The Association Between Viadent® Use and Oral Leukoplakia—Results of a Matched Case-control Study

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Abstract

Objectives: *Several oral pathologists have described oral leukoplakia of the maxillary vestibule in patients with no traditional risk factors for the condition. On questioning these patients, it was determined that Viadent® mouthrinse or Viadent® toothpaste was commonly used by them. A hypothesis was developed that Viadent® or a component of Viadent® caused the lesions. This paper evaluates the association between oral leukoplakia and use of Viadent® products.* ***Methods:*** *A matched case-control study was designed to test the hypothesis that use of Viadent® products increases an individual's risk of oral leukoplakia. Cases included 58 patients diagnosed with oral leukoplakia identified through the biopsy service at the Ohio State University, College of Dentistry, Oral Pathology Section. The matched control was a friend or relative of the patient. Cases and controls were administered a questionnaire about their use of Viadent®, and other known risk factors for leukoplakia such as tobacco and excessive alcohol use.* ***Results:*** *An age difference was seen between cases and controls, the cases being older (P<.001). After controlling for confounding factors, results of exact conditional logistic regression analyses showed that use of Viadent® products was a risk indicator for oral leukoplakia (odds ratio=10.0; 95% confidence interval=2.0, 89.2).* ***Conclusions:*** *Viadent® use is a risk indicator for oral leukoplakia, confirming our previous findings. [J Public Health Dent 2002;62(3):158-62]*

Key Words: oral leukoplakia, case-control study, sanguinarine.

Oral leukoplakia, a precancerous lesion that ranges in prevalence from 1 percent to 5 percent in the United States adult population (1,2), has been defined as a white patch that cannot be characterized as any other disease (3). The oral mucosal sites most commonly involved by leukoplakia are, in descending order, buccal mucosa, palate, tongue, lip, and floor of the mouth. From a microscopic standpoint, most leukoplakias show benign features with a thickened surface layer of keratin and normal maturational pattern of the epithelium (4). Dysplasia may also be seen in leukoplakia, with 12 percent of the lesions showing mild to moderate dysplasia, and 4.5 percent severe dysplasia (1). Oral leukoplakia is a dynamic lesion in many cases, which may either progress to invasive carcinoma or clinically regress (5). In the United States, the malignant transformation rate of oral leukoplakia has been reported to range from 6–16 percent, depending on the population studied and the length of follow-up (5).

Tobacco use has been identified as an important risk factor in the development of leukoplakia (4,6,7). Excessive alcohol use synergistically increases the risk of oral leukoplakia induced by cigarette smoking (8). Very few published studies exist that describe an association between leukoplakia and oral hygiene products. Diffuse white lesions of the oral mucosa have been reported for patients exposed to Listerine® [Warner-Lambert Company] mouthwash (9); however these lesions were not clinically consistent with leukoplakia. No clear association has been found between the use of mouthwashes and oral cancer in case-control studies when taking into account other risk factors such as alcohol and tobacco use (10).

An oral hygiene product that has recently begun to cause concern among oral and maxillofacial pathologists, as well as generate substantial controversy, is Viadent®, [Colgate Oral Pharmaceuticals] which contains sanguinarine. Sanguinarine is the principal alkaloid in an extract from the Indian bloodroot plant (*Sanguinaria canadensis* L.). Sanguinarine has been shown to have activity against bacterial dental plaque (11) and has been incorporated into both mouthwash and toothpaste preparations.

A preliminary descriptive study of maxillary vestibule leukoplakia cases reported a relationship with Viadent® use (12). Histopathologically, the lesions showed hyperkeratosis, epithelial atrophy, and chronic mucositis. About one-half showed atypia and a small percentage demonstrated mild to moderate epithelial dysplasia. This preliminary study, being a descriptive study, could not test the hypothesis that Viadent® or a component of Viadent® was associated with the lesions. Interestingly, a recent literature review concluded that the association between Viadent® use and oral leukoplakia is spurious (13).

Review of the existing clinical literature on Viadent® and oral leukoplakia by the authors was inconclusive and deemed lacking, so a case-control study was designed to address the issue. The specific aim of the study was to assess the use of Viadent® mouthwash and toothpaste in patients diagnosed with oral leukoplakia, comparing them to individuals without oral leukoplakia. One hundred and forty-eight cases and an equal number of

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controls took part in the study. The control group was individuals attending the student clinics at the College of Dentistry, Ohio State University, who were referred to the Section of Oral and Maxillofacial Pathology, and evaluated by one of the oral pathologists for a condition other than oral leukoplakia. Controls were not matched to cases. Results of crude, stratified, and logistic regression analyses of the case-control study showed that use of Viadent® paste, rinse, or both paste and rinse was a risk indicator for oral leukoplakia (odds ratio [OR]=9.72; 95% confidence interval [CI]=4.72, 21.64). A dose-response relationship also was seen between oral leukoplakia and form of Viadent® used, daily frequency of Viadent® use, or number of years Viadent® was used (14).

To further evaluate the association between Viadent® use and oral leukoplakia, a second arm was added, a matched case-control study using a control group of individuals who were friends or relatives of the cases. The aim of this paper is to report on the second part of the study.

Methods

A retrospective matched case-control methodology was used to study the association between Viadent® use and oral leukoplakia. All cases of oral leukoplakia diagnosed between January 1997 through December 1998 that fit the case definition were identified using records from the biopsy service, Section of Oral and Maxillofacial Pathology, College of Dentistry, Ohio State University. An individual was defined as a case of leukoplakia if the biopsy showed hyperorthokeratosis, epithelial atrophy, and epithelial atypia or dysplasia.

The matched controls were friends or relatives of the case. Controls were identified by the case. All cases that participated in the first part of the study were mailed two questionnaires and asked to give the questionnaire to a close friend or relative.

Data were collected by two methods: a self-administered mailed questionnaire for exposure data, and record review or clinical examination for clinical data. The questionnaire developed for this study included demographic information such as age and sex; use of Viadent® rinse and paste, frequency and duration of use; and use of smoked and smokeless tobacco products and alcohol, including frequency and duration. For the cases, clinical data that were collected included site and size of lesions. To ensure that the controls did not have oral leukoplakia, their dentists were contacted to find out if they had a lesion at their last dental examination, or they were examined at the College of Dentistry by one of the coauthors (C.M.A.), an oral pathologist. To evaluate reliability, the questionnaire was readministered to 5 percent of the sample.

Statistical Analyses

Clinical data and the questionnaire data were coded and then entered using a custom-designed program in Epi-Info Version 6. In this study, we defined use of Viadent®, tobacco, or alcohol as any current or past use of these substances. Use of Viadent® was further characterized by daily frequency of use and years of duration. New variables and dummy variables were derived, and descriptive analyses were performed using Epi-Info. The data were then exported into LogXact Turbo for further analyses (15).

Exact conditional logistic tests (16) were used to account for the matched study design and the small number of discordant pairs. Univariate analyses were performed to compute the measure of the association between dichotomous outcome (case or control) and predictor variables (age, sex, use of Viadent® products, tobacco, alcohol, and use of an oral prosthesis). These were also used to inform the multivariate analyses. Only those variables that had significant univariate associations were used in the multivariate analyses, except for tobacco use. Tobacco use was not significant in

TABLE 1
Distribution of Demographic Variables, Viadent®, Tobacco, Alcohol, and Dental Prosthesis Use in Cases and Controls

	Cases (*N*=58)		Controls (*N*=58)		
	No. or Mean±SD	%	No. or Mean±SD	%	*P*-value
Demographic variables					
Age (mean)	62.4±12.7		50.7±16.8		<.001*
Female	40	70	44	75.9	.41
Viadent® use					
Used Viadent®	27	46.6	17	29.3	.04*
Type					
Paste	6	10.3	7	12.1	.84
Rinse	6	10.3	6	10.3	.66
Both	15	25.9	4	6.9	.006*
Mean duration of use (years)					
Paste	4.5±3.8		4.1±4.0		.73
Rinse	3.7±3.7		1.5±2.7		.04*
Tobacco use					
Used tobacco products	32	55.2	30	51.7	.71
Current user	15	25.9	12	20.7	.53
Past user	17	29.3	18	31.0	.97
Alcohol use					
Used alcohol products	26	44.8	36	62.1	.06
Frequency					
Daily	13	22.4	10	17.2	.49
Occasional	13	22.4	26	44.8	.01*
Use of oral prosthesis	13	22.4	11	19.0	.65

*Statistically significant *P*-values.
Proportions may not add up to 100%.

univariate analyses, but was used as an independent variable because it is an important risk factor for oral leukoplakia. Finally, the hypothesis that there is no difference in Viadent® use between cases and controls was tested. The final model simultaneously controlled for age, tobacco use, and alcohol use.

Results

Fifty-eight cases and matched controls took part in the study. So as not to lose any data, all questionnaires returned by controls were used in the study. As a result, a case could have more than one matched control. The response rate for this matched case-control study was 39.2 percent.

The mean±SD age of the cases was 62.4±12.7 years, which was substantially and significantly older ($P<.001$) than the controls (50.8±16.3) (Table 1). There was no difference in the sex distribution, tobacco use, or denture use between the cases and control groups. In a significantly higher proportion of the matched pairs, the cases had used Viadent® products, while the controls had not. The number of discordant case-control pairs of Viadent® users was 19; of smokers, 14; of alcohol users, 17; and of denture users, 11. The percentage agreement for questionnaire reliability was 95.5 percent, and the kappa statistic was 0.90.

In the matched univariate analyses, age, sex, use of Viadent® products, tobacco, alcohol, and oral prosthesis was evaluated in cases and controls. Results of these analyses are reported in Table 2. The use of Viadent® products was statistically significantly higher in the cases than the controls, with an odds ratio of 3.8 (95% CI=1.4, 11.8). The odds of being a case were higher (OR=7.0) in those who had used both Viadent® paste and rinse than those who had used Viadent® paste (OR=2.0) or rinse (OR=2.3) alone. Duration of Viadent® products use and frequency of Viadent® products use also was increased in the oral leukoplakia cases when compared to the controls as seen in Table 2. There was a slightly increased odds ratio for males, those who used tobacco products, and oral prostheses; however, none of these were statistically significant. Use of alcohol had a protective effect (OR=0.5; 95% CI=0.2, 1.0). Results of univariate analyses showed that use of Viadent® was a risk indicator in oral leukoplakia.

TABLE 2
Univariate Analyses

	Odds Ratio	95% Confidence Interval
Age (years)	1.1	(1.05, 1.2)
Sex (male)	1.2	(0.6, 2.8)
Viadent® use—paste, rinse, or both	3.8	(1.4, 11.8)*
Viadent® use—paste only	2.0	(0.3, 16.1)
Viadent® use—rinse only	2.3	(0.4, 13.0)
Viadent® use—paste and rinse	7.0	(1.8, 40.4)*
Duration of Viadent® use (years)	1.2	(1.1, 1.4)*
Daily frequency of Viadent® use	2.3	(1.4, 4.7)*
Dose—daily frequency X duration of Viadent® use	1.1	(1.05, 1.3)*
Tobacco use (smoked and smokeless)	1.2	(0.5, 3.3)
Alcohol use	0.5	(0.2, 1.0)
Oral prosthesis	1.3	(0.5, 5.0)

*Statistically significant odds ratios.

TABLE 3
Multivariate Analyses: Exact Conditional Logistic Regression Model for Association Between Oral Leukoplakia and Use of Viadent® Products

Independent Variable	Parameter Estimate	Pr> Chi-square	Odds Ratio	95% CI
Age	0.1	<.0001	1.1	(1.05, 1.17)*
Alcohol use	–1.5	.02	0.2	(0.04, 0.82)*
Toacco use	0.9	.29	2.5	(0.6, 12.1)
Use of Viadent® products	2.3	.002	10.0	(2.0, 89.2)*

*Statistically significant odds ratios.

TABLE 4
Multivariate Analyses: Exact Conditional Logistic Regression Model for Dose-response Relation Between Oral Leukoplakia and Use of Viadent® Products

Independent Variable	Parameter Estimate	Pr> Chi-square	Odds Ratio	95% CI
Age	0.1	<.0001	1.1	(1.1, 1.2)*
Alcohol use	–1.4	.07	0.3	(0.04, 1.1)
Tobacco use	0.7	.58	2.0	(0.4, 13.6)
Frequency of use of Viadent® products	1.6	<.0001	4.7	(1.7, 20.9)*

*Statistically significant odds ratios.

Results of exact conditional logistic regression (Table 3), simultaneously controlling for the differences in the distribution of age previously seen, and other confounding factors such as tobacco and alcohol use showed that those patients who had used Viadent® products were 10.0 times (95% CI=2.0, 89.2) more likely have oral leukoplakia. Age and alcohol use were the other statistically significant risk indicators, with the risk of being a case increasing by 1.1 for every year (95% CI=1.05, 1.2). Those who consumed alcohol were less likely to be cases

(OR=0.2; 95% CI=0.04, 0.82).

Because of the smaller sample size, the issue of dose-response was not addressed to the same extent as had previously been done with the larger unmatched case-control study (14). Table 4 shows the results of the dose-response analyses for daily frequency of Viadent® product use. The risk of being a case increased 4.7 times with each increase in the daily frequency of use (95% CI=1.7, 20.9).

Potential interactions were not tested here because of the small sample size and in our previous analyses none were found significant (14).

Discussion

Munro and colleagues (13), in their review of the literature on Viadent® use and oral leukoplakia, concluded that the association between Viadent® and oral leukoplakia is spurious. However, it needs to be pointed out that 73 of 126 (58%) references in their literature review were reports submitted to Vipont Pharmaceuticals Inc. that were not published in peer-reviewed journals. Also, most of the literature reviewed dealt with animal studies, suggesting that inferences dealing directly with the human population might be viewed with a degree of skepticism. Furthermore, the clinical papers reviewed were studies of efficacy and effectiveness, not studies of toxicity and safety (17-20). Two of these studies (18-20) did find some amount of soft tissue irritation during product usage. None of the studies reviewed were longer than a six-month duration, which does not address the issue of chronic effects of Viadent®. Oral leukoplakia is a chronic condition; thus, reviewing data from short-term studies and extrapolating the findings to the ability of Viadent® to cause a chronic condition is not appropriate.

The present study is a formal, analytical epidemiologic investigation of oral leukoplakia and use of Viadent® products using a matched case-control study design that builds on our previous case-control study. Although the cases used in the present study were the same as those used in our previous study, the present study also addresses issues raised by Munro and colleagues (13) in their critique of previous studies investigating the association between oral leukoplakia and use of Viadent® products. The hypothesis that there is no difference in Viadent® use between cases and controls was formally tested using exact conditional logistic regression, simultaneously controlling for age and use of tobacco or alcohol. Measures of effect were computed using odds ratios with 95 percent confidence intervals.

Selection bias, information bias, and confounding were also addressed in the study, and measures were taken to reduce the potential effects of any of these on the study results. To address selection bias, all patients referred to the Section of Oral and Maxillofacial Pathology within a given time period, and who fit the definition of cases, were approached to take part in the study. Selection of a good control group in a case-control study is a difficult issue. An ideal control should be as similar as possible to the case, except that they do not have the condition being studied. By using a matched control, and asking the case to identify controls that were either their friend or relative, we were able to ascertain that the cases and controls in this study were very similar, including similar backgrounds. This, however, could have resulted in overmatching and is seen in the difference in use of Viadent® products by the control groups in the two studies. A much higher proportion of controls (25%) in the present study used Viadent® products than in our previous study (9.5%) (14). This overmatching could have resulted in an underestimate of the true magnitude of the association between Viadent® products and oral leukoplakia. Even so, use of Viadent® products was statistically significantly associated with oral leukoplakia.

To address the issue of information bias, cases and controls were all self-administered the same questionnaire with high reliability. As with any questionnaire, recall with the respondent is an issue. Since the cases and controls were not aware of the exact purpose of the study, except that it was to study the causes of white oral lesions, the recall error or bias, if any, is expected to be random error. Further, a kappa statistic of 0.90 for the questionnaire indicates high reliability of the data.

Even after these precautions were taken, including controlling for the effects of confounding, results of exact conditional logistic regression analyses showed that the cases were 10 times more likely to have used Viadent® products. Age was again a significant risk indicator in this study. The risk of having oral leukoplakia increased as age increased. A dose-response relation was also seen in this study.

Tobacco and alcohol use have been previously identified as risk factors in oral leukoplakia (3,4,6,7). The association between oral leukoplakia and the use of tobacco products and alcohol were explored in this study. Several different tobacco variables were used, including any tobacco use versus no use and smoked or smokeless tobacco products versus no use. None of these variables were associated with a significantly increased risk of developing oral leukoplakia in the present study. One reason for this finding may be that the cases and controls were very similar in their use of tobacco products. The alcohol variables evaluated in this study were alcohol use versus no use. Those reporting use of alcohol were less likely to be a case.

Although more stringent criteria were used in the present matched case-control study, allowing for tighter control of potential confounding factors such as age and use of alcohol or tobacco, the results of this study are similar to our previous case-control study (14). In both studies, the cases were statistically significantly more likely to have used Viadent® products. The only other statistically significant risk indicator in both studies was age. The magnitude of the effect seen in both studies was also similar. The magnitude of the effect or the strength of the association seen in the both these studies, therefore, cannot be considered spurious.

The results of this study show that the use of Viadent® products is a risk indicator for oral leukoplakia, confirming our previous results. More case-control studies need to be done in different populations. If the results of these studies are consistent, then they should be followed by a cohort study. The cohort study would enable us to establish temporal sequence, strength of association, and consistency of findings—three requirements for establishing causal effect. Simultaneously, we also would need to establish biological plausibility or mechanistic data, either through an exhaustive review of the literature or animal experiments. In a thorough 1997 review, Das and Khanna (21) concluded that san-

guinarine and its metabolites were likely to be carcinogenic.

In summary, results of this matched case-control study showed that use of Viadent® paste, rinse, or both paste and rinse was a risk indicator for oral leukoplakia (OR=10.0; 95% CI=2.0, 89.2), confirming our previous findings.

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