Cutaneous Drug Reactions in patients admitted to the Dermatology Unit at the University Hospital of the West Indies, Kingston, Jamaica

AD East-Innis, DS Thompson

ABSTRACT

Objective: *Cutaneous reactions are among the most common adverse reactions to drugs. The purpose of this study is to examine the aetiology and outcome of cutaneous drug reactions among patients admitted to the Dermatology Ward at the University Hospital of the West Indies.*

Subjects and Methods: *This was a retrospective study looking at all patients who were admitted with a diagnosis of a cutaneous drug eruption from January 1, 1997 to December 31, 2005. Data included patient demographics, date of admission to hospital, duration of hospitalization and a detailed drug history including any previous episodes of drug sensitivity. All drugs reportedly ingested by the patients up to three months prior to their cutaneous reaction were documented and the period of time between drug ingestion and the appearance of skin lesions was also noted. Clinical diagnosis, co-morbidities, histopathological diagnosis, final outcome and all ensuing disabilities were noted. The data retrieved were collated and analyzed using SPSS 12.0.*

Results: *The results showed a female to male ratio of 2.2:1. The categories of drugs most commonly implicated were antimicrobials followed by anti-epileptic drugs and nonsteroidal anti-inflammatory drugs. The most common form of drug eruption requiring admission was the exanthematous drug eruption followed by erythema multiforme, toxic epidermal necrolysis and Stevens-Johnson syndrome.*

Conclusion: *In general, the causative agents identified and the types of drug eruptions were similar to those found in previous studies. However, the anti-epileptic drugs, phenytoin and carbamazepine, ranked among the most commonly implicated drugs which differ significantly from other studies.*

Reacciones Cutáneas Medicamentosas en Pacientes Ingresados en la Unidad de Dermatología del Hospital Universitario de West Indies, Kingston, Jamaica

AD East-Innis, DS Thompson

RESUMEN

Las reacciones cutáneas se hallan entre las reacciones adversas más comunes frente a los medicamentos. El propósito de este estudio fue examinar la etiología y la evolución clínica de las reacciones cutáneas medicamentosas entre pacientes ingresados a la sala de dermatología en el Hospital Universitario de West Indies.

Métodos: *Este es un estudio retrospectivo que pasa revista a todos los pacientes que fueron ingresados con diagnóstico de erupción cutánea desde el 1ero. de enero de 1997 al 31 de diciembre de 2005.*

Resultados: *Los resultados mostraron una proporción hembra-varón de 2.2:1. Las categorías de los medicamentos más frecuentemente implicados fueron los antimicrobianos, seguidos por los medicamentos antiepilépticos y los antiinflamatorios no esteroideos. La forma más común de erupción que requirió ingreso a causa de medicamentos, fue la erupción exantemática medicamentosa seguida por el eritema multiforme, la necrólisis epidérmica tóxica, y el síndrome de Stevens-Johnson.*

Conclusión: *En general, los agentes causativos identificados y los tipos de erupciones medicamentosas, fueron similares a los hallados en estudios previos. Sin embargo, los antiepilépticos conocidos como fenitoína y carbamazepina, estuvieron entre los medicamentos más comúnmente implicados, presentándose en tal sentido una diferencia significativa con los otros estudios.*

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From: Department of Medicine, The University of the West Indies, Kingston 7, Jamaica, West Indies.

Correspondence: Dr AD East-Innis, Department of Medicine, The University of the West Indies, Kingston 7, Jamaica, West Indies. Fax: (876) 977-0691, e-mail: medicine@uwimona.edu.jm.

INTRODUCTION

The skin is a well-recognized target organ for drug reactions. It may be the only organ affected or it may be one of several organs targeted by the drug. The skin manifestations of drug sensitivity are myriad and run the gamut from solitary or localized skin lesions to extensive and disabling skin failure with systemic involvement. Any drug ingested can elicit a cutaneous drug reaction but some are more frequently implicated than others. In one series, antimicrobials were most frequently incriminated (42%), followed by nonsteroidal anti-inflammatory drugs (27%) and drugs regulating central nervous system function (NS) [10%)] (1).

Hospital dermatologists are frequently called to see patients who are thought to have developed drug reactions. Many of these patients require admission or transfer to a dermatology ward to stabilize and treat their skin and systemic symptoms. Therefore, drug reactions may account for a significant percentage of dermatology admissions and, by extension, will utilize a proportionally significant amount of hospital resources. As some cutaneous drug reactions are life-threatening, these disorders may ultimately contribute to hospital mortality figures. Studies show that adverse cutaneous drug eruptions affect 2–3% of hospitalized patients, with female patients being more often affected (1). Other authors estimate that 1 of every 1000 hospitalized patients has a serious cutaneous drug reaction (2).

Until the scope and extent of cutaneous drug reactions are thoroughly evaluated, it would be difficult to estimate their significance. However, the cost to the patient can be great. Apart from the immediate threat to the patient's mortality, there are also the long term sequelae and disabilities to contend with, loss of income from hospitalization and convalescence and the cost of inpatient and follow-up care. Permanent disabilities such as blindness are also likely to affect employment and the patient's subsequent quality of life.

Drug reactions also incur significant healthcare costs. Inevitably, drug reactions complicate the patients' clinical course and prolong the hospital stay leading to greater use of laboratory resources to monitor the patients' clinical progress and prolongation of the period in which medical personnel have to remain involved in the management. This demand on clinical and material resources translates into a real cost to healthcare facilities.

The purpose of this study is to examine the aetiology and outcome of cutaneous drug reactions among inpatients of the Dermatology Ward at the University Hospital of the West Indies (UHWI).

SUBJECTS AND METHOD

The study was conducted retrospectively. The dermatology admissions recorded for a nine-year period were reviewed. All patients who were admitted with a suspected diagnosis of cutaneous drug eruption from January 1, 1997 to December 31, 2005 were included in the study. A data collection sheet was designed for the purpose of organizing the data collection process. Data included patient demographics, date of admission to hospital and duration of hospitalization and a detailed drug history including any previous episodes of drug sensitivity. All drugs reportedly ingested by the patients up to three months prior to their cutaneous reaction were documented and the period of time between drug ingestion and the appearance of skin lesions was also noted. Medication started within 8 weeks of the onset of lesions was deemed, most likely, to have caused the eruption. The rationale for choosing this period was because drug hypersensitivity syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis may take up to 8 weeks to manifest themselves (3). Additionally, clinical diagnosis, co-morbidities, histopathological diagnosis, final outcome and all ensuing disabilities were noted. The data retrieved were collated and analyzed using SPSS 12.0.

RESULTS

Four patients' records could not be located. Therefore, some data on these patients had to be obtained from other sources. During the period of January 1, 1997 to December 31, 2005, there were 959 dermatological admissions of which 101 were due to cutaneous drug reactions (CDRs). They therefore comprised 10.5% of dermatological admissions.

The ages of patients with CDRs ranged from 5 to 82 years with a mean age of 36.4 years. There were 70 females and 31 males with a female to male ratio of 2.2:1. Twenty-seven per cent (27%) had a previous history of drug hypersensitivity. However, only twenty per cent (20%) had a history of previous CDRs as the manifestation of their drug hypersensitivity. Thirteen and a half per cent (13.5%) had reacted to the same drug or class of drugs for which they had reported previous hypersensitivity.

The number of drugs implicated in each patient ranged from one to four. The most commonly suspected drugs were phenytoin, carbamazepine and amoxicillin (Table 1). Amoxicillin-clavulanic acid, cotrimoxazole, diclofenac sodium, diclofenac potassium and chlorpropamide were also commonly implicated (Table 1). However, a wide variety of drugs were less commonly incriminated. The categories of drugs most often suspected were antimicrobials (46.3%) followed by anti-epileptic drugs (24.4%) and nonsteroidal anti-inflammatory drugs [9.7%] (Table 2).

By far, the most common form of drug eruption requiring admission was the exanthematous drug eruption (42.6%) followed by erythema multiforme (12.9%), toxic epidermal necrolysis (10.9%) and Steven-Johnson syndrome (9.9%). Other manifestations included erythroderma, cutaneous vasculitis, urticaria, bullous drug eruptions and serum sickness-like reaction (Table 3). Hospital records and other data for two patients could not be located to clarify clinical manifestations and thus these were simply termed "cutaneous drug

Table 1: Drugs implicated in CDR and the number of patients affected

Drugs Implicated	No.	Drugs Implicated	No.	Drugs Implicated	No.
Phenytoin	15	Erythromycin	2	Doxycycline	1
Carbamazepine	15	Metamizol sodium	2	Celecoxib	1
Amoxicillin	15	Metronidazole	2	Hydroxychloroquine	1
Amoxicillin + clavulanic acid	11	Metronidazole + miconazole pessary	2	Captopril	1
Cotrimoxazole	8	Roxithromycin	1	Terbinafine	1
Diclofenac Na	6	Cefuroxime	1	Haloperidol	1
Diclofenac K	5	Acetaminophen	1	Ethinyloestradiol + cyproterone acetate	1
Chlorpropamide	5	Tetracycline	1	Cefadroxil	1
Penicillin	4	Nifedipine	1	Norfloxacin	1
Glibenclamide	3	Metformin	1	Minocycline	1
Cloxacillin	2	Glipizide	1	Nevirapine	1
Ceftriaxone	2	Gentamicin	1	Unnamed analgesic	1
Enalapril	2	Tramadol	1	Unnamed Sulfonylurea	1

Table 2: Drug categories implicated in CDRs and the number of patients affected

Drug Categories Implicated	Number of Patients
Antimicrobials	57 (46.3%)
Anti-epileptic	30 (24.4%)
NSAIDs	12 (9.7%)
Sulfonylurea antidiabetic	10 (8.1%)
Other analgesics	4 (3.3%)
Antihypertensive	4 (3.3%)
Others	5 (4.1%)
Unknown analgesic	1 (0.8%)

NSAIDs = nonsteroidal anti-inflammatory drugs

Table 3: Types of cutaneous drug reactions (CDRs) and the number of patients affected

Types of CDRs	No. of Patients
Exanthematous drug reaction	43 (42.6%)
Erythema multiforme	13 (12.9%)
TEN	11 (10.9%)
SJS	10 (9.9%)
Exfoliative dermatitis	7 (6.9%)
Cutaneous vasculitis	4 (3.9%)
Eczematous drug reaction	4 (3.9%)
Fixed drug eruption	3 (3.0%)
Cutaneous drug reaction	2 (2.0%)
Urticaria	2 (2.0%)
Bullous drug eruption	1 (1.0%)
Serum sickness-like reaction	1 (1.0%)

reactions". Bullous drug-induced lesions which were not toxic epidermal necrolysis, Stevens-Johnson syndrome or fixed drug eruption were termed "bullous drug eruption".

The length of hospital stay ranged from 1 to 71 days with a mean of 12 days. Thirty-five patients (34.6%) had short-term complications. The number of short-term complications per patient ranged from one to four. The most common was hepatitis, followed by renal impairment and ophthalmologic complications which included conjunctivitis, symblephara and corneal abrasion. Less common complications included anaemia, glucose intolerance, hypertension, gastritis, haematuria, pancytopaenia and thrombocytopaenia (Table 4). Three patients had long-term complications: two had persistent hepatitis and one patient had both labial fusion and dyschromia.

Table 4: Short term complications of CDRs

Short-term Complications	No. of Patients	Percentage of Patients
Hepatitis	25	24.7%
Renal impairment	5	4.9%
Conjunctivitis	3	2.9%
Symblephara	2	1.9%
Anaemia	2	1.9%
Corneal abrasion	1	1%
Glucose intolerance	1	1%
Hypertension	1	1%
Gastritis	1	1%
Haematuria	1	1%
Pancytopaenia	1	1%
Thrombocytopaenia	1	1%
Hyponatraemia	1	1%
Hypokalaemia	1	1%

The total number of deaths among dermatology patients with these problems during the period was 17 while that among patients with adverse cutaneous drug reactions was 4. Therefore the mortality among dermatology patients was 1.8% while that among patients with CDRs was 3.9%, that is, deaths among CDRs was approximately twice that

among other dermatology patients. Of the 4 patients that died, 3 had toxic epidermal necrolysis and 1 had an exanthematous drug eruption.

DISCUSSION

As in a previous study, female patients outnumbered male patients (1). In this report, the ratio was 2:1. However, in others, the numbers were almost equal (4, 5). One possibility to explain the gender difference is that women may be more likely to consult doctors and therefore more likely to be prescribed medication leading to higher drug consumption.

The study also suggests that at least 13.5% of cases were preventable as they had reacted to the same drug or same class of drugs as they had in the past. A similar study done in a hospital setting showed that 15% were preventable for the same reason as in the present study (4). Patient education and wearing of drug-alert bracelets and necklaces are crucial in reducing this number.

It is not surprising that amoxicillin and the amoxicillin/clavulanic acid combination are among the most common causative drugs as the Boston Collaborative Drug Study (BCDS) identified amoxicillin at that time as having the highest reaction rate (1). However, the present study differed from all the other studies quoted, as in this study phenytoin and carbamazepine were also among the most commonly implicated drugs. It is of note that in the BCDS, phenytoin was listed among drugs used in 100 to 499 patients with no allergic skin reaction, whereas in this study it was one of the most commonly implicated drugs. In another study, anticonvulsants were rarely involved (4) and they were not identified at all as causative agents in a study in India (7). One possibility is that there is an increased genetic susceptibility within the study population to cutaneous eruptions secondary to phenytoin and carbamazepine. An association between the HLA-B*1502 allele and cutaneous reactions to carbamazepine, phenytoin and lamotrigine in Han Chinese in Hong Kong has been demonstrated (8). It is possible that similar genes may predispose persons in other ethnic groups to these reactions. Further studies, therefore, need to be done on the Jamaican population to investigate whether there is indeed increased relative risk of cutaneous drug reactions to these anti-epileptic drugs and to identify a common factor or factors in the individuals affected.

Like this study, other studies have shown that the majority of cutaneous drug reactions are exanthematous (1, 4). Urticaria which occurs quite commonly and in most other studies was second only to exanthematous reactions in frequency, did not occur as often as expected in this study, most likely because most cases of urticaria are not admitted to hospital (4, 5).

Mortality among dermatology inpatients is low but cutaneous drug reactions contribute significantly to this figure. This study did not explore underlying medical conditions but in other studies HIV infection, immunosuppression, connective tissue disease and history of drug eruptions were identified as risk factors for CDRs (3, 5).

The study was limited in that it was restricted to those patients admitted to the Dermatology Ward for severe cutaneous drug reactions. This excluded patients who developed severe cutaneous drug eruptions while in hospital such as those which occurred on the Internal Medicine wards, Intensive Care Unit and Paediatric wards. Further prospective studies are required to capture these data.

In summary, antimicrobials are the most common cause of serious cutaneous drug reactions requiring admission to hospital from this study. This is in keeping with other studies done in other countries. However, anti-epileptic drugs are the second most commonly implicated agents unlike in other studies and this warrants further research in this population.

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