

CLINICAL PATTERN OF COMMON CUTANEOUS DRUG REACTIONS DUE TO SYSTEMIC ANTIBIOTICS IN PATIENTS ATTENDED KHARTOUM DERMATOLOGY AND VENEREAL DISEASES TEACHING HOSPITAL – SUDAN

Mohammed Helmy Faris Shalayel^{*1}, Ietimad Abdelsalam Mohamed Ayed² and Yousif Mohammed Kordofani³

¹Professor of Biochemistry and Specialist of Dermatology and Venereology, Najran University, KSA.

²Pharmacology Department, Faculty of Medicine and Health Sciences, Omdurman Islamic University, Sudan.

³Professor of Dermatology, University of Bahri.

Article Received on
01 Sept. 2016,

Revised on 21 Sept. 2016,
Accepted on 12 Oct. 2016

DOI: 10.20959/wjpr201611-7195

***Corresponding Author**

**Prof. Dr. Mohammed
Helmy Faris Shalayel**

Professor of Biochemistry
and Specialist of
Dermatology and
Venereology, Najran
University, KSA.

ABSTRACT

A prospective descriptive hospital-based study was conducted in Khartoum Dermatology and Venereal diseases Teaching Hospital in the period from October 2015 to April 2016. The objectives of the study were to reveal the different clinical types of cutaneous drug reactions due to systemic antibiotics and to show the most common offending drugs causing cutaneous drug reactions. The study included 41 patients; 28 female patients (68.3%) and 13 male patients (31.7%). The age mean of patients was 38.44 ± 14.26 (mean $\pm$ S.D.) ranging between 4 – 70 years. Of patients included in the study, 35 patients (85.4 %) had past history of drug reactions while only 6 ones (14.6 %) did not have. Our study revealed that the highest offending antibiotic implicated to cause drug reaction was ciprofloxacin (41.5%) followed

by the antimalarial artesunate and sulfadoxine-pyrimethamine (12.2%), septrin (sulfamethoxazole/Trimethoprim) (9.8%), norfloxacin (7.3%), ceftriaxone (4.9%), penicillin (4.9%), amoxicillin (4.9), ampicillin/cloxacillin (ampiclox) (2.4%), amoxicillin/clavulanate (amoclan) (2.4%), tetracycline (2.4%), erythromycin (2.4%), and Clarithromycin(2.4%). Maculopapular rash was seen in 16 cases (39%), SJS was found in 7 cases (17.07%), TEN in 7 cases (17.07%), SJS/TEN overlap in 4 cases (9.8%), EM-major in 6 cases (14.6%) and

fixed drug eruption (FDE) in 1 case (2.4%). It was concluded that Antibiotics comprise the major impact of the drug family and inpatient and outpatient prescriptions and thus are the most irrationally prescribed drug class. So implementation of antibiotic guidelines for the hospital scenario and strict adherence should be ensured to promote the rational use.

KEY WORDS: Adverse cutaneous drug reactions (ACDRs); Steven Johnson Syndrome (SJS); toxic epidermolysis necrolysis (TEN); erythema multiforme (EM); Antibiotics.

INTRODUCTION

Cutaneous drug reactions are the most frequently occurring adverse reactions to drugs^[1] however, data on outpatient cutaneous adverse drug events (CADEs) are limited.^[2] Among hospitalized patients, the incidence of these reactions ranges from 1 to 3%. The frequency of cutaneous reactions to specific drugs may exceed 10%. These reactions may range from mildly discomforting to those that are life-threatening. Anti-infective and anticonvulsant agents are among the drugs most commonly associated with adverse reactions in the skin.^[1]

Adverse cutaneous drug reactions (ACDRs) are responsible for approximately 3% of all disabling injuries during hospitalization. Many of the commonly used drugs have reaction rates over 1%. There is a wide spectrum of cutaneous adverse drug reactions varying from transient maculopapular rash to fatal toxic epidermal necrolysis (TEN). The pattern of cutaneous adverse drug eruptions and the drugs responsible for them keep changing every year.^[3-6]

Our study aimed to determine the different clinical types of cutaneous drug reactions due to systemic antibiotics and to show the most common offending drugs causing cutaneous drug reactions in Sudanese patients attended Khartoum Dermatology and Venereal diseases Teaching Hospital – Sudan.

PATIENTS AND METHODOLOGY

This study was prospective descriptive hospital -based study. The study was conducted in Khartoum Dermatology and Venereal Diseases Teaching Hospital in the period from October 2015 to April 2016. Forty-one patients participated in the study. Data were collected using previously designed and pre-coded questionnaire.

All patients were assured that all their obtained information will be handled in a confidential atmosphere and it will not affect their life after taking verbal and written consent. All the

human studies were carried out according to the guidelines of the Animal and Human Ethical Committee of Omdurman Islamic University.

Preliminary information such as age, sex, marital status, level of education, tribe, residence, and occupation were noted. A detailed history regarding presenting symptoms, intensity and duration, and other symptoms if any, were elicited and recorded. Also, history of debilitating conditions, diabetes mellitus, hypertension, chronic illness, blood transfusion, hospitalization were elicited. Thorough drug history was recorded regarding history of implicated drugs that may cause cutaneous drug reaction like antibiotics, NSAIDs, opioids, antiepileptic, corticosteroids and other drugs. Patients with cutaneous drug reaction due to medications other than antibiotics were excluded from the study.

A thorough dermatological examination regarding the clinical pattern of the lesions was performed.

All the patients were treated according to the time of visit after appearance of skin lesions.

Statistical analysis was performed using Statistical Package for Social Science (SPSS). A descriptive analysis was done for all questionnaire parameters.

RESULTS

The study included 13 males (31.7%) and 28 females (68.3%). Twenty-one patients (51.2) were from the North, 13 patients (31.7%) from the West, 1 patient (2.4) from the East and 6 patients (14.6%) were from the Centre of Sudan.

Age distributions of the patients included in the study are shown in table 1. Percentages of the each implicated antibiotic among the offending antibiotics that caused drug reactions are shown in figure 1.

Of patients included in the study, 35 patients (85.4 %) had past history of drug reactions while only 6 ones (14.6 %) did not have.

The different types of drug reactions, name of implicated antibiotics' groups, and percentage of the each implicated antibiotic among the offending antibiotics that caused drug reactions seen in our study are explained in table 2, table 3, and figure 1 respectively. The highest frequency was for maculopapular rash followed by, Steven Johnson Syndrome (SJS), toxic epidermolysis necrolysis (TEN), SJS/TEN overlap reaction, erythema multiforme (EM) major, and fixed drug reaction.

Table 1: Frequency and percentage of age groups of the study

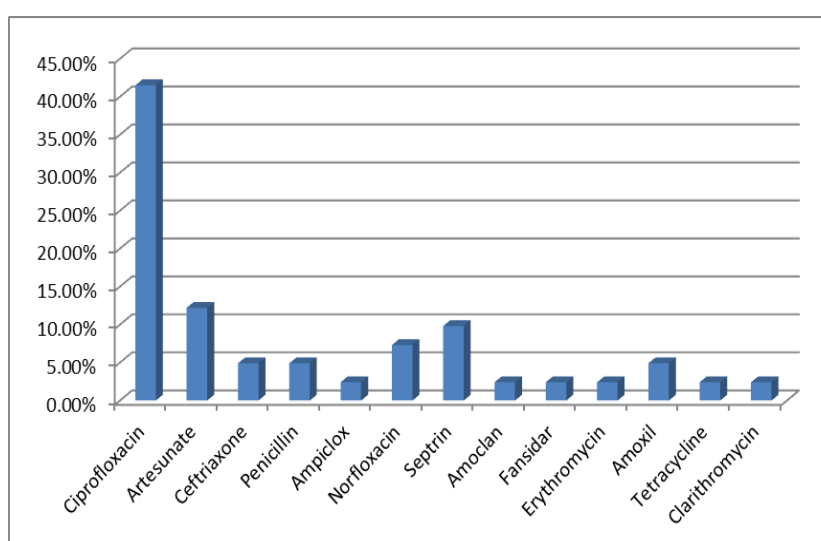
Age	Frequency	Percent
1- 9	1	2.44 %
10 – 29	12	29.27 %
30 – 40	6	14.6 %
41 – 50	14	34.1 %
More than 50	8	19.5 %
Total	41	100 %

Table 2: Types of drug reactions and their percentages in the study

Type of Reaction	Frequency	Percent
Maculopapular rash	16	39.0%
SJS	7	17.07%
TEN	7	17.07%
SJS/TEN Overlap	4	9.8%
EM. Major	6	14.6%
Fixed Drug Eruption	1	2.4%
Total	41	100%

Table 3: Name of offending antibiotics' groups

Offending antibiotics' groups	Frequency	Percent
Quinolones	20	57.14%
Drugs Containing Sulpha (septrin, artesunate)	9	25.71%
Penicillins	6	17.14%
Cephalosporins	2	4.88
Macrolides	2	4.88
Tetracycline	1	2.44
Beta lactamase inhibitors	1	2.44
Total	41	100%

**Figure 1: Percentage of the each implicated antibiotic among the offending antibiotics that caused drug reactions**

DISCUSSION

Drug interactions play a vital role in the incidence of adverse drug reactions in the community and hospitals.^[7] The skin is most commonly involved organ in adverse drug reactions. Although few cutaneous adverse drug reactions (CADRs) are potentially life threatening and cause significant morbidity and mortality, most CADRs have favourable course and generally resolve after discontinuation of the offending agent. Consequently, most of the patients with CADRs are likely to present and get treated in an outpatient setting, making prospective surveillance of CADRs in an outpatient setting essential.^[8]

Our results showed that male to female ratio was 1: 2.15. Moreover, clinical patterns of drug reaction revealed that maculopapular rash and SJS was found in 23 cases (56.07%), TEN in 7 cases (17.07%), SJS/TEN overlap in 4 cases (9.8%), EM-major in 6 cases (14.6%) and fixed drug eruption (FDE) in 1 case (2.4%). This finding is in concordance with some previous results. Pawar et al (2015)^[9] reported in their study that male to female ratio for CARDs was 1:2.33 and maculopapular rash was commonly encountered CARD in 76.67% of cases followed by urticaria (8.89%), SJS(4.4%) and FDE (3.33%).

Dimri et al (2016) reported that females were affected more than males as gender variation as seen in incidence of CADRs (W: M: 66: 45, 59.5%: 40.5%).^[10] Hence, this may support that the greater consumption of medications by women and the unbalanced sex ratio in the elderly population may at least partly account for the excess of reports in women.^[11]

It was observed that lesser number of adverse drug reaction in Children than adult like other study.^[10,12] Here it might be due to the reason that children are usually treated with lesser number of drugs and have normal kidney and liver function. Most of ADRs cases were seen in age 41- 50 years (14 cases, 34.1%) while, 8 cases (19.5%) were their ages were above 50. Like our observations, some previous studies have shown more percentage of ADRs in elderly patients only when they were interviewed (20%), otherwise percentage was too less on spontaneous reporting (7%).^[13] Other factors like variation in awareness of health care among the regional population and approachability to health care centre may be responsible for difference in reporting of ADRs among elderly patients. The clinical manifestations of drug eruptions can range from mild maculopapular exanthema to severe cutaneous adverse drug reactions (SCAR), including drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) which are rare but occasionally fatal.^[14] Two groups of mechanisms are

involved in the pathogenesis of drug reactions: immunological, with all 4 types of hypersensitivity reactions; and non-immunological, accounting for at least 75% of all drug reactions.^[15]

Regarding types of reactions and clinical pattern of drug reaction, our study revealed that maculopapular rash was seen in 16 cases (39%), SJS was found in 7 cases (17.07%), TEN in 7 cases (17.07%), SJS/TEN overlap in 4 cases (9.8%), EM-major in 6 cases (14.6%) and fixed drug eruption (FDE) in 1 case (2.4%). Pawar *et al* (2015) showed that maculopapular rash was most commonly encountered cutaneous adverse drug reaction in 76.67% of cases followed by urticaria(8.89%), SJS(4.4 %), and FDE (3.33%)^[8] whereas, Anjaneyan *et al* showed that the most common ACDRs were maculopapular rash (25%) followed by fixed drug eruptions (23%) and urticaria (22%).^[16]

Antibiotics are among the most commonly prescribed medications in the world that commonly used to manage microbial infections. This is however, accompanied by the risk of developing adverse drug reaction, impacting the safety with which the antibiotic can be used. Among the culprit antibiotics that caused cutaneous adverse drug reaction in our study, quinolones represented 57.14%, antibiotics containing sulpha (like artesunate and sulfamethoxazole-trimethoprim) represented 25.71%, penicillins represented 17.14%, cephalosporins and macrolides represented 4.88% for each, and tetracyclines and beta lactamase inhibitors represented 2.44% for each. Antibiotic-related cutaneous drug reactions represent a common cause of dermatological consultations among hospitalized patients, and it is difficult to verify the major culprit antibiotic because of the concomitant use of multiple systemic antibiotics. Antibiotic allergy may present as immediate or delayed hypersensitivity reactions. Immediate reactions are usually immunoglobulin E (IgE) mediated, whereas severe cutaneous adverse reactions (SCARs) are T-cell-mediated delayed hypersensitivity reactions. With the availability of newer systemic antibiotics and frequent combined antibiotic use for severe infection or sepsis, the appropriate selection of alternative antibiotics for treating antibiotic-related SCARs in patients with underlying infections represents a challenge for physicians^[16] especially when there is a history of adverse reaction.^[17]

Antibiotics generally do not directly stimulate the immune system, because of their small molecular size. These small chemicals may bind with larger molecules to create a hapten-carrier complex. Penicillins have been extensively studied for their propensity to induce various types of immune-mediated hypersensitivity reactions. Once the β -lactam ring opens,

it can bind with lysine to create the major determinant for allergic sensitivity, the penicilloyl-protein complex. Cephalosporins may cause allergic reactions through mechanisms similar to penicillins, but the cross-reactivity of penicillin allergy to these other classes is quite controversial. Early studies of crossover allergy rates of cephalosporins likely used reagents contaminated with trace amounts of penicillins, leading to high rates of crossover allergy.^[18,19]

Lin *et al* (2014) reported that the most common causes of SCARs were penicillins and cephalosporins for SJS/TEN and acute generalized exanthematouspustulosis (AGEP).^[20]

A previous study of self-reported antibiotic allergy prevalence among 411 543 outpatients in San Diego County, California, found that 9.0% of patients had a penicillin allergy documented in their medical record.^[21]

Regarding the onset of drug reaction, it was found that onset of < 1 week after offending drug administration was seen in 53.7% of cases while, onset of 1-2 week after drug administration, was seen in 41.5% of cases and onset of > 2weeks was seen in 4.9% of cases. Similar studies reported similar results. Dimiri *et al* (2016) reported that the onset and duration of individual reactions ranged between 1 to 21 days. Maximum number of affected patients (77.5%) had reaction for seven days whereas 15.3% patients had reactions for 8 to 15 days. So, most of the patients were relieved from the symptoms within one week. Significant associations have been observed in between various types of cutaneous reaction and duration of reaction (in days).^[10]

CONCLUSION AND RECOMMENDATIONS

Adverse Drug Reactions are one of the drug related problems in the hospital setting and is a challenge for ensuring drug safety. Maculopapular rash was likely the most common clinical pattern (39%) followed by SJS (17.07%), TEN (17.07%), EM-major (14.6%), SJS/TEN overlap (9.8%), and fixed drug eruption (FDE) (2.4%). Among the offending antibiotics implicated to cause adverse drug reactions, quinolones represented the highest frequency (57.14%) followed by antibiotics containing sulpha (like artesunate and sulfamethoxazole-trimethoprim) which represented 25.71%, penicillins represented 17.14%, cephalosporins and macrolides represented 4.88% for each, and tetracyclines and beta lactamase inhibitors represented 2.44% for each.

Expanded and bigger sample-sized additional studies are required to clarify full understanding of the mechanisms of allergy and adverse drug reactions. Pharmacogenomics studies are recommended to pave the way for pre-treatment screening for potentially severe drug hypersensitivity reaction and further work in the field of management procedures of cutaneous adverse drug reaction is highly anticipated.

REFERENCES

1. Svensson CK, Cowen EW, and Gaspari AA. Cutaneous drug reactions. *Pharmacological Reviews*. 2001; 5(3): 357-379.
2. Koelblinger P, Dabade TS, Gustafson CJ et al. Skin Manifestations of Outpatient Adverse Drug Events in the United States: A National Analysis. *J Cutan Med Surg*. 2013; 17(4): 269-275.
3. Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. *Indian J DermatolVenereolLepr*. 2004; 70: 20-24.
4. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994; 331: 1272-85.
5. Sharma VK, Sethuraman G. Adverse cutaneous reactions to drugs: an overview. *J Postgrad Med*. 1996; 42: 15-22.
6. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: Clinical pattern and causative agents-A six-year series from Chandigarh, India. *J Postgrad Med* 2001; 47: 95-9.
7. Lucca JM, Ramesh M, Ram D, Kishor M. Incidence and predictors of adverse drug reactions caused by drug-drug interactions in psychiatric patients: An empirical study. *Trop J Med Res*. 2016; 19: 29-35.
8. Pawar MP, Pore SM, Pradhan SN, Burute SR, Bhoi UY, Ramanand SJ. Nevirapine: Most Common Cause of Cutaneous Adverse Drug Reactions in an Outpatient Department of a Tertiary Care Hospital. *J ClinDiagn Res*. 2015; 9(11): FC17-20. doi: 10.7860/JCDR/2015/13672.6768.
9. Powers JH. Increasing the efficiency of clinical trials of antimicrobials: the scientific basis of substantial evidence of effectiveness of drugs. *Clin Infect Dis*. 2007; 45: S153–62.
10. Dimri D, Raina RS, Thapliyal S, Thawani V. Retrospective Analysis of Pattern of Cutaneous Adverse Drug Reactions in Tertiary Hospital of PauriGarhwal. *Journal of*

- Clinical and Diagnostic Research. 2016; 10(5): FC01-FC06. DOI: 10.7860/JCDR/2016/16938.7736.
11. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol*. 1999; 48(6): 839–46.
 12. Gonzalez Martin G, Caroca CM, Paris E. Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study. *Int J Clin Pharmacol Ther*. 1998; 36(10): 530–33.
 13. Somers A, Petrovic M, Robays H, Bogaert M. Reporting adverse drug reactions on a geriatric ward: a pilot project. *Eur J Clin Pharmacol*. 2003; 58(10): 707–14.
 14. Chung, WH, Wang CW and Dao RL. Severe cutaneous adverse drug reactions. *The Journal of Dermatology*. 2016. doi: 10.1111/1346-8138.13430.
 15. Raviglione MC, Pablos-Mendez A, Battan R. Clinical features and management of severe dermatological reactions to drugs. *Drug Saf*. 1990; 5(1): 39-64.
 16. Anjaneyan G, Gupta R, Vora Rv. Clinical study of adverse cutaneous drug reactions at a rural based tertiary care centre in Gujarat. *Natl J Physiol Pharm Pharmacol*. 2013; 3(2): 129-136. doi:10.5455/njppp.2013.3.120-127.
 17. Davey P, Legendre, Christina A, Muzny, Gailen D, Marshall, and Edwin Swiatlo. Antibiotic Hypersensitivity Reactions and Approaches to Desensitization. *Clin Infect Dis*. 2014; 58(8): 1140-1148. doi:10.1093/cid/cit949.
 18. Pichichero ME. Cephalosporins can be prescribed safely for penicillin allergic patients. *J Fam Pract*. 2006; 55: 106–12.
 19. Legendre DP, Muzny CA, Marshall GD, Swiatlo E. Antibiotic hypersensitivity reactions and approaches to desensitization. *Clinical infectious diseases*. 2014; 58: 1140- 1148.
 20. Lin Y, Yang C, Sindy H, Lin J, Hui CR, Tsai Y, Wu T, Huang C, Kao K, Hu H, Chiu C, Hung S, and Chung W. Severe Cutaneous Adverse Reactions Related to Systemic Antibiotics. *Clin Infect Dis*. (2014) 58 (10): 1377-1385 first published online March 5, 2014 doi:10.1093/cid/ciu126.
 21. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med*. 2009; 122: 778 e1-7.