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CLINICAL REPORT

Oral Challenge in Patients with Suspected Cutaneous Adverse Drug Reactions: Findings in 784 Patients During a 25-year-period

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The aim of this study was to analyse the usefulness of oral challenge test with different drugs in confirming cutaneous adverse drug reactions in routine clinical practice. During the years 1975–2000 a total of 1001 challenges were carried out in 784 patients. Patients with serious drug reactions were excluded and those with positive skin test reactions were challenged only in dubious cases. Of 1001 challenges, 136 (13%) patients developed a positive challenge reaction. Antimicrobial drugs were most commonly suspected, accounting for 67% of challenges and 66% of the positive reactions. Exanthema was the most common skin reaction (72%), followed by fixed drug eruption (16%) and urticaria (12%). One serious challenge reaction with salazosulfapyridine was seen. We conclude that the challenge test is most useful as a tolerance test or to exclude drug hypersensitivity. It may be useful to complete studies of adverse drug reactions in patients with a history of exanthema, if other diagnostic methods are not available or if other diagnostic tests yield negative results. Out-patient protocol can be used in most cases. ***Key words: drug hypersensitivity; cutaneous adverse drug reaction; oral challenge.***

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The prevalence of adverse drug reactions (ADRs) is increasing (1) and cutaneous ADRs (CADRs) are among the most common reactions. ADRs have been estimated to develop in 2–7% of hospitalized patients (2, 3) and are suspected to be caused by antimicrobial agents in about one-quarter (4). The incidence is dependent on the hospital department, being highest in departments of infectious diseases and lower in surgical departments (5).

Suspected drug allergies often cause unnecessary limitations for future drug therapies and if neglected can lead to unnecessary and even severe ADRs. Diagnostic tools to confirm drug allergy, sometimes after a long delay, are limited. Systemic challenge may be the most reliable way to exclude or confirm the allergic drug reaction (6). In this study the results of challenges carried out in clinical practice during the years 1975–2000 in a department of dermatology were analysed.

MATERIALS AND METHODS

Patients

From 1975 to 2000 a total of 1001 systemic drug provocation tests in 784 patients was carried out in the Dermatology Department of Turku University Central Hospital to exclude or confirm suspected CADR. In only a few occasional cases the acute skin reaction was seen in the clinic. The patients were referred from other clinics or by physicians in general practice or private clinics. As $<5\%$ of the acute reactions were seen by dermatologists, the suspected previous reaction pattern was based on available data and the history of the patient. The previous reaction pattern was suspected exanthema in 51%, urticaria or angioedema in 10% and fixed drug eruption (FDE) in 5%. In 337 cases (34% of the cases) the diagnosis of the skin reaction could not be set on the basis of the clinical history. Patients with a history of severe symptoms such as Stevens-Johnson syndrome, toxic epidermal necrolysis, serious angioedema and those with systemic symptoms were not challenged.

The indication for drug challenge was often the exclusion of drug hypersensitivity or exclusion of simultaneous sensitivity to structurally related drugs in patients with an evident or proven hypersensitivity. Generally the skin test positive patients were not challenged. Patients with dubious positive skin test reactions were challenged in 17 cases and those with negative skin tests in 209 cases. The skin test findings of this clinical material have been published published before (7).

The age range of the patients was 17–79 years (mean 48 years) and the ratio of females to males was 2.5:1. For evaluation of the importance of different drugs in suspected and proven allergies, the study period is divided into three time periods covering 1975–1984, 1985–1994 and 1995–2000. Each provocation test was performed as part of an individual clinical examination and all the patients gave their oral informed consent before the challenge.

Oral challenge

When the challenge was started the patient had to be free of any infections or skin symptoms. Antihistamines were not allowed during the 5 preceding days and immunosuppressive drugs (e.g. corticosteroids) were not allowed in the preceding 4 weeks. Patients with poorly controlled cardiac, renal, hepatic or other systemic disease or with uncontrolled asthma were not challenged.

Before the year 1995 the patients were always hospitalized for drug challenge. The patients were observed in the hospital for 1–5 days. Skin reactions, blood pressure, heart rate and body temperature were monitored. From 1995 onwards, patients were allowed to go home at 3–4 hours after the

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challenge dose and returned to hospital immediately if they observed some reaction. In the hospital the course of the challenge and follow-up was otherwise similar.

During the first day the patient received placebo, which was repeated once or twice, if needed. The drug challenge was started with one-quarter or one-tenth of the regular lowest dose of the drug depending on the history of the individual CADR. The higher starting doses (one-quarter) were used only in cases of evident exanthema. The dose was doubled every 1–4 h until the regular dose was reached. Thus, two to four doses of the active drug were administered during one challenge day. When the regular daily drug dose was achieved and administered two to four times without any new symptoms the exposure was considered negative. After 1995 the patient continued with regular daily doses for 3–7 days at home, reporting with a phone call in negative cases. If any signs appeared, the patient was asked to call immediately and they were always checked in the hospital.

Statistics

Frequencies of challenges with individual drugs and occurrence of positive challenge reactions were compared by using the χ^2 test.

RESULTS

Tables I and II present the number of provocations and positive results with the various skin patterns during the three time periods. Altogether 1001 challenges were carried out in 784 patients and 136 (13.5%) positive reactions developed: 97/136 (71%) exanthema, 22/136 (16%) FDE and 17/136 (12%) urticaria.

The number of challenges diminished somewhat over time, but the frequency of positive results decreased even more from 16% before 1985 to 13% between 1985 and 1994, and to 9% after 1994.

Challenges with antimicrobial drugs (Table I)

Challenges with antimicrobial drugs were carried out in 681/1001 cases (68%) and positive reactions were seen in 13% (90/681), accounting for 66% of all positive results.

Sulphonamides or/and trimethoprim were commonly suspected during the first two periods; through 1975 to 1994 sulphonamide challenges decreased significantly ($p<0.0001$) in the course of the study periods and the same was true with trimethoprim challenges ($p<0.0001$). The proportion of sulphonamides as a cause of positive challenges decreased significantly ($p<0.03$). Exanthema was the most common reaction pattern elicited with these drugs.

V-penicillin, ampicillin or amoxicillin were investigated in 24–28% of all cases, but positive challenges decreased significantly after 1994 ($p<0.005$). During all periods amoxicillin caused reactions most often (in 17–25%), each of them representing exanthema. V-penicillin elicited exanthema in 4.4% of challenges (8/181). Cephalosporin challenges started after 1985 and 3/80 positives were seen; two cases of exanthema after cephalexin and one urticaria after cefadroxil.

In challenges with macrolides, one positive urticaria was seen after erythromycin (1/37) and 6/35 (17%) FDEs after tetracycline or doxycycline. Nitrofurantoin challenges showed a decreasing tendency after 1985 and 8 positive reactions were seen (equal numbers of exanthema and urticaria). Clindamycin and metronidazole were used six times in challenges and both of them elicited exanthema in

Table I. *Oral provocation tests and positive challenge reactions to antimicrobial drugs during three time periods from 1975 to 2000*

	1975–1984		1985–1994		1995–2000		Challenge reactions 1975–2000		
Agent tested	*n*	+ (%)	*n*	+ (%)	*n*	+ (%)	Exanthema	Urticaria	FDE
Sulphonamide (S)	92	22 (24)	34	4 (12)	1		26		
Trimethoprim(T)	71	12 (17)	35	6 (17)	6		11	2	5
S + T					2	1 (50)	1		
Penicillin	81	4 (5)	50	3 (6)	50	1 (2)	8		
Amoxicillin	12	3 (25)	23	5 (22)	18	3 (17)	11		
Ampicillin	7	1 (14)	2				1		
Cephalexin			13	1 (8)	32	1 (3)	2		
Cefadroxil			6	1 (16)	19			1	
Cephuroxime			2		8				
Macrolides	9	1 (11)	14		14			1	
Tetracyclines	7	1 (14)	20	3 (15)	8	2 (25)			6
Nitrofurantoin	17	6 (35)	5	1 (20)	4	1 (25)	4	4	
Clindamycin			2	1 (50)	4	1 (25)	2		
Metronidazole			2	1 (50)	4	1 (25)	2		
Ciprofloxacin			2	1 (50)	3			1	
Gentamicin			1	1 (100)			1		
Cloxacillin			1	1 (100)			1		
Total	296	50 (17)	212	29 (13)	173	11(6)	70	9	11

n, number of challenges; +, number of positive challenge reactions; FDE, fixed drug eruption.

Table II. *Oral provocations and positive challenge reactions to diverse non-antimicrobial drugs in three time periods*

	1975–1984		1985–1994		1995–2000		Challenge reactions 1975–2000		
Agent tested	*n*	+ (%)	*n*	+ (%)	*n*	+ (%)	Exanthema	Urticaria	FDE
NSAIDs									
ASA	33	5 (15)	32	1 (3)	3	1 (33)		5	2
Phenazone salicylate	4	1 (25)	5	2 (40)				3	
Paracetamol			4	1 (25)	5	2 (40)		1	2
Ibuprofen			3	1 (33)	6	1 (17)		1	1
Ketoprofen			6		7	2 (29)	2		
Anti-epileptics									
Carbamazepine	4	3 (75)	4	3 (75)			3		3
Phenytoin	5	3 (60)	5	3 (60)			6		
Other drugs									
Captopril	4	2 (50)	3	1 (33)			3		
Diltiazem	3	2 (66)	3	1 (33)			3		
Lansoprazole					3	1 (33)		1	
Allopurinol	2		6	1 (17)	5	1 (20)	2		
Salazosulfapyridine	4		4	1 (25)	6	2 (33)	3		
Pseudoephedrine					4	2 (50)	2		
Furosemide	7	1 (14)	6		4		1		
Diverse	50	1 (2)	49	1 (2)	31		2		
Total	116	18 (15)	130	16 (12)	74	12 (16)	27	11	8

n, number of challenges; +, number of positive challenge reactions; FDE, fixed drug eruption; ASA, acetylsalicylic acid; NSAIDs, non-steroidal anti-inflammatory drugs.

2/6 cases. Both cloxacillin and gentamicin resulted in one exanthema.

Challenges with non-antimicrobial drugs (Table II)

Non-steroidal anti-inflammatory drugs (NSAIDs) were used in challenges in 108/1001 (11%) cases and 17/108 (16%) were positive. Acetylsalicylic acid (ASA) provocations were carried out in 65 patients before 1995 and in only 3 therafter. In all, 7/68 positive ASA challenges were seen, 5 with urticaria and 2 with FDE. Patients were challenged with phenazone salicylate, paracetamol, ibuprofen and ketoprofen and 10/36 positives were seen – most often FDE or urticaria and two exanthema after ketoprofen.

Phenytoin or carbamazepine yielded exanthema or FDE in 12/18 challenges. After 1994 no challenge with anti-epileptics was carried out.

Among cardiovascular drugs, captopril caused 3/7 and dilthiazem 3/5 exanthemas before 1995; no challenge was carried out thereafter. Instead, patients were occasionally challenged with allopurinol, salazosulfapyridine and furosemide after 1995, and they caused exanthema in 2/13, 3/14 and 1/17 patients, respectively. One patient, challenged for 10 days with salazosulfapyridine, developed severe exanthema with increase of liver enzymes. The enzyme values, indicating clear-cut liver damage, peaked after 3 weeks but recovered gradually thereafter. Pseudoephedrine, only used in challenges after 1995, elicited exanthema in two of four patients.

DISCUSSION

Positive challenge reactions, especially to antimicrobial agents, decreased during the last period analysed in this study. The reason for that is not clear. From patient records it is obvious that the role of the oral challenge test has evolved more towards verifying the tolerability of an essential drug or to excluding a CADR rather than proving it. Also the therapeutic alternatives were more commonly challenged. Improved availability of alternative choices, for example for antibiotics and anti-epileptics from even different chemical families of drugs, has also made the challenge tests unnecessary more often. Use of skin testing also decreased positive challenge reactions. Only 2% of all patients challenged had had a dubious positive skin test.

Immunologic drug exanthema may be elicited by different mechanisms (8) and neither skin testing nor lymphocyte transformation tests reliably exclude drug hypersensitivity. Patients with skin test negative results required oral challenge in certain cases. During the study period the lymphocyte transformation test was not available for routine diagnosis in the hospital, although it is considered a useful diagnostic method (9).

Different patient populations have been challenged in earlier studies and more than half of the challenges were positive in two previous studies when highly selected patients were challenged (10, 11); FDE was seen most often as a challenge reaction in those studies. Because of the typical history of FDE and increased use of skin tests, suspected FDE was the reason for challenge in

only a minority of our patients. Unexpected FDE was seen twice. Oral challenge in cases with suspected FDE should be avoided, because serious generalized, bullous, mucocutaneous FDE may be elicited (12, 13). In this material urticaria was the unexpected reaction most often, as only 6/17 patients had a history of suspected urticaria. The differential diagnosis between exanthema and urticaria is often difficult for general practitioners and some patients had not even visited any doctor at the time of the acute CADR. Although the history is suggestive for exanthema, precautions for an immediate reaction are necessary in each challenge. In our study exanthema was the most common skin reaction, corresponding to certain earlier reports (14, 15).

In this study the acute reaction had often occurred 1–10 years ago. Shorter 1–2-day challenges were sometimes carried out before 1995, in spite of a history of exanthema. Thus, some false negatives were possible. On the other hand, desensitization may have developed in some cases, as described with certain antimicrobial agents in particular (16). Unfortunately, the intervals between the first challenge dose and the appearance of the first symptoms in positive challenges were not systematically registered. However, the reaction appeared most often on the second day, whereas urticaria usually appeared on the first day after one to three doses. Four patients who developed exanthema 3 or more days after the beginning of the challenge had a history of suspected amoxicillin exanthema from more than 5 years ago.

An adequate diagnosis of the earlier suspected CADR is most important to avoid serious reactions. Although most cases of Stevens-Johnson syndrome or some cases of toxic epidermal necrolysis may not be immunologic and/or related to the drug, the challenge in those cases was not accepted. The patient who in the course of 10 days developed serious multisystem reaction after salazosulfapyridine had a history of slight, macular exanthema without systemic symptoms. In man, salazosulfapyridine is mainly metabolized to sulfapyridine and 5-ASA and the half-life of either component does not explain the slow reaction. Similar reactions to salazosulfapyridine have been reported (17). When a challenge in suspected cases of CADR to salazosulfapyridine or sulphonamides is considered, careful evaluation of alternative treatment choices should be done first. If salazosulfapyridine challenge is started, the patient should be followed intensively for 3 weeks with regular checking of liver enzymes two to three times weekly.

Among the patients with a history of CADR the sulphonamides as a cause showed a decreasing tendency, which probably is partly explained by a decrease in consumption. From 1980 to 1990 the defined daily dose (DDD)/1000 inhibitants/day of sulphonamides in combination with trimethoprim or alone decreased from 3.34 to 1.85 (18, 19) and further to 0.73 by the year 2000, when only the combination was marketed (20). Because positive reactions to sulphonamides were reproducible in every fourth patient before 1985, tighter indications for the challenge were indicated and an apparent decrease was seen during the last period. Increased choices for antimicrobials have made sulphonamide challenges unnecessary, except for certain infections in AIDS patients.

Beta-lactams are still important antimicrobials. The consumption of these drugs has mainly increased in the course of the 1980s to 2000 (18–20). Allergy to penicillin or aminopenicillins was confirmed in 8% (20/243) of suspected cases, corresponding to earlier reports (21, 22). Before 1995, three patients who developed exanthema after penicillin or amoxicillin had only been prick tested to exclude immediate-type reactions. Compared with penicillins, cephalosporins less commonly elicited positive challenge reactions, as was expected from earlier studies (23, 24). Exanthema was seen twice in patients with a dubious positive patch test rection. Since the beginning of the 1990s it has been common to challenge those with a history of suspected penicillin hypersensitivity to first-generation cephalosporins, which are expected to be tolerated.

IgE-mediated allergic reactions to macrolide antibiotics have been infrequently reported (25, 26) and 1/97 developed urticaria after erythromycin challenge. Different ADRs to nitrofurantoin have been reported (27). In this study 26 nitrofurantoin challenges were carried out, with 4 each of exanthema and urticaria reactions, which was a good fit with the history. The use of nitrofurantoin has decreased as also evidenced in the follow-up of the three time periods (18–20). Although the consumption of trimethoprim only decreased from 1.75 DDD/1000 inhabitant/day in 1990 to 1.52 in 2000, trimethoprim challenges were not carried out after 1995 to the same extent as they were 10–20 years earlier. This is probably due to a high likelihood of positive challenge reactions in patients with such history. Challenge reactions were exanthema, FDE or urticaria, as expected (28). Although fluoroquinolones may elicit variable skin reactions (29), in our study only five patients were challenged and one developed urticaria. Probably fluoroquinolones most generally can be replaced by other medicines. Clindamycin or metronidazole have been used in challenges since 1990 and both of them elicited exanthema as reported earlier (30, 31). Doxycycline commonly elicited FDE, as expected (32).

ASA challenges were frequent during the first study period and other NSAIDs during the further follow-up periods. Positive reactions often appeared as urticaria and non-immunologic mechanisms of cyclo-oxygenase inhibition appear to be important (33). Today ASA challenge is only carried out in exceptional cases and needs particular caution. Ketoprofen caused exanthema

in two patients who were probably sensitized from topical use, known as a most common sensitization route (34). FDE reactions caused by phenazone salicylate, ibuprofen and paracetamol have been reported previously (13, 35).

Oral challenges with anti-epileptics yielded positive reactions in more than half of the challenged patients until 1995. Carbamazepine and phenytoin are known as common causes of CADRs (9). These drugs also elicit reliable positive patch test reactions. Alternatives for these drugs are sodium valproate, lamotrigine and phenobarbital, which elicit allergic reactions less frequently (36, 37).

Exanthema elicited by captopril and diltiazem has been reported earlier (38, 39). Neither of them, however, was used in challenges after 1994, probably reflecting decreased use, when the pharmaceutical industry had developed new alternatives with less side effects In contrast, new treatment choices have not been developed for the treatment of gout. Occasional exanthema reactions were elicited by allopurinol, as expected (31).

In conclusion, systemic challenge in cases of suspected CADRs has become a method to exclude drug hypersensitivity or to prove the tolerability of an essential drug, whereas the opposite is seldom required. Guidelines to carry out drug provocation testing were reported recently (6). Skin tests and *in vitro* tests are always first-line investigations when drug hypersensitivity is suspected. In test negative cases or when skin tests cannot be performed and the lymphocyte transformation test is not available or is negative, challenge is the only method to exclude allergy. In our experience out-patient provocations can be carried out with good results, when patients with a history of serious reactions are excluded. During the long follow-up period only one serious reaction was seen, which could not be foreseen on the basis of patient history. Certain drugs – especially salazosulfapyridine – should be challenged only with particular indications and the response should be monitored carefully for 3 weeks.

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