

HPV's Link to Head and Neck Cancer Examined

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SAN FRANCISCO — While the relationship of the human papillomavirus to cervical cancer is well known among the public and in the medical profession, it is less commonly recognized that oral HPV appears to be associated with head and neck cancers. Even among the cognoscenti, there is a good deal of confusion about the details of this association.

At the Seventh International Conference on Head and Neck Cancer, Dr. Maureen L. Gillison of Johns Hopkins University, Baltimore, reviewed current studies to answer some of the most frequently asked questions about HPV and cancers of the head and neck: **► Which HPV types are most associated with cancers of the head and neck? HPV-16 is the most common cause of cervical cancer, accounting for about 54% of these cancers, followed by HPV-18 and HPV-45. HPV-16 may be even more prominent among cancers of the head and neck, with a 92% association in one study.**

► What risk of cancer is associated with oral HPV infection? Published studies show little agreement on the magnitude of the risk associated with oral HPV-16, although all the studies that Dr. Gillison reviewed found statistically significant increases. The odds ratios in published studies range from 1.7 for all the head and neck cancers to 32.3 for cancers of the oropharynx to 99.3 for cancers of the tonsil. Dr. Gillison estimated the overall increase in the risk of oropharyngeal cancer from HPV-16 infection to be about 15-fold over the risk in people who are not infected.

► How common is oral HPV infection? Estimates of the prevalence of HPV infection in control populations range from 3% to 18%. **► What are the risk factors for oral HPV infection?** As in urogenital infection, sexual behavior appears to be the prime culprit

in oral HPV infection, although peripartum transmission has been documented. Several studies have found HPV-16-positive head and neck cancers to be associated with a history of sexually transmitted disease, a history of casual sex, infrequent condom use, infrequent barrier use during oral sex, the number of sexual partners, and the number of oral sex partners.

► How does oral infection relate to cervical infection? Oral HPV infection is about three times as likely in women with

cervical infections, but in the overwhelming majority of these women—94% according to one study—different types of HPV are responsible for their oral and urogenital infections.

► How long is a patient with HPV-positive cancer infectious? Studies have found oral HPV infections to persist for about 2 years following treatment for head and neck cancers. These infections have not been associated with recurrences or second primary cancers, however.

► Will the HPV vaccine have any effect on oral HPV infection? There is no direct evidence bearing on this question, but the indirect evidence is encouraging. Following vaccination, HPV-16 IgG can be detected in oral fluid, and oral HPV-16 is seropositive with cervical HPV-16.

Dr. Gillison serves as a consultant to, receives research funding from, and collaborates with scientists employed by Merck & Co. The conference was sponsored by the American Head and Neck Society. ■

Verdeso™ (desonide) Foam, 0.05%

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Rx Only
FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE
CONTRAINDICATIONS

The use of Verdeso Foam is contraindicated in patients who are hypersensitive to desonide or to any ingredient in this preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of topical corticosteroids over large body surface areas, prolonged use, or the addition of occlusive dressings. Therefore, patients applying a topical corticosteroid to a large body surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression (see Laboratory Tests). If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic corticosteroid supplementation, see prescribing information for those products.

The effect of Verdeso Foam on HPA axis function was investigated in pediatric patients in one study. In this study, patients with atopic dermatitis covering at least 25% of their body applied Verdeso Foam twice daily for 4 weeks. Three out of 75 patients (4%) displayed adrenal suppression after 4 weeks of use based on the cosyntropin stimulation test. The laboratory suppression was transient; all subjects had returned to normal when tested 4 weeks post treatment.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses because of their larger skin surface area to body mass ratios (See PRECAUTIONS: Pediatric Use).

If irritation develops, Verdeso Foam should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noticing a clinical exacerbation, as with most products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, the use of an appropriate antifungal, antibacterial or antiviral agent should be instituted. If a favorable response does not occur promptly, use of Verdeso Foam should be discontinued until the infection has been adequately controlled.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes or other mucous membranes. The medication should not be dispensed directly onto the face. Dispense in hands and gently massage into affected areas of the face until the medication disappears. For areas other than the face, the medication may be dispensed directly on the affected area. Wash hands after use.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged, otherwise covered, or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report any signs of local or systemic adverse reactions to the physician.
5. Patients should inform their physicians that they are using Verdeso Foam if surgery is contemplated.
6. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, contact the physician.

Laboratory Tests: The cosyntropin (ACTH₁₋₂₄) stimulation test may be helpful in evaluating patients for HPA axis suppression.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic or photo-carcinogenic potential of Verdeso Foam or the effect on fertility of desonide.

Desonide revealed no evidence of mutagenic potential based on the results of two in vitro genotoxicity tests (Ames assay, mouse lymphoma cell assay) and an in vivo genotoxicity test (mouse micronucleus assay).

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

There are no adequate and well-controlled studies of Verdeso Foam in pregnant women. Therefore, Verdeso Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No long-term reproductive studies in animals have been performed with Verdeso Foam. Dermal embryofetal development studies were conducted in rats and rabbits with a desonide cream, 0.05% formulation. Topical doses of 0.2, 0.6 and 2.0 g cream/kg/day of a desonide cream, 0.05% formulation or 2.0 g/kg of the cream base were administered topically to pregnant rats (gestational days 6-15) and pregnant rabbits (gestational days 6-18). Maternal body weight loss was noted at all dose levels of the desonide cream, 0.05% formulation in rats and rabbits. Teratogenic effects characteristic of corticosteroids were noted in both species. The desonide cream, 0.05% formulation was teratogenic in rats at topical doses of 0.6 and 2.0 g cream/kg/day and in rabbits at a topical dose of 2.0 g cream/kg/day. No teratogenic effects were noted for the desonide cream, 0.05% formulation at a topical dose of 0.2 g cream/kg/day in rats and at a topical dose of 0.6 g cream/kg/day in rabbits. These doses (0.2 g cream/kg/day in rats and 0.6 g cream/kg/day in rabbits) are similar to the maximum recommended human dose based on body surface area comparisons.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when Verdeso Foam is administered to a nursing woman.

Pediatric Use: Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children. HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

The effect of Verdeso Foam on HPA axis function was investigated in pediatric patients, ages 6 months to 17 years, in one study. In this study, patients with atopic dermatitis covering at least 25% of their body applied Verdeso Foam twice daily for 4 weeks. Three out of 75 patients (4%) displayed adrenal suppression after 4 weeks of use based on the ACTH stimulation test. The suppression was transient; all subjects' cortisol levels had returned to normal when tested 4 weeks post treatment.

Safety of Verdeso Foam has not been evaluated in pediatric patients below the age of 3 months.

Geriatric Use: Clinical studies of Verdeso Foam did not include any subjects aged 65 or over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In a controlled clinical study of 581 patients 3 months to 17 years of age, adverse events occurred at the application site in 6% of subjects treated with Verdeso Foam and 14% of subjects treated with vehicle foam. Other commonly reported adverse events for Verdeso Foam and vehicle foam are noted in Table 1.

Table 1 - Commonly Occurring Adverse Events

Adverse Event	Verdeso Foam (N=387)	Vehicle Foam (N=194)
System Organ Class		
General disorders and administration site conditions	32 (8%)	31 (16%)
Application site burning	11 (3%)	15 (8%)
Application site atrophy	5 (1%)	0 (0%)
Application site dermatitis	2 (1%)	1 (1%)
Application site reaction	3 (1%)	6 (3%)
Infections and infestations	79 (20%)	38 (20%)
Upper respiratory tract infection	37 (10%)	12 (6%)
Pharyngitis	2 (1%)	0 (0%)
Pharyngitis streptococcal	2 (1%)	1 (1%)
Viral infection	6 (2%)	0 (0%)
Nervous System Disorder	7 (2%)	1 (1%)
Headache	7 (2%)	1 (1%)
Psychiatric Disorder	3 (1%)	0 (0%)
Irritability	2 (1%)	0 (0%)
Respiratory, Thoracic and Mediastinal Disorders	27 (7%)	7 (4%)
Asthma	3 (1%)	0 (0%)
Cough	14 (4%)	3 (2%)
Skin and Subcutaneous Tissue Disorders	10 (3%)	6 (3%)
Dermatitis contact	3 (1%)	2 (1%)
Telangiectasia	3 (1%)	0 (0%)

Elevated blood pressure was observed in 6 (2%) subjects receiving Verdeso Foam and 1 (1%) subject receiving vehicle foam. Other local adverse events occurred at rates less than 1.0%. The majority of adverse reactions were transient and mild to moderate in severity, and they were not affected by age, race or gender. The following additional local adverse reactions have been reported with topical corticosteroids. They may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, striae and miliaria.

OVERDOSAGE

Topically applied Verdeso Foam can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

WARNING

FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.

Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C).

Avoid contact with eyes or other mucous membranes.

Keep out of reach of children.

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Renowned Educator Gets Lifetime Award

The Dermatology Foundation has conferred its Lifetime Career Educator Award on Dr. Irwin M. Braverman, professor of dermatology at Yale University School of Medicine. According to the foundation, "The award celebrates Dr. Braverman's distinguished career and the high standard he has set for the next generation of teachers in all areas of dermatology." For more information, visit www.dermatologyfoundation.org, and select Press. ■