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ORIGINAL RESEARCH ARTICLE

Cutaneous Adverse Drug Reactions in the Elderly: a Retrospective Analysis in Thailand

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Abstract

Background Elderly people tend to be sicker than young people. They also take more medications, increasing the risk of adverse drug reactions (ADRs), which are one of the leading causes of morbidity and mortality in this age group. Knowledge of cutaneous ADRs from medicine use in the elderly population is limited.

Objective The aim of this study was to investigate demographic data, causative drugs and cutaneous manifestations of ADRs in elderly patients.

Methods A retrospective analysis was conducted involving elderly patients aged >60 years with cutaneous ADRs in the period from 2002 to 2012. We analyzed data with respect to demographic data, clinical data, outcomes, and risk factors for serious reactions.

Results A total of 400 patient records were included. The mean age was 73.6 years, and 53 % were women. The common reactions were maculopapular rash (65 %) and angioedema with/without urticaria (11.3 %). Antibiotics (42.8 %) and non-steroidal anti-inflammatory drugs (9.5 %) were common causative drugs. Serious cutaneous ADRs were found in 16.5 %.

Conclusion Our results show that multiple underlying medical conditions, especially cerebrovascular diseases, are risk factors for serious cutaneous ADRs in elderly patients. These findings emphasize the need for awareness about cutaneous drug reactions in elderly patients.

Key Points

Antibiotics, followed by non-steroidal anti-inflammatory drugs, were found to be the most frequent causative agents in cutaneous adverse reactions in elderly patients.

Maculopapular rash is the most common cutaneous adverse drug eruption in elderly patients.

Multiple underlying diseases, especially cerebrovascular diseases, are risk factors for serious cutaneous adverse reactions in elderly patients.

1 Introduction

Nowadays, the number of people aged older than 60 years old is increasing worldwide. The prevalence of illness, especially for chronic diseases, is also high in the elderly; many people in this age group are likely to have several health problems that require medication for the rest of their lives. The incidence of adverse drug reactions (ADRs) was significantly higher in the elderly than in other age groups, perhaps because these elderly patients are often sicker and require more medications [1, 2]. A previous published study showed that 20–40 % of elderly patients use at least five medications, so called polypharmacy or multiple-drug therapy [3], which may increase the risk of ADRs, morbidity and mortality [4, 5]. Furthermore, the pathological and physiological processes of aging are important factors

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that can directly impact ADRs in the elderly [6–8]. Thirty-seven percent of the patients with ADRs in the emergency department were over 65 years old. Moreover, 3–5 % of elderly inpatients were admitted because of ADRs [9, 10]. Although many studies about correlations between age and ADRs have been reported, the data on elderly patients with cutaneous ADRs are still limited [3–6, 8–13]. Therefore, the aim of this study was to investigate demographic data, causative drugs and cutaneous manifestations of ADRs in elderly patients.

2 Methods

This study was approved by the Siriraj Institutional Review Board, Siriraj Hospital, Mahidol University, Bangkok, Thailand. We retrospectively reviewed the data records of patients who were diagnosed as having cutaneous ADRs at the ADR center of Siriraj Hospital between January 2002 and February 2012. A total of 3,571 patients diagnosed as having cutaneous ADRs were reviewed. Patients aged older than 60 years old were classified as elderly, as per the World Health Organization's (WHO's) definition, and were included in this study [14]. The exclusion criteria were as follows: missing important information, including underlying diseases, causative drugs, and the causality assessment levels. The cutaneous reactions were diagnosed by attending physicians and dermatologists together with well-trained pharmacologists from the ADR center to identify the causality assessment levels—certain, probable, possible, unlikely, unclassified and unclassifiable—according to the WHO guidelines [15].

1. *Certain* means that the adverse reaction has occurred during the time period corresponding with the drug usage. In addition, the reaction could not be explained by pre-existing disease, other concomitantly used drugs or other chemical substances. Furthermore, the adverse reaction obviously improved or disappeared after the patient stopped using the drug, but recurred after they started using it again. Thus, the pharmacological mechanism of the adverse event is clearly evident as an explanation.
2. *Probable* means that the adverse reaction has occurred during the time period corresponding with the drug usage and is probably not associated with pre-existing disease, concomitantly used drugs or other chemical substances. When the patient stopped using the drug, the adverse reaction improved or disappeared. However, information about repeat drug use may not be available.
3. *Possible* means that the adverse reaction has occurred during the time period corresponding with the drug use, but may be explained by pre-existing disease, concomitantly used drugs or other chemical substances. Information about the patient stopping use of the drug is not complete or is not available.
4. *Unlikely* means that the adverse reaction has occurred during a time period that does not correspond with the drug use and may be explained by pre-existing disease, concomitantly used drugs or other chemical substances.
5. *Unclassified* means that more data are essential for a proper assessment or that the additional data are under examination.
6. *Unclassifiable* means that the information available is insufficient or contradictory and does not allow a judgment to be made about the relationship between the health product and the adverse event. Data cannot be supplemented or verified.

Demographic data including history of food allergy, atopy, underlying diseases, current medications, and history of previous cutaneous ADRs were collected. Patients who received five or more drugs were defined as having multiple-drug therapy. The cutaneous manifestations were classified into two groups: serious cutaneous reactions and non-serious cutaneous reactions. Angioedema with or without urticaria, drug hypersensitivity syndrome, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), anaphylaxis, acute generalized exanthematous pustulosis (AGEP) and drug-induced vasculitis were considered to be serious drug reactions [16]. The clinical course of cutaneous reactions and the causative drugs were also recorded.

2.1 Statistical Analysis

Demographic data, clinical characteristics, management and outcome were analyzed by descriptive analysis. The Chi-squared test and Fisher's exact test were used for the categorical data. The Mann–Whitney *U* test was used in a comparison of median time and duration data between serious and non-serious reactions. Odds ratios were calculated if the clinical data were significant. A *P* value of < 0.05 was considered to be statistically significant. Predictive Analytics SoftWare (PASW), version 18.0, Statistical Package for the Social Sciences (SPSS) Inc., Chicago, IL, USA, was used for the statistical analysis in this study.

3 Results

Patient records for 400 patients diagnosed as having cutaneous ADRs were identified. The mean age was 73.6 ± 6.6 years (range 62–96 years). Females (53 %) had a minimal higher prevalence of cutaneous reactions than

males (47 %). Of the 95 patients whose data on atopy were accessible, 24.2 % had a history of atopic diathesis. Eighty percent of the patients had underlying diseases. The most common underlying disease was hypertension (53.2 %), followed by dyslipidemia (28.8 %) and cancer (23.8 %). Fifty-four percent of the patients received multiple-drug therapy (five or more medications), while 18 % of the patients received a single drug. Sixteen percent of the patients had a previous history of cutaneous ADRs, which manifested as maculopapular (MP) rash (73.4 %) and angioedema (12.5 %), respectively. HIV test were performed in 114 patients (28.5 %) and revealed positive results in two patients (0.5 %) (Table 1). Table 2 demonstrates cutaneous ADRs of 400 patients. By using the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) causality categories assessment, 80.2 %, 18.2 % and 1.5 % of 400 patients had their reactions classified as possible, probable and certain classification, respectively. MP rash was the most common (65 %), followed by angioedema with or without urticaria (11.3 %) and urticaria alone (8 %).

All causative drugs are shown in Table 3. The most common causative drugs were antibiotics (42.8 %), non-steroidal anti-inflammatory drugs (NSAIDs) (9.5 %) and contrast medias (9.3 %). Cephalosporins, penicillins and quinolones were the three most common antibiotics causing cutaneous ADRs in elderly patients. In the NSAIDs drug group, cyclooxygenase (COX)-II inhibitors were more likely to cause cutaneous reactions than COX-I inhibitors.

Regarding patients with MP rash, both males and females were affected equally (Table 4). The mean age was 73.8 ± 6.6 years. Only 11.9 % of the patients had previous cutaneous ADRs. The median duration from drug intake to the reaction was 3 days, ranging from immediately to 3 months. Most of the patients had no mucosal or systemic involvement. Antibiotics were the most frequent drugs causing MP rash, which affected about half of the patients (48.1 %) in this group. Most of the patients (93.1 %) had complete recovery, with a median time of improvement of 3 days and no death in this group.

Regarding patients with angioedema (with or without urticaria) and urticaria alone, females (61 %) showed a higher prevalence than males (39 %). Previous cutaneous ADRs were detected in 35.1 % of either angioedema or urticaria patients, a prevalence three times greater than that in the MP rash patients. Antibiotics (39 %), NSAIDs (16.9 %) and contrast media (16.9 %) were the most frequent causative drugs. The reactions occurred immediately or up to 30 days after the drug administration. Almost a quarter of patients (24.7 %) had systemic involvements. Two patients (2.6 %) needed intramuscular adrenaline injection because of anaphylaxis. Most of the patients (96.1 %) had complete recovery; two patients (2.6 %) died (Table 4).

Serious cutaneous ADRs were detected in 16.5 %. There was no significant difference between male and female patients with respect to the severity of cutaneous ADRs in the elderly patients (Table 5). Histories of atopy and food allergy did not affect the severity of reactions, nor did multiple-drug therapy. On the other hand, patients with previous cutaneous ADRs had a significantly higher chance of having serious cutaneous ADRs ($P = 0.002$, odds ratio 2.6). The durations from drug intake to the event were 2 and 3 days for serious and non-serious cutaneous reactions, respectively. The most common causative drugs of severe ADRs were antibiotics (27.3 %), followed by NSAIDs (21.2 %), contrast media (10.6 %) and anti-convulsants (9.1 %), respectively. Antibiotics (45.8 %), contrast media (9.0 %), anti-hypertensives (7.8 %) and NSAIDs (7.2 %), respectively, were the most common causative drugs of non-severe ADRs. From univariate analysis, patients with liver and cerebrovascular diseases had a higher risk of serious cutaneous ADRs than non-serious cutaneous ADRs ($P = 0.048$ and 0.02, respectively), but multivariate analysis showed that only cerebrovascular diseases posed a risk regarding experiencing serious cutaneous reactions ($P = 0.048$). In addition, patients with multiple underlying diseases have an increased risk of severe cutaneous ADRs ($P = 0.007$). About 40 % of patients with serious cutaneous reactions and 3 % of patients with non-serious cutaneous reactions were admitted ($P < 0.0001$). Moreover, 4.6 % of serious cutaneous ADR patients passed away, which was a significantly worse outcome than that seen in the non-serious cutaneous reactions group ($P = 0.03$) (Table 5).

4 Discussion

Cutaneous ADRs are important problems in elderly patients. Elderly patients show the highest prevalence rate of cutaneous ADRs per 1,000 new referrals (13.6/1,000 new referrals) [17]. Females are usually the predominate gender that experience ADRs in many studies in all age group as well as in this study [2, 11, 18–20]. Similar to other studies, atopic diathesis was not a predisposing factor for drug hypersensitivity [21, 22]. In this study, we could not find any association between history of atopy and any specific types of reactions. The number of underlying diseases was reported as the significant risk factor for ADRs [23]. Most patients in this study had underlying diseases, and 78.2 % of these patients have more than one underlying disease. The number of prescribed medications has previously been reported as an ADR risk factor [3, 9, 12, 13, 20]. Compared with the US population, Thai elderly patients in this study took multiple-drug therapy more than US patients did (54 and 20 %, respectively) [24, 25].

Table 1 Demographic and clinical data of elderly patients with cutaneous adverse drug reactions

Characteristics	No. of patients (%)[a]
Gender	
Male	188 (47.0)
Female	212 (53.0)
Age	
Mean age (range)	73.6 ± 6.6 years (62.0–96.0)
History of atopy ($N = 95$)	23 (24.2)
Asthma	16 (16.5)
Allergic rhinitis	11 (11.5)
Allergic conjunctivitis	4 (4.2)
Atopic dermatitis	3 (3.1)
Underlying disease[b] ($N = 400$)	
Hypertension	213 (53.2)
Dyslipidemia	115 (28.8)
Cancer	95 (23.8)
Diabetes mellitus	89 (22.2)
Heart diseases	78 (19.5)
Cerebrovascular diseases	41 (10.2)
Renal diseases	33 (8.2)
Gastrointestinal diseases	18 (4.5)
Liver diseases	14 (3.5)
None	87 (21.8)
Current medicine ($N = 400$)	
1 current medication	72 (18.0)
2–4 drugs therapy	112 (28.0)
≥5 drugs therapy (multidrug therapy)	216 (54.0)
History of previous cutaneous adverse drug reactions ($N = 400$)	
Have history of previous cutaneous adverse drug reaction	64 (16.0)
Maculopapular rash	47/64 (73.4)
Angioedema	8/64 (12.5)
Urticaria	4/64 (6.3)
Exfoliative dermatitis	2/64 (3.1)
Stevens-Johnson syndrome/toxic epidermal necrolysis	1/64 (1.6)
Pruritus	1/64 (1.6)
No history of previous cutaneous adverse drug reactions	336 (84.0)
HIV status ($N = 400$)	
Positive	2 (0.5)
Negative	112 (28.0)
Unknown	286 (71.5)
Patients visited ($N = 400$)	
Outpatient department	282 (70.5)
Inpatient department	118 (29.5)

HIV human immunodeficiency virus

[a] Unless otherwise stated

[b] Patient might have more than one underlying disease

Perhaps, Thai elderly patients have a greater chance of taking non-prescribed medications, which may affect the risk of ADRs.

Similar to general populations, most patients had non-serious and non-life-threatening conditions. MP rash was the most frequent cutaneous ADR, followed by urticaria and/or angioedema [26–28]. For MP rash, the median duration from drug intake to the event was 3 days, which was shorter than that previously reported in Thai patients (older than 15 years old) (9 days) [28]. Drug detoxification and elimination in elderly patients may be slower because of the age-related decline in liver and renal function, which may cause a rise in drug levels [29]. The faster rising of drug levels in the circulatory system may induce ADRs earlier in the elderly than in general populations. Elderly patients with MP rash had a similarly good outcome to those of other age group patients with MP rash [28].

Angioedema and urticaria rank as second and third most frequent reactions in this study, similar to previous reports [30]. Drug-induced angioedema can be associated with urticaria in about 50 % of patients and may be followed by a serious, life-threatening conditions such as anaphylaxis [31]. We found that angioedema and urticaria were more common in females and approximately one-third of urticaria and/or angioedema patients had experienced previous cutaneous ADRs, which is similar to previously reported data in patients older than 18 years of age with drug-induced urticaria [32]. Chen et al. [33] reported females tend to have more frequent anaphylaxis, urticaria and angioedema induced by drugs than men. However, some studies found no significant difference between genders [33–35].

A previous study in China reported that allopurinol was the most common causative drug in cutaneous ADRs in the elderly [36]. However, the patterns of cutaneous ADRs may vary greatly between countries. Similar to the results of a previous study in Thai patients older than 15 years of age in 2005 [28], antibiotics and NSAIDs were responsible for most of these eruptions, which accounted for more than 50 % of all of the reported ADRs. Cephalosporins were more frequent causative drugs than penicillins. This can be explained by the fact that our study was performed in a tertiary hospital in which third-generation cephalosporins were frequently prescribed and penicillins were not widely used. NSAIDs, including aspirin, were the second most frequent drug group causing cutaneous reactions. Kasemsarn et al. [37] studied cutaneous reactions to NSAIDs; ibuprofen, diclofenac (COX-I inhibitors) and celecoxib (COX-II inhibitor) were the most frequent drugs causing cutaneous reactions in Thai patients (mean age 47.9 years). Our study revealed that COX-II inhibitors were a little more frequent than COX-I inhibitors, which may be explained by the risk of gastrointestinal irritation in elderly

Table 2 Cutaneous manifestations of adverse drug reactions in the elderly

	No. of patients (%)
Cutaneous adverse drug reactions ($N = 400$)	
Maculopapular rash	260 (65.0)
Angioedema	45 (11.3)
Angioedema alone	41 (10.3)
Angioedema with urticaria	4 (1.0)
Urticaria alone	32 (8.0)
Pruritus	22 (5.5)
Erythema multiforme	8 (2.0)
Exfoliative dermatitis	8 (2.0)
Stevens-Johnson syndrome/toxic epidermal necrolysis	6 (1.5)
Drug hypersensitivity syndrome	6 (1.5)
Photosensitive dermatitis	6 (1.5)
Fixed drug eruption	4 (1.0)
Vasculitis	1 (0.2)
Bullous pemphigoid	1 (0.2)
Acute generalized exanthematous pustulosis	1 (0.2)
WHO-UMC causality	
Certain	6 (1.5)
Probable	73 (18.2)
Possible	321 (80.2)

WHO-UMC World Health Organization–Uppsala Monitoring Centre

patients. Physicians might favor prescribing COX-II inhibitors over COX-I inhibitors. Rutnin et al. [32] has studied drug-induced urticaria in Thai patients (mean age 44.8 years, range 18–82 years); antibiotics, NSAIDs, opioids and muscle relaxants were the four most frequent causative drugs. In this study, contrast media and anti-secretory acid agents were more frequent than opioids; this can be explained by the different frequency of drug use between the elderly and younger adults. Because of a high prevalence of illness, elderly patients need radiocontrast agents for investigations, and anti-secretory acid agents are usually prescribed for patients who have gastric diseases or are receiving anti-platelet drugs and NSAIDs. Our data demonstrated that NSAIDs were the causative agents in 21.2 % of patients with severe cutaneous reactions, but only 7.2 % of patients with non-severe cutaneous ADRs. Patients with cutaneous ADRs to NSAIDs have a higher chance of severe reactions than of non-severe cutaneous ADRs. Angioedema was the cutaneous manifestation in 13 of 14 patients with severe cutaneous reactions to NSAIDs.

Compared with a previous study in Thai patients older than 15 years, the rate of serious cutaneous ADRs in the elderly was higher (8 and 16.5 %, respectively). We also classified patients into two age groups and found no

Table 3 Causative drugs causing cutaneous adverse drug reactions in elderly patients

Characteristics	No. of patients (%)
Antibiotics	171 (42.8)
Cephalosporins	50 (12.5)
Ceftriaxone	21
Cefazolin	12
Ceftazidime	6
Cephalexin	4
Cefoperazone	2
Cefaclor	1
Cefepime	1
Cefoxitin	1
Cefditoren	1
Cefdinir	1
Penicillins	31 (7.8)
Piperacillin/tazobactam	8
Dicloxacillin	7
Amoxycillin	6
Amoxycillin/clavulanic acid	4
Penicillin	4
Cloxacillin	1
Ampicillin/sulbactam	1
Quinolones	30 (7.5)
Ciprofloxacin	18
Ofloxacin	6
Levofloxacin	5
Norfloxacin	1
Glycopeptide	14 (3.5)
Vancomycin	13
Teicoplanin	1
Lincosamide	10 (2.5)
Clindamycin	10
Carbapenem	18 (4.5)
Meropenem	10
Imipenem/cilastatin	4
Imipenem	3
Ertapenem	1
Sulfonamides	5 (1.3)
Trimethoprim/sulfamethoxazole	3
Sulfadiazine	2
Aminoglycoside	3 (0.8)
Gentamicin	1
Amikacin	1
Streptomycin	1
Macrolide	3 (0.8)
Clarithromycin	3
Polymixin	3 (0.8)
Colistin	3
Tetracyclines	2 (0.5)
Tetracycline	2
Nitroimidazoles	2 (0.5)
Metronidazole	2

Table 3 continued

Characteristics	No. of patients (%)
NSAIDs	38 (9.5)
COX-I inhibitors	17 (4.2)
Aspirin	4
Diclofenac	4
Ibuprofen	4
Mefenamic acid	2
Naproxen	1
Piroxicam	1
Loxoprofen	1
COX-II inhibitors	21 (5.2)
Celecoxib	8
Etoricoxib	7
Nimesulide	4
Meloxicam	2
Contrast media	37 (9.3)
Iopromide	26
Iobitridol	5
Iohexol	3
Ioxaglate	2
Iodixanol	1
Anti-hypertensives	28 (7.0)
Calcium channel blocker	
Amlodipine	8
Manidipine	2
Nifedipine	1
Cinnarizine	1
Felodipine	1
Diuretic	
Furosemide	4
Hydrochlorothiazide	2
Hydrochlorothiazide/amiloride	1
ACEI	
Enalapril	3
Beta-blocker	
Atenolol	1
Propanolol	1
ARB	
Olmesartan	1
Lorsartan	1
Alpha-1 blocker	
Doxazocin	1
Opioids	27 (6.8)
Tramadol	21
Morphine	4
Fentanyl	1
Pethidine	1
Anti-convulsant	23 (5.8)
Phenytoin	17
Carbamazepine	2
Sodium valproate	2
Gabapentin	1
Pregabalin	1

Table 3 continued

Characteristics	No. of patients (%)
Gastric antisecretories	20 (5.0)
Omeprazole	12
Esomeprozole	3
Pantoprazole	2
Ranitidine	2
Rabeprazole	1
Anti-gout	9 (2.3)
Allopurinol	9
Anti-cancer	7 (1.8)
Oxaliplatin	2
Methotrexate	1
Carboplatin	1
Cyclophosphamide	1
Imatinib	1
Thalidomide	1
Lipid-lowering agents	5 (1.3)
Simvastatin	4
Atorvastatin	1
Anti-diabetic medications	3 (0.8)
Gliclazide	1
Glipizide	1
Pioglitazone	1
Anti-fungals	3 (0.8)
Amphotericin B	1
Caspofungin	1
Clotrimazole	1
Anti-psychotics	3 (0.8)
Quetiapine fumarate	1
Haloperidol	1
Imipramine	1
Miscellaneous	26 (6.5)
Paracetamol	3
Rifampicin	3
Domperidone	3
Pseudoephedrine	2
Lidocaine	2
Albumin	1
Tolterodine tartrate	1
Isosorbide dinitrate	1
Orphenadrine	1
Tolperisone	1
Cyproheptadine	1
Warfarin	1
Vitamin D	1
Anti-glaucoma eye drop	1
Finasteride	1
Bisphosphonate	1
Permixon	1
Leuprorelin	1

ACEI angiotensin-converting-enzyme inhibitor, *ARB* angiotensin II receptor blockers, *COX* cyclooxygenase, *NSAIDs* non-steroidal anti-inflammatory drugs

Table 4 Demographic data and clinical course of two most common cutaneous adverse drug reactions in the elderly

Characteristics	Reaction			
	Maculopapular rash ($N = 260$), N (%)[a]		Angioedema with or without urticaria and urticaria alone ($N = 77$), N (%)[a]	
Sex				
Male	126 (48.5)		30 (39.0)	
Female	134 (51.5)		47 (61.0)	
Age (years)				
Mean age (range)	73.8 ± 6.6 (62.0–96.0)		74.2 ± 6.1 (63.0–94.0)	
Multidrug therapy (≥5 drugs)	140 (53.8)		36 (46.8)	
Previous drug allergy	31 (11.9)		27 (35.1)	
Duration from drug intake to cutaneous reaction				
Median duration (range) (days)	3 (immediate–90)		1 (immediate–30)	
Mucosal involvement	3 (1.2)		5 (6.5)	
Systemic involvement	9 (3.5)		19 (24.7)	
Common causative drugs				
	Antibiotics	125 (48.1)	Antibiotics	30 (39.0)
	NSAIDs	21 (8.1)	NSAIDs	13 (16.9)
	Anti-hypertensives	21 (8.1)	Contrast media	13 (16.9)
	Opioids	20 (7.7)	Gastric antisecretories	5 (6.5)
	Contrast media	18 (6.9)	Opioids	4 (5.2)
	Others	55 (21.1)	Others	12 (15.5)
Treatment				
Antihistamine	184 (70.8)		61 (79.2)	
Systemic steroids	37 (14.2)		30 (39.0)	
Topical steroids	88 (33.8)		9 (11.7)	
Emollient	18 (6.9)		0 (0)	
Adrenaline	0 (0)		2 (2.6)	
No treatment	61 (23.5)		13 (16.9)	
Outcome				
Completely recover	242 (93.1)		74 (96.1)	
Loss to follow-up	18 (6.9)		1 (1.3)	
Death	0 (0)		2 (2.6)	
Time of improvement				
Median (range) (days)	3 (1–30)		1 (1–10)	

NSAIDs non-steroidal anti-inflammatory drugs

[a] Unless otherwise stated

significant difference between patients aged younger or older than 75 years old. Gender and age were not factors affecting the severity of reactions in this study. Patients aged younger than 75 years old were not more likely to develop serious reactions than older elderly. Bruneau et al. [38] has studied the ADRs in the elderly in France and revealed similar results to our study, that there were no differences in past history, severity of effects or medications between age groups.

Pharmacodynamics and pharmacokinetics also change in the elderly [29]. The age-related decline in renal function in elderly patients may also predispose them to exaggerated ADRs. A previous study found that one-third of ADRs in elderly patients were related to renal impairment, especially in very old women. However, most of the patients in that study had non-cutaneous reactions [19]. Another study has also shown that renal dysfunction was a predictor for ADRs among elderly patients [13]. However, we could not find significant differences in renal impairment in severe or non-severe cutaneous ADRs. The correlation between liver disease and the risk of ADRs is still controversial [39–42]. Despite the univariate analysis showing a higher risk for elderly liver dysfunction patients developing cutaneous ADRs, the multivariate analysis did

Table 5 Demographic and clinical data in elderly patients with serious and non-serious cutaneous adverse drug reactions

	Serious adverse drug reaction ($N = 66$), N (%)[a]	Non-serious adverse drug reaction ($N = 334$), N (%)[a]	P value, univariate analysis	P value, multivariate analysis
Sex			0.278	
Male	27 (40.9)	161 (48.2)		
Female	39 (59.1)	173 (51.8)		
Age (years)				
Mean age	72.8 ± 6.2	73.8 ± 6.6	0.25	
Age group			0.21	
62–75	47 (71.2)	211 (63.2)		
76–96	19 (28.8)	123 (26.8)		
History of atopy ($N = 95$)	5 (26.3)	18 (23.7)	0.81	
History of food allergy with cutaneous reaction ($N = 400$)	0 (0)	7 (2.1)	0.60	
Multidrug therapy	36 (54.5)	180 (53.9)	0.92	
Previous drug allergy	19 (28.8)	45 (13.5)	0.002* (OR = 2.60, 1.39–4.82)	
Median duration from drug intake (range) (days)	2 (immediate–60)	3 (immediate–300)	0.02*	
Underlying disease				
Hypertension	41 (62.1)	172 (51.5)	0.11	
Dyslipidemia	24 (36.4)	91 (27.2)	0.14	
Coronary heart disease	13 (19.7)	65 (19.5)	0.97	
Diabetes	18 (27.3)	71 (21.3)	0.28	
Renal diseases	4 (6.1)	29 (8.7)	0.48	
Liver diseases	5 (7.6)	9 (2.7)	0.048*	0.14
Cerebrovascular diseases	12 (18.2)	29 (8.7)	0.02* (OR = 2.33, 1.12–4.86)	0.048*
Gastrointestinal diseases	4 (6.1)	14 (4.2)	0.50	
Malignancy	17 (25.8)	78 (23.4)	0.68	
No underlying disease	7 (10.6)	80 (24.0)	0.02* (OR = 2.65, 1.17–6.04)	
Underlying diseases ≥2 diagnosis	43 (65.2)	157 (47.0)	0.007* (OR = 2.13, 1.22–3.70)	
Department visited			0.47	
Inpatient department	17 (25.8)	101 (30.2)		
Outpatient department	49 (74.2)	233 (69.8)		
Admission (outpatients only; $N = 282$)			<0.0001*	
Admitted	19/49 (38.8)	6/233 (2.6)		
Not admitted	30/49 (61.2)	227/233 (97.4)		
Outcome ($N = 372$)			0.03*	
Completely recover	62 (95.4)	304 (99.0)		
Death	3 (4.6)	3 (1.0)		

Serious drug reactions: angioedema with or without urticaria, drug hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, acute generalized exanthematous pustulosis, vasculitis

OR odds ratio

* $p < 0.05$

[a] Unless otherwise stated

not show a risk of developing severe skin reactions in patients with liver impairment. Multivariate analysis showed that cerebrovascular disease was the only independent predictor of severe cutaneous ADRs. Gravante et al. [43] demonstrated an increasing frequency of TEN in patients with cancer. With regard to the limited number of TEN patients in our study, we did not find this correlation. Only one of six TEN patients in our study had cancer. In addition, we found that the patients suffering from multiple conditions had a higher risk of developing severe cutaneous ADRs. In this study, the number of drugs used was not significantly associated with the severity of cutaneous ADRs.

A previous study showed that HIV-positive patients were more prone to cutaneous drug reactions than the general population [44]. In this study, data about HIV status were limited. We could not draw any conclusions about the association between HIV status and cutaneous ADRs in elderly patients.

5 Conclusion

Cutaneous ADRs are important problems in elderly patients. Changes in drug pharmacodynamics and pharmacokinetics in this age group may predispose patients to more frequent or severe ADRs. Monitoring elderly patients for cutaneous ADRs may be helpful to decrease the occurrence and the severity of reactions.

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