

Delayed Occurrence of a Severe Cutaneous Reaction in a Multiple Sclerosis Patient Taking Interferon Beta-1b

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ABSTRACT

We report a case of a patient treated for relapsing multiple sclerosis (MS) with interferon beta-1b who developed a severe vasculitic-like skin reaction 9 months after initiation of interferon therapy. Prompt discontinuation of interferon beta-1b and institution of corticosteroid therapy was associated with complete resolution of the cutaneous lesions. Other potential causative agents were excluded by penicillin skin sensitivity testing or continuing use in the absence of adverse reactions. We conclude that a vasculitic-like cutaneous reaction to interferon beta-1b may occur long after institution of therapy in some MS patients. We review other case reports of severe cutaneous reactions associated with interferon beta-1b therapy in MS patients that suggest that susceptibility cofactors may be important elements in the occurrence of these reactions, and consider whether other medications commonly used in MS patients could have such a role. (Allergy and Asthma Proc 19:85–88, 1998)

Interferon beta-1b has been used widely in the treatment of multiple sclerosis (MS) patients with relapsing forms of the disease since 1993. A multicenter placebo controlled clinical trial employing two dosage regimens in 372 patients

demonstrated efficacy of this agent in reducing both frequency and severity of attacks in MS patients with relapsing disease leading to its release. In the course of that trial, several common and usually self-limited side effects were noted in substantial numbers of the treated participants, including flu-like symptoms and local cutaneous reactions at the sites of subcutaneous injection. Injection-site reactions were noted initially in 80% of individuals in the high dose regimen currently used clinically and 63% of the lower dose regimen. These reactions diminished in frequency with continued use but were still seen in 44 to 50% of the individuals followed for 4 or 5 years. In most instances these cutaneous reactions consisted of local erythema.^{1,2} With more widespread use, injection-site necrosis and painful nodules were reported in a few cases after therapy of 6–19 weeks.^{3,4} We recently encountered a patient who developed a vasculitic type cutaneous reaction to interferon beta-1b after 9 months of previously tolerated therapy.

CASE REPORT

A 34-year-old woman with relapsing multiple sclerosis was begun on interferon beta-1b therapy 4 years after onset of her first symptoms of MS. In 2½ years before initiation of therapy she had four distinct relapses consisting of optic neuritis affecting either eye and myelopathy. Past medical history was also notable for migraine headaches, and coarctation of the aorta which was surgically repaired. Initial flu-like symptoms attenuated over 3 months, although she continued to have some malaise and headaches after administration and injection-site erythema. An attack of optic neuritis occurred 3 months after initiation of interferon beta-1b. She developed diarrhea while on therapy and

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was diagnosed to have lactose intolerance, with response to dietary modification. Nine and one half months after initiation of interferon therapy, she presented with an acute painful, purpuric reaction involving her limbs, trunk, and face, evolving over several hours from a warm, erythematous, pruritic reaction at injection sites from the previous week to a generalized, raised, erythematous plaque-like reaction (Figs. 1 and 2). Three warm erythematous lesions were present on her abdomen at sites of previous injections. Two weeks earlier she had been given dicloxacillin and topical erythromycin ointment briefly for conjunctivitis. She had received penicillin previously without reaction. Other medications included baclofen, amantadine, intermittent oxybutynin and hyoscyamine, all of which she subsequently continued without adverse reaction.

Physical examination revealed no fever or mucosal lesions, conjunctival injection, cardiopulmonary abnormalities, or hepatosplenomegaly. Neurologic examination revealed moderate spastic ataxia and paraparesis (MRC 4/5) and a Marcus Gunn pupil on the right unchanged from her stable neurologic examination 3 weeks earlier. Laboratory studies including a sedimentation rate, blood count, and chemistry profile were normal. The interferon beta-1b was discontinued and she was treated with prednisone 35 mg for 1 week, followed by a 3-week tapering reduction. The rash resolved over a 2-week period without formation of ulcers or bullae, and without recurrence after discontinuation of the prednisone.

Subsequent immediate skin testing for penicillin allergy revealed negative prick and intradermal reactions to major (PrePen, Schwarz Pharma Inc, Milwaukee WI) and minor determinants (benzylpenicillin G, sodium penicilloate and

benzylpenicilloyl-n-propylamine). Oral challenge with 250 mg of penicillin V failed to produce any untoward reaction.

DISCUSSION

Injection-site reactions are common in MS patients using subcutaneously administered interferon beta-1b. Five types of reactions have been noted in the report of a consensus conference reviewing its indications and use: local erythema, bruising, and pain likely related to injection technique, cutaneous and subcutaneous infection also likely related to injection technique, subcutaneous atrophy and uncommonly, necrosis with secondary infection.⁵ Attention to injection technique may reduce the frequency of some reactions but persistence of erythematous reactions at injection sites appears to occur in about half of patients at 4 to 5 years of follow-up.² In a study after release of interferon beta-1b, mild skin reactions were noted in 47 and 44% of patients with relapsing/remitting and relapsing/progressive clinical patterns respectively; however, they were seen less frequently in a small number of patients with chronic progressive disease.⁶ One might speculate whether more pronounced immune activation in patients with relapsing disease is related to the occurrence and perhaps the severity of these cutaneous reactions.

Interferons are classified by their source as leucocyte (alpha), fibroblast (beta), or immune (gamma), the latter derived from T lymphocytes and natural killer cells. Interferons alpha and beta share receptor sites, some homology, and immunologic effects and appear to have antagonistic immunomodulating properties to interferon gamma, which has been shown to induce attacks in MS patients. Interferon

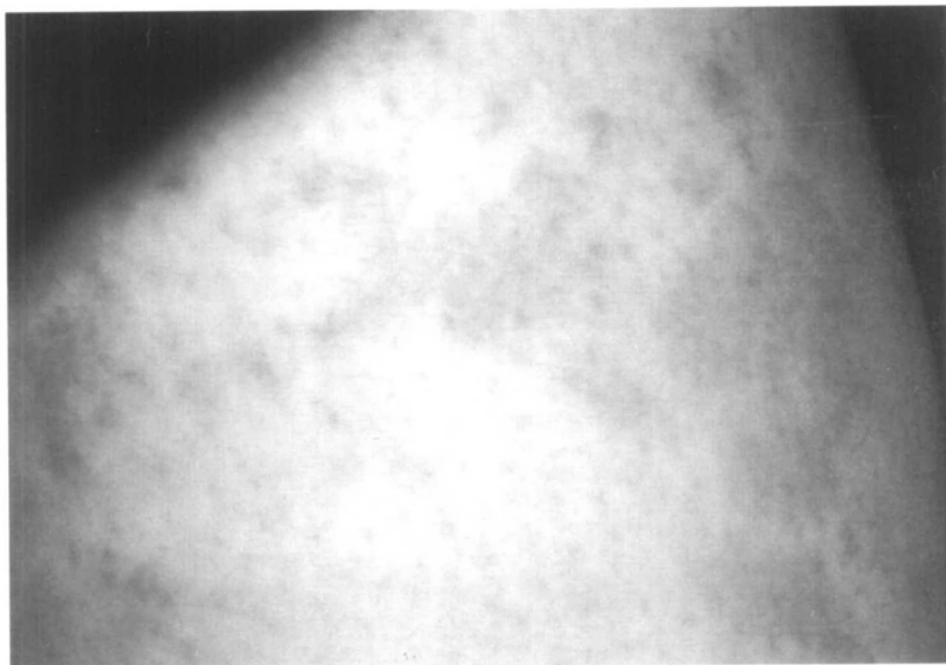


Figure 1. Contralateral leg demonstrating raised plaque-like erythematous lesions and erythematous papules. Prednisone 35 mg daily had been administered for 5 days at the time of this photograph.

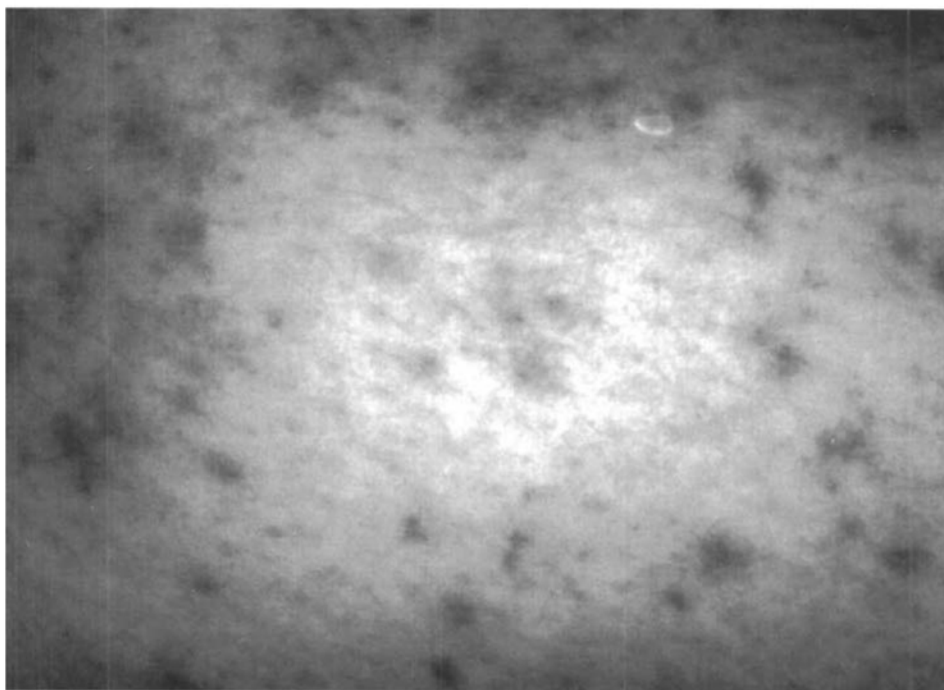


Figure 2. Example of maculopapular erythematous lesions on contralateral thigh. Prednisone had been administered as in Figure 1.

alpha and beta enhance CD8 suppressor T lymphocyte effects and CD8 cytotoxicity.⁷

Necrotizing cutaneous lesions which may occur in 1 to 3% of individuals given interferon beta-1b also have been described with interferon alpha in MS patients and patients treated for leukemia or Kaposi's sarcoma in AIDS. Similar dermatopathology consisting of perivascular and interstitial lymphocytic and histiocytic infiltrates with focal vascular thrombosis have been described in patients treated with both interferon beta-1b and interferon alpha.^{3,8} While the mechanism by which interferon beta-1b induces cutaneous necrosis and ulceration is unknown, the infrequency of occurrence and multiplicity of involved sites suggest that it is not due to injection-trauma, but rather reflects an underlying susceptibility, perhaps in conjunction with cofactors, as continued use in at least one patient has not been associated with persistent ulceration. It has been suggested that the pain occurring soon after injection at sites of necrosis may be related to local vasospasm.⁴ Sheremata et al. described a prominent vascular pattern resembling livedo reticularis surrounding the region of necrotic ulceration in their case.³

Our patient presented with a cutaneous reaction that differed from those previously described. The onset occurred much longer following initiation of therapy and differed in appearance from previous reports. The generalized raised erythematous rash and purpura that followed an initial local painful erythema at sites of recent injection suggests an immune mediated systemic response typical of a vasculitic reaction. It is possible that prompt discontinuation of interferon beta-1b and institution of corticosteroid therapy prevented development of a necrotizing process which might have included ulcerative lesions such as those previously described. Several reports have described pa-

tients given interferon alpha who developed or suffered reactivation of inflammatory rheumatologic disorders including systemic lupus and rheumatoid arthritis.⁹ The presence of other diseases limits interpretation of causation of the rheumatologic features of the flu-like reactions commonly seen with interferon therapy, and their persistence in some patients more than a year later² could suggest activation of generalized immune responses established by susceptibility or cofactor, which could result in serositis or cutaneous vasculitis. The high molecular weight of interferon beta-1b (>19kd) allows for the possibility of immune complex formation. If this is the case, the rarity of such reactions might reflect the small dosage administered in comparison to other immune therapeutic agents such as equine antithymocyte globulin, which may precipitate serum sickness.¹⁰

Other medications that might have been implicated in the occurrence of our patient's cutaneous reaction have either been eliminated by penicillin skin testing and readministration or by continuation in the absence of adverse effect. It is of possible interest that she began the use of amantadine a few weeks before the onset of the reaction, though she has subsequently continued it in the absence of interferon beta therapy without incident.

In summary, our case indicates the potential for a vasculitic type cutaneous reaction during long-term interferon beta-1b therapy. Prompt discontinuation of interferon beta-1b and institution of corticosteroids was associated with rapid and complete resolution of the cutaneous symptoms. The potential for interactive effects of interferon beta with other agents commonly used in MS patients such as amantadine is not established by this report but should be monitored in light of this case and previous reports sugges-

tive of a vasospastic process in necrotizing cutaneous ulceration. The possibility that interferon beta might induce generalized immune reactions affecting other organs in susceptible individuals is speculative and intriguing.

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2. Data on file.

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A starting dose of 2 sprays in each nostril twice daily is recommended. If greater control of symptoms is needed, the dose may be increased to 2 sprays in each nostril 3 times a day. For adults, maximum total daily doses should not exceed 8 sprays in each nostril per day (400 mcg/day).

After the desired clinical effect is obtained, the maintenance dose should be reduced to the smallest amount necessary to control the symptoms. Some patients with perennial rhinitis may be maintained on as little as 1 spray in each nostril per day. It is always desirable to titrate an individual patient to the minimum effective dose to reduce the possibility of side effects.

NASAREL and NASALIDE should not be considered to be identical. Physicians should consider the observed differences in the mean responses in terms of side effects (see ADVERSE REACTIONS) and flunisolide absorption (see PHARMACOKINETICS) in treating individual patients.

For pediatric patients 6 to 14 years of age, the recommended starting dose of NASAREL is 1 spray (25 mcg) in each nostril 3 times a day (total dose 150 mcg/day) or 2 sprays (50 mcg) in each nostril 2 times a day (total dose 200 mcg/day). Maximum daily doses should not exceed 4 sprays in each nostril per day (total dose 200 mcg/day) as the safety and efficacy of higher doses have not been established. NASAREL is not recommended for use in pediatric patients less than 6 years of age as the safety and efficacy have not been assessed in this age group.

INDICATIONS AND USAGE: NASAREL is indicated for the management of the symptoms of seasonal or perennial rhinitis.

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients.

NASAREL should not be used in the presence of untreated localized infection involving the nasal mucosa.

WARNINGS: The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition, some patients may experience symptoms of withdrawal, eg, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to NASAREL should be carefully monitored to avoid acute adrenal insufficiency in response to stress.

Careful attention must also be given to patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may exacerbate their symptoms.

The use of NASAREL with systemic prednisone as alternate day therapy or with daily doses of less than 7.5 mg could increase the likelihood of hypothalamic-pituitary-adrenal axis suppression compared to a therapeutic dose of either one alone. Therefore, NASAREL treatment should be used with caution in patients already on prednisone regimens for any disease.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG Prescribing Information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS: General: In clinical studies with flunisolide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops it may require treatment with appropriate local therapy or discontinuance of treatment with NASAREL.

Since there is no evidence that exceeding the maximum recommended dose of NASAREL is more effective, higher doses should be avoided.

Patients should be advised to clear their nasal passages of secretions prior to use. NASAREL should not be used in the presence of untreated local infection involving the nasal mucosa.

Flunisolide should be used with caution, if at all, in patients with active or quiescent tuberculosis infections, fungal, bacterial or systemic viral infections or ocular herpes simplex.

As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances with the use of flunisolide nasal solutions. Temporary or permanent loss of the sense of smell and taste have also been reported with the use of flunisolide nasal solutions.

Because of the inhibitory effect of corticosteroids on wound healing, a nasal corticosteroid should be used with caution in patients

NASAREL[®] (flunisolide)

who have experienced recent nasal septal ulcers, recurrent epistaxis, nasal surgery or trauma, until healing has occurred.

Although systemic corticoid effects typical of Cushing's syndrome are minimal with recommended doses of topical steroids, this potential increases with excessive doses. If recommended doses are exceeded with long-term use, or if individuals are particularly sensitive, symptoms of hypercorticism could occur including suppression of hypothalamic-pituitary-adrenal function and/or retardation of growth in pediatric patients. Therefore, larger than recommended doses of NASAREL should be avoided.

Information for Patients: Patients should use NASAREL at regular intervals since its effectiveness depends on its regular use. Patients should take the medication as directed and should not exceed the prescribed dose. A decrease in symptoms can be expected to occur within a few days of initiating therapy in allergic rhinitis patients. Patients should contact their physician if the condition worsens, if sneezing or nasal irritation occurs, or if symptoms do not improve by 3 weeks.

Persons taking immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying Patient Instructions carefully.

Carcinogenesis: Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of the drug. Flunisolide was administered to mice at doses of 5, 50 and 500 µg/kg/day (15, 150 and 1500 µg/m², respectively) and to rats at doses of 0.5, 1 and 2.5 µg/kg/day (3.0, 5.9 and 14.8 µg/m², respectively). There was an increase in the incidence of benign pulmonary adenomas in mice, but not in rats.

Female rats receiving the highest oral dose had an increased incidence of mammary adenocarcinoma compared to control rats. An increased incidence of this tumor type has been reported for other corticosteroids.

Impairment of Fertility: Female rats receiving high doses of flunisolide (200 µg/kg/day or 1180 µg/m² body surface area) showed some evidence of impaired fertility. Reproductive performance in the low (8 µg/kg/day or 47.2 µg/m²) and mid-dose (40 µg/kg/day or 236 µg/m²) groups was comparable to controls.

Pregnancy: Teratogenic Effects: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day (480 µg/m² and 1180 µg/m²) respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

Pediatric Use: NASAREL is not recommended for use in pediatric patients less than 6 years of age as safety and efficacy, including possible adverse effects on growth, have not been assessed in this age group. For pediatric patients 6 years of age and over, recommended maximum daily doses should not be exceeded in order to minimize the risk of systemic corticoid effects, including potential growth retardation. (See INDIVIDUALIZATION OF DOSAGE and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS: The adverse event rates listed below are based on symptoms spontaneously reported in multidose controlled clinical trials in comparing NASAREL and NASALIDE for treatment of allergic rhinitis. In patients receiving NASAREL the most common adverse events were transient aftertaste (17%) and transient nasal burning and stinging (13%). These symptoms did not usually interfere with treatment.

Adverse Event Rates for NASAREL:

Incidence Greater than 1% (probably causally related)
Respiratory: Nasal burning/stinging (13%), epistaxis*, nasal dryness, pharyngitis, cough increased
Gastrointestinal: Nausea
Special Senses: Aftertaste (17%)
Incidence 1% or Less (probably causally related)
Respiratory: Hoarseness
Special Senses: Abnormal sense of smell
Incidence 1% or Less (causal relationship unknown)*
Respiratory: Sinusitis

Adverse Event Rates for NASALIDE:

Incidence Greater than 1% (probably causally related)
Respiratory: Nasal burning/stinging (44%), epistaxis*, nasal dryness*, pharyngitis*, cough increased
Gastrointestinal: Nausea
Special Senses: Aftertaste (8%)
Incidence 1% or Less (probably causally related)
Respiratory: Hoarseness, nasal ulcer
Incidence 1% or Less (causal relationship unknown)*
Respiratory: Sinusitis

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

*Reactions occurred under circumstances where the causal relationship has not been clearly established; they are presented as alerting information for physicians.

OVERDOSAGE: In mice, rats and dogs, intravenous flunisolide at doses up to 4 mg/kg showed no effect. One spray bottle contains 6.25 mg of flunisolide; therefore, acute overdosage is unlikely.

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