CASE REPORT

Levamisole Causing a Fixed Drug Eruption

Sandra Knowles and Neil H. Shear

INTRODUCTION

Levamisole, an anthelmintic agent, has been used as an immunostimulant since 1972. It has also been investigated in various disease states including rheumatoid arthritis, leprosy, and colon cancer. The most frequently reported adverse effects include gastrointestinal symptoms, febrile illness, fatigue, agranulocytosis, and skin reactions[1]. Skin rash has occurred in up to 15% of rheumatoid arthritis patients treated with levamisole[2]. Other cutaneous reactions include erythema multiforme, erythema nodosum[3], and lichenoid skin eruptions[4]. This case represents the first published report describing a fixed drug eruption (FDE) caused by levamisole.

CASE

A 68 year-old woman was diagnosed with Duke's C colon carcinoma, for which treatment with 5-fluorouracil (5-FU) 450 mg/m^2/week, and levamisole 50 mg tid for three consecutive days every other week was prescribed. Concurrent medication therapy included domperidone as needed for nausea and vomiting. After four courses of levamisole and eight courses of 5-FU, an itchy lesion was noted on the right leg. The skin lesion was described as red spots, approximately 2 cm in diameter, that faded with time to a brown colour. The lesion tended to be slightly pruritic and recurred in the same place with each treatment course. The "spots" appeared about eight hours after receiving chemotherapy and levamisole. The lesion improved over the next week with the application of 1% hydrocortisone cream. During the next two months, the lesions remained bothersome for the patient and she continued to apply the steroid cream. After the eighth course of levamisole, the skin lesions appeared on the shoulder area. As with each previous cycle, the lesions faded prior to the next cycle of levamisole. On the basis of this presentation, a diagnosis of a FDE was made.

In order to prove that the skin lesions were due to the levamisole and not 5-FU, levamisole was not given for the llth and 12th cycle. During this time. the lesions completely resolved. The levamisole was restarted after this time and the lesions reappeared. Domperidone, the only other agent being taken by the patient, was discontinued prior to the levamisole challenge. Shortly thereafter, because of a lack of response, the chemotherapy was discontinued.

DISCUSSION

Fixed drug eruptions were first described in 1894 as a result of antipyrine ingestion. Many drugs have been implicated as a cause of FDE including tetracycline, acetaminophen, quinidine, metronidazole, dimenhydrinate, phenolphthalein, and barbiturates[5-8]. The appearance of a FDE may involve more than one drug. The two drugs may be chemically related (e.g., demeclocycline and tetracycline) or chemically unrelated compounds (e.g., tetracycline and oxphenbutazone)[6,8]. A literature search using Medline® and Embase®, revealed no other reports of levamisole causing a FDE.

Fixed drug eruptions recur in the same skin area after readministering the causative medication. They usually appear as solitary pruritic, erythematous, bright red or dusky red macules that may evolve into an edematous plaque. In some patients, multiple lesions may be present. Mucosal

Sandra Knowles, B.Sc.Phm., is a Pharmacist, Adverse Drug Reaction Clinic, Sunnybrook Health Science Centre, North York, Ontario
Neil H. Shear, M.D., FRCP (C), is the Director, Adverse Drug Reaction Clinic and the Director, Division of Clinical Pharmacology, Sunnybrook Health Science Centre.
Address correspondence to: Sandra Knowles, Adverse Drug Reaction Clinic, Sunnybrook Health Science Centre, University of Toronto, 2075 Bayview Avenue, North York, Ontario, M4N 3M5

surfaces may be involved with blistering and erosion. After the initial acute phase, residual hyperpigmentation develops over a period of a week, with the lesions varying in colour from brown to black[6,7]. Some patients may complain of burning or stinging in the affected skin sites. Systemic manifestations are present in approximately 25% of cases, and can include fever, malaise, and abdominal symptoms. Antihistamines appear to have no effect on FDEs[6].

Fixed drug eruptions are most common on the genitalia and in the perianal area, although they can occur anywhere on the skin surface. The onset of a FDE can be sudden, developing within 30 minutes to 8 hours after ingestion of the medication. In other cases, the reaction may be delayed up to 15-16 hours after drug provocation. The lesions persist for a few days to a few weeks. In patients who continue to receive the offending drug, the number of sites may gradually increase[5-8].

Some patients with FDE demonstrate a refractory period of a few weeks to several months during which time the implicated drug does not produce a recurrence of the eruption. The mechanism for this refractory period is unknown, although it has been suggested that it may represent desensitization[5-8].

Several investigations have been carried out to aid in the diagnosis of FDE. These have included light and electron microscopy studies, patch testing, autotransplantation, and immunological studies. Unfortunately, no conclusive tests are available nor has the pathogenesis of a FDE been fully elucidated. A challenge or provocation test with the suspected drug may be useful in confirming the diagnosis[9,10]

In this patient, levamisole was implicated in causing her lesions. The cutaneous reaction occurred after four courses of levamisole and was consistent with that of a FDE. Although no biopsies or other studies were performed in the patient, a diagnosis of FDE due to levamisole was based on the clinical appearance and the positive results upon drug rechallenge.

REFERENCES

1. Symoens J, Veys E, Mielants M, et al. Adverse reactions to levamisole. *Cancer Treat Rep* 1978;62:1721-30.
2. Anon. Multicentre Study Group. Levamisole in rheumatoid arthritis. *Lancet* 1978;II:1007-12.
3. Lionel NDW. Anthelminthic drugs. In: Dukes MNG, Elis J, eds. Side effects of drugs, Annual 7. Amsterdam: *Excerpta Medica*; 1983:317.
4. Kirby JD, Black M, McGibbon D. Levamisole-induced lichenoid eruptions. *J R Soc Med* 1980;73:208-11.
5. Korkij W, Soltani K. Fixed drug eruption: a brief review. Arch Dermatol 1984;120:520-4.
6. Sehgal VN, Gangwani OP. Fixed drug eruption: current concepts. *Int J. Dermatol* 1987;26:67-72.
7. Commens C. Fixed drug eruption. *Aust J Derm* 1983;24:1-8.
8. Bork K. Cutaneous side effects of drugs. Philadelphia: *WB Saunders*;1988:98-108.
9. Kauppinen K, Stubb S. Fixed eruptions: causative drugs and challenge tests. *Br J Derm* 1985;112:575-8.
10. Sehgal VN, Rege VL, Kharangate VN. Fixed drug eruptions caused by medications: a report from India. *Int J Dermatol* 1978;17:78-81.