



## A Case of Bupropion-Induced Toxic Epidermal Necrolysis (TEN)

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### Abstract

Toxic Epidermal Necrolysis (TEN), which has high mortality, is an acute mucocutaneous disease with bullous lesions in the skin, eyes and mucosae. It often develops due to medications. Bupropion is an antidepressant that blocks neural dopamine and the noradrenaline reuptake. Its slow-release form is used in smoking cessation treatments. In the literature, Bupropion-induced side effects have been reported such as urticaria angioedema, erythema multiforme, and acute generalized eczematous pustulosis. We found it appropriate to present our case of Bupropion-induced toxic epidermal necrolysis, which has not yet been presented in the literature.

**Keywords:** Toxic epidermal necrolysis; Urticarial; Bupropion; Immunoglobulin

### Introduction

Toxic Epidermal Necrolysis (TEN), which has high mortality, is an acute mucocutaneous disease consisting of bullous lesions in the skin, eyes, and mucosae [1]. A pathogenesis of the disease has yet to be fully understood although it has been thought that the deterioration of the control mechanism of the keratinocyte apoptosis and the increase in fas ligand expression in the keratinocytes play a fundamental role in the triggering of necrosis [2]. The difference between Stevens Johnson Syndrome (SJS) and TEN is based on the involvement of the body surface percentage (percentage of epidermal detachment or the potential to detach). It must be distinguished that if the involvement of the body surface is less than 10%, between 10-30%, and more than 30%, they are accepted as respectively a SJS, 'SJS/TEN overlap and TEN) [3]. SJS and TEN are accepted as idiosyncratic drug reactions. They often develop due to drugs [4]. Many medications have been reported in association with SJS/TEN although the most common drugs are the sulfonamide group of antibiotics, anticonvulsant drugs, allopurinol, non-steroidal anti-inflammatory drugs, and nevirapine.

Bupropion is an antidepressant that blocks neural dopamine and noradrenaline reuptake [5]. Its slow-release form is used in smoking cessation treatments. Bupropion SR is the first non-nicotine pharmacological agent which has been used for smoking cessation. The side effects associated with Bupropion such as urticaria, angioedema, erythema multiforme, and acute generalized eczematous pustulosis have been reported in the literature [6,7].

### Case Presentation

A 38-year-old female patient was complaining of widespread redness (rash) and denudation of the skin, sores in her mouth, and stinging in her eyes. She was admitted to ICU with a diagnosis of TEN. She had a history of smoking for 10 years and was treated with Bupropion for 14 days. She did not have any contributing factors in her background or her family history. There were no previous drug allergies, hypersensitivity reactions, or any history of atopy or skin reactions. Her physical examination revealed a blood pressure of 130/80 mmHg, pulse rate of 122 per minute, and a body temperature of 36.9°C. The dermatological examination showed approximately 80% of her body had erythematous, and maculopapular eruptions with a tendency to merge (Figure 1). There was also more than 30% of the involvement area that had bullous lesions. There were erosions in the eyes, oral, and genital mucosa (Figure 2). The laboratory investigations were as follows: Hemoglobin 15.4g/dl, White blood cells 6900/mm<sup>3</sup>, Platelet 154000/mm<sup>3</sup>, CRP 149.8mg/L, Glucose 163mg/dl, Urea 26.4mg/dl, Creatinine 0.7mg/dl, ALT 120 u/L, and the Serum bicarbonate was found to be 19.2mmol/L. The SCORTEN score was assessed as 3 (Table 1).

She was treated with IVIG at a dose of 40mg/day for total of 3 days (sum of 120mg), methylprednisolone at a dose of 1mg/kg/day (80mg), oral antihistamine, nutritional support,

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**Table 1:** SCORTEN score and accompanying mortality rates<sup>1</sup>.

Parameters	Individual Points	SCORTEN Score (sum of individual points)	Mortality Rate (%)
Age $\geq$ 40 years	1	0 - 1	3.2
Presence of malignancy	1	2	12.1
BUN > 28 mg/dl (>10mmol/L)	1	3	35.3
Serum Glucose > 252mg/dl (> 14mmol/L)	1	4	58.3
Heart rate $\geq$ 120 per minute	1	$\geq$ 5	90
Serum Bicarbonate < 20mmol/L	1		
Body surface epidermal detachment > 10 %	1		

<sup>1</sup>'Yes' answers to the parameter are worth one point each 'No' answers are worth zero.

<sup>2</sup>Note: SCORTEN is the severity of the disease score. This scale is recommended to be used within 24 hours of the patient's first visit and on the 3<sup>rd</sup> day. The value in the paediatric age group is not fully known yet.

The SCORTEN score is explained in Table 1. Our patient's heart rate  $\geq$  122, Serum bicarbonate < 20, and involvement of the body surface area > 10.

and on the advice of the infectious diseases department an I.V. Ceftriaxone therapy was started. In addition, topical steroid cream, eau borique dressing, antibiotic cream, and a sterile wound dressing were applied. Consultations with an ophthalmologist, an infectious diseases specialist, an internist, a plastic surgeon, and a gynecologist were carried out. Antibiotic eye drops and artificial tears were used for the eye lesions. A hemoculture, urine culture, and swab cultures from the open wounds were conducted, but no microbial growth was detected. The antibiotic therapy was completed in 10 days, and the systemic steroid therapy was gradually tapered and stopped at the end of three weeks. From her follow-ups, it was found that her skin lesions had started to regress. At the end of the second week, she was transferred from the ICU to dermatology unit because lesions were regressing due to the therapy. She was discharged with a full recovery on the 4<sup>th</sup> week. She is continuing with her follow-ups, and except for mild-sclerosis on her skin she has no other morbidity (Figure 3).

## Discussion

In TEN, it is believed that immune-related cytotoxic reactions destroy keratinocytes. The damage in keratinocytes due to drugs occurs when CD4 and CD8 + T lymphocytes infiltrate into the skin and release cytokines such as perforin, granzyme B, IL12, and interferon gamma, which activate cytotoxic T lymphocytes. Active cytotoxic T lymphocytes play important roles in triggering apoptosis [8,9]. The keratinocyte necrosis in TEN is the result of a change in the control mechanism of the death receptor FAS (CD95), which is located on the cell surface of the keratinocytes and its specific FAS ligand conjunction [10,11].

Currently, there is no standard treatment accepted for TEN. There have been many immunosuppressive or immunomodulatory treatment modalities used, including; systemic corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine, plasmapheresis, and tumour necrosis factor alpha inhibitors. However, the data associated with these treatments is limited and also controversial. It has been shown that IVIG, which has been used recently in TEN treatments, contains antibodies that block FAS in vitro, and inhibits apoptosis by blocking the formation of the FAS-FASL compound [11,12]. However, there are some opinions that argue that the duration of necrolysis and the prevalence and mortality rates in patients treated with IVIG are not different from what is expected from other treatments [13]. Systemic steroids usage in TEN has also been used for many years. In the EUROSCAR study, there was no significant mortality differences detected when comparing the group treated with steroid, IVIG, or combinations of these treatments, with

the only supportive treatment group. This study was carried out with 281 patients.

The SCORTEN scale was developed to assess TEN, which is widely used to predict the severity of the disease and the mortality rate accordingly. It is extremely important that patients with a SCORTEN score 3 (mortality rate: 35.3%) or higher are transferred quickly to the burn unit or intensive care unit.

Smoking is one of the most significant health problems of today which causes serious morbidity and mortality. Bupropion is a new generation antidepressant that mainly blocks neuronal dopamine and noradrenalin reuptake. It is also effective on serotonin reuptake. It is being used in major depressive disorders and bipolar disorder treatment. Bupropion's slow release form has been successfully used since 1997 in smoking cessation treatment and is generally well-tolerated. Bupropion is widely used in smoking cessation outpatient clinics.

The major side effects of Bupropion are headaches, insomnia, convulsions, dry mouth, and skin reactions. In clinical studies, hypersensitivity reactions due to Bupropion have been reported in 3% [8]. The symptoms often develop between the 10<sup>th</sup> to 20<sup>th</sup> days of the treatment. Hypersensitivity reactions are usually accompanied by itching, redness, and urticaria. Other rare side effects such as angioedema, serum-like reactions, erythema multiforme, and anaphylaxis have also been reported. In our case, Bupropion-induced TEN developed. Bupropion is generally well-tolerated, but it does, on occasion, cause serious hypersensitivity reactions, which we should be aware of and thus, inform patients accordingly. In our case report, we would like to draw attention to the fact that the side effect of Bupropion may cause TEN, which to date, has not been reported in the literature.

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