Metallic Taste as a Side Effect of Topical Fluorouracil Use

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ABSTRACT

Topical fluorouracil is widely used for the treatment of precancerous and cancerous lesions of the skin. The most common side effect of this medication is localized irritant dermatitis. The authors report a case of dysgeusia with metallic taste as a side effect of this medication. While not previously seen with topical use, this is not an uncommon side effect seen with systemic administration of 5-fluorouracil. The etiology of dysgeusia from chemotherapeutic agents and systemic absorption of fluorouracil is discussed.

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INTRODUCTION

5-fluorouracil is a chemotherapeutic agent used in the treatment of both systemic and cutaneous neoplasms. Its topical formulation is FDA-approved for the treatment of actinic keratoses and superficial basal cell carcinomas. Topical fluorouracil is available in 0.5%, 1%, and 5% concentrations. Depending on the formulation and condition being treated, instructions for use range from daily to twice-daily application for two to 12 weeks. While the development of a bitter or metallic taste is a known side effect of systemic administration of 5-fluorouracil, we report the first case of this side effect associated with its topical use.

CASE REPORT

The patient is a 64-year-old Caucasian woman who presented with a 4 mm scaly, red lesion on her right external naris that she reported as being present for several months. The lesion had previously been treated with cryotherapy, but it persisted. Biopsy of the lesion revealed squamous cell carcinoma in situ. After a thorough discussion of treatment options, the patient opted to have treatment with 5% topical fluorouracil. The patient was instructed to apply the medication to the lesion twice a day for six weeks. Three days into treatment, the patient developed a metallic taste in her mouth, which was constantly present. She denied application of the medication to her nasal or oral mucosa. With the exception of the fluorouracil cream, the patient had no other changes in her medications. The dysgeusia did not interfere with her ability to eat or drink. The sensation lasted for four days before resolving on its own without further sequelae. She continued use of the medication as initially directed. At follow up six weeks following initiation of the medication, the patient's squamous cell carcinoma in situ showed full clinical resolution. She has been free of recurrence at 18 months of follow up.

DISCUSSION

Systemic 5-fluorouracil has been used for treatment of solid organ tumors of the breast, colon, liver and ovary since its development in the 1950s. Its primary mechanism of action is through interference with DNA synthesis. After cell entry, fluorouracil becomes ribosylated and phosophorylated and binds the enzyme thymidylate synthetase. This binding prevents the conversion of deoxyuridine-5 monophosphate to thymidine-5 monophosphate, thereby truncating cellular mitotic activity.[1,2]

Topical formulations of fluorouracil were first introduced in the early 1960s after it was noted that patients being treated for internal malignancies with 5-fluorouracil had disappearance of their actinic keratoses.[3] Topical fluorouracil has subsequently been used to treat a variety of cutaneous neoplastic conditions, including squamous cell carcinoma in situ as in our patient.[4,5,6]

The most common side effect of topical use is the development of an irritant dermatitis with erythema and erosions associated with burning and stinging at the site of application. Photosensitivity is also commonly seen.[7] Rare side effects include allergic contact dermatitis,[8] formation of telangiectasias,[9,10] herpes simplex virus reactivation,[9,10] conjunctivitis[11] and onycholysis.[12] While the manufacturer of 5% topical 5-fluorouracil lists medicinal taste

as a potential gastrointestinal side effect of the medication,[13] to our knowledge, this is the first report of metallic taste associated with topical use of topical 5-fluorouracil in the literature.

Dysgeusia, which developed during topical fluorouracil treatment for squamous cell carcinoma in situ, was fortunately a self-limited side effect in our patient. Given that this medication is frequently applied over larger body surface areas than in our patient, those prescribing this medication should be aware of rare but potentially serious side effects of this medication due to its systemic absorption.

Systemic administration of 5-fluorouracil, however, has been implicated in the development of dysgeusia in 2–7 percent of patients receiving this medication.[14,15] Altered taste sensation is a commonly reported problem among cancer patients receiving systemic chemotherapy, with up to 75 percent of chemotherapy patients reporting such changes.[16,17] The mechanism behind these disturbances is not well understood but is thought to involve damage to cells responsible for taste. The medication may destroy taste receptor cells within taste buds.[18] These cells have a high turnover rate of 10 days and are susceptible to toxicity from chemotherapeutic agents.[19] These medications may also affect neuronal cells leading to disruption of afferent taste pathways.[18]

Initial studies in absorption of radiolabeled, topical 5% 5-fluorouracil showed that ~6 percent of the topical dose is systemically absorbed.[20] Other studies showed absorption to be only 2.6 percent, but diseased skin had 15–75 times greater absorption compared to healthy skin.[21,22] While our patient only applied 5-fluorouracil to a limited body surface area, systemic absorption of the medication likely accounts for her transient dysgeusia. Other common side effects of systemic 5-fluorouracil include myelosuppresion, mucositis and diarrhea. Life-threatening toxicity due to topical application of 5-fluorouracil for treatment of basal cell carcinoma has been reported.[23] In that case, the patient was found to have a deficiency of dihydropyrimidine dehydrogenase (DHD), the initial rate-limiting enzyme in the metabolism of fluorouracil, which led to severe hematological and gastrointestinal toxicity. While the DHD status of our patient is unknown, we do not recommend use of fluorouracil over any larger surface area in this patient in the future due to the potential for more serious side effects.

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DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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