [14-17]. The tragic outcome of this case motivated the writing of this report and the review of the current recommendations on skin testing with penicillin.

Except for a few of the tertiary centres, most hospitals in the Middle East do not apply the current screening techniques for penicillin sensitivity and still use old methods. Routinely, testing is carried out on all patients who are going to receive penicillin. In the older technique, the skin test is performed directly by intradermal injection of a one-tenth or higher concentration of the drug to be used, without a prior prick test or control. This is known to result in exposure to a higher dose of the allergenic material. The predictive value of this traditional technique for preventing allergic reactions to penicillin is not accurately known. Hence, sensitivity screening to penicillin is underestimated and severe allergic reactions cannot be avoided.

Recommendations for patients with suspected allergies to penicillin are now continuously updated and it is very important that they are implemented in order to minimize fatalities [7,20]. These recommend that there should be an established sound indication for the penicillin therapy and that it should only be used if alternative antibiotics are not available. A skin test should only be performed to screen individ-

uals where a previous history of allergy to the drug is clear or is not known and if alternative antibiotics are not available. An allergist or well trained medical worker should be the one to conduct allergy tests. Only standard extracts, which include major and minor determinants of penicillin, should be used. The major determinant is commercially available, e.g. Pre-pen® (Hollister-Stier Laboratories, United States of America). The minor determinants include benzylpenicillin (penicillin-G), benzylpenicilloate and benzylpenilloate. Unfortunately, the last two reagents are only made in a few highly specialized laboratories and only recently have some of them become available commercially on a limited basis.

Proper allergy skin tests should be conducted with a positive control (histamine) and a negative control (saline) to avoid false-negative results in patients on antihistamines or false-positive results associated with dermatographism or other disorders respectively. Testing should also begin with the prick technique before the intradermal test to avoid systemic reactions to the latter in highly sensitive patients. The prick test should be conducted with non-irritant dilutions such as 3 mg penicillin/mL. If this is negative, one can proceed with 1/100 dilution for the intradermal test with 0.2 mL, and if this is negative with 1/10 dilution after 15 minutes each. If all of these are negative, then the drug can be administered safely in most cases. Because fatal reactions in such cases have rarely been reported, it is advisable that patients be observed in a medical facility for at least 30 minutes after any systemic injection. An open challenge test with oral doses of the suspected drug is rarely required to confirm the possibility of any allergic reaction. This technique is hazardous and must only be conducted by qualified personnel in a med-

ical facility where they can manage any acute allergic reactions.

Airway management, endotracheal intubation tools and basic drugs needed for cardiopulmonary resuscitation should be available in medical facilities where parenteral drugs are given [20,21]. In the setting of acute anaphylaxis, epinephrine is a life-saving drug and should be given at doses of 0.3–0.5 mL of 1:1000, either subcutaneously or intramuscularly immediately [21,22].

It is important to start proper skin testing with the prick or scratch technique before the intradermal injection with penicillin extracts. Patients who have a positive prick skin test or intradermal skin test to penicillin should avoid all penicillin-like products, including semi-synthetic ones like amoxicillin and ampicillin. Additionally, they should avoid all cephalosporin compounds because of their cross-reactivity with penicillin [3,4]. These patients are advised to wear a medical alert bracelet or hold cards with information of penicillin allergy.

Because of the risk of sensitization and anaphylaxis to penicillin, the skin test should not be routinely conducted for all individuals who will receive penicillin. Candidates for the skin test are patients who report any previous reaction to penicillin, those who do not know, or those for whom a history of allergic reaction cannot be obtained (e.g. patients in a coma).

The other important problem in the management of anaphylaxis is delay in the administration of epinephrine, subcutaneously or intramuscularly [23]. Early use of subcutaneous epinephrine or intramuscular epinephrine in acute anaphylactic reaction is the drug most often reported to save lives [21,22]. Intravenous epinephrine is the drug form most commonly used in severe

anaphylactic shock when there is loss of consciousness or cardiac arrest.

Because of the rarity of severe allergic reactions, physicians are sometimes slow to deliver the appropriate treatment. Hence, it is the duty of the specialists in the field of allergy to continuously update primary and secondary health care practitioners. Using the media for health education is also highly recommended to raise public awareness of penicillin allergy.

Conclusion

Although skin testing appears to be safe, systemic reactions have been observed and fatalities reported. As far as possible, medical care providers should implement the latest recommendations regarding skin testing for the diagnosis of drug hypersensitivity. When penicillin is clinically indicated, it is recommended to use diluted standard extracts that include the major and minor determinants. Additionally, the use of proper controls should not be ignored, and the skin prick test should precede the intradermal test. The importance of early administration of epinephrine for acute anaphylactic reactions cannot be over-emphasized. It is to be hoped that promoting the recent guidelines will lead to the prevention of systemic allergic reactions and fatalities due to the penicillin skin test or to penicillin administration.

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What does a national drug policy help to achieve?

The goals and objectives of a national drug policy (NDP) will depend upon the country situation and its priorities. In the broadest sense an NDP should: make essential drugs available and affordable to all those who need them; ensure safety, efficacy and quality of drugs available; promote the national use of drugs by both prescribers and consumers; be concerned with efficiency, equity and substantiality. The policy must also take into account such areas as production, international collaboration, property rights and the role of pharmacists.

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