Skin Testing before Antibiotic Administration – Is there a Scientific basis?

Pradeep Narayan¹, Emmanuel Rupert²

Abstract

The practice of skin testing prior to administration of antibiotics in the absence of a history of allergy is non-existent in the western world. Reports on skin testing in the absence of known allergy are unheard of in the medical literature. The practice of giving a test dose prior to administration of the antibiotic is also practiced very sporadically and has no scientific basis. Despite this in India in most major institutions both in government and private hospitals, general practice set up and small and medium nursing homes, skin testing prior to administration of antibiotics remains extremely common and is even considered to be negligent if not practiced.

In this review the evidence for skin testing and test dose before antibiotic administration has been examined. Based on the evidence available skin testing should be restricted to patients with a history of prior penicillin allergy for whom penicillin or other B-lactam antibiotic is the drug of choice and there is no suitable alternative.¹ There is no need to do skin testing without a history of penicillin allergy even if the drug is to be administered parenterally. Test dose administration does not protect patients from anaphylactic reactions and hence the practice has no scientific basis.

Introduction

E ven t h o u g h i t h a s b e e n recommended that skin testing should be restricted only to patients with a history of prior penicillin allergy for whom penicillin or other B-lactam antibiotic is the drug of choice and there is no suitable alternative¹ the practice of skin test has been deeply ingrained in the psyche of the health care providers including doctors as well as nursing staff. Currently in most hospital in India “Skin testing” refers to injecting a small amount of the antibiotic in question in varying dilution. There is no definite protocol for the dilution across institutions nor is there consensus about the injection being given intra-dermally or subcutaneously. Following the injection the area is examined for induration or features of systemic hypersensitivity reactions. The time one has to wait before confirming that the patient is not allergic to the antibiotic in question is also variable. There is no evidence in the literature that this practice is useful in reducing rates of anaphylactic reactions and the practice has been in vogue purely as part of the culture of administering antibiotics in institutions in our part of the world.

Test dose administration is often practiced by anesthetists and other medical practitioners whereby a small amount of the antibiotic in question is administered intravenously and after a non-defined period of wait the remaining antibiotic is administered. The logic behind this practice is that by test dose administration even if the patient had hypersensitivity reaction the dose of antigenic challenge is limited therefore minimizing the chance of a full-blown anaphylaxis.

Scientific basis of Skin testing

At the outset it has to be clarified that skin testing in the patients with no history of previous allergic reaction to antibiotics and those with a positive history are two completely different scenarios. While clinically significant IgE-mediated penicillin allergy can be safely confirmed or refuted using skin testing with penicilloyl-poly-lysine and native penicillin G in presence of positive history of allergy²,³ its utility as a screening tool in all patients without any history of allergic reaction is questionable.

There are two main arguments against skin test or test dose in patients with no previous history of allergy to penicillin or any other antibiotic.

Firstly, anaphylaxis is a generalized hypersensitivity reaction which may be IgE or non-IgE mediated. Thus, the presentation can be within 1 hour (IgE mediated) or beyond 1 hour (non-IgE mediated). So, the time we generally wait before giving the antibiotic after a skin test or a test dose does not assure that the patient is not allergic to the antibiotic in question and will not have a hypersensitivity reaction.

Secondly, hypersensitivity reactions are dose independent. Rawlins and Thompson classified adverse drug reactions into two types. Type A reactions which are dose dependent and are predictable and type B reactions which are dose independent and unpredictable. Hypersensitivity reactions to antibiotics belong to the type B of adverse drug reactions and thus are dose independent.¹ This has been further confirmed by Wills and Brown who classified drug reactions into 9 types and suggested that hypersensitivity reactions are a type H reaction which are neither pharmacologically predictable, nor are they dose related.³

Moreover, while parenteral administration appears the most likely
route to induce anaphylaxis, it has been reported to occur following parenteral, oral, topical, or inhalation routes.

Lastly, skin tests (in presence of penicillin allergy) have been well validated mainly for β-lactam but less well validated for other classes of antibiotics. Routine cephalosporin skin testing should be restricted to research settings. If skin test is negative, an oral amoxicillin challenge can be given. Acute tolerance of an oral therapeutic dose of a penicillin class antibiotic is the current gold standard test for a lack of clinically significant IgE-mediated penicillin allergy.

Pathology of Penicillin allergy

Adverse Drug Reactions (ADRs) account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalized patients. Drug allergy is relatively uncommon, accounting for less than 10% of all ADRs. Hypersensitivity reactions represent about one third of all adverse drug reactions.

The course of penicillin hypersensitivity is unpredictable with an individual tolerating penicillin earlier may show allergy on subsequent administration and those allergic earlier may not have problems on subsequent administration.

According to the World Allergy Organization drug allergies based on timing of symptoms can be classified into immediate and delayed. Immediate reactions occur within 1 hour after the drug administration and delayed reactions occur more than 1 hour after the last drug administration. Immediate reactions can range from urticaria to anaphylactic shock and may be mediated by specific IgE antibodies. Delayed reactions are usually manifested as a maculopapular rash and specific T lymphocytes may be involved in this type of reaction.

Antibiotics can be classified as β-lactam and non-β-lactam. The β-lactams share a 4-membered β-lactam ring and are consist of 2 major classes (penicillins and cephalosporins) and 4 minor ones (carbapenems, monobactams, oxacephems, and clavams). Non-β-lactam antibiotics have different chemical structures and some of the commonly used non-β-lactam antibiotics include quinolones, macrolides, aminoglycosides, sulfonamides, rifamycins, and clindamycin.

IgE-mediated reactions involve drug allergens binding to IgE antibodies, which are attached to mast cells and basophils, resulting in IgE cross-linking, cell activation and release of preformed and newly formed mediators. Non-IgE-mediated drug allergy most commonly are T-cell-mediated reactions.

True incidence of Penicillin allergy

β-lactam are the most widely used antibiotic worldwide. It is also the most commonly reported cause of drug allergy, with a prevalence rate of 0.7 to 10% in adults and children. However it has been shown that 95% of patients with a history of penicillin allergy were considered not to be allergic in large scale follow up studies using various tests to confirm the diagnosis. Based on the recommendations of the European Network of Drug Allergy / European Academy of Allergy and Clinical Immunology: assessment of β-lactam hypersensitivity includes a detailed clinical history, in vitro quantification of specific IgE-antibodies, skin tests, and drug provocation test (DPT).

Those patients with non suggestive or unknown histories have a penicillin skin-test positivity rate of less than 2%. Among all patients labeled penicillin-allergic, the frequency of serious reactions to cephalosporin administration is less than 1%. Over diagnosis of drug allergy leads to the unnecessary use of broader spectrum and expensive antibiotics contributing to the emergence of multidrug resistant pathogens. Equally, underdiagnosis of antibiotic allergy can have serious and sometimes fatal consequences.

Tests to assess Penicillin allergy

A positive skin prick test (SPT) is defined as mean weal diameter greater than 3 mm (associated with a flare response) compared to the negative control after 15 to 20 minutes.

A positive intradermal test (IDT) while being more sensitive to the SPT it is also more prone to anaphylaxis. Similar to the SPT it is defined as an increase in the mean weal diameter of ≥3 mm compared to the baseline diameter for the negative control after 15 to 20 minutes. It is performed by injecting 0.02 to 0.05 mL of an allergen intradermally, raising a small bleb measuring 3 mm in diameter. Readings should be taken both after 15 to 20 minutes and after 24 and 72 hours for evaluation of non-immediate reactions.

Drug provocation tests (DPT) are used to objectively reproduce the patient’s symptoms and signs of hypersensitivity using the suspected agent. DPT involves administering the drug using slow, incremental dose escalations and observing for the presence or absence of an objective reaction. However, a positive test does not confirm allergy (i.e. an immune-mediated reaction). It should be done only under strict supervision.

Anaphylaxis during general anaesthesia

Neuromuscular blocking agents account for over half of all cases of anaphylaxis. However anaphylaxis due to latex and antibiotics are on the rise. Anaphylaxis to fentanyl and neostigmine has also been reported. Researchers examining patients undergoing anaphylaxis during anesthesia have suggested that screening patients without a prior history of allergic drug reactions is not recommended because there is a discrepancy between skin pick test results and clinical outcomes.

Antibiotic hypersensitivity in children

Immediate hypersensitivity to as β-lactam is particularly rare in children, but identification of these patients is particularly important because these reactions can be life threatening. The decreased frequency of allergic drug reactions in children may be secondary to several factors, including fewer drug exposures, generally reduced allergic reactivity, less vigorous antibody response, and differences in drug metabolism.

Penicillin allergy in Cardiac Surgery

The Society of Thoracic Surgeons guidelines for prescribing antibiotics in presence of penicillin allergy recommend that “In patients with a history of an immunoglobulin-E (IgE)–mediated reaction to penicillin or cephalosporin (anaphylaxis, hives, or angioedema), vancomycin should be given preoperatively and for no more than 48 hours. Alternatively, skin testing may be performed in these patients and, if negative, a cephalosporin regimen administered (Class I, Level of Evidence A).” However for patients “with a history of a non-IgE
mediated reaction to penicillin (such as a simple rash) or an unclear history either vancomycin or a cephalosporin is recommended for prophylaxis with the understanding that these patients have a low incidence of significant allergic reactions to cephalosporins (Class I, Level of Evidence B).2,26

Desensitization
This is a specialist area and has to be done by experts in the field. Oral route is the safest, however it can be performed by intravenous, or subcutaneous routes as well. Desensitisations have been performed safely even in pregnant women.29

Summary
Over diagnosis of drug allergy leads to the unnecessary use of broader spectrum and expensive antibiotics and majority of patients with a history of penicillin allergy prove not to be allergic in large. Skin testing in the current form does not protect patients from anaphylaxis and there is no scientific basis for the practice.

Recommended antibiotic administration protocol
Based on the guideline the suggested protocol for antibiotic administration starts with a clinical history. A history of drug and antibiotic allergy has to be elicited. In the absence of history of allergy to antibiotics (usually penicillin group) no skin testing or test dose is required.

If the patient provides a history of allergy to penicillin then alternative appropriate antibiotic should be used.

The alternative antibiotics include - Cephalosporins and other non-penicillin beta-lactams. They have been used safely in individuals, even with confirmed penicillin allergy. Currently it is believed that there is little, if any, clinically significant immunologic cross-reactivity between penicillin and other beta-lactams.2

Another safe option would be to use non-beta Lactams like Vancomycin.

In the unique situation of penicillin being the only drug of choice and the patient gives a history of penicillin allergy one has to seek specialist advice. A skin test and a course of desensitization vis. a vis. administration of penicillin or cephalosporin has to be taken based on the clinical condition of the patient and how convincing the history of allergy to penicillin is. It also has to be borne in mind that almost 85% patients previously allergic to penicillin may be able to tolerate the drug on re-administration, indicating the potential transient nature of the condition.3

However, this has to be discussed with the patient, the family and other involved clinicians before reaching a consensus and has to be dealt with on a case to case basis.

References