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Research Article

Toxic Epidermal Necrolysis, Stevens - Johnson syndrome and Erythema Multiform associated with Chlorpheniramine

Mulugeta Russom[1*], Merhawi Debesai1, Mehari Zeregabr[1], Filmon Tesfai[2], Gelila Abrham[3]

[*1]Eritrean Pharmacovigilance Centre, Ministry of Health, Eritrea

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

[3]Tesseney Hospital, Tesseney, Eritrea

[*]**Corresponding author:** Mulugeta Russom, Eritrean Pharmacovigilance Centre, Ministry of Health, Asmara, Eritrea. Tel: +2917197450; Email: satiswt@gmail.com

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Abstract

Introduction: Stevens - Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Erythema Multiform (EM) are very rare but potentially fatal cutaneous reactions. As of the publication of this case report, the association of Chlorpheniramine and the serious cutaneous reactions EM, SJS and TEN is not documented in literature. However, inthe international adverse drug reaction database (VigiBase) we found a total of 53 cases of EM, SJS, and TEN submitted from different parts of the world including Eritrea. This case study, based on data retrieved from VigiBase, was therefore aimed at assessing the causal association of TEN, SJS and EM with the use of Chlorpheniramine.

Method: Search was made in the VigiBase, using VigiLyze with 'Chlorpheniramine', 'Chlorpheniramine maleate' and 'Chlorphenamine' as drug substance and 'EryhthemaMutiforme', 'Stevens-Johnson syndrome' and 'Toxic epidermal Necrolysis' as reactionMedDRA terms. Possible duplicates were eliminated using VigiMatch. Retrieved cases were then subjected to causality assessment using Austin Bradford-Hill criteria.

Results: From 1973 to April 2017, a total of 53 serious cutaneous reactions including SJS (26), EM (14), TEN (8) and epidermal Necrolysis (5) were reported to the global database. Chlorpheniramine was the only suspected drug in 15 of the cases with no concomitants except for one case. The median time to onset was found to be three days and in four of the cases, reaction outcome was marked as 'fatal' and in 13 as 'not yet recovered'.

Conclusion: This case series assessment found a suggestive causal association between Chlorpheniramine and the serious cutaneous reactions under discussion.

Introduction

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are life-threatening cutaneous reactions mostly manifested with drugs [1-9]; though larger cases of Erythema Multiform (EM) can be explained with certain infections [10]. These serious cutaneous reactions are generally characterized by targetoid erythematous lesions, epidermal Necrolysis, skin sloughing and detachment that usually involves the trunk, face and mucous membranes including the eyes, genitals and lips with varying degrees [11]. They are very rare events with an average incidence proportion of one case per million populations per year [2,12].

Chlorpheniramine is used in the symptomatic control of allergic conditions which respond to antihistamines including hay fever, urticaria, vasomotor rhinitis, food allergy, drug and serum reactions, pruritus vulvae, pruritus aniand insect bites [13]. As of the publication of this cases report, the association of Chlorphe-

niramine and the serious cutaneous reactions EM, SJS and TEN is not documented in literature, even as a case report. Summary of Product Characteristics (SPC) of Chlorpheniramine manufactured by different companies also do not include the aforementioned reactions as possible adverse effects [13-16]. Only allergic reactions including exfoliative dermatitis, photosensitivity, skin rash and urticaria are adequately labeled in the SPCs. However, reports from international adverse drug reaction database, VigiBase, indicate that a total of 53 cases of EM, SJS, TEN and epidermal Necrolysis have been reported from different parts of the world including Eritrea. This assessment therefore aimed at drawing more attention to the possible risk of TEN, SJS and EM associated with the use of Chlorpheniramine based on data retrieved from VigiBase. This case series assessment was inspired by a single incident of TEN associated with the use of Chlorpheniramine and calamine lotion reported to the Eritrean Pharmacovigilance Centre. Both drugs are not known to cause the reaction.

Methods

Search was made on April 15, 2017 in the global adverse drug reaction database, VigiBase, using VigiLyze, an analysis tool developed by the Uppsala Monitoring Centre. 'Chlorpheniramine,' 'Chlorpheniramine maleate' and 'Chlorphenamine' were used as a drug substance and 'EryhthemaMutiforme', 'Stevens-Johnson syndrome' and 'Toxic epidermal Necrolysis' as reactionMedDRA terms. Possible duplicates were eliminated using VigiMatch, a tool also developed by the Uppsala Monitoring Centre to eliminate duplicate safety reports. By running the search criteria, reactions with single suspect, seriousness, completeness score of the reports, Information Component (IC) value, dechallenge and rechallenge information of the cases were retrieved. The cases were then exported to excel spreadsheet for further analysis. Median age, sex and reaction time to onset were calculated. Besides, to eliminate possible alternative causes, cases with single suspected drug (Chlorpheniramine) were extracted and tabulated separately.

Summary of the case from Eritrea

On 25th July of 2012, an 11 years old male patient was taken to the nearest hospital with a chief complaint of generalized body rash and itching. The rash reportedly started four days before the visit. He was given Chlorpheniramine 4mg orally and calamine lotion 60 ml to treat a suspected allergic reaction. Seven days after treatment with both calamine lotion and Chlorpheniramine, the patient began to develop flue like symptoms, fever and his skin started to peel off (specially the abdomen and the back). While the rash for which the treatment was initiated exhibited worsening symptoms. On his second visit to the hospital, the child exhibited progressive skin manifestations. The itching was intensified both in severity and coverage, starting from the face extending through the upper chest all the way down to the lower extremities. The abdomen and legs developed vesicular and bullous lesions. The patient had no pertinent familial or personal history of allergic reaction to Chlorpheniramine or calamine lotion and no previous history of eczema or skin allergy was reported. At his second visit, before the initiation of therapy for the complications he developed, his pulse and respiratory rates were measured 24 beats per minute (b/min) and 104b/min respectively.

Percussion examinations of the chest, back and abdomen could not be performed as the skin reaction in these areas was extremely sever. Physical musculoskeletal and skin examinations revealed generalized skin lesion and hyper-pigmentation with peeling off skin on the back, neck and abdomen. The face (HEENT) was generally hypo-pigmented with erythematous and wet lesions on the mouth. Generally, the patient developed multiple lesions of the skin and mucosal epithelia, in which the eyes were specially Necrolysis. The skin epithelial tissue exfoliation was extensive with an estimated coverage of 70% of the total body surface area. This involved conjunctival, gastrointestinal, genital, mouth and other mucous membranes. Laboratory examination results were used to rule out diabetes and all suspected infectious diseases. Lastly, the patient was diagnosed with TEN. During his stay in the hospital, the patient was treated with antibiotic drugs namely ceftriaxone, crystalline penicillin and cloxacillin, IV fluids as well as transfusion of packed red blood cells.

Hydrocortisone 25mg followed by prednisolone 20mg tablet daily was given to treat inflammation. To manage the burn, the patient was treated with silver nitrate ointment. Moreover Aspirin, Ibuprofen and Antacid syrup were given orally whenever deemed necessary, coupled with continuous wound dressing for over a week. Over the course of his treatment, laboratory tests, apart from being used to rule out infectious diseases, were used to rationalize management interventions. These tests included complete blood count, liver function test, liver ultrasonography, renal function test and electrolyte concentration tests. The patient was discharged after 52 days of hospitalization with complete recovery from TEN.

Results

From 1973 to April 2017, a total of 53 serious cutaneous reactions including Stevens-Johnson syndrome (26), Erythema multiform (14), toxic epidermal Necrolysis (8) and epidermal Necrolysis (5) were reported to the global database. The reactions were reported from six continents and 17 countries namely Thailand (21) United Kingdom (5), South Korea (4), Malaysia (3), Vietnam (3), USA (3), Australia (2), India (2), Indonesia (2), Brazil (1), Burkina Faso (1), Eritrea (1), France (1), Madagascar (1) Mexico (1), New Zealand (1) and Turkey (1). The cases were 25 males, 27 females and one of unknown sex. Age was reported in 49 of the 53 cases and the median age was 26 years (ranges from one month to 84 years). A positive statistical signal (IC025) was noted with SJS (IC025=0.21) and TEN (IC025=0.49). The reports had a median completeness score of 0.57 in the scale of 0.0 to 1.0.

Chlorpheniramine was the only suspected drug in 15 of the cases and in only one of these 15 cases betamethasone and paracetamol were reported as concomitants. Other drugs were co-reported with Chlorpheniramine in the rest of the cases (n=38) either as concomitant or co-suspected. From the reports where Chlorpheniramine is the only suspected drug, five were reported as SJS, seven as EM, two as TEN and one as Epidermal Necrolysis (EN). The time to reaction onset was reported in 40 of the cases. The median time to onset was found to be three days, ranging from one day to 25 days following the initiation of Chlorpheniramine. In 21 of the cases, of which six were TEN, nine SJS and six EM, reaction abated following discontinuation of the drug of interest (Table 1,2). The exact number of cases subjected to rechallenge was unknown; however, a positive rechallenge was reported for one case. Reaction also stopped with sequelae in five of the cases. In four of the cases, reaction outcome was marked as 'fatal 'and in 13 as 'not yet recovered'.

S.No	Sex	Age	Concomitants	Med DRA Term	Time to Onset-Days	Outcome
1.	Male	31	None	TEN	4	Not recovered
2.	Female	4	None	TEN	N.A	Recovering
3.	Male	14	None	TEN	N.A	Recovered
4.	Female	44	None	SJS	1	Recovered
5.	Female	43	None	SJS	4	Not recovered
6.	Male	4	None	SJS	6	Not recovered
7.	Female	48	Betamethasone, Paracetamol	SJS	N.A	Recovered
8.	Male	30	None	SJS	3	Unknown
9.	Male	61	None	EM, Pruritus	N.A	Recovered
10.	Male	26	None	EM, Dermatitis bullous	1	Not recovered
11.	Female	14	None	EM, Pruritus	7	Not recovered
12.	Male	12-Jan	None	EM	1	Recovered
13.	Female	1	None	EM	3	Recovered
14.	Female	40	None	EM	1	Not recovered
15.	Male	1	None	EM	1	Recovered

Table 1: Cases of EM, SJS and TEN where Chlorpheniramine was the only suspect drug.

S. No	Sex	Age	Other suspected (S) or concomitants (C)	Reaction Term (Med DRA)	Time to Onset-Days	Outcome
1	Female	84	Lisinopril (S), Pseudoephedrine (S), Clarithromycin (S), Latanoprost (S)	TEN/SJS, Sepsis	N.A	Fatal
2	N.A	N.A	Montelukast (S), Piperacillin (S), Tazobactam (S), and eight other suspects	TEN, Dermatitis bullous	NA	Recovered
3	Male	11	Calamine Lotion (S)	TEN	1	Recovered
4	Male	31	None	TEN	4	Not recovered
5	Male	13	Amoxicillin (S), Paracetamol (S)	TEN	20	Not recovered
6	Male	16	Paracetamol (S), Co-trimoxazole(S), Guaifenesin (S)	TEN	3	Recovered
7	Female	N.A	Paracetamol (S), Co-trimoxazole (S), Benzylpenicillin (S)	TEN	3	Fatal
8	Male	13	Phenoxy methyl penicillin (S), Cefotaxime (C), Paracetamol ©	TEN	1	Recovered with sequelae
9	Female	4	Chlorphenamine	TEN	N.A	Recovering
10	Female	38	Dextromethorphan (S), Paracetamol (C)	TEN	1	Recovered with sequelae

11	Female	7	Ceftazidime (S), Vancomycin (S), Paracetamol (S), Codeine (S), Ciclosporin (S)	TEN	25	Not recovered
12	Female	50	Valproic acid (S), Amoxicillin (S), Paracetamol (S), Oxolamine (S),	TEN	N.A	Recovered
13	Male	14	None	TEN	N.A	Recovered
14	Male	54	Simvastatin (S), Furosemide (S), Sulfadiazine (S), And other 43 drugs co-reported 31 as suspects and 12 as concomitants	TEN	N.A	Unknown
15	Female	48	Clindamycin (S)	SJS, Cholestasis	N.A	Recovered
16	Male	40	Paracetamol (S), Azithromycin (S)	SJS	9	Recovering
17	Female	45	Azithromycin (S), Ciprofloxacin (S)	SJS	7	Recovered
18	Female	44	None	SJS	1	Recovered
19	Male	33	Tolperisone (S)	SJS	2	Recovered
20	Female	23	Paracetamol (S), Amoxicillin (S)	SJS	8	Recovered
21	Female	43	None	SJS	4	Not recovered
22	Male	4	None	SJS	6	Not recovered
23	Female	75	Levomepromazine (S), Nortriptyline (C)	SJS	20	Fatal
24	Female	18	Homeopathic preparation (S), Paracetamol (S)	SJS	1	Not recovered
25	Male	32	Amoxicillin (S), Metamizole (C), Paracetamol (C), Co-trimoxazole (C), Dexamethasone (C)	SJS	2	Recovered with sequelae
26	Male	12-Aug	Dicloxacillin (S)	SJS	5	Not recovered
27	Female	65	Bromhexine (S), Glibenclamide (S), Aminophylline (S), Prednisolone (C)	SJS	2	Not recovered
28	Female	48	Betamethasone (C), Paracetamol (C)	SJS	N.A	Recovered
29	Male	15	Ampicillin (S), Diazepam (S), Prednisolone (C)	SJS	2	Recovered
30	Male	57	Allopurinol (S), Colchicine (C)	SJS	8	Recovered
31	Female	35	Co-trimoxazole (S), Lincomycin (S)	SJS	11	Unknown
32	Male	4	Amoxicillin (S), Paracetamol (S)	SJS	2	Not recovered
33	Female	N.A	Paracetamol (S)	SJS	3	Recovered
34	Female	62	Dimenhydrinate (S)	SJS	7	Unknown
35	Male	30	None	SJS	3	Unknown
36	Male	3	Azithromycin (S), Ascorbic acid (S), Retinol (S), Vitamin B nos (S), Vitamin D nos (S), Paracetamol (S), Nicotinamide (S)	SJS	N.A	Unknown
37	Female	25	Paracetamol (S)	SJS	N.A	Unknown
38	Female	25	Paracetamol (S)	SJS	N.A	Unknown
39	Male		Phenylpropanolamine (S), Atropa belladonna (S), and six other suspects	SJS	N.A	Recovering
40	Male	75	Glibenclamide (S), Terbinafine (S)	EM, Pyrexia, Eosinophilia, Urticaria	3	Not recovered
41	Male	2	Cetirizin (S), Co-trimoxazol(S), Paracetamol (S)	EM, Pruritus, Fatigue	1	Recovered
42	Female	2	Amoxillin (S), Co-trimoxazol (S), Paracetamol (S)	EM, Pruritus, Fatigue	1	Unknown

43	Female	2	Paracetamol (S)	EM, Pruritus	4	Recovered with sequelae
44	Male	61	None	EM, Pruritus	N.A	Recovered
45	Male	26	None	EM, Dermatitis bullous	1	Not recovered
46	Female	14	None	EM, Pruritus	7	Not recovered
47	Male	12-Jan	None	EM	1	Recovered
48	Female	1	None	EM	3	Recovered
49	Male	78	Hydroxyzine (S), Dextromethorphan (S), Bromhexine (C), Paracetamol ©	EM	1	Recovered with sequelae
50	Female	40	None	EM	1	Not recovered
51	Female	55	Amoxicillin (S), Bromhexine (C), Indometacin (C), and other seven drugs(C)	EM	1	Recovered
52	Male	1	Chlorphenamine	EM	1	Recovered
53	Female	51	Cefoperazone (S), Sulbactam (S), Acetylcysteine (S), Ceftriaxone (S), Furosemide (S), Ranitidine (S), Vancomyci(S), Vecuronium (S)	EM	2	Unknown
TEN - Toxic Epidermal Necrolysis SJS - Stevens - Johnson syndrome EM - Erythema Multiform N.A - Not Available						

Table 2: Cases of EM, SJS and TEN associated with the used of Chlorpheniramine.

Discussion

TEN, SJS and EM are very rare but highly fatal cutaneous reactions. As such, this causality assessment was inspired by a single incident of TEN associated with the concomitant use of calamine lotion and Chlorpheniramine reported to the Eritrean Pharmacovigilance Center. This case series assessment, using Austin Bradford-Hill criteria, found a suggestive causal association between Chlorpheniramine and these serious cutaneous reactions. The association of Chlorpheniramine and SJS/TEN was fore grounded by a statistical signal with an IC025 value 0.49 for TEN and 0.21 for SJS. Readers should however keep in mind that a statistical signal (i.e. positive IC value) does not mean a true signal. It is only a measure of disproportionality which indicates that the reactions of interest are more frequently reported than expected thus strengthening the association. Though co-suspected or concomitant drugs were reported in majority of the cases, Chlorpheniramine was the only suspected drug reported in 15 of the cases and concomitant drugs were reported in only one case. Of these, dechallenge information was reported in six cases and all reactions abated following withdrawal of the suspected drug, Chlorpheniramine. In one of the six cases, the suspected drug was subsequently re-introduced after the reaction resolved and the rechallenge was found to be positive. This shows that there was a plausible dose-response relationship. The presences of positive dechallenge and rechallenge, therefore, strengthens the possible causal association of Chlorpheniramine with TEN, SJS and EM.

Most of the reactions reported from different parts of the world were characterized by a more or less similar clinical feature and a similar time to reaction onset following the administration of Chlorpheniramine. Besides, in the 15 cases, reactions were very specific. Patients took only Chlorpheniramine and encountered SJS, TEN, or EM with no other co-reported reactions suggesting that the reactions were specific and consistent. In the case reported from Eritrea, other possible alternative causes including history of infectious diseases, other drugs intake and previous allergy were ruled out. Even though the reactions have low background incidence, the positive IC value, specificity and consistency of the reactions, the plausible temporal association, presence of cases with positive dechallenge and rechallenge suggest a possible association of TEN, SJS and EM with the use of Chlorpheniramine.

Measuring association of risks with spontaneous reports is however very difficult and might be potentially confounded with different alternative causes. Hence, readers should interpret the association cautiously. The safety concern over the use of drugs is one of the key impetuses for staying vigilant in detecting safety signals. Even a single case of potentially fatal incident associated with the use of a particular drug or combination of drugs should be sufficient to trigger caution. For this reason, there is no minimal number of cases below which reporting should be ignored or postponed. The incidence of TEN, SJS and EM as a result of the use of Chlorpheniramine is very critical as the drug is available over the counter (i.e. without prescription). This makes the use of Chlo-

rpheniramine potentially alarming as consumers will have access to the drug with a minimal guidance from healthcare professionals. We therefore recommend healthcare professionals to advise consumers on the early signs and symptoms of TEN, SJS and EM to prevent potential risks. We also recommend further research to be conducted to substantiate the safety signal.

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