

Original Article

The Importance of Prolonged Provocation in Drug Allergy — Results From a Danish Allergy Clinic

Sara Fransson, Holger Mosbech, MD, DMSc, Mogens Kappel, MD, DMSc, Janni Hjortlund, MD, PhD, Lars K. Poulsen, PhD, DMSc, Ask D. Kvisselgaard, and Lene H. Garvey, MD, PhD *Hellerup, Denmark*

What is already known about this topic? Currently, drug provocation tests are recommended only in skin test negative patients and performed as a single challenge. Prolonged provocation to rule out nonimmediate reactions is scarcely discussed in literature and not yet addressed in guidelines.

What does this article add to our knowledge? In Denmark, drug provocation, including prolonged provocation, with culprit drug is a safe and useful method to diagnose drug allergy. Most provocations are with narrow-spectrum penicillins, reflecting the local pattern of antibiotic use.

How does this study impact current management guidelines? Prolonged provocation increases the number of patients diagnosed with nonimmediate reactions and should always be considered when drug provocation is included in allergy investigation.

BACKGROUND: Drug provocation is the “Gold Standard” in drug allergy investigation. Recent studies suggest that a negative drug provocation on first dose should be followed by a prolonged provocation over several days.

OBJECTIVE: To evaluate drug allergy investigations on the basis of drug provocation, including prolonged provocation.

METHODS: Data from adult patients investigated for drug allergy in a Danish Allergy Clinic during the period 2010 to 2014 were entered into a database. Data included clinical details and results of provocations with suspected culprit drug (for penicillins performed only in specific IgE-negative patients). If provocation was negative on first dose, treatment was continued for 3 to 10 days.

RESULTS: A total of 1,913 provocations were done in 1,659 patients, median age 46 years, of whom 1,237 (74.6%) were females. Drugs investigated were antibiotics, 1,776 (92.8%), of which 1,590 (89.5%) were penicillins; analgesics, 59 (3.1%); local anesthetics, 33 (1.7%); and other drugs, 45 (2.4%). In total, 211 of 1,913 (11.0%) provocations were positive. Causes were antibiotics, 198 (93.8%), of which 167 (84.3%) were penicillins;

analgesics, 7 (3.3%); local anesthetics, 0; and other drugs, 6 (2.8%). Only 43 (20.4%) provocations were positive on first dose, whereas 95 (45.0%) turned positive more than 3 days later. **CONCLUSIONS:** Only 11.0% of the provocations were positive. Importantly, only 1 of 5 patients tested positive on the first dose, indicating that prolonged exposure should always be considered when drug provocation is included in allergy investigations. Most provocations were with penicillins, reflecting the pattern of antibiotic use in Denmark, which differs from that in other countries, especially outside Northern Europe. © 2017 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2017;■:■-■)

Key words: Prolonged provocation; Drug challenge; Narrow-spectrum penicillin; Drug provocation test; Drug allergy; Betalactam antibiotics

Suspected drug allergy is a widespread problem with great impact on daily medical practice. Many nonallergic adverse drug effects are mislabeled allergy and both health personnel and patients fear that minor reactions may be the precursor for life-threatening anaphylaxis. Increased understanding about the relative rarity of true allergic reactions and the underlying mechanisms would be useful in putting these fears into perspective.¹ Patients with suspected drug allergy are often prescribed more expensive drugs,² have longer hospitalizations,³ and are prescribed broad-spectrum antibiotics contributing to antimicrobial resistance.⁴ Investigations to confirm or rule out allergy are therefore important.

Large epidemiological studies of drug allergy are scarce. The prevalence of alleged penicillin allergy in 2006 in a Danish hospital population was 2.6%.⁵ The true prevalence is difficult to determine because of overdiagnosing of patients who are not investigated, as well as underestimation of cases due to underreporting.⁶⁻⁹

The fact that only a small proportion of suspected allergies are confirmed on investigation is well described in literature.

Allergy Clinic, Department of Dermato-Allergology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

Conflicts of interest: L. K. Poulsen is employed by University Hospital Copenhagen; has received research support from the European Union Commission; has received payment for the development of educational presentations from ALK; and is a European Academy of Allergy and Clinical Immunology board member. L. H. Garvey has received lecture fees from ThermoFisher. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 7, 2016; revised January 19, 2017; accepted for publication February 17, 2017.

Available online ■■

Corresponding author: Sara Fransson, Allergy Clinic, Department of Dermato-Allergology, Herlev and Gentofte Hospital, University of Copenhagen, Kildegårdsvej 28, DK-2900 Hellerup, Denmark. E-mail: sara.fransson@hotmail.com.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.02.024>

Abbreviations used

ASA- Acetylsalicylic acid

IR- Immediate reaction

NIR- Nonimmediate reaction

sIgE- Specific IgE

IDT- Intradermal test

ENDA- European Network for Drug Allergy

NSAID- Nonsteroidal anti-inflammatory drug

In populations with suspected drug allergy, the confirmed penicillin allergy rate differs between 28.7%¹⁰ in Denmark, using the European Network for Drug Allergy (ENDA) guidelines, and 13.5%¹¹ in Slovenia, using local guidelines. In the United States, the reported rate is lower, with less than 10% being diagnosed with penicillin allergy after a suspected reaction.^{12,13} The reported differences between countries and centers seem related to differences in investigation protocols,^{10,11,14-19} populations,^{20,21} and patterns of antibiotic use.^{22,23}

In many countries, betalactam antibiotics is the most common drug group suspected of causing allergy, followed by other antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs).^{3,7,17,24} Narrow-spectrum penicillins are the most frequently prescribed drugs in Denmark,²⁵ due to low price, favorable side effect profile, and low risk of inducing resistance. Broad-spectrum antibiotics, especially aminopenicillins, are more commonly used in countries outside Northern Europe because of higher incidence of resistance to narrow-spectrum penicillins.²²

As opposed to American guidelines,¹³ European guidelines²⁶⁻²⁸ suggest different investigation protocols for immediate reactions (IRs) (<1 hour of drug intake) and nonimmediate reactions (NIRs) (>1 hour after drug intake) on the basis of history of the suspected reaction. However, a recent study questioned patient recall and showed that clinical history cannot be used to predict whether reactions will be IRs or NIRs.¹⁰ Investigation protocols in most allergy centers use skin tests: Skin prick tests and intradermal tests (IDTs) for IRs and patch tests/late reading of IDTs for NIRs. Drug provocation, or drug challenge, is usually performed only if skin test results are negative. Drug provocation is the "Gold Standard" with good diagnostic value.²⁹ Recently, prolonged provocation, that is, a repeated dose provocation over several days, has been introduced in another Danish center for adult patients. Results suggest that a negative drug provocation on first dose does not rule out a NIR, which can be diagnosed during prolonged provocation.^{10,15} This has also been suggested in children from other parts of Europe.^{30,31} However, the issue of prolonged provocation is not yet addressed in guidelines.

In our clinic, data on allergy investigation using drug provocation tests, including prolonged provocation with culprit drugs, have been collected since 2010. The aim of this study was to evaluate the results from drug allergy investigations in our clinic during the period 2010 to 2014. This is the largest study of prolonged provocation in drug allergy investigation reported so far.

METHODS

Data from adult patients undergoing drug provocation as part of investigations for drug allergy (excluding perioperative reactions) in the Allergy Clinic, Gentofte Hospital, Denmark, during the period 2010 to 2014 were collected prospectively in a database. Data were

collected in case record forms filled in by the attending physician, inspired by the ENDA guidelines.³² Contraindications for provocation followed recommendations in the ENDA position paper on drug provocation.²⁸ Patients with suspected allergy to penicillins underwent drug provocation only if specific IgE (sIgE) for penicillins were negative.

Drug allergy investigation at the clinic includes clinical history, analysis of sIgE (for penicillins), and drug provocation with culprit drug if known (Figure 1). Skin testing is not presently included in the standard investigation protocol in the region. sIgE is measured using the ImmunoCAP method (ThermoFisher Scientific, Uppsala, Sweden) with a cutoff value of more than 0.35 kUA/L. sIgE analysis is carried out for penicillin V, penicillin G, ampicillin, and amoxicillin (all commercially available) and in addition for penicillin degradation products (minor determinants), a noncommercially available test that our clinic has special access to on a research basis. If sIgE to 1 or more penicillins is detected, further testing is usually abandoned because of a suspected high probability of a clinical allergy and the patient is issued with a warning card against penicillins. Data from these patients are not entered into the provocation database. An exception was made in 8 cases in which sIgE was slightly elevated to only 1 penicillin, and the patient had a strong clinical indication for needing penicillins. If no sIgE is found, the patient undergoes drug provocation with suspected culprit drug. If culprit type of penicillin is unknown, provocation with penicillin V is performed.

Drug provocation is performed under observation including access to emergency room facilities. Intravenous access is obtained when provocation is considered high risk either because of history of a severe IR or because of comorbidities. The provocation is either titrated or nontitrated, depending on the estimated risk of inducing a reaction on the basis of severity of the reaction and the patient's comorbidities. The route of provocation is usually the original route of administration, that is, mainly oral, or in a few cases intravenous and subcutaneous.

Titrated provocation is usually performed in three 10-fold steps 30 to 45 minutes apart depending on the route of administration, starting with 1:100 dilution of therapeutic dose and ending with full therapeutic dose.

Nontitrated provocation is performed with a single full therapeutic dose. Both types of provocation are followed by 2-hour observation in the clinic. If provocation is negative, an IR is ruled out and in most cases provocation is continued at home for 3 to 10 days, to match timing of exposure and symptom onset of the initial reaction. For the purpose of this study, *immediate reactions* are defined as developing within the observation time at the clinic, that is, less than 2 hours after the first full dose. *Nonimmediate reactions* are defined as developing after 2 hours. A provocation is considered positive, for both IRs and NIRs, on the development of objective symptoms. For IRs, this would be rash/urticaria with or without pruritus, and very rarely, respiratory and/or circulatory symptoms and for NIRs typically maculopapular exanthema. Subjective symptoms only are not considered sufficient to diagnose a clinical allergy. NIRs are generally confined to the skin and patients are issued with a written treatment plan for out-of-hours treatment plus antihistamines and in many cases steroids on leaving the clinic. If patients develop symptoms they are instructed to call the clinic, where they will speak to a doctor who assesses their reported symptoms and gives advice about treatment.

Download English Version:

<https://daneshyari.com/en/article/5647516>

Download Persian Version:

<https://daneshyari.com/article/5647516>

[Daneshyari.com](https://daneshyari.com)