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Review Article

Assessment of drug hypersensitivity with non-irritating concentrations of antibacterial agents for allergic skin tests: a review

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ABSTRACT

Hypersensitivity reactions to antibiotics are common with a prevalence of 6-10% of all adverse reactions. There is a lack of guidelines and standardization of skin tests for the screening of hypersensitivity to all antibiotics, in terms of the methodology, dose and time of evaluation of the tests. Literature from Europe and America suggests the use of non-irritating concentration (NIC) of antibiotics for skin testing such as intra dermal test (IDT), skin prick test (SPT). These are concentrations at which the drug is unlikely to produce irritation by virtue of its chemical nature resulting in false positive reactions. These concentrations have been validated by trials in their populations. Due to the increase of antibiotic resistance in our country, declaring a patient allergic to a specific class of antibiotics based on positive skin tests can further narrow the therapeutic armory. These individuals have an increased incidence of infections with resistant organisms as well as increased cost of hospitalization. This is due to the use of alternative broad spectrum antibiotics. Therefore, there is a need for a standardized protocol for the use of skin tests in screening of hypersensitivity, with validated NIC of all antibacterial agents. The aim of this article is to review literature of protocols for assessment of drug hypersensitivity with NIC of antibacterial drugs for SPT, IDT and also establish the need for research in this area in our country.

Keywords: Hypersensitivity, Skin prick test, Intradermal tests, Antibacterials, Non-irritating concentration

INTRODUCTION

Adverse drug reactions are harmful or unpleasant reactions, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. Adverse drug reactions are of six types, dose-related (augmented), non-dose related (bizarre), dose-related and time-related (chronic), time-related (delayed), withdrawal (end of use), and failure of therapy (failure). Hypersensitivity reactions are bizarre type of reactions, which can range from itching to life-threatening conditions like anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis.[1]

Hypersensitivity reactions to antibiotics are common with a prevalence of 6-10% of all adverse reactions.[2] These adverse reactions are more common with beta-lactam group of antibiotics,[3] but with the increased use of non-beta lactam antibiotics, there is increasing evidence of adverse reactions attributable to them. It is a common clinical problem, yet there is a lack of guidelines and standardization of skin tests for the screening of hypersensitivity to all antibiotics,[4] in terms of the methodology, dose and time of evaluation of the tests.

In the clinical scenario an arbitrary intra dermal test (IDT) with 0.05-0.2 ml of formulation in the flexor aspect of the forearm, is of routine practice.[5] This may not hold true for all antibiotics, as the chemical nature of the formulation may induce a false positive reaction. Literature from Europe and America suggests the use of non-irritating concentration (NIC) of antibiotics for skin testing such as IDT, skin prick test (SPT). These are concentrations at which the drug is unlikely to produce irritation by virtue of its chemical nature resulting in false positive reactions. These concentrations have been validated by trials in their populations.[2,6-8]

Due to the increase of antibiotic resistance in our country and narrow sensitivity patterns of resistant organisms, declaring a patient allergic to a specific class of antibiotics based on positive skin tests can further narrow the therapeutic armory.

It is known that patients labeled as "allergic" to penicillin, without formal investigations and tests have an increased incidence of infections with resistant organisms like *Clostridium difficile*, methicillin resistant *Staphylococcus aureus*, and vancomycin resistant enterococci, as well as increased cost of hospitalization. This is due to the use of alternative broad spectrum antibiotics as evidenced in previous cohort studies.[9,10] Therefore, there is a need for a standardized protocol for the use of skin tests in screening of hypersensitivity, with validated NIC of all antibiotics. The aim of this article is to review the literature of protocols for assessment of drug hypersensitivity with NIC of antibacterial drugs for SPT, IDT and also establish the need for research in this area in our country.

Pathophysiology of hypersensitivity to antibacterial agents

Hypersensitivity reactions to antibacterial agents are of two types: immediate and non-immediate type. Immediate type is immunoglobulin E (IgE) mediated reaction; occurs within 1 hr of administering the antibiotic and usually manifest as urticaria, angioedema, conjunctivitis, bronchospasm and anaphylactic shock. Whereas non-immediate type is a T-cell dependent reaction, which occur after 1 hr of administration of the drug and manifest as maculopapular rashes, exanthema, delayed urticaria, fixed drug eruptions, exfoliative dermatitis, erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis.[2,4]

Assessment of hypersensitivity

Assessment of hypersensitivity can be done by taking patients history, doing in vivo tests like the SPT, IDT and patch test; and in vitro tests such as basophil activation test (BAT), lymphocyte toxicity test, lymphocyte activation test, and drug provocation test.[2,7]

Immediate reactions can be detected by in vivo tests such as SPT and IDT assessed at 15 mins. This can be further confirmed by in vitro tests like serum specific IgE, flow cytometric BAT. Non-immediate reactions can be detected by a late reading of IDT at 24 hrs, 48 hrs and 72 hrs, which can be confirmed by patch testing and in vitro tests such as lymphocyte transformation test, enzyme linked immunospot.[11]

Beta lactam antibiotics

Penicillins and cephalosporins are both implicated in beta-lactam induced hypersensitivity reactions. The reported incidence of penicillin allergy ranges from 1% to 10%, the true incidence of life-threatening anaphylactic reactions ranging between 0.004% and 0.015% (13). Patients are labeled as allergic to penicillin without an in-depth investigation as to the nature of their reaction; many patients who report an allergy to penicillin do not meet the criteria for a true drug allergy. This is largely due to a lack of guidelines. Cephalosporins have an incidence of allergy from 1% to 10% and have cross reactivity of 10% with those who have a history of penicillin allergy.[8] Carbapenemes and monobactams have a low rate of cross-reactivity in patients with penicillin allergy.[8,12]

Suggested evaluation of immediate and delayed hypersensitivity in beta-lactam antibiotics

European guidelines formulated by the European Academy of Allergy and Clinical Immunology Interest Group on Drug Allergy and American practice parameters have proposed the use of non-irritating concentrations for penicillins (Table 1) and cephalosporins (Table 2) for skin hypersensitivity testing. These have been validated in their populations[4,6,7] and in Figure 1 is a suggested algorithm for the evaluation of immediate hypersensitivity reactions to beta-lactams.

To evaluate immediate hypersensitivity for beta-lactams the proposed algorithm in Figure 1, suggests the use of SPT. For which the results are read at 20 mins, if negative the patient should be successively evaluated by intradermal test, results of which should be read at 20 mins. If the patient is negative

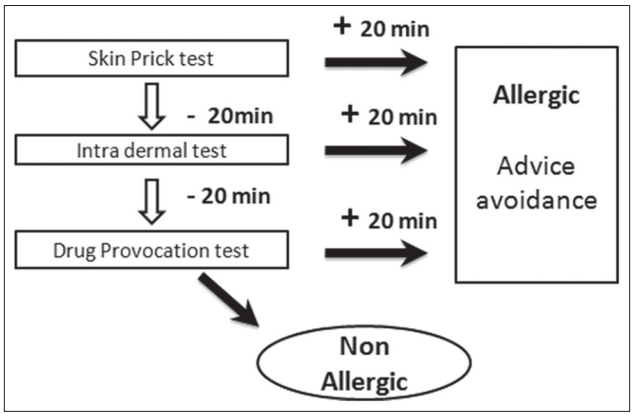

Figure 1: Algorithm for evaluation of immediate hypersensitivity in beta-lactam antibiotics.[2,4]

Table 1: Non-irritating concentrations of penicillins for IDT/SPT.

Generic name	Non-irritating concentration (IDT/SPT)[2,7]	Dilution to be used for (IDT/SPT)[6]
Penicilloyl-poly-L-lysine	5×10^{-5} mM	NA
Minor determinant mixture	2×10^{-2} mM	NA
Benzylpenicillin	10.000 IU	NA
Ampicillin	20 mg/ml	1:10
Amoxicillin	20 mg/ml	1:10
Amoxi-clavulanic acid	20 mg/ml	1:10
Ticarcillin	20 mg/ml	1:10
Piperacillin	20 mg/ml	1:10

IDT: Intra dermal test, SPT: Skin prick test

for both the skin tests, it should be followed by, "drug provocation test" which is the gold standard for evaluating immediate hypersensitivity. If positive to the SPT or IDT the patient is considered allergic, and clinically should be advised avoidance of the beta lactam. To evaluate delayed hypersensitivity for beta-lactams the proposed algorithm in Figure 2 is similar with the exception of, a late reading of intradermal test at 24 hrs and 48 hrs.

Suggested evaluation of immediate and delayed hypersensitivity to non-beta lactam antibiotics

Allergic reactions to non-beta lactam antibiotics can cause morbidity and rarely, mortality. The overall incidence of hypersensitivity reactions to these agents is estimated to be

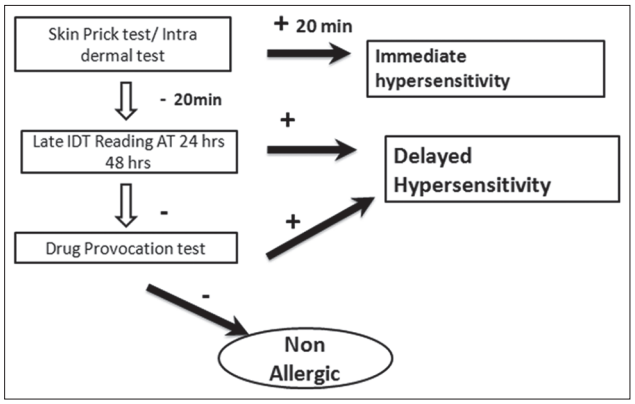

Figure 2: Algorithm for evaluation of delayed hypersensitivity to beta-lactam antibiotics.[2,4,8]

Table 2: Non-irritating concentrations of cephalosporins[2,7-8] for IDT/SPT.

Generic name	Non-irritating concentration (IDT/SPT)	Dilution of the full strength (IDT/SPT)
Cefazolin	33 mg/ml	1:10
Cefuroxime Cefoxitin Cefotaxime Ceftriaxone Ceftizoxime Ceftazidime Cefoperazone Cefpirome Ceftazidime Cefoperazone Cefpirome	2 mg-20 mg/ml	1:10
Cefepime	2 mg/ml	
Non-irritating concentrations of monobactams, carbepenemes[2,8] for IDT/SPT.		
Aztreonam	2 mg/ml in normal saline solution	
Imipenem	0.5-1 mg/ml	
Meropenem	1 mg/ml	

IDT: Intra dermal test, SPT: Skin prick test

1-3%.[8] There is a lack of standardized guidelines for skin hypersensitivity testing for non-beta lactams. The chemical nature of the drug itself may elicit a false positive reactions at higher concentrations.[7] The following NIC have been suggested in literature (Table 3).

A review by Brockow et al., suggested the use of an algorithm (Figure 3) for evaluation of immediate and delayed hypersensitivity to non-beta-lactam antibiotics, with NIC suggested in literature.[4,6,7]

For patients with a clinical history of allergy to antibiotics, the algorithm suggests the successive use of SPT, intradermal test and drug provocation test, for evaluating immediate hypersensitivity. Delayed hypersensitivity to non-beta-lactams is evaluated by patch test and drug provocation test.

Drawbacks of skin testing

Skin testing may sensitize a few patients; a negative skin test may turn positive after a few weeks. This is common in individuals with history of atopy and food allergies.[13] Some

Table 3: Non-irritating concentrations of non-beta-lactams for IDT/SPT.

Aminoglycosides[6,7]	Suggested Non irritating concentrations
Gentamycin	4 mg/ml for IDT/SPT 1:10 Dilution of the full strength
Streptomycin	0.1 mg/ml to 20 mg/ml for IDT/ SPT
Tobramycin	4 mg/ml for IDT/SPT 1:10 dilution of the full strength
Quinolones[2]	**Suggested non-irritating concentrations**
Ciprofloxacin	2 mg/ml SPT 0.006 mg/ml IDT
Levofloxacin	5 mg/ml SPT 0.05 mg/ml IDT
Moxifloxacin	5 mg/ML SPT 0.004 mg/mL IDT
Others[2,7,6]	**Suggested Non irritating concentrations**
Cotrimoxazole	800 µg/mL 1:100 dilution of the full strength
Clindamycin	15 mg/mL 1:10 dilution of the full strength
Vancomycin	5 µg/mL 1:10000 dilution of the full strength
Erythromycin	50 µg/mL 1:1000 dilution of the full strength

IDT: Intra dermal test, SPT: Skin prick test

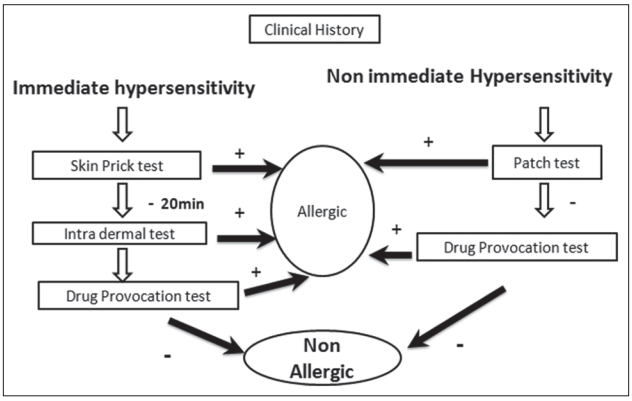

Figure 3: Algorithm for evaluation of immediate and delayed hypersensitivity to non-beta-lactam antibiotics.[2,8,4]

patients experience systemic reactions after percutaneous and epicutaneous skin testing; they have been case reports of anaphylaxis after skin testing.[4] The sensitivity and specificity of SPT and IDT is variable for different antibiotics, which limits it value as a diagnostic tool.

Current Asian practice patterns of skin testing to antibacterial agents

There are surveys suggesting ambiguity in clinical practice regarding the use of skin testing for hypersensitivity to antibacterial agents. A survey of current practice of allergic skin testing in tertiary and secondary hospitals in Korea[14] by Lee et al. found that "antibiotic skin testing protocols were variable and differed with regard to the type and concentrations of antibiotics, the volume injected, and the interpretation of the results." Another survey in the U.A.E by Abdulazeez et al.,[15] also suggest that there is a wide variation among clinicians with regard to the dose and method used for IDT/SPT and in absence of a policy for antibiotic skin testing, application of the procedure is haphazard and may be performed when it is not indicated.

There is a lack of literature on practice patterns in India, but there are many case reports that raise the clinicians concern. A case report by Kumar et al. of a life-threatening anaphylaxis to ceftriaxone despite a negative skin test, asks the question whether the false negatives of skin test can be reduced.[16] Samanta et al. in a case report of amikacin induced preoperative anaphylaxis, raises the question "Should we proceed for skin test before amikacin/aminoglycoside injection?" as the standardized testing protocols are not available.[17] Bhagwat and Saxena describes a Grade V anaphylactic reaction to preoperative ceftriaxone, despite a negative skin test. Stating that incidence of anaphylactic reaction during anesthesia has been reported as 1:6000-1:20000, where antibiotics are responsible for 8.3% of the reactions.[18]

There is evidence to suggest that the hypersensitivity to antibiotics varies with race and ethnicity. The incidence of such reactions varies between countries,[19] which is supported by Guéant et al. "The genetic factors involved in IgE-mediated mechanisms have been studied mainly in beta-lactam reactions, and they appear to be related to human leukocyte antigen presentation (HLA A2 and DRw52)."[20] The NIC suggested in the European and American guidelines, have been determined by trials in a relatively few number of patients in their populations, these concentrations may not be valid for clinical practice in India.

In the above surveys and reports, it is evident that there is wide variation of practice and ambiguity regarding the conduct and predictive value of skin tests. In developing country like India these tests are of great importance as in vitro tests may not be economically viable. Thus validating the NIC for all antibiotics in the Indian population, and developing protocols for skin testing to increase its sensitivity and specificity is of great importance.

CONCLUSION

There is a lack of standardized guidelines for assessing hypersensitivity to antibiotics in our country; this can indirectly contribute to emergence of drug resistance. The NIC suggested in literature may not hold good for clinical practice in India, as they have not been tried in our populations. Further research, focusing on validation of NIC in Indian population and harmonization of hypersensitivity testing procedures by developing standardized testing protocols is needed.

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