CLINICAL REPORT

The Prevalence of Acute Cutaneous Drug Reactions in a Scandinavian University Hospital

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To investigate the epidemiology of acute cutaneous adverse drug reactions, a cross-sectional study was designed with four visits, equally distributed over one year, to all clinical departments of a large university hospital in order to find patients with possible drug-induced exanthema of less than 2 weeks' duration. Patients were examined clinically and offered investigation for possible drug allergy, including blood tests, and skin tests when appropriate. Subsequent drug challenge tests were performed in selected cases. Finally, the history and test results were evaluated to determine the imputability of each drug as the possible culprit. In a cohort of 11,371 in- and out-patients, 131 were referred for evaluation. Twenty-nine cases of acute cutaneous drug reactions were identified, giving a prevalence of 0.33% in in-patients, 0.14% in out-patients, and 0.25% overall. Twenty-five percent of the case patients died within 6 months after the study period. The most common type of skin reactions were symmetrically distributed maculo-papular exanthema and eczematous eruptions. Several more rare types of skin reactions were each represented by a single case. β-lactam antibiotics and chemotherapeutics were the most common eliciting drugs. The prevalence was lower than reported previously, but similar to a recent study. However, prospective studies are few and rarely performed in large hospital settings. Furthermore, variations in the pharmaco-therapeutic traditions between countries may affect the outcome of such studies. *Key words: drug allergy; drug eruption; pharmaco-epidemiology; pharmaco-vigilance.*

Cutaneous drug reactions (CDR) are common and significant complications of treatment of patients and have implications for patient health and the healthcare economy (1). For example, the choice of antibiotic therapy in a patient with suspected penicillin allergy may lead to the use of more expensive and more toxic antibiotics (2–4). Approximately 2–3% of hospitalized medical patients are reported to have a CDR (5, 6), although a recent European study found a prevalence of 0.36% in a hospital population (7).

Different pharmaco-therapeutic cultures exist between countries, as illustrated by the variation in sales of antibiotics in the European Union (EU) (8). Furthermore, during The Boston Collaborative Drug Surveillance Program it appeared that hospitalized American patients received twice as many drugs as a matched group in Scotland (9). National/regional studies are thus called for, and the epidemiology of CDR has not been investigated in Scandinavia. The objective of the present study was to determine the prevalence of specific acute CDR (ACDR) at Odense University Hospital and to register the observed cutaneous reactions, eliciting drugs, and referring departments.

MATERIALS AND METHODS

This was a cross-sectional study with four visits of one day's duration to all clinical departments at Odense University Hospital, which has 1107 beds and more than 1000 out-patient consultations a day. The exact number of patients was retrieved by the hospital statistics department by computerized search for patients hospitalized on the days of the study. Included patients had a high imputability of an ACDR as defined by Moore et al. (10), and ACDR being defined as an undesirable morphological skin change with or without systemic involvement, with a history of less than 2 weeks, developed after local or systemic administration of drugs in dosages commonly used in prevention, diagnosis or treatment of disease or modification of physiological functions. The time from first exposure to first cutaneous manifestation of a possible drug rash should not exceed 3 months.

All departments were visited once every season of the year 2002–2003: winter (November 15th – January 23rd), spring (February 4th – April 16th), summer (April 29th – June 27th) and autumn (September 4th – November 11th), in order to reduce bias caused by seasonal variations in the use of certain drugs. Bed wards as well as out-patient clinics were visited. Written information was distributed to the chairpersons of all departments. The medical and nursing staff were informed and reminded of the study protocol at staff meetings weeks in advance, the evening before each visit, and on three or more occasions during the day of each visit. The exact date of visit was revealed the evening before each visit. On the days of each visit posters for staff and patients were displayed in the bed wards and out-patient clinics.

Patients fulfilling inclusion criteria were offered investigation for drug allergy. History was taken using a questionnaire for recording medical history with emphasis on the exanthema, and drug intake over the last 3 months. Clinical examination was performed by a consultant dermatologist. A series of routine blood analyses for diagnostic and differential diagnostic purposes were performed upon referral: haemoglobin, leukocyte eosinophil count and s-CRP, s-creatinine, s-ALAT, s-tryptase, and, upon elective investigation > 4 weeks later: basophil his-

tamine release, and specific IgE if commercially available. For a number of diagnostic entities supplementary haematological, biochemical and serological sampling, and microbial investigations were performed for diagnostic and differential diagnostic purposes. Skin biopsy was performed in selected cases upon inclusion, and patch tests, skin prick tests (SPT), intradermal tests and drug challenge tests upon elective investigation. Finally, the history and findings of the examinations were evaluated in a retrospective determination of the imputability of each drug as the possible culprit. The imputability analysis was performed by the authors and imputability was described as: certain/likely, possible, and unlikely. ACDR was defined as cases with the imputability score of "certain/likely".

Specific IgE was measured when available (CAP Pharmacia, Stockholm, Sweden). Basophil histamine release was measured for all suspected drugs (11) (RefLab, Copenhagen, Denmark). SPT were performed using commercially available formulations of the suspected drugs. SPT was performed in concentrations of 1:1 except in cases of suspected type 1 reactions where dilutions starting from 1:10.000 were used. Histamine HCl 10 mg/ml (ALK-Abelló, Hørsholm, Denmark) was used as positive control and isotonic saline as negative control. Intradermal tests (0.05 ml) with suspected drugs were performed on the upper arm in concentrations of 1:10.000 – 1:1 of commercially available sterile formulations for injections. Whenever a positive test was seen, a minimum of 20 control tests were performed to ensure that the test material was not irritant giving rise to unspecific reactions. Patch tests were performed using standard technique with Finn Chambers on Scanpor (Epitest Ltd Oy, Tuusula, Finland & Alpharma AS, Oslo, Norway) and pure drugs in 10%, pet./aq./eth. (Chemotechnique, Malmö, Sweden). Drugs not available in this formulation were tested using commercially available formulations of the drugs in 30% pet./aq./eth. (12). Patch tests were read on D3 and D5–7 according to ICDRG recommendations (13). Oral or intravenous drug challenge tests was performed according to history in dilutions of 1:10.000 – 1:1 of one therapeutic dosage, when all aforementioned tests were negative, unless contraindicated (14).

Prevalence rates were calculated for each department. Statistical analysis was performed using Fisher's exact test. The level of significance was set to 5%.

The study was approved by the regional ethical board (VF20020165) and informed written consent for all the diagnostic procedures was obtained from all patients.

RESULTS

The four visits yielded a cohort of 11,371 in- and out-patients. A total of 131 patients were referred for evaluation. Fifty-seven fulfilled inclusion criteria, 43 were included, whereas 14 did not agree to participate in the investigation programme. Eighteen of 43 completed the investigation programme and 21 withdrew consent prior to finalization. Four died prior to elective investigations (Fig. 1). The mean age of the included patients was 58 years (range 4–91 years). The sex-ratio (F/M) was 1.2 (16/13). The mean age of patients with established ACDR was 59.2 years, range 4–91 years and sex-ratio 1.3 (12/9).

Five of the 18 patients completing the investigation programme had positive tests (Table I). In 5 of 13 test negative cases, an ACDR was likely based on history, clinical examination, *in vitro* tests, and skin biopsy in spite of negative skin tests and drug challenge.

Among the 21 patients not completing the investigation, 7 were concluded to be drug-induced from history, clinical examination, *in vitro* tests and skin biopsy.

All 4 patients who died prior to elective investigations had an ACDR based on history, clinical examination, *in vitro* tests, and skin biopsy.

Eight of the 14 who initially did not consent to participate in the subsequent investigation programme had ACDR based on history and clinical examination alone (Fig. 1). Only demographic parameters of these patients have been included in the analysis. Imputability scores for the 57 patients evaluated were: certain/likely: 29 (56.7%) and possible/unlikely: 28 (43.3%).

The prevalence of ACDR was 0.33% (24/7192) among in-patients, 0.14% (6/4179) in out-patients, and the overall prevalence (in- and out-patients) 0.25% (29/11,371). The prevalence of ACDR varied between departments from 0% in most departments to 6.66% in the intensive care units (Table II).

The most common reactions were maculo-papular rashes or eczema. There was a large group of rarer reactions, each represented by single cases (Table III). In two cases the ACDR was responsible for hospitalization (toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS)). β-lactam antibiotics and chemotherapeutics were the most frequent eliciting agents (Table IV).
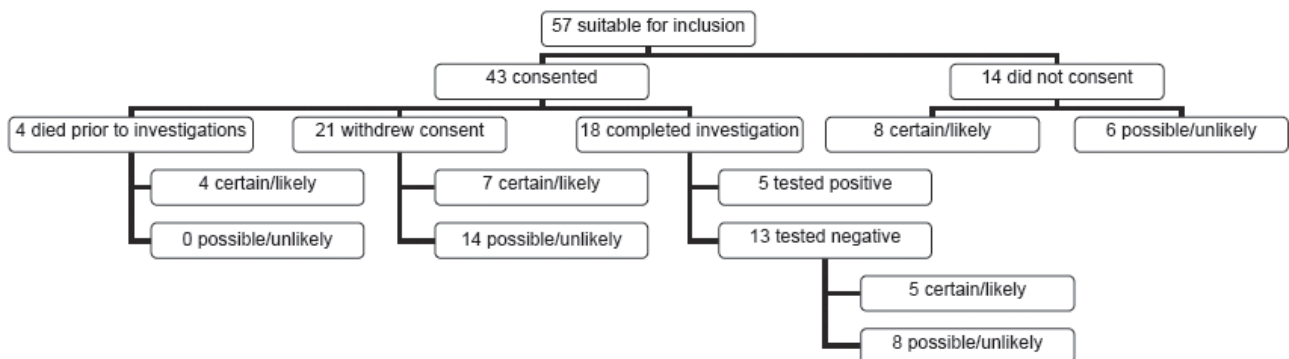
Fig. 1. Distribution of all patients included in the study.

Table I. *Positive tests in drug allergy investigations of patients with acute cutaneous drug reactions (ACDR) and controls (non-ACDR)*

	Number of positive tests (no. performed) in:	
	ACDR patients (n=21)	Non-ACDR patients (n=22)
Histopathology[a]	12 (17)	7 (16)
Tissue eosinophilia	13 (17)	6 (16)
Peripheral eosinophilia	7 (20)	3 (18)
S-tryptase	5[b] (21)	0 (17)
Specific IgE[c]	0 (29)	0 (16)
Histamine release[d]	0 (30)	2[e] (11)
Patch test	2[f] (74)	0 (68)
Skin prick test	0 (53)	0 (27)
Intradermal test	2[g] (26)	0 (11)
Drug challenge test	4[h] (24)	0 (13)

[a]Suggestive histopathology is defined as cutaneous drug reaction being suggested specifically in the report from the dermato-pathologist.
[b]Baseline tryptase was measured in 3 of the 5 cases (1 peri-orbital dermatitis, 2 eczema, 2 maculo-papular rashes) and was elevated in 2 diagnosed with sub-clinical mastocytosis. Values were between 15.9 and 33.3 µg/l. The remaining 2 patients died before re-test was feasible.
[c]CAP Pharmacia, Stockholm, Sweden.
[d]Two false-positive tests. Tests did not correlate with drug challenge test.
[e]Same patient.
[f]Ampicillin 1, amoxicillin 1.
[g]Lidocaine 1, citanest-octapressin 1.
[h]Cefuroxime 1, donepezil 1, peginterferon α-2a 1, topical lidocaine/prilocaine 1 (the same patient who had positive intradermal test).

Four patients with ACDR had a history of allergy or positive SPT to inhalant allergens, compared with one in the groups with lower drug imputability ($p = 0.18$). Three had a history of contact allergy or positive TRUE test, compared with three in the lower imputability groups ($p=1.00$). One patient with ACDR had both

Table III. *Acute cutaneous drug reactions by diagnosis*

Clinical diagnosis	n (%)	Drugs
Maculo-papular rashes	13 (44.8)	Ampicillin 3, chemo 2[a], cefuroxime 2, dicloxacillin 1, lamotrigine 1, pivampicillin 2, sulfamethizole 1
Eczema	4 (13.7)	Chemo 2, donepezil 1, lidocaine 1[a]
Urticaria	1 (3.4)	Cefuroxime
DRESS	1 (3.4)	Furosemide or allopurinol[a]
Erythema	2 (6.8)	5-flourouracil 1[a]
Hyperpigmentation	1 (3.4)	6-mercaptopurine or cytarabin
Local reaction	1 (3.4)	β-human chorionic gonadotropin
Palmo-plantar erythema	1 (3.4)	Cyclophosphamide
Peri-orbital dermatitis	1 (3.4)	Benzalkonium chloride
Psoriasis	1 (3.4)	Peginterferon α-2a
Purpura	2 (6.8)	Eptifibatid 1, heparin 1
TEN	1 (3.4)	Cefuroxime or ciprofloxacin
Total	29 (100)	

[a]A single culprit drug was not identified in altogether 6 cases.
DRESS: drug reaction with eosinophilia and systemic symptoms;
TEN: toxic epidermal necrolysis;
Chemo: chemotherapeutics.

inhalant allergy and contact allergy. Eight with ACDR stated previous reactions to drugs, compared with six in the lower imputability groups ($p=0.52$).

ACDR was more common among medical than surgical patients (Table II) ($p=0.03$), although significance was lost when in- and out-patients were evaluated separately. The prevalence varied between seasons: winter 10/2808 (0.35%), spring 9/2849 (0.31%), summer 9/2939 (0.30%), and autumn 1/2775 (0.03%). Thirty-six were referred in winter, 49 in spring, 27 in summer and 19 in autumn.

Twelve of 43 (28%) of the patients included, and 25% of the patients diagnosed with ACDR died within

Table II. *Prevalence of acute cutaneous drug reactions (ACDRs) in different departments*

Department	No. of ACDR	Prevalence		
		In-patients (%)	Out-patients (%)	Overall prevalence (%)
Cardiology	1	0.29	0	0.17
Gastroenterology, surgical	1	0.36	0	0.21
Geriatrics	4	1.51	0.52	1.56
Gynaecology/obstetrics	1	0.26	0	0.15
Haematology	3	3.15	0	1.48
Intensive care unit	3	6.66	0	6.66
Internal medicine	5	0.79	0.43	0.59
Nephrology	1	0	1.28	0.73
Neurology	1	0.62	0	0.22
Neurosurgery	1	2.27	0	0.59
Nuclear medicine	1	0.66	0	0.66
Oncology	2	0	1.30	0.22
Ophthalmology	1	0.33	0	0.30
Orthopaedics	1	0.19	0	0.11
Paediatrics	3	1.55	0	0.53
Medical, total[a]	11	0.48	0.27	0.39
Surgical, total[b]	5	0.44	0	0.22
Total	29	0.33	0.14	0.26

Departments not listed here which had no reactions: clinical psychology, dermatology, environmental medicine, ear nose and throat, adult psychiatry, and children's psychiatry.
[a]Medical departments: cardiology, endocrinology, medical gastroenterology, geriatrics, haematology, internal medicine, nephrology, neurology,
[b]Surgical departments: Dental surgery, surgical gastroenterology, neurosurgery, orthopaedics, plastic surgery, thoracic and vascular surgery, urology.

Table IV. *Drug groups implicated in acute cutaneous drug reactions*

Drug	*n* (%)
β-lactam antibiotics	12 (41.3)
Chemotherapeutics	5 (17.2)
Diuretics	2 (6.8)
Sulpha antibiotics	2 (6.8)
Quinolones	2 (6.8)
Anti-convulsives	1 (3.4)
Cytokines	1 (3.4)
β-human chorionic gonadotrophin	1 (3.4)
Donepezil	1 (3.4)
Local anaesthetics	1 (3.4)
Excipients	1 (3.4)
Total	29

6 months after the study period. No correlation between ACDR and the deaths could be established except in a single patient dying during the course of TEN.

Para-clinical investigations

Results from routine blood tests did not influence the final diagnosis of ACDR.

In 13 cases imputability was established based on history, histopathology and haematology, biochemistry and serology alone.

5 received chemotherapy and had reactions known from the literature (15). One received ampicillin during a PCR-confirmed Epstein-Barr viral infection. One had a maculo-papular rash from sulpha-methizole/trimethoprim and erythromycin treatment of a urinary tract infection, supported by histopathology and peripheral eosinophilia. One known penicillin-allergic patient had a maculo-papular rash during cefuroxime treatment of erysipelas, supported by histopathology and peripheral eosinophilia. One patient with epilepsy developed a maculo-papular rash on re-administration of her anticonvulsive drugs after having been admitted in a delirious state where lamotrigine and levetiracetam had been unintentionally paused. One patient developed a maculo-papular rash supported by histopathology and peripheral eosinophilia during treatment with penicillin and cefuroxime for erysipelas. One patient with known allergy to benzalconium chloride had periorbital dermatitis after treatment with eye drops preserved with benzalconium chloride and did not consent to finish the planned investigations. One patient with known allergy to sulphamethizole had a maculo-papular rash supported by histopathology and peripheral eosinophilia during accidental treatment of urinary infection with sulpha-methizole. One patient had a maculo-papular rash supported by histopathology and peripheral eosinophilia during pivampicillin treatment for the same reason.

One patient developed DRESS after increasing the daily dosage of furosemide to 320 mg but died from congestive heart failure prior to investigation. One patient with a history of hypersensitivity to cefuroxime and ciprofloxacin had TEN confirmed by histopathology during accidental treatment of severe gastroenteritis with both drugs but died prior to investigation.

For 8 included patients not consenting to any elective investigations, imputability was established on history and objective examination. One known penicillin allergic female geriatric patient developed a maculo-papular rash following cefuroxime treatment. One patient with mononucleosis developed a rash after ampicillin and amoxicillin treatment. One patient developed a maculo-papular rash during dicloxacillin treatment of a surgical wound after osteosynthesis of a traumatic fracture.

One trombocytopenic nephropatic patient developed purpura following heparinization of a central venous line. One comatose multi-traumatized patient developed generalized erythema after several operative procedures in general anaesthesia, prophylactic antibiotics, and radio-contrast injections. One HIV-positive patient developed a maculo-papular rash during ampicillin treatment of an abscess of the kidney. One patient with myelodysplastic syndrome developed a maculo-papular rash during pivampicillin treatment. One patient treated with β-hCG in the fertility clinic developed an eczematous local reaction at the site of injection overnight.

DISCUSSION

The prevalence of ACDR in in-patients was similar to data from a recent French study (7), and the most common reaction pattern was a maculo-papular rash. The most frequent eliciting drug group was the penicillins. Our findings on most common reactions and eliciting drugs are in agreement with previous reports (5, 6), where the prevalences were 2–3% (2.2 and 2.7, respectively) in medical in-patients. However, in our study the prevalence in medical in-patients was 0.33%. The rate of ACDR was highest in the intensive care units and the departments of haematology and geriatrics.

Seasonal variation in the prevalence has been described, with a peak in winter (7). This could not be confirmed in this study.

Sex ratios with a predominance of female patients have been described (16), as has predominance of males (7).

We found no over-representation of patients with previously diagnosed allergies among the patients with ACDR, although higher prevalences of atopic symptoms in patients with a previous systemic drug reaction have been reported (17).

The prevalence of ACDR in out-patients was low, as expected. Little has been published on CDR in out-patients. Apaydin et al. (18) reported an incidence of CDR in out-patients of 1.2% and 0.1% in in-patients. This is contrary to our findings.

Only 2 patients in this study developed severe reactions (DRESS and TEN). The rare occurrence is in agreement with other reports (5, 18–20), but in contrast to the study by Fiszenson-Albala et al. (7), who found 34% severe eruptions in their 48 cases.

The differences in prevalence of specific ACDR and eliciting drugs between the present and other studies is probably explained by differing pharmaco-therapeutic cultures across countries and even hospitals. Thus, caution is advocated when attempting to superimpose conclusions from one part of the world into the context of another.

The number of tested patients with high drug imputability is too small for meaningful values for sensitivity and specificity to be calculated for any of the diagnostic procedures compared with the imputability analysis. Furthermore, each individual test is used in determining imputability, which makes validation of the individual test problematic. The value of the diagnostic tests was

disappointingly small, with only 2/74 positive patch tests, 0/53 skin prick tests and 2/26 intradermal tests among 43 ACDR patients. While the tests may be of value in the investigation of specific reactions, we were unable to prove them of value in routine testing. This is perhaps due to the fact that reactions where some of these tests are validated were too few. Since test results were used in establishing imputability, calculations of sensitivity, specificity, and predictive values would be biased. However, there is no tendency towards a significant diagnostic power for any of the procedures. Barbaud et al. (19) found that 72% could be diagnosed by patch tests, SPT, and intradermal tests. Only 2 of our patients were diagnosed by skin testing. Specific IgE, histamine release, and SPT yielded no true positive results. Drug challenge test gave the most positive reactions, confirming its place in drug allergy testing (14). However, 4 patients were diagnosed with ACDR in spite of a negative drug challenge test. False negative reactions are possible in delayed type reactions if only skin tests and drug challenge tests lasting one day are performed, as was the case in this study (21). Other tests, such as the lymphocyte stimulation test, have been employed in the investigation of drug allergies. However, this test was not available to us.

The possible sources of bias in the present study are numerous: a relatively high number of patients dropped out. These may have been the most severely affected or the most severely ill (selection bias). Selection also took place at the level of diagnosis: due to the short observation period in each department, patients with rashes of a relatively long duration are relatively over-represented compared with patients suffering from shorter lasting rashes, such as urticaria or angioedema. Also, referral bias may have occurred on two levels: non-dermatologically trained physicians and nurses may have failed to recognize mild eruptions, and referring doctors and nurses may have failed to refer relevant patients, despite an exhaustive information and motivation campaign in all participating departments. Physicians may have been more likely to monitor patients with histories of drug allergy, and investigators looking explicitly for ACDR may have been more likely to decide for ACDR in patients where imputability is not sufficient (diagnostic suspicion bias).

The evaluation of CDR is complex. The imputability concept of "The French Pharmaco-Vigilance System" (10) is systematic and clearly specifies individual factors of importance for the establishment of drug imputability, but are not to be confused with diagnostic criteria for ACDR. However, while the imputability concept states how intrinsic and extrinsic factors are weighted against each other, it neither states how much weight individual test results have, nor says anything about the quality and amount (or lack) of literature on similar reactions. In our experience this may cause inter-observer differences in the evaluation of suspected ACDR cases.

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