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EPIDERMOLYTIC ADVERSE CUTANEOUS DRUG REACTIONS DUE TO SYSTEMIC ANTIBIOTICS – ONSET AND MUCOUS MEMBRANES' AFFECTION

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ABSTRACT

A wide spectrum of cutaneous manifestations ranging from maculopapular rashes to toxic epidermal necrolysis (TEN), considered being two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions can be caused by different classes of antibiotics. Toxic epidermal necrolysis (TEN) and Stevens Johnson Syndrome (SJS) are characterized by mucocutaneous tenderness and typically hemorrhagic erosions, erythema and more or less severe epidermal detachment presenting as blisters and areas of denuded skin. Our prospective descriptive hospital -based study aimed to determine the prevalence of epidermolytic adverse cutaneous drug reactions among other cutaneous adverse drug reactions due to systemic antibiotics with highlights on onset and mucous membranes affection in Sudanese patients attended Khartoum Dermatology and Venereal diseases Teaching Hospital – Sudan. Mucous membranes' affection existed in 100 % of patients. Ocular along with oral mucosal affections were the predominant sites. Percentages of only oral affection, mouth and genitalia, mouth and eyes, eyes and genitalia, all mucous membranes, eyes alone, and genitalia alone were 34.1%, 22%, 14.6%, 12.2%, 12.2%, 2.4%, and 2.4%% respectively. Epidermolytic adverse cutaneous eruption represented 58.6% of all cutaneous drug reactions due to antibiotics. **It was concluded that** epidermolytic adverse cutaneous drug eruptions are common cutaneous adverse drug reactions (CADRs) and represented 58.6% of all cutaneous drug reactions due to antibiotics. Ocular along with oral mucosal membranes (41.5 % and

34.1%) were the predominant sites of mucosal affection. Onset of < 1 week after offending drug administration was seen in most of patients (53.7%).

KEY WORDS: Cutaneous Adverse Drug Reactions (CADRs); Steven Johnson Syndrome (SJS); Toxic Epidermolysis Necrolysis (TEN); Erythema Multiforme (EM); Antibiotics.

INTRODUCTION

Toxic epidermal necrolysis (TEN) and Stevens Johnson Syndrome (SJS) are severe adverse cutaneous drug reactions that predominantly involve the skin and mucous membranes. Both are rare, with TEN and SJS affecting approximately 1or 2/1,000,000 annually, and are considered medical emergencies as they are potentially fatal. They are characterized by mucocutaneous tenderness and typically hemorrhagic erosions, erythema and more or less severe epidermal detachment presenting as blisters and areas of denuded skin. Currently, TEN and SJS are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions[1], differing only by their extent of skin detachment.[2]

Initial symptoms of toxic epidermal necrolysis (TEN) and Stevens Johnson Syndrome (SJS) can be unspecific and include symptoms such as fever, stinging eyes and discomfort upon swallowing. Typically, these symptoms precede cutaneous manifestations by a few days.[3]

Our study aimed to determine the prevalence of epidermolytic adverse cutaneous drug reactions among other cutaneous adverse drug reactions due to systemic antibiotics with highlights on onset and mucous membranes affection 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

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 epidermolytic drug reactions, name of implicated antibiotics, diagnosis and morphology of lesions seen in our study are explained in table 1. Epidermolytic adverse cutaneous eruption represented 58.6% of all cutaneous drug reactions due to antibiotics (table2).

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.

Results of mucous membranes affection are listed in table 3 and figure 1.

Table 1: Overall lesions morphology and diagnosis seen in patients with epidermolytic drug reactions due to different antibiotics

Offending drug	Number of cases	Diagnosis	Lesion morphology
Ciprofloxacin	17	Fixed drug eruption, EM-major, SJS, TEN	Erosion, Scales, Bullae, Patch, Hyperpigmentation, Target cell, Papule,
Artisunate	5	EM-major, SJS, TEN	Erosion, Patch, Crust, Bullae, Erythema,

			Target lesion
Penicillins	3	EM-major, SJS	Erosion, Papule, Bullae, Crust, Erythema, Target lesions
Sulfamethoxazole-Trimethoprim (cotrimoxazole) or Seprtin	3	SJS, TEN, SJS/TEN overlap	Erosion, Bullae, Erythema
Norfloxacin	3	TEN	Erosion, Vesicle, Bullae, Erythema,
Amoxicillin	2	SJS, TEN	Crust, Patch, Erythema, Erosion, Vesicle, Papule, Plaque, Target Lesion
Ceftriaxone	2	SJS, TEN	Erosion, Crust, Macule, Scale
Ampiclox (Ampicillin/Cloxacillin)	1	SJS	Crust, Patch, Erythema, Erosion, Vesicle, Papule, Target lesion
Amoclan (Amoxicillin/Clavulenic acid)	1	EM-major	Macule, Plaque, Bullae, Erosion, Hyperpigmentation
Fansidar (sulfadoxine and pyrimethamine)	1	SJS	Erythema, Bullae, Plaque, Erosion
Erythromycin	1	EM-major	Erythema, Target lesion
Clarithromycin	1	TEN	Erosion, Bullae, Patch, Erythema, Peeling
Tetracycline	1	SJS/TEN overlap	Bullae, Erosion, Target lesion

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%

***Epidermolytic adverse cutaneous drug reactions**

Table 3: Results of mucous membranes affection

Affected mucous membranes	Frequency	Percent
Oral	14	34.1%
Eye	1	2.4%
Genitalia	1	2.4%
Oral & Eye	6	14.6%
Oral & Genitalia	9	22.0%
Eye & Genitalia	5	12.2%
All	5	12.2%
Total	**41**	**100%**

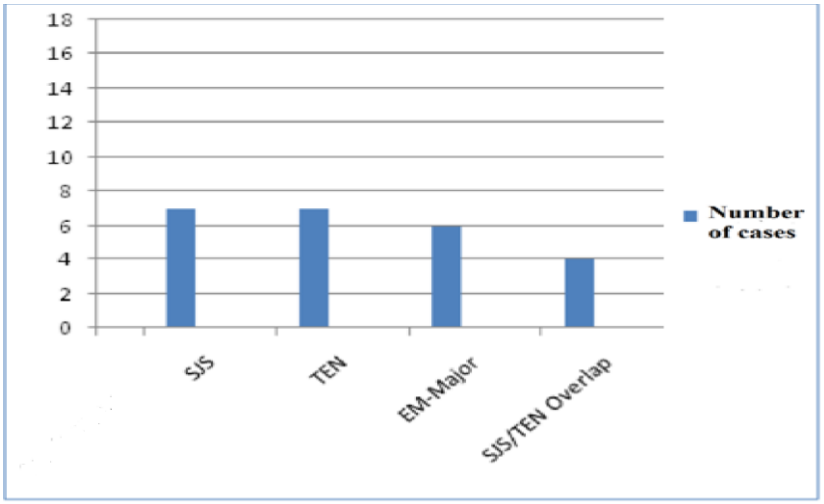

Figure 1: Types of epidermolytic drug reactions and frequency

DISCUSSION

Cutaneous adverse drug reactions (CADRs) have been seen to be one of the most common adverse drug reactions (ADRs) in various studies. A wide spectrum of cutaneous manifestations ranging from maculopapular rashes to toxic epidermal necrolysis (TEN) can be caused by different classes of drugs. Studies have found the overall incidence of CADRs in developed countries as 1-3%, while the incidence in developing countries is thought to be higher between 2% and 5%.[4] Clinicians come across many instances of suspected CADRs in different forms. Therefore, not only the dermatologist, but the practicing physician should be familiar with these conditions to enable early diagnosis and prompt withdrawal of the causative drug to prevent mortality.[5] Our results showed that SJS was found in 23 cases (56.07%), TEN in 7 cases (17.07%), SJS/TEN overlap in 4 cases (9.8%), and EM-major in 6 cases (14.6%). 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.[6] The widespread epidermolysis and blistering of TEN results from keratinocyte apoptosis and an organized series of biochemical reactions leading to cell changes and cell death.[7]

Our results revealed that the most implicated antibiotics in causing epidermolytic drug reactions were ciprofloxacin (17 cases, 41.46%), the antimalarial artesunate (5 cases, 12.19%), penicillins, cotrimoxazole and norflox prospective descriptive hospital -based study acin (3 cases for each, 7.31% for each), amoxicillin and ceftriaxone (2 cases for each, 4.87 %

for each) ampicillin/cloxacillin, amoxicillin/alavulenic acid, sulfadoxine and pyrimethamine, erythromycin, clarithromycine and tetracycline (1 patient for each, 2.44%).

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.[8]

The World Allergy Organization (WAO) has recommended categorizing immunologic drug reactions based upon the timing of the appearance of symptoms.[9] True allergic reactions to amoxicillin are mediated by the immune system and are classified into immediate (developing within 30 to 60 minutes of drug ingestion) or non-immediate (beyond 1 hour of ingestion) type reactions.[10,11] Non-immediate reactions occur more than 1 hour after ingestion of antibiotic and usually last several days.[12] For the most part, they are mild, self-resolving maculopapular exanthemas or hives.[11] Rarely, non-immediate reactions may present with exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).[13]

It is important to differentiate between immediate and non-immediate reactions given their different pathogenic mechanisms and management.[10] The immediate reactions are considered to be immunoglobulin E (IgE)-mediated responses and non-immediate reactions are thought to be T cell mediated.[11] Unfortunately, the pathogenesis of allergic reactions to antibiotics in general and amoxicillin in particular is not well characterized; in addition to IgE and T cell-mediated mechanisms it has been suggested that certain antibiotics can bind non-covalently to antigen-interacting structures, such as the T cell receptor or major histocompatibility complex, and cause a direct stimulation of the immune response. The term p-i concept (or pharmacological interaction with immune receptors) has been coined for the latter.[14] Antibiotics are small-sized molecules that are assumed to be non-immunogenic, and hence numerous hypotheses have been advanced to account for their ability to activate the immune system.[15,16]

Results of mucous membranes affection showed its occurrence in 100 % of patients. Typically, mucous membrane erosions (seen in 90% of cases) generally precede the skin lesions by 1-3 days. The most frequently affected mucosal membrane is the oropharynx, followed by the eyes and genitalia. Oral cavity involvement usually presents as a sore or

burning sensation. Intake may be limited because of pain associated with the oropharyngeal lesions.[17]

Ocular along with oral mucosal affections were the predominant sites. Percentages of only oral affection, mouth and genitalia, mouth and eyes, eyes and genitalia, all mucous membranes, eyes alone, and genitalia alone were (34.1%, 22%, 14.6%, 12.2%, 12.2%, 2.4%, and 2.4%% respectively). Thus ocular affection occurred in 41.5% of patients. Our findings are in concordance with some previous studies. Ocular complications generally result from abnormal keratinization of the tarsal conjunctiva. A Sjogren like syndrome with decreased lacrimal secretion causes dry eye and predisposes to corneal abrasions and corneal scarring with neovascularization.[18] A study by Power and colleagues found that 50% of patients with TEN developed ocular complications.[19]

Early sites of cutaneous involvement are the presternal region of the trunk and the face, but also the palms and soles. Involvement (erythema and erosions) of the buccal, genital and/or ocular mucosa occurs in more than 90% of patients, and in some cases the respiratory and gastrointestinal tracts are also affected.[20] Ocular involvement at the onset of disease is frequent, and can range from acute conjunctivitis, eyelid edema, erythema, crusts, and ocular discharge, to conjunctival membrane or pseduomembrane formation or corneal erosion, and, in severe cases, to cicatrizing lesions, symblepharon, fornix foreshortening, and corneal ulceration.[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.

Most cases of TEN are drug induced, typically occurring within 1-3 weeks of therapy initiation and rarely occurring after more than 8 weeks. Therefore, a detailed medication history, focusing on medications that have been recently started, is a vital component of the patient's history.[17]

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).[22]

CONCLUSION

Epidermolytic adverse cutaneous drug eruptions are common cutaneous adverse drug reactions (CADRs) and represented 58.6% of all cutaneous drug reactions due to antibiotics. Ocular along with oral mucosal membranes (41.5 % and 34.1%) were the predominant sites of mucosal affection. Onset of < 1 week after offending drug administration was seen in most of patients (53.7%).

Conduction of other studies with bigger sample size is recommended to reveal the complex interplay between host, drug, and other potential factors such as infectious diseases and/or environmental factors.

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