

# Cutaneous reactions simulating erythema multiforme and Stevens Johnson syndrome due to occupational exposure to a plant-growth regulator

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## ABSTRACT

**Background:** In India, hydrogen cyanamide (Dormex®) is a plant growth regulator used mainly for the bud-breaking of grapevines. The use of this chemical may result in severe cutaneous reactions simulating erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). **Methods:** Studies were conducted on four seasonal grapevine workers who developed severe cutaneous reactions following the unprotected use of Dormex® (hydrogen cyanamide). **Results:** Two of the patients had EM-like skin lesions and the other two developed SJS-TEN-like skin lesions. A latent period of 5-7 days existed between the contact with the chemical and the development of the skin lesions. The histopathological picture was suggestive of EM. All the patients responded to systemic steroids and antihistamines. **Conclusions:** Hydrogen cyanamide may act as a hapten, initiating cytotoxic immunological attack on keratinocytes, resulting in EM- and SJS-TEN-like clinical picture. Awareness regarding such severe cutaneous reactions due to the inappropriate handling of Dormex® is required. The use of personal protection equipments while handling agricultural chemicals is essential.

**Key Words:** Skin reactions, Dormex®, Hydrogen cyanamide

## INTRODUCTION

Hydrogen cyanamide (Dormex®) is a plant growth regulator used to enhance the flowering of seasonal plants.<sup>[1]</sup> Vineyard workers use this product routinely to ensure the optimum growth of grapes. The northern districts of Karnataka state of India are famous for excellent quality grape production because of the arid climate. During the time of blooming, usually, poor people are employed on the basis of daily wages for applying Dormex® to the buds. These workers do not use personal protection equipments while handling the chemical due to lack of awareness regarding its adverse effects.

Mild skin lesions have been described as a result of the inadvertent handling of Dormex®. Severe cutaneous reactions simulating erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have

been reported for the first time among fifteen such workers from this region.<sup>[2]</sup> Hydrogen cyanamide may also cause serious systemic effects such as headache, palpitation, vomiting, respiratory distress, hypotension, altered sensorium, disulfiram-like reaction and ocular irritation.<sup>[3]</sup> Here, cutaneous reactions resulting from Dormex® in four seasonal grapevine workers are described.

## METHODS

Four patients, who attended the dermatology out-patient department of a tertiary care hospital during October to December 2006 with skin lesions following the handling of Dormex®, were studied. Detailed history regarding exposure to the chemical and evolution of the skin lesions were elicited. Two patients required hospitalization because of extensive skin involvement whereas the other two were

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managed on outpatient basis. A skin biopsy was taken from the first patient with milder involvement. Tzanck smear was prepared from the skin lesions of the third and fourth patients with bullous lesions. The patients were treated with systemic corticosteroids and antihistamines. Counseling was done regarding the usage of personal protection measures while using such chemicals. Occurrence of these cases was brought to the notice of the local health units in order to ensure preventive action.

## RESULTS

Autumn and early winter (September to early December) are the usual seasons for applying Dormex® in grapevines, and all the four patients presented during this time. They were working in the vineyard for the first time. Patient profile and details of the clinical features are presented in Table 1.

All the four patients sprinkled the chemical manually without using any personal protection gears. However, they gave history of washing hands and feet following the work using soap and water. There was an interval of 5-7 days between the handling of Dormex® and the appearance of the symptoms. The third patient developed the symptoms following cleaning of a utensil that he had used to pour the liquid Dormex® 5 days ago. The conditions started as burning and stinging sensation over the involved areas followed by the appearance of itchy, erythematous papules. In two patients, some of the papules developed central necrosis simulating atypical target lesions [Figure 1]. In both the male patients the lesions progressed to form flaccid vesicles and bullae even over the covered body parts such as the trunk. Nikolsky's sign was positive. These lesions ruptured to form denuded areas simulating SJS-TEN [Figure 2]. Mucous membranes were not involved. There was no systemic involvement in any of the patients. The fourth patient gave the history that 25 of his coworkers developed stinging and burning sensation following the handling of Dormex®.

Hematoxylin and eosin (H and E) stained histopathological section of the skin biopsy from an EM-like lesion showed vacuolar degeneration of the basal cell layer, satellite cells and apoptotic keratinocytes. There was lymphocytic infiltrate at the dermoepidermal interface, which was consistent



Figure 1: Atypical target-like lesions in case 2



Figure 2: Extensive denudation of the skin in case 4

with the histopathological features of EM. Tzanck smear was performed from freshly denuded area in both male patients and it revealed rounded keratinocytes and abundant inflammatory cells.

All the patients were treated with systemic corticosteroids and antihistamines. The EM-like lesions in the female patients resolved in 7 days. Patients with vesiculobullous lesions simulating SJS-TEN required hospitalization in the dermatology intensive care unit and the management for acute skin failure. These lesions healed by two weeks with postinflammatory hyperpigmentation. Patient counseling was

Table 1: Details of patients with skin lesions due to Dormex®

No.	Age/sex	Duration	Exposure to dormex	Sites involved	Morphology of lesions
1.	18 years/F	8 days	15 days back	Distal extremities	Erythema multiforme-like
2.	40 years//F	2 weeks	3 weeks back	Trunk and extremities	Erythema multiforme-like
3.	40 years/M	10 days	15 days back	Face, back, extremities	Stevens-Johnson syndrome - toxic epidermal necrolysis like
4.	28 years/M	8 days	15 days back	Trunk and extremities	Stevens-Johnson syndrome - toxic epidermal necrolysis like

done regarding the safe usage of agricultural chemicals.

## DISCUSSION

The principal active ingredient of Dormex<sup>®</sup> is hydrogen cyanamide (49%, w/w).<sup>[1]</sup> It has been marketed in India since 1989 as a growth-promoter of grapes. The product label on the container (marketed in India) provides a warning only regarding the skin and eye irritations. However, the inadvertent use of Dormex<sup>®</sup> is known to cause dermatological manifestations more than just "irritation," such as erythema, pruritus, caustic burns and maculopapular rash.<sup>[3]</sup> It can also cause sensitization following skin contact.<sup>[3]</sup> In an earlier occasion, a similar inappropriate use of this chemical in this area of north Karnataka led to development of EM and SJS-TEN-like skin lesions in fifteen grape-vine workers.<sup>[2]</sup> Whether these lesions belonged to classical EM-SJS-TEN spectrum of diseases or contact EM-like eruptions due to Dormex<sup>®</sup> remained elusive.<sup>[2]</sup> All the four patients described here, had EM-like lesions initially, and these lesions finally developed into SJS-TEN-like lesions in two of them.

Pathomechanism involved in the development of such lesions following exposure to Dormex<sup>®</sup> is not clear. There was a lag period of 5-7 days between the contact with Dormex<sup>®</sup> and the development of skin lesions in all the patients, suggesting an underlying immune mechanism rather than an irritant contact dermatitis. Initially, EM-like lesions were observed.

Histopathologically, there was evidence of satellite cell necrosis and apoptotic bodies. Two of the patients developed clinical features simulating SJS-TEN even on covered body parts that are unlikely to have direct contact with the chemical. All these factors led us to presume that these lesions might have developed by a mechanism similar to classical EM and SJS-TEN. Hydrogen cyanamide molecules (Mol. wt.: 42 kDa) might have acted as haptens, binding to the keratinocytes and rendering them antigenic. This might have initiated a cytotoxic immunologic attack on the keratinocytes expressing this nonself antigen as it occurs in herpes simplex virus or drug induced classical form of the disease.

Reports of systemic and cutaneous toxicity due to the inappropriate use of Dormex<sup>®</sup> are available.<sup>[3,4]</sup> Majority of these reports is from Italy, where the sale and use of

the compound was temporarily withheld in February 2002.<sup>[4]</sup> Subsequently, in June 2003, it was re-introduced following the enhancement of the precautionary measures. However, even after this measure, there were incidents of adverse effects following the occupational exposure of the chemical.<sup>[4]</sup> This highlights the urgent need of educating the agricultural laborers regarding the safe use of hydrogen cyanamide.

In India, the awareness campaigns for agricultural workers regarding the safe usage of chemicals and fertilizers are not conducted routinely. Due to illiteracy, the workers remain unaware of the precautionary information given on product label. Poverty forces them to work with chemicals such as Dormex<sup>®</sup> without any personal protection equipments in exchange of minimum daily wages. Lack of surveillance/notification systems to track agricultural chemical poisoning has worsened the situation as many cases go unrecorded by health authorities. Hence, there is a lack of awareness regarding these serious side effects of Dormex<sup>®</sup> even among physicians.

This report and an earlier report<sup>[2]</sup> on the serious cutaneous reactions due to Dormex<sup>®</sup> should be an eye-opener for the agricultural and health authorities. The product label of Dormex<sup>®</sup> should mention such severe cutaneous reactions. Regular or seasonal awareness campaigns for agricultural workers regarding the side effects of fertilizers and plant growth regulators and their proper usage may avert such untoward reactions in future.

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