

Data Strengthen Link Between HPV, Oral Cancer

BY BRUCE K. DIXON
Chicago Bureau

Researchers in Montreal have reported new evidence supporting a strong causal association between human papillomavirus infection and tonsil-related oral cancers.

The study also found that human papillomavirus (HPV) 16 seropositivity contributes substantial independent risk prediction. "HPV 16 seropositivity may thus

serve as a surrogate marker for the total-ity of HPV exposure that is relevant in oral carcinogenesis," wrote Dr. Javier Pintos and his associates from the division of cancer epidemiology at McGill University.

Additionally, while some researchers have reported a positive correlation between markers of sexual activity and oral cancers, this study found no such association (Oral Oncol. 2008;44:242-50).

The investigation, as part of a multicenter study coordinated by the International

Agency for Research on Cancer, followed a hospital-based case-control design.

A total of 72 patients with newly diagnosed squamous cell carcinoma of the mouth and 129 controls were recruited. Among patients, the most common cancer site was the tongue (21 patients), followed by the floor of the mouth (12) and palatine tonsil (12), "other" and "unspecified" parts of the mouth (18), the palate (4), the gums (2), the oropharynx (2), and the inner lip (1), Dr. Pintos and his coinvestigators said.

Patients ranged in age from 25 to 84 years, though most were between 55 and 74; men accounted for more than 70%.

As expected, tobacco smoking and alcohol consumption were higher among patients, compared with controls. Controls were selected from the same hospitals where patients had been recruited but did not have personal histories of cancer nor admitting conditions related to tobacco or alcohol. Heavy smokers (more than 49 pack-years) represented 39% of patients and 16% of controls, and more than half of patients and 17% of controls were categorized as heavy drinkers.

HPV DNA was detected in 6 of 129 controls (5%) and 14 of 72 patients (19%). Most viral infections among patients harbored high-risk HPV types (13 of 14 samples), compared with 4 of the 6 HPV-positive controls, the investigators said, adding that HPV 16, which was not detected among controls, was found in 13 of the 14 positive samples from the oral cancer arm.

Other studies have found that, in the oral cavity, the tonsils appear to be preferentially infected by HPV, the authors said. "In addition to the epidemiological evidence, there is consistent biological evidence that HPV-positive cancers arising from the palatine and lingual tonsils are a distinct entity etiologically linked to infection by high-risk HPV types, especially HPV 16."

On the other hand, there is scant biological evidence linking HPV infection and cancers of the oral cavity not related to the lingual and palatine tonsils, and the proportion of nontonsillar cancers of the mouth attributable to HPV infection is likely to be small, they wrote.

"The association found in this investigation between HPV and cancers of the palatine tonsils and base of tongue seem to be genuine," the authors said, noting that the association is independent from the influence of smoking and alcohol, the two established causal factors for oral cancers.

The validity of the association was further supported through the consistent use of both polymerase chain reaction and serologic techniques, Dr. Pintos and his associates wrote.

The study was funded by the National Cancer Institute of Canada. The authors had no conflicts of interest to declare. ■

METROGEL®

(metronidazole gel), 1%
BRIEF SUMMARY

For topical use only. Not for oral, ophthalmic or intravaginal use.

INDICATIONS AND USAGE

METROGEL® (metronidazole gel), 1% is indicated for the topical treatment of inflammatory lesions of rosacea.

CONTRAINDICATIONS

METROGEL® (metronidazole gel), 1% is contraindicated in those patients with a history of hypersensitivity to metronidazole or to any other ingredient in this formulation.

PRECAUTIONS

General: Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local skin irritation occurs, patients should be directed to use the medication less often or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia.

Information for Patients: Patients using METROGEL® (metronidazole gel), 1% should receive the following information and instructions:

1. This medication is to be used as directed.
2. It is for external use only.
3. Avoid contact with the eyes.
4. Cleanse affected area(s) before applying METROGEL® (metronidazole gel), 1%.
5. This medication should not be used for any other condition than that for which it is prescribed.
6. Patients should report any adverse reaction to their physicians.

Drug Interaction: Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin, resulting in a prolongation of prothrombin time. Drug interactions should be kept in mind when METROGEL® (metronidazole gel), 1% is prescribed for patients who are receiving anticoagulant treatment, although they are less likely to occur with topical metronidazole administration because of low absorption.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats, but not in studies involving hamsters. In several long-term studies in mice, oral doses of approximately 225 mg/m²/day or greater (approximately 37 times the human topical dose on a mg/m² basis) were associated with an increase in pulmonary tumors and lymphomas. Several long-term oral studies in the rat have shown statistically significant increases in mammary and hepatic tumors at doses >885 mg/m²/day (144 times the human dose).

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-related increase in the frequency of micronuclei was observed in mice after intraperitoneal injections. An increase in chromosomal aberrations in peripheral blood lymphocytes was reported in patients with Crohn's disease who were treated with 200 to 1200 mg/day of metronidazole for 1 to 24 months. However, in another study, no increase in chromosomal aberrations in circulating lymphocytes was observed in patients with Crohn's disease treated with the drug for 8 months.

In one published study, using albino hairless mice, intraperitoneal administration of metronidazole at a dose of 45 mg/m²/day (approximately 7 times the human topical dose on a mg/m² basis) was associated with an increase in ultraviolet radiation-induced skin carcinogenesis. Neither dermal carcinogenicity nor photocarcinogenicity studies have been performed with METROGEL® (metronidazole gel), 1% or any marketed metronidazole formulations.

Pregnancy: Teratogenic Effects: Pregnancy Category B. There are no adequate and well-controlled studies with the use of METROGEL® (metronidazole gel), 1% in pregnant women.

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral administration of metronidazole in rats or mice at 200 and 20 times, respectively, the expected clinical dose. However, oral metronidazole has shown carcinogenic activity in rodents. Because animal reproduction studies are not always predictive of human response, METROGEL® (metronidazole gel), 1% should be used during pregnancy only if clearly needed.

Nursing Mothers: After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels taken after topical metronidazole application are significantly lower than those achieved after oral metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the risk to the infant.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: While specific clinical trials in the geriatric population have not been conducted, sixty-six patients aged 65 years and older treated with METROGEL® (metronidazole gel), 1% over ten weeks showed comparable safety and efficacy as compared to the general study population.

ADVERSE REACTIONS

In a controlled clinical trial, 557 patients used METROGEL® (metronidazole gel), 1% and 189 patients used the gel vehicle once daily. The following table summarizes adverse reactions that occur at a rate of ≥1% in the clinical trials:

System Organ Class/Preferred Term	Metronidazole Gel, 1% N=557	Gel Vehicle N=189
Patients with at least one AE	186 (33.4)	51 (27.0)
Infections and infestations	76 (13.6)	28 (14.8)
Bronchitis	6 (1.1)	3 (1.6)
Influenza	8 (1.4)	1 (0.5)
Nasopharyngitis	17 (3.1)	8 (4.2)
Sinusitis	8 (1.4)	3 (1.6)
Upper respiratory tract infection	14 (2.5)	4 (2.1)
Urinary tract infection	6 (1.1)	1 (0.5)
Vaginal mycosis	1 (0.2)	2 (1.1)
Musculoskeletal and connective tissue disorders	19 (3.4)	5 (2.6)
Back pain	3 (0.5)	2 (1.1)
Neoplasms	4 (0.7)	2 (1.1)
Basal cell carcinoma	1 (0.2)	2 (1.1)
Nervous system disorders	18 (3.2)	3 (1.6)
Headache	12 (2.2)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	22 (3.9)	5 (2.6)
Nasal congestion	6 (1.1)	3 (1.6)
Skin and subcutaneous tissue disorders	36 (6.5)	12 (6.3)
Contact dermatitis	7 (1.3)	1 (0.5)
Dry skin	6 (1.1)	3 (1.6)
Vascular disorders	8 (1.4)	1 (0.5)
Hypertension	6 (1.1)	1 (0.5)

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The following table summarizes the highest scores of local cutaneous signs and symptoms of irritation that were worse than baseline:

Sign/Symptom	Metronidazole Gel, 1% N=544	Gel Vehicle N=184
Dryness	138 (25.4)	63 (34.2)
Mild	93 (17.1)	41 (22.3)
Moderate	42 (7.7)	20 (10.9)
Severe	3 (0.6)	2 (1.1)
Scaling	134 (24.6)	60 (32.6)
Mild	88 (16.2)	32 (17.4)
Moderate	43 (7.9)	27 (14.7)
Severe	3 (0.6)	1 (0.5)
Pruritus	86 (15.8)	35 (19.0)
Mild	53 (9.7)	21 (11.4)
Moderate	27 (5.0)	13 (7.1)
Severe	6 (1.1)	1 (0.5)
Stinging/burning	56 (10.3)	28 (15.2)
Mild	39 (7.2)	18 (9.8)
Moderate	7 (1.3)	9 (4.9)
Severe	10 (1.8)	1 (0.5)

The following additional adverse experiences have been reported with the topical use of metronidazole: skin irritation, transient redness, metallic taste, tingling or numbness of extremities, and nausea.

OVERDOSAGE: There are no reported human experiences with overdosage of METROGEL® (metronidazole gel), 1%. Topically applied metronidazole can be absorbed in sufficient amount to produce systemic effects.

DOSAGE AND ADMINISTRATION: Areas to be treated should be cleansed before application of METROGEL® (metronidazole gel), 1%. Apply and rub in a thin film of METROGEL® (metronidazole gel), 1% once daily to entire affected area(s). Patients may use cosmetics after application of METROGEL® (metronidazole gel), 1%.

HOW SUPPLIED: METROGEL® (metronidazole gel), 1% is available in a 45 gram and 60 gram tube.

45 gram tube - NDC 0299-3820-45

60 gram tube - NDC 0299-3820-60

Keep out of the reach of children.

Storage Conditions: Store at controlled room temperature: 20° to 25°C (68° to 77°F), excursions permitted between 59° and 86°F (15°-30°C).

Prescribing Information as of December 2005.

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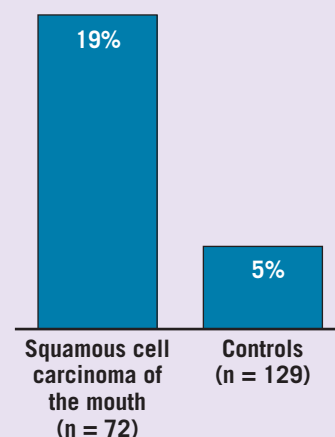
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2. MediMedia; Formulary Compass, July 2007

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14501 N. Freeway
Fort Worth, TX 76177
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Percentage of Patients With Human Papillomavirus



Source: Oral Oncology