Evaluation of Systemic Provocation Tests in Patients with Suspected Allergic and Pseudoallergic Drug Reactions

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In order to examine the diagnostic value of systemic provocation tests, we studied 56 inpatients hospitalized for identification of the agent eliciting previous severe allergic or pseudoallergic reactions to non-steroidal anti-inflammatory drugs, local anaesthetics or antibiotics. Skin tests were positive in only 4 patients reacting to antibiotics and propyphenazone and were always negative for local anaesthetics ($n = 32$). Only 4 of 26 patients reacted to oral or subcutaneous provocation, 3 times to penicillin and once each to mepivacain, propyphenazone and cyanocobalamine when the suspected drug was tested. In the remaining 30 patients, who for safety reasons were tested only with alternative drugs, none had positive reactions, but 11 patients reported non-specific symptoms, as did 9 of 21 patients given placebo. Systemic provocation tests for drug allergy thus gave few positive results. However, these tests should always be done together with placebo testing for validation of results, and they remain indispensable for identification of alternative, well-tolerated drugs. *Key words: drug allergy; pseudoallergy; psychological reactions; placebo testing; local anaesthetics; non-steroidal anti-inflammatory drugs; antibiotics.*

Unwanted drug reactions constitute a major problem in pharmacological therapy. Their frequency ranges from $15-30\%$ among hospitalized patients, and 15% are due to immunologically mediated mechanisms (1). Pseudoallergic or anaphylactoid reactions, defined by their symptomatology which clinically mimics classical allergic reactions without known associated immunological mechanisms (2, 3), probably make up the major part of the remaining non-pharmacological reactions. These are observed with a broad range of agents, including, in particular, non-steroidal anti-inflammatory drugs (NSAID) and local anaesthetics (3, 4.)

The identification of specific drugs as causing clinical reactions is complicated by many confounding factors. Thus, patients frequently take several drugs or a combination of drugs, and clinical reactions can develop after the drug has been well-tolerated for a long time. Furthermore, the chemical nature and metabolism of different drugs varies widely, varying also among different individuals, and the clinical symptomatology can be highly divergent for the same drug, both with regard to the target organ and the severity of the reaction (4). Despite major efforts, the pathomechanisms of many drug reactions are unclear and as a consequence, diagnostic laboratory tests are available for only a small subgroup of drugs, specifically for those involving IgE-mediated mechanisms ($2-8$).

In view of this situation and the potentially life-threatening nature of drug reactions, *in vivo* provocation tests have been resorted to as a major diagnostic approach (6, $8-12$). In such a procedure, the patients are exposed to the suspected or (more frequently) alternative drugs via the same route by which the drug is normally administered. The overall value of such a procedure is, however, uncertain. An additional problem with such tests is that the patient may be emotionally upset due to his or her past experience during severe clinical reactions ($11-13$). Also, 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 (14, 15).

In order to shed further light on these problems, we have evaluated the outcome of provocation tests performed at our institution with patients referred for the clarification of suspected type I allergic or pseudoallergic reactions to drugs, using a defined scheme (6, 16). The data show that placebo testing is indispensable, that the overall yield of positive reactions is low and that alternative, well-tolerated drugs can always be identified.

MATERIAL and METHODS

All patients hospitalized between 1992 and 1994 for provocation testing to rule out immediate type hypersensitivity to drugs were included in the study. They had to be free of symptoms, without underlying diseases or risk factors, such as asthma or urticaria (10, 17), and not under the influence of drugs suppressing the test reactions, such as antihistamines or corticosteroids. Tests were performed according to a previously published, defined scheme (Table I) (6, 16). Briefly, after taking an initial careful history, patients were thoroughly instructed with regard to the test procedure, possible associated symptomatology and about the importance of blinded testing throughout. The patients then gave written informed consent. Skin tests were performed only in patients with suspected immunological reactions and, for safety reasons, in all patients with past reactions during local anaesthesia, as described earlier (6, 18). On day 2, patients received placebo in order to get accustomed to the test procedure, to lower their anxiety level and to help them interpret unspecific symptoms. Thereafter, one drug was tested each day, starting with the drug that was least and ending with the one most suspected to have elicited the patient's reaction. Placebo testing was omitted when the patient did not consent to stay long enough in hospital, in favour of completing testing of suspected or alternative drugs. Similarly, provocation tests with the suspected drug were not included in the schedule when the eliciting drug had been identified beyond doubt, when the patient refused positive testing, or when previous reactions had been very severe or even life-threatening.

Testing was always done in a hospital ward where the medical and nursing staff were trained for emergency therapy, where supervision was optimal and where emergency equipment was close by. On the morning of each test day, patients were given intravenous physiologi-

Table I. *Diagnostic scheme for hospitalized patients with suspected drug allergy*

Day of hospital stay	Diagnostic procedure
Day 1	History, skin tests
Day 2	Placebo
Days 3 – [a]	Non-implicated, alternative drugs[b]
Last day	Suspected drug
Day of discharge	Discussion of results, proposal for future treatment alternatives and advice to avoid certain drugs or drug classes

[a] number of days depends on the number of suspected and alternative drugs to be tested in each individual patient.
[b] drugs least suspected to have caused reactions were tested in ascending order of likelihood, only one drug being tested per day.

cal saline via either an indwelling or a daily renewed intravenous catheter. Infusion was maintained for 6 h after the last exposure. For blinding of the patient, all clues regarding the type of agent given were avoided. Thus, oral provocation tests were carried out with bland capsules containing placebo or different concentrations of the test drug, prepared by the hospital pharmacy, and for subcutaneous injections during anaesthetic testing, an unlabelled syringe containing drug or placebo was used, although the pharmacological effect of the local anaesthetic was a potential source of unblinding. Unless unavailable, tests were done with pure ingredients and not commercial preparations in order to exclude the effects of additives or additional pharmacologically active drugs, such as vasoconstrictants in local anaesthetics.

Only 1 drug or placebo was tested per day, with several applications. The initial dose of drugs was generally 0.1% of the full normal dose. Subsequent applications with ascending doses occurred at defined 30 min to 2 h intervals, based on the pharmacokinetics of the test drug (16), until twice the normal daily dose was reached. Generally, patients were given 5 provocation tests per day. Before each new exposure, vital signs were taken and the patient was questioned regarding possible symptoms. These were recorded on a test sheet in the hospital record.

If, in the judgement of the physician, a positive reaction had occurred, testing was interrupted for at least 1 day, depending on the severity of the reaction. In case of major intervention with rescue medication, testing was postponed for several days, even some weeks, with intermittent hospital discharge. Provocation tests were restarted with those drugs chemically and pharmacologically least related to the eliciting drug.

If reactions were doubtful and if this was medically indicated, the same reagent was to be re-tested at a later time in the test series.

At the end of testing, the patient and his or her private physician or dentist were informed about the outcome of the tests and advised on future applications of the test drugs, based on negative reactions.

RESULTS

Most of the 56 patients evaluated were middle-aged (mean 40.8 years) and female ($n = 41$). Their mean duration of hospital stay was 8.6 days. The majority of patients were admitted because of suspected NSAID-induced intolerance reactions, including mainly aspirin, diclofenac and paracetamol ($n = 23$), followed by reactions to local anaesthetics ($n = 16$) and antibiotics ($n = 14$), particularly penicillin, sulphonamides and doxycycline. One patient each had reacted to dexamethasone, benzodiole and ferric sulphate. In 33 patients, reactions had presented with symptoms of anaphylactic shock, while in the remainder other symptoms commonly associated with type-I allergy (urticaria, flush, shortness of breath) had been observed.

Skin tests were positive in only 4 of 32 tested patients, namely against penicillin, erythromycin, clindamycin and propyphenazone, and they were always negative for local anaesthetics (Table II).

In 27 patients, only negative systemic provocation tests with alternative drugs, i.e. other classes of NSAIDs, such as paracetamol instead of aspirin, or for antibiotics, macrolides and chinolone derivatives, were done because of severe previous clinical reactions. In 24 patients, positive as well as negative testing was done, and in 5 patients, only positive tests were performed, either because no alternative drugs were available or desired, or because patients had no time for an extended hospitalization. Patients with positive prick test reactions were not challenged with the same drug for safety reasons.

Overall, the majority of patients failed to react during oral or subcutaneous provocation tests (Table II). Only 3 of 29 patients exposed to the suspected eliciting drug had unequivocally positive reactions to penicillin and one each to scandicain, propyphenazone and cyanocobalamine (vitamin B12) (Table III). Symptoms generally mimicked on a minor scale the previous clinical reactions and were readily controlled with emergency medication.

Non-specific symptoms, such as palpitation, restlessness, sweating and sensations of heat and of a lump in the throat, were reported by 42.9% of patients during placebo testing and by 19.6% on drug testing (Table II). In case of doubt, the unspecific nature of these symptoms was confirmed by repeated testing of the same drug at a later date.

DISCUSSION

The present data show that systemic provocation tests performed according to strict rules and with proper precautions

Table II. *Overall test results in patients with suspected drug intolerance or allergy*

Methods of testing	Number of patients tested	Type of reaction	Number of patients
Prick tests	32	Positive	4
Intracutaneous tests	16	Negative	16
All provocations with drugs	56	Positive	6
		Negative	41
		Non-specific	11
Provocation, placebo	21	Negative	12
		Non-specific	9

Table III. *Numbers of patients tested and reacting to different test drugs during systemic provocation tests*

Test drugs	Number of patients tested	Number of positive reactions
Local anaesthetics	6	1
Antibiotics	6	3
Analgetics	12	1
Other drugs[a]	5	1

[a] caffeine, dexamethasone, ferric sulphate, benzodiole and cyanocobalamine.

are very safe, although the diagnostic yield is low, with only 6 of 29 (17.9%) patients reacting to the suspected eliciting drug. This implies that the patient was either admitted with the wrong diagnosis or that the test procedure, as also currently propagated by others (19, 20), is inadequate. Our positive yield might have been higher if patients with severe clinical reactions had also been tested with the implicated drug, but this is difficult to justify on ethical grounds. Nevertheless, only 33.3% (80/240) of patients with suspected reactions to NSAID, including aspirin, have recently been reported by another group to react to oral challenge (21), and even fewer patients (3/177 or 1.6%) reacted to subcutaneous challenge with local anaesthetics (22), using the same schedule as reported here. A low yield of <1% with local anaesthetics is also cited in a recent review of the older literature (20). Increased positive provocation tests would thus be justified against this background.

As in our study, all patients with suspected reactivity to local anaesthetics also failed to react with immediate type reactions on skin testing (22), suggesting that the underlying pathomechanisms are primarily pseudoallergic in nature. Prick or intracutaneous skin testing is thus not warranted in these patients, as also holds for patients with suspected reactivity to NSAID where skin tests are not only falsely negative, but even healthy controls may have positive tests (16, 22–24). The only exception, as also evident from our data, is propyphenazone where IgE antibodies have been implicated in the past (25–27). Skin tests are furthermore indicated when antibiotics or several other drugs apart from NSAID or local anaesthetics are considered (Table II) (28).

In view of the limited possibilities for *in vitro* diagnostic tests and the lack of availability of simple *in vivo* tests for most substances, the low yield of positive systemic provocation tests is disappointing. This might be due to special circumstances prevailing at the time of the clinical reaction which are no longer present at the time of challenge testing, such as associated viral diseases (14) or a high level of anxiety during dental procedures (20). The pharmacological action of adrenalin in local anaesthetics might have added to this anxiety, with provocation of cardiovascular reactions when larger doses are administered. Reactions to preservatives in commercial preparations should also always be considered, although thorough investigations of such agents with oral challenges also yielded no or only rare positive data in a large patient population (20, 22).

Although for safety reasons, provocation tests with the implicated drug were not pursued in about half of our patients, testing of alternative drugs was of considerable value for these patients since it provided them with a safe means to treat their disease with agents having pharmacological effects comparable to those of the drug they had reacted to clinically. This is particularly important for patients suffering from chronic diseases such as epilepsy or chronic intractable pain, in situations where long-term prophylaxis is required, or in patients needing extensive, painful oral surgical procedures.

In recent years, there has been growing awareness of a close link between the nervous system and the immune system, explaining even some acute type-I allergic reactions on the basis of Pavlovian conditioning (29, 30). We have tried to take account of this and to reduce anxiety levels and the associated non-specific symptomatology during systemic provocation tests by starting the test schedule with placebo whenever possible. A sizeable number of patients (42.9%) reported some non-specific symptoms in response to placebo, with a lower incidence (19.6%) during subsequent provocations. The non-specific nature of these symptoms could generally be readily differentiated from true allergic-type reactions by an experienced physician. It should nevertheless be kept in mind that psychological factors can be a major component of classical allergic symptoms, although the nature of doubtful reactions can generally be clarified by repeated testing under blinded conditions.

In conclusion, while systemic provocation tests remain an invaluable tool in patients with drug reactions, their overall diagnostic yield is low, and they are uneconomical. Major progress is to be expected only with a better understanding of the pathomechanisms involved, particularly with regard to the nature of pseudoallergic reactions. Until simpler tests are available, however, we suggest that systemic provocation tests should be done with very selected, urgently needed drugs, starting always with blinded placebo testing to alleviate the patient's anxiety and thus to increase the validity of subsequent drug testing. Furthermore, confirmation of suspected drug reactions should be sought whenever possible and in at least a single blinded setting.

REFERENCES

1. Hoigné R, Lawson DH, Weber E. Risk factors for adverse drug reactions – epidemiological approaches. Eur J Clin Pharmacol 1990; 39: 321–325.
2. Dukor P, Kallos P. Pseudo-allergic reactions. Basel: Karger, 1985.
3. Schlumberger HD. Pseudoallergic reactions to drugs and chemicals. Ann Allergy 1983; 51: 317–324.
4. Parker CW. Allergic drug responses – mechanisms and unresolved problems. CRC Crit Rev Toxicol 1972; 1: 261–266.
5. Schnyder B, Pichler WJ. T-Zellaktivierung bei Arzneimittelallergien. Allergologie 1997; 20: 58–62.
6. Zuberbier T, Henz BM. Diagnosis of urticaria. In: Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. Urticaria, clinical, diagnostic and therapeutic aspects. Berlin: Springer, 1997: 139–159.
7. McDonald JR, Mathison DA, Stevenson DD. Aspirin intolerance in asthma: detection by oral challenge. J Allergy Clin Immunol 1972; 50: 198–207.
8. Patterson R. Diagnosis and treatment of drug allergy. J Allergy Clin Immunol 1988; 81: 380–384.
9. DeShazo RD, Nelson HS. An approach to the patient with a history of local anesthetic hypersensitivity: Experience with 90 patients. J Allergy Clin Immunol 1979; 63: 387–394.
10. Delaney JC. The diagnosis of aspirin idiosyncrasy by analgesic challenge. Clin Allergy 1976; 6: 177–181.

11. Ring J. Diagnostik von Arzneimittel-bedingten Unverträglichkeitsreaktionen. Hautarzt suppl 1987; 38: 16–22.
12. Patterson R, DeSwarte RD, Greenberger PA, Grammer LC. Drug allergy and protocols for management of drug allergies. N Engl Reg Allergy Proc 1986; 7: 325–342.
13. Vervloet D, Charpin D, Pradal M. Atopy and drug allergy. ACI News 1992; 4: 39–42.
14. Calhoun WJ, Dick EC, Schwartz LB, Busse WW. A common cold virus, rhinovirus 16, potentiates airway inflammation after segmental antigen bronchoprovocation in allergic subjects. J Clin Invest 1994; 94: 2200–2208.
15. Zuberbier T, Iffländer J, Semmler C, Czarnetzki BM. Acute urticaria – clinical aspects and therapeutic responsiveness. Acta Derm Venereol (Stockh) 1996; 76: 295–297.
16. Vieth B, Ochmann G, Czarnetzki BM. Anaphylaktoide (pseudoallergische) Reaktionen – Neue Wege zur Diagnose der chronisch rezidivierenden Urtikaria. In Macher E, Czarnetzki BM, Knop J, eds. Jahrbuch der Dermatologie. Münster: Regensberg & Biermann, 1986: 97–106.
17. Wüthrich B, Fabro L. Acetylsalicylsäure- und Lebensmitteladditiva-Intoleranz bei Urtikaria, Asthma bronchiale und chronischer Rhinopathie. Schweiz Med Wochenschr 1981; 111: 1445–1450.
18. Grabbe J, Zuberbier T, Wagenpfeil S, Czarnetzki BM. Skin prick tests to common allergens in adult atopic eczema and rhinitis patients: reproducibility on duplicate and repeated testing. Dermatology 1993; 186: 113–117.
19. Bleck O, Vieluf D. Pseudo-allergische Reaktionen auf nichtsteroidale Antiphlogistika und Analgetika. Allergologie 1997; 20: 375–384.
20. Rueff F, Przybilla B. Lokalanästetika-Unverträglichkeit. Allergologie 1997; 20: 385–392.
21. Quiralte J, Blanco C, Castillo R, Delgado J, Carrillo T. Intolerance to nonsteroidal antiinflammatory drugs: Results of controlled drug challenges in 98 patients. J Allergy Clin Immunol 1996; 98: 678–685.
22. Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. J Allergy Clin Immunol 1996; 97: 933–937.
23. Czarnetzki BM. Urticaria. Berlin: Springer-Verlag, 1986.
24. Mathews KP, Lovell RG, Sheldon JM. The problem of aspirin allergy with a report on skin testing with salicylate-containing human sera. J Lab Clin Med 1950; 36: 416–421.
25. Wiedow O, Brasch J, Christophers E. Orale Expositionstestungen bei nicht Aspirin-bedingten Analgetikaintoleranzen. Hautarzt 1996; 47: 901–908.
26. Fabro L, Wüthrich B, Wälti M. Acetylsalicylsäure- and Pyrazol-Allergie oder Pseudo-Allergie. Z Hautkr 1985; 62: 470–478.
27. Szczeklik A, Gryglewski RJ, Czerniewska-Mysik G, Pieto R. Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. BMJ 1977; 2: 231–232.
28. Eichler G, Merk HF. Unerwünschte Arzneimittelreaktionen auf Antibiotika. Allergologie 1997; 20: 368–374.
29. Theoharides TC. The mast cell: a neuroimmunoendocrine master player. Int J Tiss Reac 1996; 18: 1–21.
30. MacQueen G, Marshall J, Perdue M, Siegel S, Bienenstock J. Pavlovian conditioning of rat mucosal mast cells to secrete rat mast cell protease II. Science 1989; 243: 83–85.