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Incidence and risk factors for cutaneous adverse drug reactions in an intensive care unit†

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ABSTRACT

Objective. To evaluate the incidence of adverse cutaneous drug reactions in intensive care unit patients. **Design.** Cohort study. **Setting.** General adult intensive care unit of an institutional tertiary care hospital. **Patients.** Patients in the intensive care unit during a consecutive 8-month period were examined for adverse cutaneous drug reactions. **Results.** Patients in the intensive care unit have an incidence of 11.6% of adverse cutaneous drug reactions. Associated risk factors were female gender, obesity, age over 60 and immune dysregulation (systemic lupus erythematosus, dysthyroidism, and antiphospholipid antibodies syndrome). Few patients had previous history of adverse cutaneous drug reactions. Antimicrobials were the main drug involved. Morbilliform rash followed by urticary were the most frequently observed reactions. Interestingly, over 50% of patients with massive edema –independent of etiology– died. **Conclusions.** Intensive care unit patients are particularly at risk for developing an adverse cutaneous drug reaction.

Key words. Cutaneous drug reactions. Hospital epidemiology. Intensive care unit.

Incidencia y factores de riesgo en las reacciones adversas medicamentosas de tipo cutáneo en la unidad de cuidados intensivos

RESUMEN

Se realizó un estudio de cohorte en la Unidad de Terapia Intensiva (UTI) de un hospital de tercer nivel para evaluar la incidencia de reacciones cutáneas adversas a drogas. Se examinaron todos los pacientes internados en dicha unidad durante un periodo consecutivo de ocho meses. Observamos una incidencia de reacciones adversas a medicamentos de 11.6%. Los factores de riesgo asociados fueron sexo femenino, obesidad, edad mayor a 60 años y alteraciones inmunológicas (lupus eritematoso sistémico, distiroidismo y síndrome de antifosfolípido). Los antimicrobianos fueron los principales medicamentos involucrados. La erupción morbiliforme y la urticaria fueron las reacciones más frecuentes. Un hallazgo interesante fue que más de 50% de los pacientes con anasarca fallecieron. Concluimos que los pacientes internados en la UTI son particularmente susceptibles para desarrollar una reacción adversa cutánea a medicamentos.

Palabras clave. *Farmacodermias. Epidemiología hospitalaria. Terapia intensiva.*

INTRODUCTION

Adverse cutaneous drug reactions (ACDR) occur in approximately 2%-6% of all patients treated;[1-6] morbilliform rashes represent the majority of ACDR (95%), followed by urticaria (5%).[7-11] Although virtually any drug is capable of eliciting an adverse cutaneous reaction, the most frequently implicated agents are antimicrobials and non-steroidal anti-inflammatory drugs (NSAID)[3,6,7,12-15] Although the latency period for presenting an ACDR is variable, most reactions appear within the first week of treatment.[7] Thirty percent of patients hospitalized for over a month present at least one cutaneous reac-

† Note: We have recently been advised that this project was chosen by the International Student Research Foundation as one of the five finalists among 396 International Research Projects.

tion following drug administration[2,16] and this results in longer hospital stay, greater cost, and almost twice the morbidity than for the rest of the hospitalized population. Severe ACDR were the fourth cause of death among hospitalized patients in the United States in 1994 and its incidence has remained stable during the last 30 years.[10,11,17]

The most frequent underlying predisposing factors for the presentation of ACDR are asthma,[2,6,18] pregnancy,[4,19] hepatic failure,[20-22] renal failure,[23-25] systemic lupus erythematosus,[22] infection by Herpes Virus 6-7,[23,26] AIDS,[5,23] and other immune dysregulations.[27,28]

We designed a prospective study to evaluate the incidence and risk factors involved in cutaneous adverse drug reactions among ICU patients.

MATERIALS AND METHODS

An observational, prospective cohort study from March 1st-October 31st 2003 at the general ICU of an adult tertiary care center was conducted. Prior approval by our Institutional Review Board, all patients were physically examined twice a day. A certified dermatologist clinically diagnosed cutaneous adverse drug reactions. All patients in the ICU were seen daily and the following were recorded: age, gender, number of days in the ICU, underlying diseases and administered drugs. In addition, the following were recorded in those who developed an ACDR: personal or familiar history of adverse reactions to drugs, dermatological diagnosis, evolution of the dermatosis, and patient follow-up. Suspicious drugs were chosen by their frequency in the literature.

All patients were followed until skin problem resolution, hospital discharge or death. Frequency, median, mean and mode were obtained with the SPSS program and the Epi Info 6.0 program was used to calculate odds ratio, p and χ^2 of the possible risk factors for presenting an ACDR.

RESULTS

190 patients were hospitalized at the general ICU during our 8-month study period. ACDR occurred in 22 (11.6%), and of these, 45% were over 60, 36.3% were 40-60 years of age and 18.1% were 20-40 years old. No pediatric patients are seen at this Institution. Six (27%) developed the reaction within the first four days of hospitalization in the ICU. The majority of patients were females (n = 15; 68.2%). Mean duration of stay at the ICU was 4 days, 1.8 days more than patients without ACDR, which was statistically significant.

The most common underlying diagnosis were: dysthyroidism (hypo-hyperthyroidism) in 15 patients

Table 1. Underlying diseases.

Underlying diseases	Patients with ACDR		Patients without ACDR				
	n	%	n	%	OR	95% CI	p value
Dysthyroidism	15	68.18	6	3.57	57.86	15.09 - 240.4	<0.001
Obesity	12	54.54	35	20.8	4.56	1.67 - 12.57	<0.0001
SLE *	11	50	7	4.16	23	6.59 - 83.73	<0.001
Sepsis	9	40.9	19	11.3	5.43	1.84 - 15.98	<0.001
AAS *	3	13.6	3	1.78	8.68	1.28 - 59.39	<0.002
Cardiac failure	6	27	38	22.62	1.28	0.41 - 3.82	0.621
Dyslipidemia	5	22	47	28	0.76	0.23 - 2.35	0.603
Diabetes mellitus	4	18.1	80	47.6	0.008	0.07 - 0.81	0.008
Severe neutropenia	4	18.1	19	11.3	1.74	0.45 - 6.29	0.352
Hypertension	4	18.1	86	51.2	0.21	0.06 - 0.7	0.0035
Pneumonia	4	18.1	61	36.3	0.39	0.11 - 1.30	0.091
Peptic ulcer disease	4	18.1	39	23.21	0.74	0.20 - 2.50	0.595
Pleural effusion	3	13.6	27	16	0.82	0.18 - 3.24	0.768
Pancreatitis	2	9	23	13.7	0.63	0.10 - 3.09	0.548
Respiratory failure	2	9	12	7.14	1.30	0 - 6.86	0.742
Renal failure	1	4.5	7	4.16	1.1	0.17 - 7.08	0.933
Others	1	4.5	7	4.16	1.1	0.17 - 7.08	0.933

* SLE = systemic lupus erythematosus * AAS = antiphospholipid antibodies syndrome.

Table 2. Drug-induced dermatoses.

Dermatosis	Patients	
	n	%
Maculo-papular rash	13	59.1
Erythema multiforme	5	22.7
Stevens-Johnson syndrome	2	9.1
Urticaria	1	4.5
Fixed drug eruption	1	4.5

Table 3. Risk factors for presenting an ACDR at the ICU.

Risk factor	OR	95% CI	p value
Female gender	2.36	0.92 - 5.02	< 0.001
Age over 60	2.42	0.99 - 4.69	< 0.008
Obesity	4.56	1.67 - 12.57	< 0.0001
Sepsis	5.43	1.84 - 15.98	< 0.001
SLE*	23.00	6.59 - 83.73	< 0.001
AAS**	8.68	1.28 - 59.39	< 0.002
Dysthyroidism	57.86	15.09 - 240.40	< 0.0001
Being at the ICU	17.77	9.84 - 31.98	< 0.0001

* SLE = systemic lupus erythematosus. ** AAS = antiphospholipid antibodies syndrome.

(68.18%), obesity in 12 (54.5%) patients (BMI >30), systemic lupus erythematosus in 11 patients (50%) and sepsis in 9 patients (40.9%). Patients with SLE or antiphospholipid antibodies syndrome were under corticosteroid treatment. Interestingly, 3 (50%) of the 6 patients with antiphospholipid antibodies syndrome developed ACDR. Other underlying diseases are shown in table 1. Diagnoses were taken from the patients' clinical records.

Most reactions (n = 18; 81.8%) were attributed to antimicrobials, mainly cephalosporins (33.3%), and the second most common offending drug group were NSAID (10 patients-45%); other drugs implicated were angiotensin converter enzyme inhibitors (ACE) administered to 7 (31.8%) patients and diuretics to 6 (27.2%) patients**.** Although anticonvulsant seizure drugs are commonly implicated in ACDR none of the 19 patients that received them presented an ACDR.

Seventeen patients (77%) had no previous person-al or familiar history of ACDR. The most frequent ACDR seen was morbilliform rash (59%); other ACDR are shown in table 2. Odds ratio for risk factors associated to ACDR are shown in table 3.

One hundred and thirty patients (68.42%) had some degree of edema, of which 71 (54.61%) died.

Of the 168 patients that did not present an ACDR during their hospitalization at the ICU, 83 (49.4%) were females and 85 (50.5%) males. Forty-nine (29.16%) were between 20 and 40 years old, 96 (57.14%) between 40 and 60 years, and 23 (13.7%) over age 60.

These patients with no ACDR had several underlying diseases (see Table 1). Ninety-four (55.9%) were taking antimicrobials, 63 (37.5%) patients were taking NSAID, 36 (21.42%) patients were taking ACE and 61 patients (36.3%) were taking diuretics.

Twelve (7.14%) patients had previous personal of familiar history of adverse drug reactions.

DISCUSSION

The incidence of ACDR in ICU patients was 11.6% and most were attributed to antimicrobials and secondly to NSAID; a majority appeared within the first 4 days of hospitalization at the ICU and cleared 24-48 h after the suspicious drug was withdrawn.

The risk factors associated to the development of ACDR were female gender, age over 60, being hospitalized in the ICU, obesity, and immune dysregulations such as systemic lupus erythematosus, dysthyroidism, and antiphospholipid antibodies syndrome.

Immune dysregulation was an important risk factor for developing an ACDR; autoimmune conditions such as SLE, AAS, and dysthyroidism were the most prevalent underlying diseases in our population with ACDR. Only 3 patients with AIDS were hospitalized in the intensive care unit during the study period and none presented ACDR, though evidently no conclusions can be drawn.

Obesity was an important risk factor for drug interactions; over 50% of the patients with ACDR were obese (BMI>30). A decreased metabolism of isoform 3A4 is seen in obese patients, resulting in an indirect inhibition of CYP3A4, one of the isoenzymes of cytochrome P-450.[29] This may predispose to more adverse drug reactions and drug interactions in obese patients than in non-obese ones.

According to a recently published study of ACDR during a 5-year period, the risk for developing an adverse cutaneous reaction to drugs in patients with a positive family history for these reactions is 14% compared to 1.2% for those without a family history.[30] In our study only 23% of the patients with an ACDR had a positive personal or family history.

The frequency of adverse cutaneous reactions increases with age, being more common in patients over 60.[30-32] They are 35% more frequent in women independent of age and are 50% more common in senescent hospitalized women. This is probably sec-

ondary to these patients' increased drug intake, particularly NSAID for arthritic pain and their greater longevity compared with men.[27, 33,34] The majority of our patients were females over 60 years of age.

A recent prospective cohort study at our Institution with 4785 non-ICU hospitalized patients found an incidence of ACDR of 0.7% (in press). We found a greater incidence of ACDR among ICU patients (11.6% vs. 0.7%), probably secondary to longer hospitalization, greater drug intake, and more severe illness. Also, hospitalization in the ICU implies many risk factors including an intrinsic "stress load" that probably alters immunity in itself.

An interesting finding was that over 60% of the patients in the ICU had massive edema, and more than half of these died. Anasarca in ICU patients can be multifactorial: heart or kidney failure, multiple organ failure or physician-induced. A drug is defined as any substance that affects the structure or functioning of a living organism;[35] thus water, when administered by a physician for therapeutic purposes, can be considered a drug. We believe this finding warrants further investigation to determine if physician-induced edema is related to an increased mortality in the ICU. In any event, edema should be considered a cutaneous sign of poor prognosis independent of its etiology.

Also of interest for further investigation is the relationship between diabetes mellitus, hypertension and a low incidence of ACDR.

The skin, though frequently neglected in an ICU setting, is an important reflection of the patient's general health status. We consider there is a need for a pharmacological surveillance program of acute cutaneous reactions specifically in ICU patients.

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