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Case Report

Loss of Smell (Anosmia) and Taste (Ageusia) in a Patient Treated with Pegylated Interferon Alfa and Ribavirin

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ABSTRACT

Introduction: Anosmia, the loss of the sense of smell, is a rare adverse event associated with interferon alpha (INF-α). Millions of patients with hepatitis B and hepatitis C virus (HCV) infection are currently treated with INF-alfa-2a daily. Only 5 cases of anosmia have been reported in the literature, and none was associated with pegylated INF-alfa.

Case summary: A 55-year-old Arab male (height, 5'1"; weight, 81 kg) with chronic HCV developed anosmia and ageusia (loss of the sense of taste) after 36 weeks of treatment for HCV with subcutaneous pegylated INF-alfa-2a 180 μg and ribavirin 1200 mg. Treatment was continued for 12 additional weeks before being discontinued. Twenty-four weeks after treatment was discontinued, HCV-RNA was undetectable and, during the same visit, the patient reported that he had regained his sense of smell a few weeks previously. The Naranjo algorithm score was 7, representing a probable association of anosmia with INF-alfa-2a treatment. Other etiologies for loss of smell and taste were ruled out.

Conclusions: We report a case of anosmia and ageusia in a patient treated with pegylated INF-alfa-2b and ribavirin for HCV infection. The patient regained his sense of smell and taste within 24 weeks of stopping treatment. (*Curr Ther Res Clin Exp.* 2007;68:271–277) Copyright © 2007 Excerpta Medica, Inc.

Key words: anosmia, pegylated interferon alfa-2a, ribavirin, hepatitis C virus.

INTRODUCTION

Interferon alpha (INF-α) is a cytokine that has antiviral, antiproliferative, and immunomodulatory effects.[1] Approximately 170 million people worldwide are infected with hepatitis C virus (HCV) and ~350 million people are infected with hepatitis B virus (HBV).[2] The US National Institute of Health has recommended

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that HBV and HCV infections should be treated with pegylated INF-alfa-2a or INF-alfa-2b for ≥24 to 48 weeks.[1] INF-alfa-2a is associated with several adverse events (AEs), including hypothyroidism, hyperthyroidism, diabetes, psychosis, depression, blood dyscrasia, and various dermatologic conditions. Although INF-α has been used extensively in the treatment of HBV and HCV infections, only 5 cases of anosmia (loss of the sense of smell) and ageusia (loss of the sense of taste) associated with the use of INF-α have been reported in the medical literature.[3–6]

The aim of this study was to report a case of loss of smell and taste in a patient with HCV treated with pegylated INF-alfa-2a and ribavirin combination treatment.

CASE SUMMARY

A 55-year-old Arab male (height, 5'1"; weight, 81 kg) was tested at the hepatitis clinic of the King Khalid University Hospital, Riyadh, Saudi Arabia, in 2004 for chronic HCV infection. The patient's medical history included stable asthma and diabetes, which required occasional use of inhaled albuterol and insulin for ~8 years, but no signs of systemic complications (ie, chronic obstructive lung disease, congestive heart failure, renal failure, or psychiatric disorders).

Physical examination was unremarkable and his vital signs (temperature, 36.8°C; blood pressure, 112/78 mm Hg; heart rate, 81) were normal. His body mass index was 33 kg/m^2. Findings on examination of his eyes, ears, nose, and throat were within normal limits, and findings on neurologic examination were grossly intact. Examination of the cardiovascular system, respiratory system, and abdomen were normal, except for truncal obesity. The spleen was not palpable, the liver span was 12 cm, and there was no evidence of ascites or lower limb edema.

Except for alanine aminotransferase (ALT) (163 U/L [normal, 10–40 U/L]), all laboratory tests were within normal limits, including sodium, potassium, magnesium, phosphorous, serum creatinine, blood urea nitrogen, albumin, bilirubin, prothrombin time, international normalized ratio, erythrocyte sedimentation rate, hemoglobin, and platelet count. HBV surface antigen, antismooth muscle antibody, and alpha-fetoprotein were all negative. The patient's liver biopsy was done just prior to the treatment and revealed grade III, stage III chronic HCV infection; HCV-RNA level was 600,000 copies/mL.

The patient was diagnosed with chronic HCV infection and treated with subcutaneous pegylated INF-alfa-2b* 180 μg plus ribavirin 1200 mg once a week for 48 weeks. The treatment was well tolerated. Hemoglobin, leukocyte count, and platelet count were maintained within normal range and did not decrease. ALT activity normalized within 3 weeks and remained normal throughout the remainder of the treatment (week 3, 26 U/L and week 48, 33 U/L, respectively).

*Trademark: Pegintron® (Schering Corporation, Kenilworth, New Jersey).

The remainders of the laboratory investigations were unremarkable. After 12 weeks of treatment, HCV-RNA, which indicates an early viral response, was undetectable.

After 36 weeks of treatment, the patient noted significant hair loss from his beard, moustache, and scalp. He also reported fatigue, flu-like symptoms, and total loss of smell and taste. He reported a "stuffy nose" but did not indicate a history of rhinitis, exposure to chemical fumes, or head trauma.

The patient was referred to an otolaryngologist, who found the man's mucous membranes, teeth, gums, and oral cavity to be normal and without any signs of infection. On examination of the nose, no nasal polyps, obstruction, inflammatory process, intranasal mass, fracture of the cribriform plate, or any form of ulceration were noted. Neurologic examination revealed normal cranial nerve function without facial paralysis or facial droop. The patient was a nonsmoker.

The patient did not complain of dry mouth, nor did he show any signs of Parkinson's (decrease in spontaneous movement, gait difficulty, postural instability, rigidity, and tremor) or Alzheimer's disease (memory loss or behavior changes). Thyroid function test and vitamin levels were not determined, and he was not taking any medication other than pegylated INF-alfa-2b and ribavirin.

Perfume and isopropyl alcohol smell identification tests, which are used to identify nerve function, were administered to the patient. He was unable to identify either smell. Anosmia was diagnosed based on his symptoms and the results of the smell tests, but ageusia was noted based on the patient's complaint.

The patient responded well to INF-alfa-2b and ribavirin; he remained on the regimen for 48 weeks. Twenty-four weeks after treatment was stopped, the patient's HCV-RNA level remained undetectable. At the same time, he reported that within the last several weeks he had regained his sense of smell and his sense of taste had improved.

The Naranjo algorithm score[7] was 6 and 7 for ageusia and anosmia, respectively, representing a probable relationship of INF-alfa-2b and ribavirin treatment.

DISCUSSION

Smell and taste are chemical senses that allow appreciation of the flavor of foods.[8] They also serve as an early warning system against toxins, polluted air, and smoke. Physiologically, these senses aid in normal digestion by triggering gastrointestinal secretions. Smell or taste dysfunction can have a significant impact on quality of life. Anosmia is a condition in which the sense of smell is reduced or lost entirely.[8] Loss of the sense of smell may be related to nasal and sinus disease, allergic rhinitis, chronic rhinitis, nasal polyps, adenoid hypertrophy, head trauma, nasal fracture, smoking, Alzheimer's or Parkinson's disease, multiple sclerosis, or old age.

Among the numerous medications[9–19] (**Table**) that can cause loss of smell and taste are angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, followed by calcium channel blockers, diuretics, and

Table. Drugs that have been associated with taste and smell disturbances.[2–12]

Amikacin	Amitriptyline	ACE-inhibitors
Auranofin	β-Blockers	Candesartan
Captopril	Cisplatin	Clozapine
Colchicine	Corticosteroids (nasal)	Doxycycline
Diltiazem	Enalapril	Fluvastatin
Gold	Imipramine	Interferon-α
Levodopa	Lithium	Lovastatin
Methimazole	Methotrexate	Midodrine
Nifedipine	Nortriptyline	Pegylated interferon
Phenytoin	Propylthiouracil	Terbinafine
Tricyclic antidepressants	Vincristine	Xylocaine (nasal)

ACE = angiotensin-converting enzyme.

hydroxymethylglutaryl-coenzyme A.[9–11] Antiproliferative agents, such as 5-fluorouracil, cyclophosphamide, methotrexate, cisplatin, and levamazole, can destroy gustatory receptors permanently while patients are taking them.[9,12,13] Also, these antiproliferative agents and corticosteroids can alter the body's immune system and initiate candidal overgrowth, causing dysgeusia.[14] Antiseizure drugs (eg, phenytoin) and psychotropic agents (eg, tricyclic antidepressants) can also significantly alter the taste sensation.[15]

Other less common causes of anosmia and ageusia include cocaine abuse, toxic chemicals, and industrial agents (eg, benzene, chlorine, sulfuric acid, paint solvents, formaldehyde, ashes, cadmium, chromium, lead, nickel).[8] Trace elements, such as zinc and copper, and nutritional deficiencies of vitamin A, vitamin B_6, and vitamin B_{12} can also cause anosmia.[9]

At least 5 cases of INF-alfa–induced anosmia and ageusia in patients undergoing treatment for HCV infection have been reported in the medical literature (MEDLINE, OVID, and EBSCOhost; search terms: *interferon*, *pegylated interferon*, *anosmia*, *loss of smell*, and *neurological adverse effects*).[3–6] Ribavirin monotherapy has never been reported to cause anosmia or ageusia.

In 2001, Manzano Alonso et al[3] reported on a patient who developed a complete loss of smell and taste while receiving INF-α for chronic HCV infection. The 33-year-old patient had been diagnosed with HCV infection based on positive HCV-RNA findings and elevated ALT activity. He was treated with INF-alfa-2b 3 million U 3 times weekly for 52 weeks. In the first month of treatment, he developed anosmia and ageusia. No abnormality was found on physical and neurologic examination, or computer tomography. However, anosmia and ageusia persisted 18 months after treatment was discontinued.

Fernandez Fernandez et al[4] reported that a patient receiving INF-α for chronic HCV infection had completely lost the senses of smell and taste.

Kraus and Vitezic[5] reported a case of INF-alfa–induced acute anosmia in a 37-year-old patient with chronic HCV infection. The patient reported difficulty

smelling after the initiation of INF-α 5 million U. Within 2 weeks, the patient had totally lost his sense of smell. Findings on radiologic and physical examinations were normal, and anosmia was still present 13 months after the discontinuation of INF-α. The authors proposed that a neurotoxic mechanism may have been responsible for this AE.

Maruyama et al[6] reported that a patient with chronic active HCV infection had developed acute anosmia while undergoing INF-α treatment. Within 10 days of starting daily treatment with INF-α 6 million U, the patient reported difficulty smelling food. Treatment was stopped after 2 months. All radiologic and physical examination findings were normal; however, the patient showed no reaction to a standard olfactory acuity test. The patient had borderline diabetes, and the association of anosmia with impaired glucose tolerance could not be ruled out. However, anosmia was probably related to the INF-α treatment, since it developed 10 days after treatment was started. Nine months after discontinuation of INF-α, the anosmia had not improved.

In 2004, Bagheri et al,[20] in their pharmacovigilance study, also had reported different adverse drug reactions (ADRs) while patients were receiving peginterferon alfa-2b plus ribavirin for viral hepatitis during the 1-year period. Among them, neurosensory ADRs, including disturbances in taste, vision, hearing, or smell, were reported 18 times in 11 (22%) patients.

Other rare neurologic AEs that have been reported after patients underwent INF-α treatment are as follows: subcorticofrontal encephalopathy and choreic movements related to recombinant INF-alfa-2b[21]; refractory akathisia after INF-α treatment, with resting and action tremor related to INF[22]; measured declines in hearing, sensation, vibration, and muscle strength while patients were taking INF-α treatment[23]; chronic inflammatory demyelinating polyneuropathy after treatment with INF-α[24,25]; Bell's palsy during INF-α treatment for chronic HCV infection in patients with hemorrhagic disorders[26]; and acute sensorineural hearing loss associated with pegylated INF-α and ribavirin combination treatment during treatment for HCV infection.[27]

The mechanism by which INF-α might induce alterations in neurons and cause anosmia is not known; however, it may be related to changes in neuroendocrine hormone levels, structural similarities and common pathways between INF and specific neuroendocrine hormones, and the immunoregulatory effects of INF.[28] Alternatively, INF-α may stimulate the manufacture of autoantibodies that damage the myelin sheath at peripheral neurons, resulting in permanent nerve damage.

Our patient had no known etiology for anosmia and ageusia. It was only during pegylated INF-alfa-2b and ribavirin treatment that the patient developed both anosmia and ageusia. He regained his senses of taste and smell when the treatment was stopped. It was not ethical to rechallenge the patient with INF-α to reconfirm the AE. Of the 5 reported cases of anosmia,[3–6] 2 patients developed anosmia within 2 weeks, and in 2 other cases, anosmia remained even after INF-α had been stopped for 9 months. Our patient regained his sense of smell 24 weeks after the completion of 48 weeks of pegylated INF-alfa-2a treatment.

CONCLUSIONS

We report a case of anosmia and ageusia in a patient treated with pegylated INF-alfa-2b and ribavirin for HCV infection. The patient regained his sense of smell and taste within 24 weeks of stopping treatment.

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