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Serious Mucocutaneous Reactions Associated with Ciprofloxacin in the Global Adverse Drug Reaction Database

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Habtom Kifle[1], Mehari Zerebagr[2], Filmon Tesfai[3], Marta Amanuel[2], Mulugeta Russom[2*]

[1]Halibet National Referral Hospital Asmara, Eritrea

[2]Eritrean Pharmacovigilance Centre, Asmara, Eritrea

[3]National Medicines and Food Administration, Asmara, Eritrea

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ABSTRACT

Introduction: Stevens–Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are acute life-threatening mucocutaneous reactions to drugs. Ciprofloxacin is one of the broad spectrum antibiotics which can cause SJS and TEN. The study is aimed at assessing the seriousness of mucocutaneous reactions associated with the use of ciprofloxacin and identifies possible risk factors. **Methods**: A retrospective data analysis was carried out on the global adverse drug reaction database on June 30, 2017. Search was made with 'ciprofloxacin' as a drug substance and 'Toxic epidermal necrolysis' and/or 'Stevens-Johnson syndrome' as MedDRA reaction terms. Data was generated using VigiLyze™, an analysis tool of the global adverse drug reaction database, developed by the Uppsala Monitoring Centre (UMC). **Results**: From 1987 to June 2017, a total of 916 cases of TEN and SJS were reported. Outcome was documented in 641 cases and reaction was marked as 'recovered' in 57%, 'not recovered' in 20% and 'fatal' in 23%. Of the reported fatal cases, 77% were aged 40 and above with female predominance (57%). Higher mortality was reported with TEN (117, 78%) compared to that of SJS. The median time to reaction onset was found to be four days. SJS was reported as 'recovered' in 222 cases following withdrawal of ciprofloxacin (i.e. positive dechallenge) and reaction recurred in ten cases with re-introduction of the drug (i.e. positive rechallenge). With TEN, positive dechallenge and rechallenge were 81 and 3 cases respectively. **Conclusion**: Fatal outcomes following mucocutaneous reactions associated with the use of ciprofloxacin were found to be significant. Older age, extent of epidermal involvement and underlying septicemia and being female were identified as possible risk factors for fatal outcomes.

INTRODUCTION

Ciprofloxacin, a widely used broad spectrum antibiotic acting on both gram negative and gram positive bacteria [1], has previously been associated with serious cutaneous reactions, such as Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) [2]. SJS and TEN are acute life-threatening mucocutaneous reactions usually caused by drugs [3]. These cutaneous reactions are characterized by extensive necrosis and detachment of the epidermis with widespread erythematous or purpuric macules or flat atypical lesions [3,4]. These two conditions are severity variants of an identical process of epidermal necrolysis (EN) and differ only in the extent of body surface involvement [3,4]. If the affected body surface area is below 10%, we diagnose it as 'SJS'; if between 10% and 30% we call it 'overlap of SJS/TEN' and 'TEN' if more than 30% of the body surface area is involved. The incidence of SJS and TEN is estimated to be 1 to 6 cases and 0.4 to 1.2 cases per million populations per year respectively [5-8].

This study was inspired by a number of life-threatening mucocutaneous reactions reported to the Eritrean Pharmacovigilance Centre. The aim of this study is therefore to analyze the seriousness and identify possible risk factors of SJS and TEN associated with Ciprofloxacin using the global adverse drug reaction database, VigiBase™.

METHODS

A retrospective data analysis was conducted on the WHO-UMC adverse drug reaction database on June 30, 2017. Search was made with 'ciprofloxacin' as a drug substance and 'TEN' and/or 'SJS' as reaction MedDRA terms. Data was generated using VigiLyze™, an analysis tool of the global adverse drug reaction database, developed by the Uppsala Monitoring Centre. Information on reactions' seriousness and outcome was captured using VigiLyze™. For further descriptive analysis, the generated data was exported to excel spreadsheet. Reaction time to onset was calculated from the time of the patient's first prescription to the occurrence of the adverse events. On the cases of 'SJS/TEN overlap' time to reaction, onset was taken from the SJS on the consideration of the fact that SJS develops earlier [9].

Ethical considerations:

According to the WHO policy and UMC guidelines [10], patients' and reporters' identity are anonymized in the adverse drug reaction global database. The principal investigator of the study, head of the Eritrean Pharmacovigilance Centre, de-identified further patient identifiers prior to analysis and only statistical datasets are shared with the study team. As the study is retrospective and National Pharmacovigilance Centers of all member states of the WHO program for international drug monitoring have free access to use the global database [10], this study does not require ethical clearance.

RESULTS

From1987 to June 2017, a total of 916 cases of SJS and TEN (358 male, 530 female and 28 unspecified sex) were reported with highest reports in 2011 and 2016. The median age of patients who encountered SJS and/or TEN was 59 years (range: 18 - 74). Reports were submitted from 87 countries of which 41.5% were reported from the European countries. The cases were 58.1% SJS, 37.1% TEN and the rest were overlap of SJS/TEN. Reactions' outcome was reported in 641 cases and it was marked as 'recovered' in 56.9% (43 cases of which recovered with sequelae), 'not yet recovered' in 19.8% and 'fatal' in 23.3% of the cases.

Around 78% of the cases with fatal outcomes were those who developed TEN following the use of Ciprofloxacin and the rest were suspected to have died of SJS. Of these fatal cases, 77% were aged above 40 years and 57% were females.

Reaction recovered following withdrawal of ciprofloxacin in 222 patients with SJS and in 81 patients with TEN. Following recovery from the first reaction, ciprofloxacin was re-introduced in some patients and SJS as well as TEN recurred in 10 and 3 patients respectively. Reporters' qualification was highlighted in 83.3% of the cases, of which 54.5% of them were physicians.

DISCUSSION

This study found that the fatality rate of the serious cutaneous reactions associated with the use of ciprofloxacin is very high. Although the cases of SJS were higher in number compared to TEN, number of deaths with TEN greatly exceeded that of SJS. This implies that the

greater the extent of the epidermal involvement, the higher the mortality. The extensive detachment of skin and mucosal areas as well as delayed referral to burn centers could probably lead to more fluid losses and high infection rates which could possibly lead to fatalities [11].

The maximum numbers of cases were seen in the 4^{th}, 5^{th} and 6^{th} decades of ages. Furosemide, co-trimoxazole, paracetamol, allopurinol, vancomycin and ceftriaxone were among the top co-reported drugs in less than 5% of the cases which could possibly have explained or aggravated the condition [12].

We observed female predominance which can possibly be explained by the increased susceptibility to infections compared to males [13-15]. Age and extent of epidermal involvement were found to be the most important prognostic factors for the occurrence of TEN and SJS. In this study, higher mortality rate was noticed in elderlies, which is consistent with findings from previous studies [16-18]. The plausible times to reaction onset, positive dechallenge and rechallenge information in some cases and the low background disease incidence suggests a possible causal association between ciprofloxacin and SJS/TEN.

Inadequate information on the comorbid conditions of the cases and reactions' outcome as well as inability to identify the route of administration of the drug were some of the limitations of our study. Besides, the fact that the cases were voluntarily reported from healthcare professionals and submitted to the global adverse drug reaction database from different parts of the world makes the denominator unknown. As such, we could not quantify the actual risk of SJS/TEN associated with Ciprofloxacin. Moreover, readers should note that the information is submitted from a variety of sources, and the likelihood that the suspected adverse reaction is drug - related is not the same in all cases and merely suspicions; not confirmed cases.

CONCLUSION

Serious cutaneous reactions related to ciprofloxacin have been associated with significant number of deaths globally. Older age, extent of epidermal involvement, underlying septicemia and female sex were associated with increased risk of fatal outcomes of these reactions. This however, requires further studies to quantify the risks and identify other possible risk factors for these mucocutaneous reactions. Prescribers should, therefore, use ciprofloxacin only when necessary and opt better treatment alternatives whenever possible.

Advice should also be given to consumers on the possible adverse effects and the early signs and symptoms of SJS and TEN to avoid complications.

Declarations

Consent for publication: All co-authors have given their consent for publication.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: All of the authors played a key role on the analysis, interpretation of the cases, write-up and editing of the manuscript.

Disclaimer: The thoughts presented in this paper are those of the authors, and do not represent the opinion of the WHO or the Uppsala Monitoring Centre.

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