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 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.

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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 labora-

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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 (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-
The present data show that systemic provocation tests performed according to strict rules and with proper precautions
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 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 J Med 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, Iflländer J, Semmler C, Czarnetzki BM. Acute urticaria — clinical aspects and therapeutic responsiveness. Acta Derm Venereol (Stockh) 1996; 76: 295–297.
16. Veth 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. Quiralt 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, Czerneijewskina-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.