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Position paper

Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations

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A drug provocation test (DPT) is the controlled administration of a drug in order to diagnose drug hypersensitivity reactions. DPTs are performed under medical surveillance, whether this drug is an alternative compound, or structurally/pharmacologically related, or the suspected drug itself. DPT is sometimes termed controlled challenge or reexposure (1), drug challenge (2), graded (2) or incremental challenge (3), test dosing (2),

rechallenge (4), or testing for tolerance (5). DPT is recommended by some specialized centers (6–9), allergy societies (2), and text books (6, 10), whereas other societies advise against performing DPTs (11), and some review articles (12) and textbooks (13) do not even mention the method. The topic DPT is controversial in general and the test procedures not validated in most instances. Therefore it is considered important to develop general guidelines for performing DPT. Specific protocols for every single drug or at least group of drugs would be helpful, where indication, contraindication, substance, dosing, grading of the reaction and test as well as scoring criteria are defined. However, the development of individual DPT protocols is impractical because of the countless drugs that may cause numerous kinds of hypersensitivity reactions, allergic and non-allergic, with different time courses, severity and outcome, the individual situation of every person, and other factors that might possibly influence the test reaction. This paper sets out general guidelines for DPT that can be adapted for the specific problem under investigation.

Aims of the Task force

Our aims are to define the rationale and general principles of DPT and to propose recommendations based on evidences from published literature data as well as on the clinical expertise of members of the ENDA (European Network for Drug Allergy), the core part of the EAACI drug hypersensitivity interest group.

DPT may help to optimize the pharmacotherapy of the patient concerned; it might also guide oneself and others on the choice of therapy for future patients or generate new scientific knowledge; only the first mentioned reason for re-challenge shall be the topic of this paper (14).

Principles of testing for drug hypersensitivity

Drug hypersensitivity reactions – comprising both allergic and non-allergic reactions (15) – are common in clinical practice and comprise about 15% of all adverse drug reactions (7, 16). Accurate identification of the responsible agent is important for future treatments to avoid labeling somebody as being "allergic" for life without good reason (12). The work-up of a suspected drug hypersensitivity includes a detailed clinical history and physical examination (17), followed by one or more of the following procedures: skin tests when available and validated (18), laboratory tests, and ultimately, provocation tests (19).

In spite of its limitations, DPT is widely considered to be the "gold standard" to establish or exclude the diagnosis of hypersensitivity to a certain substance, as it not only reproduces allergic symptoms but also any other adverse clinical manifestation irrespective of the mechanism. It thus has advantages over all other test procedures and even can prove or disprove the clinical relevance of test results as obtained with other *in vivo* and *in vitro* test methods. But DPT should be performed only if other, less dangerous test methods do not allow relevant conclusions and if the outcome might thus help clarify an otherwise obscure pathologic condition. A firm diagnosis certainly optimizes allergen avoidance and provocation procedures might thus be required to evaluate hypersensitivity reactions against certain drugs, drug metabolites and drug ingredients. However, DPT should only be considered after balancing the risk-benefit ratio in the individual patient. DPT is performed as controlled administration under medical surveillance to establish or exclude the diagnosis of a drug hypersensitivity reaction and, in selected cases, to provide alternative drugs for the patient in need. If the original reaction was delayed and/or not dangerous, DPT may be performed on an outpatient basis (20), but patients with more severe reactions should be hospitalised for DPT.

A distinction must be drawn between diagnostic DPT and therapeutic desensitization or tolerance induction procedures. By this method, a state of unresponsiveness is produced that continues as long as the drug is given and resolves within days after cessation of drug delivery (21).

Indications for DPT

Before performing any DPT, an individual risk-benefit evaluation has to be done. Caution and surveillance is mandatory in all cases. Severe reactions in the history, patients with a reduced health status or at increased risk during emergency treatment, require a guarded and especially critical evaluation. With drugs of limited future necessity for the individual patient, DPT should be avoided. The indications for DPT fall into four, partially overlapping groups:

1. to exclude hypersensitivity in non-suggestive history of drug hypersensitivity and in patients with non-specific symptoms, such as vagal symptoms under local anesthesia;
2. to provide safe pharmacologically and/or structurally non-related drugs in proven hypersensitivity such as other antibiotics in betalactam-allergic patients. This may also be helpful for anxious people who would refuse to take the recommended drug without proof of tolerance;
3. to exclude cross-reactivity of related drugs in proven hypersensitivity, for example a cephalosporin in a penicillin-allergic subject or an alternative NSAID in an aspirin-sensitive asthmatic;
4. to establish a firm diagnosis in suggestive history of drug hypersensitivity with negative, non-conclusive or non-available allergologic tests, for example a maculopapular eruption during aminopenicillin treatment with negative allergological tests.

Contraindications for DPT

DPT with a suspected drug should not be performed in pregnant women or in patients at increased risk due to co-morbidity like acute infections or uncontrolled asthma, or underlying cardiac, hepatic, renal, or other diseases, where exposure might provoke a situation which is beyond medical control. However, exceptions can be made if the drug under suspicion is essential for the patient, e.g. neurosyphilis and penicillin therapy (22). A pregnant woman suspected for local anaesthetic hypersensitivity, scheduled for epidural anaesthesia/analgesia during labour, and with negative intradermal skin tests performed in the delivery room, may undergo a DPT with the local anaesthetic in the delivery room by the anaesthetist before the insertion of the epidural catheter.

In most circumstances it is difficult to justify DPT with drugs, that are nowadays mostly obsolete like sulfonamides (except in HIV-positive persons [2]) or substances with debatable value like many herbal products or "lifestyle drugs" (14).

DPT should never be performed on patients who have experienced severe, life-threatening immunocytotoxic reactions, vasculitic syndromes, exfoliative dermatitis, erythema multiforme major/Stevens-Johnson syndrome, drug induced hypersensitivity reactions (with eosinophilia)/DRESS and toxic epidermal necrolysis (2, 23) (Table 1).

In a few conditions, the literature recommendations are heterogeneous: e.g. in fixed drug eruptions oral provocation testing seems safe even in children, if the patient suffered only single or a few lesions, but should not be attempted in patients who had generalized bullous reactions which may sometimes be difficult to distinguish from Stevens-Johnson syndrome (24, 25).

Table 1. Drug-induced reactions, where DPT is generally not recommended or contraindicated

Generalized bullous fixed drug eruptions
Acute generalized exanthematous pustulosis (AGEP)*
Toxic epidermal necrolysis (TEN)*
Stevens Johnson syndrome*
Drug hypersensitivity syndromes (with eosinophilia) / DRESS*
Systemic vasculitis
Specific organ manifestations, e.g.
– blood-cytopenia
– hepatitis
– nephritis
– pneumonitis
Severe anaphylaxis
Drug-induced autoimmune disease (systemic lupus erythematosus, pemphigus vulgaris, bullous pemphigoid, etc.)

* patch testing justified under special conditions, but not oral intake.

Test methods

Route of administration

The different routes of administrations include oral, parenteral (iv, im, sc), and topical (nasal) (26), bronchial (27), conjunctival (28), cutaneous (29), etc. application of the test substance. Although the drug should in principle be administered in the same way as it was given when the reaction occurred, the oral route is favoured if possible (2), since absorption is slower and developing adverse reactions can thus be treated earlier as compared to DPT performed by the parenteral route.

Test agents

Typically, commercial preparations are used. In case of drug combinations, as in some over the counter (OTC) preparations, the single compounds should be tested separately. The separate testing of the active ingredients and the additives has to be considered (30) as reactions may also be caused by those compounds. The proof of tolerance to a drug, however, should be assessed with the commercial preparation.

Dosage of test preparations and time intervals

They are dependent on numerous variables, including the type of drug itself, the severity of the drug hypersensitivity reaction under investigation, the route of administration, the expected time latency between application and reaction, the state of health of the individual patient, and his/her co-medication. Generally one should start with a low dose, carefully increasing this and stopping as soon as the first objective symptoms occur. If no symptoms appear, the maximum single dose of the specific drug must be achieved, and the administration of the defined daily dose is desirable. In case of a previous immediate reaction (i.e. occurring less than 1 hour after drug administration) (31) the starting dose should be between 1:10.000 and 1:10 of the therapeutic dose, dependent on the severity of the reaction; the time interval between doses should be at least 30 min, but many drugs and specific situations might require longer intervals. In case of previous non-immediate reactions (i.e. occurring more than 1 hour after the last drug administration) the starting dose should not exceed 1:100 of the therapeutic dose (20). Depending on the drug and the patient's response threshold, DPT may be completed within hours, days or, occasionally, weeks (2).

If DPT is performed in order to find an alternative drug, one should reach the maximum single therapeutic dose; in some cases it may be essential to deliver a defined daily dose over a prolonged period of time.

Time interval between reaction and provocation test

At least 5 times the drug elimination half time should be waited in order to guarantee complete elimination. The

Table 2. Drugs, that may alter reactivity and thus influence the outcome of the test if taken concomitantly (adapted from 6,18)

Medication	Route	Immediate reaction	Non-immediate reaction	Free interval
Antihistamines (H1-blockers)	oral, intravenous	+	–	5 days
Antidepressants (imipramines, phenothiazines)	oral, intravenous	+	–	5 days
Glucocorticosteroids*	topical	–	?**	?**
Long-term	oral, intravenous	±	+	3 weeks
Short-term, high-dose (> 50 mg p.e.)	oral, intravenous	±	+	1 week
Short-term, low-dose (< 50 mg p.e.)	oral, intravenous	±	-	3 days
Betablocking agents	oral	+	+	1 day
	topical (eye)	–	–	
ACE-inhibitors***	oral	+	+	1 day

* withdrawal may not be possible; ** probably irrelevant in most instances; *** controversial discussion, see text.

reaction under investigation should have resolved completely, clinically and according to lab results – if measured initially and being abnormal. Any corrective medication or co-medication that might influence the outcome of the test result (Table 2) should be completely washed out. Whereas this happens within a few days with antihistamines or intravenous steroids for the treatment of systemic reactions, a sufficient wash out time for topical steroids for treatment of contact allergy might be up to 4 weeks (32).

As a general rule, DPT should be performed not earlier than 4 weeks after the episode. But there is no defined limit and no general rule nor agreement on this topic. As an example, antibodies to penicillin may disappear from the serum within 6 to 12 months, and skin reactivity decreases over time (33), but hypersensitivity remains. For this reason, some authors recommend repetition of skin test or even rechallenge 2 to 4 weeks later (34), although this view is not generally accepted (35).

Preparation for provocation procedures

Ethical considerations. The risk-benefit ratio must be acceptable (14): the drug must be important; i.e. it has to be substantially more effective than other alternatives. The condition being treated must be serious; no alternative testing method is available or the results are inconclusive. The patient must be informed of the consequences of both the use of alternative treatments and the risks involved in DPT. The patient should give oral (or even better written) informed consent for the test (33).

Safeguards for DPT. Accurate and comprehensive records should include a sufficient description of the initial episode treated, the drug exposure as well as a detailed description of the adverse effects. An individual protocol must be prepared, the procedures must be managed by an expert. Resuscitation facilities should be available for emergencies. Monitoring must be designed in such a way that early signs of the relevant disorder arising from DPT can be detected.

Additionally an approval by an ethical committee is mandatory if the provocation procedure is performed only for scientific value or for altruistic value (i.e. so other patients might profit from the obtained knowledge) – neither topic being within the scope of this paper (14).

Certain co-medication is contraindicated if it may cause problems if emergency treatment becomes essential, e.g. ß -blocking agents (36) or that may even aggravate immediate type reactions such as ACE-inhibitors. Regarding avoidance of ACE-inhibitors (37, 38) however, the discussion is controversial: with reference to reports on hypersensitivity reactions in hemodialysis patients under ACE inhibitors (39), and due to the potential involvement of bradykinin in hypersensitivity reactions, that may be enhanced by ACE-inhibitors (40), avoiding such drugs during DPT seems reasonable.

Documentation. DPT should be regarded as a serious and potentially dangerous test procedure. Therefore it is important to document the patient's personal details, medical history, and concomitant drug therapy before DPT. Before and after the provocation, all relevant physical signs, changes in laboratory parameters, spirometry – and others if relevant for the particular patient such as electrocardiogram changes – must be recorded and retained.

Practical aspects. It is essential to have well-trained medical staff, that is immediately available in case of emergency, and facilities for continuous monitoring of the patient's condition. Intravenous access and intensive care room access/emergency treatment should be available depending on the severity of the previous reaction and the type of drug. Procedures like spirometry, monitoring of blood pressure, pulse and vital signs must be performed according to the patient's individual situation. Evolution of life-threatening reactions may make fast access to intubation essential.

DPT should be performed placebo-controlled, single blinded, and, in certain situations where psychological aspects may prevail, even double-blind. This is of

utmost importance, since even in healthy students and hospital staff without any medication but placebo capsules, 41% reported (mostly subjective) symptoms like sedation, irritation, but even nasal congestion, fever, exanthemas and urticaria within a 3-day observation period (41).

The subject's health status should be good on the day of testing, without any sign of allergy or viral infection that could stimulate an immune response – even though this might have been a potential co-factor for the original reaction.

Patients should be observed as long as severe exposure-related reactions may be expected. This depends on the type of previous drug reaction, the drug under investigation (42) and the individual situation of the patient. If mild reactions had occurred, observation after stabilisation is recommended for at least 2 hours. After severe reactions hospitalization is mandatory because of the possibility of biphasic episodes that can be lethal if not recognized early and treated adequately (43). After release, the patient should be equipped with an adequate emergency treatment if further symptoms such as urticaria seem possible (antihistamines, betamimetics, glucocorticosteroids).

In general terms a "safety first" policy should be followed and in many cases an observation period of 24 hours is desirable. Local regulations may influence these procedures.

Test performance

Several factors influence the decision for the "adequate procedure", the most important being the drug and/or drug-ingredient itself, the type of previous adverse reaction, the constitution of the patient at the time of DPT and the availability/reliability of general clinical and specific *in vitro* and *in vivo* tests. Here only general recommendations shall be given, with special examples according to the indications for testing as defined above:

1. Exclude hypersensitivity in non-suggestive history: Many patients are wrongly labeled as being "allergic", based on a suggestive history but not proven by tests; or proven by tests with limited predictive value, such as skin tests with opiates, IgE detection in aspirin hypersensitivity (44), or other non-validated biological tests. In such instances, DPT might be the most valuable aid or even the only way to free the patient from his/her "allergy".

As an example, many adverse reactions to local anaesthetics are due to non-allergic factors that include vasovagal or adrenergic responses. To exclude the rare possibility of an immune mediated-reaction, a graded exposure should be performed (2). Since however the patient may be emotionally upset due to his or her past experience during severe clinical reactions, placebo testing (45) or even "reverse placebo provocation" (46) seems indispensable in some patients where subjective symptoms prevail.

2. Provide safe alternatives in allergic patients and prove tolerance: Penicillin-allergic patients are claimed to have an approximately ten-fold increased risk of having an allergic reaction to antimicrobial drugs in classes other than penicillins and cephalosporins (47). The general approach is to select an agent structurally distinct from the agent that had caused the reaction and then introduce the drug under close supervision.

Exposure under controlled conditions might also be helpful for anxious people, either with distinct agents (e.g. other classes of antibiotics after immunologically mediated reactions) or similar drugs under pretreatment regimens for prevention (e.g. radio contrast media, however: controversial discussions [48]).

3. Exclude cross-reactivity of related drugs in proven hypersensitivity: Patients with a history of allergy to penicillin and skin test positivity are at a three times increased risk if a cephalosporin is given; therefore DPT under controlled conditions – after performing skin tests – is essential before rating cephalosporins as alternatives or classifying them as forbidden. The same is true for the frequently observed hypersensitivity reactions to NSAID in general and especially in aspirin-sensitive asthmatics, since there is no definitive skin or *in vitro* test to identify patients who may react to aspirin (44), to other NSAIDs or to 5-HT3 receptor antagonists (49). Carefully performed DPTs may thus be useful in finding safe alternatives and confirming the diagnosis.

4. Establish the diagnosis in cases of suggestive history but negative (skin or *in vitro*-) tests: For clarification of suspected drug hypersensitivity skin tests are usually the first to be performed (18,32), but frequently with negative results. The causative agent can then only be identified by DPT, as described in a case of a patient with a maculopapular eruption after intake of several drugs (50).

DPT may be performed on the same day as diagnostic skin tests are performed if the reaction under investigation was an immediate one.

Assessment of test results

A DPT can be termed positive, if it reproduces the original symptoms. If the original reaction is just manifested with subjective symptoms and challenge testing again leads to similar, non-verifiable symptoms, placebo challenge steps must be performed. If these placebo steps are negative, repetition of the previous dosing of the drug under investigation is highly recommended.

Always try to objectify the test result by exact surveillance of skin alterations (photographs are helpful) and other signs of the original drug reaction. For example, *in vivo* tests that might be applicable are rhinomanometry (in some cases with occupational rhinitis) and peak-flow and/or spirometry for respiratory symptoms, and determination of cardiovascular parameters for anaphylactic symptoms. The importance

of *in vitro* tests is frequently overestimated by non-expert physicians. General clinical tests such as a complete blood count, total platelet count or eosinophilia, the determination of mediator release (histamine in blood or methylhistamine in urine; eosinophil cationic protein and serum tryptase) can sometimes be helpful. Measuring cytokines, immune complexes, complement components, complement split factors and others are still research tools with no defined reliability for clinical use. "Specific" tests like the lymphocyte transformation test (51), the CAST-ELISA (52 pro, 53 contra) and 15-HETE-determination (54), flow cytometric basophil activation tests (55), or leukocyte cytotoxicity assays (56) may soon have a role in patient evaluation and management, but negative predictive values need to be systematically investigated first. However, one has to admit that this is equally true for DPT itself!

Scoring systems and documentation of adverse events

All clinical signs and symptoms independent of their pathogenesis have to be documented in the test protocol, including the type and severity of reaction, any prodromi, subjective and objective signs, the kinetics, parameters for systemic involvement (e.g. blood and liver parameters), the eliciting substance and its dosing. Scoring systems might be helpful in some cases, they are however not generally accepted (Table 3a,b), and not easily applicable in a clinical setting.

Whereas some methods like the "French Pharmaco-Vigilance System" (59) are based on intrinsic, patient-related and extrinsic, literature-related criteria, that are separately evaluated, other methods are based on statistical models or standardized decision trees.

Skin symptoms should best be photo-documented. The histological evaluation of drug rashes is not pathognomonic in most cases and therefore cannot generally be recommended. In some instances however, such as in lichenoid exanthemas, erythema multiforme and cutaneous vasculitis, histology might help to support the clinical diagnosis.

The corrective treatment of reactions to DPT must also be documented in the test protocol.

Management of adverse reactions

Treatment of adverse events during provocation testing depends on the type of reaction and its severity. Stop of further test drug supply is the first measure, followed by adequate general and specific procedures according to the treatment of anaphylactic reactions (43, 60). Introduction of suppressive or remittive therapy should, however, only be started when symptoms are sufficiently specific to allow calling the reaction a conclusive positive test result. Corrective treatment can not follow standardized

Table 3a. Simple algorithm for the interpretation of test results (adapted from 57)

Questions	Assessment									
Appropriate intervall agent-event	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Known reaction to agent	–	N	N	Y	Y	Y	Y	Y	Y	Y
Event reasonably explained by clinical state or other (nondrug) therapies	–	Y	N	Y	Y	N	N	N	N	N
Dechallenge attempted	–	–	–	–	–	N	Y	Y	Y	Y
Improved with dechallenge	–	–	–	–	–	–	N	Y	Y	Y
Rechallenge attempted	–	–	–	–	–	–	–	N	Y	Y
Relapse on rechallenge	–	–	–	Y	N	–	–	–	N	Y
Definite										X
Probable				X		X		X		
Possible					X				X	
Conditional/dubious			X							
Unrelated (no ADR)	X	X					X			

(Y = yes, N = no, X = allocation)

Table 3b. Criteria for the evaluation of DPT results (adapted from 58)

Symptoms, reaction	Evaluation				
Identical reaction	yes	yes	yes	no	no
Severity and extension increased, time interval shorter	yes	no	no	–	–
Severity, localization and time course identical	–	yes	no	–	–
Prodromi	–	–	–	yes	no
Interpretation of the result	P3	P2	P1	S	N

(P = positive [P3 – P1 are subgroups of positives]; S = suggestive, but not conclusive; N = negative)

procedures but has to be individualized following the general rules of emergency treatment.

Interpretation of test results and consequences

The predictive value of DPT mainly depends on the type/mechanism of reaction and the drug involved. Thus urticarial reactions under penicillin therapy are frequently reproducible whereas morbiliform eruptions after ampicillins are not – probably sometimes because of absent co-factors (35). A physician performing DPT for drug hypersensitivity reactions has to know the specific literature and needs considerable experience in order to be able to differentiate the many reasons for false-negative and false-positive test results (Table 4). These reasons are numerous but can be evaluated and avoided in most cases.

Spontaneous desensitization/tolerance induction has to be considered as an explanation for an unexpected negative DPT result – although this has not been documented in the literature.

The patient finally needs adequate documentation of those drugs that he should not receive any more and those that had been tolerated in the test. The personal use of Medic-Alert tags and/or bracelets should be encouraged. An "allergy passport" to be presented before any drug prescription in the future should be issued and contain at least:

- the (generic and company) name of drug and the active ingredient;
- the date and type of reaction and its severity;
- the method used for evaluation (e.g. history, skin test, IgE-detection, LTT, or DPT), including date and comments;
- recommended safe alternatives and the tolerated dose (in the DPT).

Limitations of drug provocation testing

There are several limitations to the seemingly straightforward procedure of DPT (Table 5): Many people do not take only one drug at a time, and certain adverse events are sometimes indicative, but hardly ever specific for a certain substance. DPT helps detect the etiology, but hardly ever the pathogenesis of the reaction, and only about 15% of the unwanted drug reactions are due to immunologically mediated mechanisms.

When performing DPT, one has to consider the considerable number of false-positive and false-negative results. A negative test does not prove tolerance for the drug in the future and a positive result might not indicate lifelong hypersensitivity. Positive test reactions might be irrelevant, if control patients cannot be studied because of ethical considerations (58). And a negative test does not exclude a drug as being the culprit for a reaction since crucial co-factors might be absent during the test procedure: the setting during the test procedure may lack certain components prevailing when the drug is normally administered, such as the anxiety often present before a dental procedure or an associated inflammatory disease, such as latent asthma, urticaria or viral infections (45, 61). In summary, there is no absolute certainty for future situations!

As the intensity of a reaction after drug hypersensitivity reactions is not absolutely predictable, a careful assessment of the necessity for DPT as well as the dosage is therefore essential.

The predictive value of DPT is dependent on the type of reaction and even more the type of drug. Thus, in a study on 204 patients with a history of anaphylactoid reactions after radiocontrast media, only 24% with an unequivocal history reacted to a test dose; 67% of these developed symptoms despite antiallergic premedication, whereas 20% of those with negative provocation test reacted again upon reexposure (62). Similarly skin-test positivity has been observed in 2 out of 216 (0.9%) (63) and in 26 out of 247 (10.5%) (64) children or adolescents re-tested more than 3 weeks after negative DPT followed by a course of the suspect beta-lactam.

The heterogeneity of side effects of a single drug as well as the enormous number of drugs on the market make it difficult to define specific test procedures for every situation; and it is even more difficult to standardize these procedures. Well-controlled protocols exist only for

Table 4. Important considerations when interpreting DPT results

Potential reasons for	
false-positive reactions	false-negative results
Psychological symptoms	Antiallergic drugs
Preexisting symptoms (e.g. urticaria)	Missing co-factors (light, co-medication, viral infection, physical exercise,...)
Drug-induced aggravation of preexisting disease	Exposure and/or observation time too short
Self infliction	Too short /too long time interval from reaction
	Dosage too low
	"Desensitization" by testing

Table 5. Risks and disadvantages of drug provocation tests

- potentially dangerous
- read out might be difficult (if subjective, unspecific symptoms prevail)
- does not clarify the pathogenic mechanism of the reaction
- not completely pathognomic reactions
- false-negative results can occur
- false-positive results can occur
- co-factors, that are essential for the clinical symptoms might be absent
- does not indicate mere sensitization which may become positive under certain circumstances

allergic contact dermatitis (29), fixed drug eruptions (25), maculopapular eruptions after aminopenicillins and cephalosporins (65, 66), immediate (67) and non-immediate reactions to betalactam antibiotics (20), urticaria and angioedema after NSAID (45), local anaesthetics (46), and a few others (68).

But safety first: Despite the development of a series of serological and cellular tests to clarify immunological sensitization of a patient to penicillin (69), they do not, in most cases, allow an absolute prospective statement on the risk involved in renewed penicillin treatment (13). Provocation tests may narrow the gap, but they do not close it.

The causality of a reaction needs stringent criteria; the message of a provocation test with all its variables regarding sensitivity and specificity depends on the diagnostic aim. A test with high sensitivity is needed when looking for explanations of suspected drug hypersensitivity reactions, but in order to prove causality high specificity would be essential. In clinical practice, it might be more useful to look for safe alternatives instead of proving that a drug was the definitive cause of the problem.

Conclusion

Accurate identification of the agent inducing a patient's hypersensitivity reaction is important. The assessment has to be based mostly on the observation of the clinical signs, their time course and, eventually, their response to antiallergic treatment, and, most importantly, to adequate test results, including DPT in some instances. Confirmation of a presumptive diagnosis by a DPT is often the only reliable way to establish a diagnosis, if other diagnostic procedures such as *in vivo* skin testing and *in vitro* laboratory tests do not lead to conclusive results. This procedure should be undertaken only with great caution and a compelling need, since DPT can also cause severe or fatal reactions.

Plans to avoid future adverse reactions and to provide safe alternative drugs should be formulated as a final phase of the management of patients with suspected drug reactions; for that purpose, an undisputed cause-relationship is essential – this frequently includes a DPT. An individual risk-benefit calculation has to be done in any case, contraindications and ethical considerations taken into account. Thus, DPT must not be performed in patients with proven sensitization except within specific studies.

The test performance should follow established criteria, and the many limitations, potentially leading to false-positive or false-negative test results, be kept in mind; even a negative DPT is no guarantee for future tolerance of the drug!

Causality and imputation have to follow defined rules; the "WHO Drug Monitoring Programme" suggests the following terms: certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessible/unclassifiable (70). Several algorithms were defined, but none fulfills all expectations (Table 3a,b), and they are rarely used in clinical practice (57, 58, 70).

The definition of the general principles for drug provocation tests in this paper should help establish specific protocols for the different groups of drugs on one hand and the different clinical signs of hypersensitivity on the other. Regarding algorithms for drug testing, a DPT should prove or disprove questionable results as obtained with other, less potentially dangerous methods, such as skin or *in vitro* tests – and thus represent the golden standard of drug testing in many clinical situations. Unfortunately, even a negative DPT may not absolutely predict tolerance upon future exposure (as is proven in food allergy testing [71]), nor prove intolerance. The aim should thus be to have such tests available that we can omit provocation tests – but this situation has not yet been achieved.

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