



CASE STUDY

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Toxic epidermal necrolysis associated with combination therapy of spironolactone and torsemide

Melcy Mary Philip^{a,*}, Kala Kesavan P^a, Jai Prakash^b

^a Patient safety pharmacovigilance Associate, Govt. TD Medical College, Vandanam, Alappuzha, Kerala, 688005, India

^b Senior Principal Scientific officer, Indian Pharmacopoeia Commission, Ghaziabad, U.P., India.

ARTICLE INFO ABSTRACT



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Introduction: Dytor plus tablet is a fixed-dose combination of torsemide and spironolactone used for generalized edema. TEN is a serious, potentially life-threatening dermatological disorder.

Methods: Here we present a case report of a 47-year-old female who was on Dytor Plus (5/50 mg) therapy once daily for generalized edema; presented to dermatology outpatient department with chief complaints of multiple erosions over oral cavity, swelling of lips with scaling, redness and burning sensation in both eyes, multiple well defined mostly erythematous rashes over the entire body since 2 days.

Results: On examination, her vital signs were stable and lab results indicate she had elevated SGOT(140 IU/L), SGPT (228 IU/L), ALP (162IU/L), and blood urea(47 mg/ml) values. The patient was diagnosed to have developed Dytor plus induced toxic epidermal necrolysis. Discontinued the medicine and prescribed with Dexamethasone injection, IgG Injection, Cefotaxime injection, Cloxacillin capsule, Cetirizine tablet, Hydroxypropyl methylcellulose eye drop, and candid mouth paint. The patient had a hospital stay of 25 days.

Conclusions: The patient improved symptomatically. Causality was assessed as per the WHO-UMC causality scale and this case was put in the probable category. This case was uploaded via vigiflow under the pharmacovigilance programme of India having report Id 2019-30695.

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Introduction

Toxic epidermal necrolysis (TEN) is a rare, more severe dermatological drug reaction as compared to a Stevens-Johnson syndrome which is less severe. The main

symptoms are severe skin peeling and blistering that progresses quickly, resulting in large raw areas that may ooze or weep (Goodmann *et al.*, 2008). Dytor Plus 5mg Tablet is a combination of two medicines Spironolactone



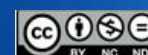
* Corresponding Author

Melcy Mary Philip
E-mail: melcyphilip20@gmail.com
Contact: +919847160339

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(50 mg) + Torsemide (5 mg) used to treat edema (fluid overload) and reduce excess fluid levels in the body while maintaining the potassium balance. Dehydration is a very common side effect as well as it lowers down the level of calcium, sodium, and magnesium in the blood. Sometimes it causes dizziness or tiredness

Generally, Oedema associated with nephrotic syndrome were treated with torsemide 100 mg co-administered with an aldosterone antagonist. No pharmacokinetic interactions have been reported following coadministration of torsemide with digoxin, spironolactone, carvedilol, or cimetidine (Dipiro *et al.*, 2002). Short term studies have shown that orally administered torsemide 5 to 20 mg/day to decrease the severity of edema and mean bodyweight to a greater extent than placebo or furosemide 40 mg in patients with chronic CHF. Torsemide 20 mg/day also achieved a greater reduction in pre-existing edema than furosemide 40 mg/day in patients with chronic CHF. Efficacy appeared to be maintained for 11 months in a longer-term dose-ranging study using torsemide 5 to 20 mg/day. Both torsemide 10 to 200 mg/day as monotherapy, and torsemide 5 to 20 mg/day plus spironolactone 50 to 200 mg/day, significantly reduced body weight and peripheral edema after up to 13 weeks treatment in patients with nephrotic syndrome. Torsemide 10 to 20 mg/day coadministered with spironolactone 100 to 200 mg/day effectively reduced edema, ascites, and bodyweight in these patients. Torsemide 10 to 20 mg/day plus potassium canrenoate 200 mg/day decreased ascites and edema in cirrhotic patients to a greater extent than either monotherapy with potassium canrenoate 400 mg/day for up to 7 days, or furosemide 25 to 50 mg/day plus potassium canrenoate 200 mg/day for 3 to 4 days. Addition of torsemide 10 to 40 mg/day to pre-existing therapy with spironolactone 50 to 400 mg/day improved ascites and edema in 73 % and 67 % of patients, respectively, after 6 months of treatment (Dunn *et al.*, 1995).

Case presentation

Dytor plus tablet is a fixed-dose combination of torsemide (which is a loop diuretic) and spironolactone (which is an antagonist of aldosterone). A 47 years old female patient was suffering from edema and started a combination therapy of torsemide (5 mg) and spironolactone (50 mg) with a dosage regimen of once a day. There was no history of any concomitant medication. The patient suffered from a serious adverse event and reported after a couple of days at the department of dermatology outdoor, with chief complaints of multiple erosions over oral cavity, swelling of lips with scaling, redness and burning sensation in both eyes, multiple well defined mostly erythematous rashes over the entire body. The patient underwent laboratory test and it was observed that her vital signs were stable and lab

result indicated that she had elevated SGOT(140 IU/L), SGPT(228 IU/L), ALP (162 IU/L) and blood urea (47 mg/ml) values. The patient was diagnosed to have developed drug-induced toxic epidermal necrolysis. The suspected drug dytor plus was withdrawn on the same date and the patient was treated medically with dexamethasone injection, IgG Injection, cefotaxime injection, cloxacillin capsule, cetirizine tablet, Hydroxypropyl methylcellulose eye drop, and candid mouth paint. The patient was getting admitted to the hospital resulting in the adverse event to be considered as a serious adverse drug reaction. The patient had a hospital stay of 25 days. The patient improved symptomatically. Causality was assessed as per the WHO-UMC causality scale and this case was put in the probable category as the de-challenge test resulted in improving the health condition of the patient. This case was reported to the National coordination center through vigiflow having a report Id 2019-30695.

Discussion

The majority of adverse effects associated with spironolactone are dose-dependent. Higher dose therapy using more than 100 mg/day is more likely to cause hyperkalemia, particularly when there is a cardiac or renal compromise. Other dose-dependent side effects include menstrual irregularities (metrorrhagia, amenorrhea, breakthrough bleeding), breast tenderness and enlargement, orthostatic hypotension, hyperkalemia, and reduced libido (Kim *et al.*, 2012).

A case has been reported for 80 years old man who was treated with spironolactone for the management of heart failure, his prostate cancer was exaggerated. After 2 weeks of spironolactone withdrawal, the patient returned to his previous condition. This indicates that spironolactone is a selective androgen receptor modulator. Hence, spironolactone should be used in caution with men with prostate cancer, and should not be used to treat edema (Sundar *et al.*, 2012).

A drug surveillance program had been conducted on 13,349 patients treated with spironolactone resulted in adverse events in 164 patients. Hyperkalemia has mostly occurred in 68 patients and an increased level of blood urea nitrogen in 161 patients. Other adverse reactions such as dehydration, hyponatremia, gastrointestinal symptoms, neurological disturbances, and skin rashes were less common (Greenblatt *et al.*, 1973).

The most common adverse reaction in women taking spironolactone was hyperkalemia but it was extremely uncommon in women age less than 45 years (1.9 % of all hyperkalemia cases). Increased Google searches and scholarly mentions in the Altmetric database for spironolactone were also associated with increased

reporting of adverse events in the FAERS database for men and women combined (Wang et al., 2020).

The causality of ADRs was assessed in a study conducted to assess the incidence, causality, and severity of diuretic-induced Adverse Drug Reactions (ADRs). About 40 out of 92 patients suffered from ADRs. Naranjo's scale identified 25 ADRs as probable, 15 as Possible, and none as unlikely or certain; the WHO scale identified 22 ADRs as Possible and 18 as Probable. Hartwig's and Seigel's scale identified 28 ADRs as moderate, 09 as Mild, and 03 as severe. This study indicates that diuretics induced ADRs could be minimized by early prediction of the symptoms (Vikas et al., 2017).

A 28-year-old female patient suffering from Acne for 5 years was prescribed with 100 mg spironolactone once daily for a month. Within 30 min following the consumption of spironolactone, the patient developed intense pruritus, conjunctivitis, angioedema, skin rash. The patient recovered from the adverse event in 3 days of medical treatment with 10 mg of cetirizine hydrochloride and 20 mg of prednisolone (Mehta et al., 2016).

A study indicated that the rash was a very rare adverse reaction associated with torsemide. Only around 3 % of the 1,048 medicines analyzed developed rashes (Ancuceanu et al., 2019).

Torsemide, a potent loop diuretic of the sulfonylurea class resulted in photosensitive lichenoid reaction in an 82 years old male patient. Adverse generalized and cutaneous reactions to this medication are uncommon and are usually mild and transient. Because of the potential risk for cross-reactivity of torsemide with the sulfonamide group of medications, torsemide should be used cautiously in sulfonamide hypersensitive patients (Byrd et al., 1997).

Conclusions

We report the first case of toxic epidermal necrolysis associated with combination therapy of spironolactone and torsemide. which helps to further demonstrate a possible link between diuretics uses while treatment of edema. Though it could not be confirmed that the adverse event has a causal relationship with the drug but still it cannot be ruled out that it cannot cause such adverse events in the future. Hence the patient should be taken care of properly with close monitoring to observe the symptoms and protect from any such adverse drug reaction.

Conflict of interest

There is no conflict of interest between the authors.

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