Food and drug provocation test

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1. Food provocation test

INTRODUCTION

The diagnosis of food allergy depends on the thorough review of the patients's medical history, results of supplemented trials of dietary elimination, and in vivo and in vitro tests for measuring specific IgE levels. However, in some cases the reliability of such procedures is suboptimal. Oral food challenges (OFCs) are procedures employed for making an accurate diagnosis of immediate and occasionally delayed adverse reactions to foods. OFCs may also be used to determine if a food allergy has resolved.

INDICATIONS for OFCs

An OFC should be performed for establishment or exclusion of a diagnosis, for scientific purposes in clinical trials, or for the determination of the threshold value or the allergenicity of foods. Fig. 1 provides an algorithm for proceeding from the suspicion of food-related symptoms to the final decision for recommending a specific therapeutic elimination diet.

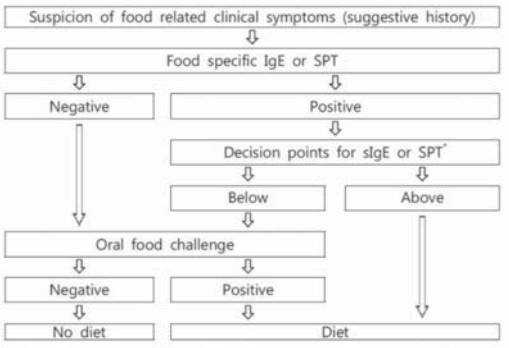

Fig. 1. How to proceed from the suspicion of food-repeated symptoms to the final decision on recommending a therapeutic specific elimination diet. *Diagnostic decision points appear to be population, age, and allergen dependent.

Types of OFCs

There has been a debate about whether OFCs should be done in an open or double-blind fashion. In an open OFC, the food is given in its natural form. For a single-blind OFC, the food or placebo is given in a vehicle that disguises the appearance and the taste of the food. The patient is unaware of the nature of the food given, whereas staff involved in the procedure have this information. For DBPCFCs, none of the parties involved is aware of the composition of the product. Common clinical indications for OFC and the corresponding procedures are shown in Table 1.

Table 1. Clinical indications for OFCs and the corresponding procedures

Challenge	Procedure
Anaphylaxis proven or highly probable (together with proof of specific IgE)	No oral food challenge; diet
Questionable anaphylaxis (with or without proof of IgE)	Open challenge; inpatient basis
Typical oral allergy syndrome with corresponding sensitization	No oral food challenge; diet?
No improvement of clinical symptoms under elimination (or oligo-allergenic) diet	No oral food challenge; no diet?
Introduction of new foods in sensitized infants (before exposure)	DBPCFC or open challenge*
Rechallenge after (long-term) avoidance of a food (to investigate possible acquired tolerance)	DBPCFC or open challenge*
Expected late phase clinical reactions (eg, in children with atopic eczema)	DBPCFC
Subjective symptoms (eg, abdominal discomfort, nausea)	DBPCFC

*Depending on type of symptoms (eg, presence of atopic eczema).

Preparation for OFCs

There are several issues to be considered prior to an OFC in patients. These can be divided into patient-related and procedure-related parameters (Table 2)

Table 2. Several issues to be Determined prior to commencing a food Challenge in a patient

Patient related parameters
age of the patient
clinical features of the suspected reaction
severity of the reaction
dosing (start dose, increment, top dose)
timing between challenges
regimen (in-patient or out-patient)
special considerations (concomitant factors) such as a possible influence of concomitant exercise (or intake of drugs such as β-blockers, ACE-inhibitors or aspirin, alcohol, antihistamines, corticosteroids)
Procedure related parameters
settings (trained personnel)
safety measures
informed consent procedures
blinding procedure
statistical evaluation

Dosing schedule for OFC

In 1 approach, the total amount administered during a gradually escalating OFC equals 8-10 g of the dry food, 16-26 g of meat or fish, and 100 mL of the wet food. The challenge food is mixed with the vehicle and administered in gradually increasing increments every 15 minutes. This time interval is preferred because most acute reactions occur within 15 minutes; however, the dosing interval must be adjusted on the basis of a patient's history. The starting dose should be evaluated based on the patient's history and available data from the literature. (Table 3)

Table 3. Proposed Starting Dose for Different Foods

Food	Dose
Peanut	0.1 mg
Milk	0. 1 mL
Egg	1 mg
Cod	5 mg
Wheat	100 mg
Soy	1 mg
Shrimp	5 mg
Hazelnut	0.1 mg
The actual starting dose must always be considered in the actual patient.	

Interpretation of OFC

Despite controlled conditions, it is sometimes difficult to determine whether clinical symptoms are

sufficiently clear to make a decision. Niggemann et al. proposed a decision tree for various situations during an OFC procedure, which is reproduced in Fig. 2.

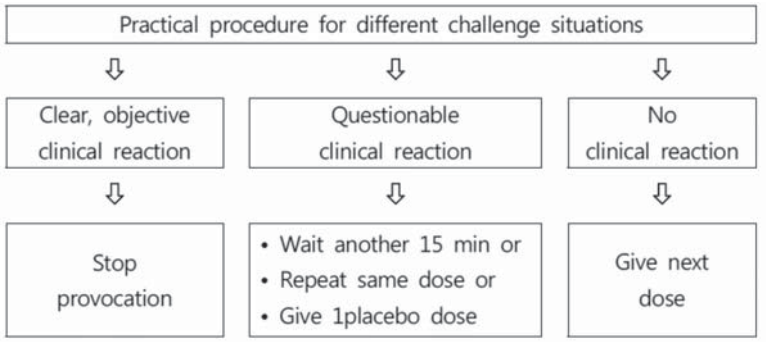

Fig. 2. Decision tree for various situations during oral food challenge procedure.

2. Drug provocation test

Drug provocation test (DPT) is the controlled administration of a drug to diagnose immune or non-immune-mediated drug hypersensitivity and the last step for accurate recognition of drug hypersensitivity reactions in the absence of informative alternative diagnostic tests. (Table 1)

Table 1. drug provocation tests.

Definition: Controlled administration of a drug to diagnose drug hypersensitivity and the last step for accurate recognition of drug hypersensitivity reactions if the previous diagnostic evaluations are negative or unavailable.
Requirements: • Trained personnel, who know how to perform tests, are ready to recognize and treat symptoms and signs of a hypersensitivity reaction • Equipment for emergency resuscitations
Methods • Informed consent • Commercial agents are usually used • Route of administration: Oral, parenteral, cutaneous, bronchial, etc. • Starting dose depends on severity and immediate/non-immediate timing of index reaction (1/10000–1/10) • Interval: 30–90 min

The provocative drug is either an alternative, a structurally/pharmacologically related drug or the culprit drug itself. A DPT is performed if other less critical or less difficult tests fail to yield conclusive decisions. In each clinical presentation, “to provoke or not to provoke” a patient should be decided after balancing the risk-benefit ratio. Several factors may influence not only the decision but also the protocol for a DPT, such as the chronology of the index clinical reaction (immediate vs.non-immediate), the severity of the clinical

reaction (anaphylaxis vs. mild reactions), the population involved (children vs. adults) and the facilities of the medical center (including intensive care unit). A definite diagnosis of drug hypersensitivity reaction, in fact, may become a clinical necessity that many drug courses may be required over a lifetime, usually as an emergency. The advantages and the disadvantages of DPT are summarized below (Table 2).

There are many limitations which prevent DPT to be a part of the routine clinical practice. Although DPT is considered as the "gold standard" for the diagnosis of drug hypersensitivity reactions, such tests are interfered by the risk of life-threatening reactions and contraindicated in severe drug reactions (i.e., bullous drug eruptions, systemic vasculitis, blood cytopenia, nephritis, etc.) in patients using _-blockers or ACE-inhibitors or, are troublesome for patients with hypersensitivity to neuromuscular blocking agents (Table 3).

Table 2. Advantages and disadvantages of DPT

Advantages	Disadvantages
Confirmation or exclusion of diagnosis of drug hypersensitivity	Potentially dangerous
Less use of more expensive alternatives	DPT protocol is chosen based on patients′/parents′ report about the reaction suffered
Less use of broad spectrum antibiotics, decreased risk of antibiotic resistance	False positive and false negative results may occur
Reduced cost of drug allergy algorithm	Cofactors may be absent
Generally good safety profile	Potential risk of resensitization
Acceptable for most patients	Although gold standard, many contraindications to perform DPT may be present
Avoidance of unnecessary desensitizations	Lack of standardized protocols, especially for non-immediate reactions
Provision of safe alternative	Subjective symptoms could be difficult to interpret
Decreased social burden of drug allergy	Lack of objective and reliable biomarkers (e.g., serum tryptase)
	Negative results may not be sufficient to reuse the culprit drug
	Need experienced personnel and well-established clinical settings

Table 3. Circumstances in which DPTs are contraindicated or not preferred.

Patient related factors • Uncontrolled asthma • Uncontrolled underlying chronic disease • Pregnancy • Use of β-blockers • If underlying heart disease is a contraindication for the use of adrenaline
Index drug hypersensitivity reaction • Vasculitis syndromes • Bullous exanthemas (Steven Johnson syndrome, toxic epidermal necrolysis, bullous fixed drug eruptions, etc.) • Acute generalized exanthematous pustulosis • Drug-induced autoimmune disease (systemic lupus erythematosus, pemphigus vulgaris, etc.) • Drug induced hypersensitivity syndromes (DRESS) • Involvement of specific organ systems (hepatitis, nephritis, blood dyscrasias, etc.) • Severe anaphylaxis
Culprit drug • Unlikely to be needed and several structurally unrelated alternatives exist

There is usually a lack of uniformity not only in selection of the diagnostic tests but also in management of drug allergy in daily practice of clinicians around the world. In a survey study, distributed through the International Allergy Societies, it was stated that 64% of respondents considered DPT extremely useful for both the exclusion and the confirmation of B-lactam allergy. Nevertheless, the methodology of how to conduct challenges, for example, the dosing of the antibiotic during a challenge on the first day, how to choose alternative drug in the case of amoxicillin allergy, and the location of DPT were not consistent. In summary, drug allergy is increasing in the 21st century and we are encountered with numerous challenges during the management of patients with drug hypersensitivity reactions. DPT is still required for the accurate diagnosis of many drug HSRs, as well as to evaluate the tolerability of alternative medications. The DPT will preserve its valuable contribution in the drug allergy management until better alternatives are proposed due to the risks it poses, costs, the time required, and the need for experienced healthcare personnel and service. There is still a gap in the standardization of procedures of DPT and interpretation of test results. Despite negative DPT results, implementation of the culprit drug in routine clinical practice is sometimes lacking. As experience grows, the development of shorter, inexpensive and less risky DPT methods will lead to a better quality of the health service and thus the established application of these methods.

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