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Influence of the buccal application site of a bioadhesive slow-release tablet on salivary miconazole concentrations in irradiated patients

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Abstract

Cancer patients, irradiated in the neck region, often develop oral candidosis and a substantial decrease in salivary flow after irradiation. As the use of a bioadhesive buccal tablet containing miconazole nitrate has been shown to be effective in the treatment of oral candidosis, the influence of the application site on the buccal levels of miconazole nitrate was studied. The t_{max}, the adhesion time and $T^{>MIC}$ were significantly higher ($P < 0.05$) when the gingiva was chosen as the application site in comparison with the cheek. The C_{max}, t_{max} and AUC were not significantly different. The gingiva is the application site of choice in irradiated patients even with a decreased salivary flow.

Keywords: Bioadhesion; Buccal; Miconazole; Irradiation

Bioadhesive dosage forms can be applied at different sites in the oral cavity. In a previous study the bioadhesion and the slow-release characteristics of a bioadhesive buccal tablet containing miconazole nitrate were evaluated in healthy volunteers at different application sites (gingiva, cheek and palate) and in comatose intubated patients at the cheek and the gingiva (Bouckaert et al., 1993). This study revealed that the gingiva appeared to be the best site for the application of the bioadhesive formulation in healthy volunteers with a normal salivary flow, while the cheek was the optimal application site in comatose patients. The adhesion time and the salivary miconazole levels were both higher within the volunteers in comparison with the comatose patients, probably due to differences in amount of saliva produced and/or in mouth movements.

Cancer patients, irradiated in the neck region, often develop oral *Candida* infections as a secondary effect. As these patients show a reduced salivary flow, the influence of the application site within the oral cavity for a bioadhesive tablet containing miconazole nitrate was studied.

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Table 1
Clinical details of the patients

Patient	Sex	Age	Diagnosis of the tumour	Radiation dose at parotis (Gy)
CF	m	81	parotis metastasis	20
DCA	m	83supraglotti c larynx	18	
FC	m	43	floor of mouth	46
BC	m	84	tonsil oropharynx	44
GP	f	68	ethmoid sinus	36
DSW	m	60	floor of mouth	52

The bioadhesive tablet formulation contained 10.0 mg miconazole nitrate (Sigma Chemical Co., St. Louis, MO, USA), 82.8 mg thermally modified maize starch (drum-dried waxy maize starch (DDWM), Cerestar, Vilvoorde, Belgium), 5.0 mg Carbopol 934 (B.F. Goodrich Co., Cleveland, OH, USA), 2.0 mg sodium benzoate (Flandria, Zwijnaarde, Belgium) and 0.2 mg silicium dioxide (Pharmachemic, Antwerpen, Belgium). The powders were blended for 10 min in a Turbula mixer (Type T2A, W.A. Bachofen, Basel, Switzerland) and were directly compressed at a pressure of 150 MPa on an eccentric press (Korsch, type EKO, Frankfurt, Germany), equipped with 7-mm flat punches. The tablets were 2 mm thick.

Six patients of both sexes (five male, one female; aged 43–84) participated in this cross-over study. The approval of the Ethics Committee of the Gent Medical School was obtained. In all volunteers the tablet was placed first on the attached gingiva in the region of the right upper canine and, after an interval of 2 days, on the right cheek buccal mucosa in the region of the last upper molar. The tablet was fixed with slight manual pressure. Next, the tablet was moistened with the tongue to prevent sticking of the tablet to other parts in the mouth. All patients were irradiated in the neck region (30–60 Gy) because of an underlying tumour. Clinical details of the patients are shown in Table 1. The adhesion time was defined as the interval between the moment of application and the moment the bioadhesive tablet was no longer visible. Saliva (2 ml) was collected prior to the application of the formulation (blank) and 120, 240, 360, 480 and 600 min after application of the tablet. The saliva was collected by spontaneous flow into a borosilicate tube (16 × 125, Corning, NY, USA) over a 2-min period (1 min before and 1 min after the given time). Care was taken that the tongue did not contact the tablet during the 10 min before sampling in order to avoid an abnormally high drug level. The saliva samples were stored at −20°C pending analysis.

Miconazole nitrate concentrations in saliva were determined by HPLC as described by Bouckaert et al. (1992). An internal standard solution (IS) 40 μl, containing 1.0 mg ml^{-1} econazole nitrate (Janssen Pharmaceutica, Beerse, Belgium) in methanol and 160 μl methanol were added to 800 ml saliva in a borosilicate tube (12 × 75 mm, Corning, NY, USA). After vortexing, 1 ml acetonitrile was added. The mixture was vortexed for 1 min and centrifuged for 2 × 5 min at 1500 g. Next, 20-μl supernatants were injected onto a reversed phase column (Lichrospher 100 RP 18, 5 μm, Merck, Darmstadt, Germany) and eluted with a mobile phase consisting of methanol/tetrahydrofuran/2.5 mM aqueous acetate buffer, pH 5 (75/5/20: v/v/v). The flow rate was 1 ml min^{-1} and the temperature ambient. The UV-detector (D-4000 Merck) was set at 220 nm. Linearity of the calibration curve was obtained in a concentration range from 0 to 100 μg ml^{-1} ($y = 0.023x$; $r^2 = 0.9988$). The detection limit was 0.098 μg ml^{-1}. The precision ($n = 5$) at the concentration of 50 μg ml^{-1} had a coefficient of variation of 1.76% (within run) and 3.68% (run by run).

The results are given as means with (S.D.). The maximal salivary concentration C_{max}, the time to reach the maximal salivary concentration (t_{max}), and the time period above the MIC value ($T^{>MIC}$) for miconazole nitrate against *Candida*

albicans ATCC no. 10231 (5 μg ml^{-1}) were determined from the concentration-time curves. When the salivary concentration at the last sampling time was still above 5 μg ml^{-1}, this time was taken as the endpoint of $T^{>MIC}$. The area under the curve (AUC) was calculated as AUC_{sal} (0 → 12 h) using the ABSPLOTS programme (Shumaker et al., 1988). The AUC and $T^{>MIC}$ values for both application sites were statistically evaluated using the two-tailed Wilcoxon test (Siegel and Castellan, 1988).

Both application sites in the oral cavity were well accepted by the patients. No tablet had to be removed due to local irritations. All patients wore a dental prosthesis but no problems were observed with the prosthesis when the tablet was applied on the gingiva. Some problems were seen with the dental prosthesis in the patients applying the tablet on the cheek.

The mean adhesion time of the tablet on the gingiva was 610 min (range 390–870 min). In one patient the tablet came lose by removing the dental prosthesis. The adhesion time on the cheek was much shorter due to the fact that in all patients the tablet came loose and was swallowed during the meal taken 4 h after application.

For the tablet placed on the gingiva, the drug was slowly released from the bioadhesive formulation resulting in elevated salivary miconazole nitrate concentrations during more than 12 h. This was in contrast with the cheek where initially higher miconazole nitrate levels were seen, followed by a dramatic decrease in salivary miconazole nitrate levels 4 h after application due to the detachement of the dosage form (Fig. 1). The values of C_{max}, t_{max}, AUC, $T^{>MIC}$ and the adhesion time are given in Table 2. The t_{max}, the adhesion time and $T^{>MIC}$ were significantly higher when the gingiva was chosen as the application site ($P < 0.05$, two-tailed Wilcoxon test).

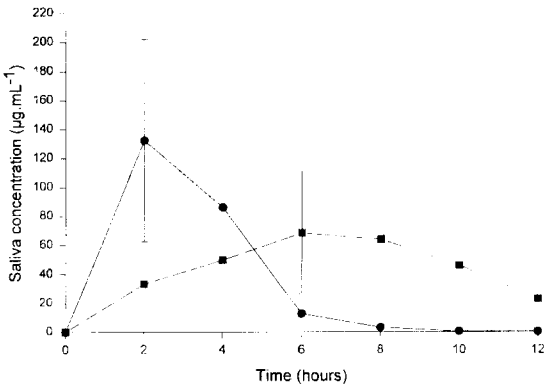

Fig. 1. Mean (S.D.; $n = 6$) salivary miconazole nitrate concentrations after administration of 10 mg miconazole nitrate as a slow-release bioadhesive tablet applied on the gingiva (□) and the cheek (○) in cancer patients irradiated at the neck region.

Patients irradiated to the neck region, due to an underlying tumour, mostly suffer from oral candidosis (Guentzel et al., 1985); besides that, a decrease of 50% in salivary flow is reported after a total irradiation dose of 10 Gy (Mosseman, 1983). A previous study (Bouckaert et al., 1993) showed that salivary flow and mouth movements could play an important role in adhesion time and drug release of the bioadhesive formulation. In healthy volunteers the gingiva was the application site of choice, while in comatose patients the cheek appeared to be the best application site. From this study it could be concluded that the amount of saliva produced was a very important parameter to obtain minimal miconazole nitrate levels to treat oral candidosis. As cancer patients irradiated in the neck region often show a reduced salivary flow, the influence of the application site could be of influence on the levels of miconazole nitrate obtained.

Table 2
The mean AUC, t_{max}, C_{max} and $T^{>MIC}$ values for both application sites ($n = 6$; mean with (S.D.))

	AUC (mg min^{-1} ml^{-1})	Adhesion time (h)	t_{max} (h)	C_{max} (μg ml^{-1}	$T^{>MIC}$ (h)
Gingiva	33.72 (17.4)	10.2 (3.1)[a]	4.7 (2.1)[a]	86.4 (48.8)[a]	12 (0)[a]
Cheek	29.02 (16.8)	4 (0)	2 (0)	123.2 (69.7)	5.3 (1.6)

[a]Significantly different ($p < 0.05$, two-tailed Wilcoxon test).

When the tablet was applied at the gingiva in the irradiated patients comparable results were obtained for the evaluated parameters as in the previous study with healthy volunteers. In comparison with the study on the comatose intubated patients the gingival site in the irradiated patients revealed dramatically higher miconazole nitrate levels. This can be explained by the fact that, within the group of irradiated patients, speaking, drinking and eating resulted in the contact of small amounts of saliva with the tablet; this was also because of the so-called 'playing with the tablet' with the tongue. Finally a small reservoir of saliva, formed on the dental prosthesis at the gingiva, induces a faster swelling and release rate from the tablet.

When evaluating the cheek as the application site, a significant reduction in adhesion time was noted in comparison to the gingiva. This could be explained by the fact that during eating food sticks to the dental prosthesis and that while the patients are trying to remove the food with their tongue or by removing the prosthesis, the tablet was detached and swallowed. Although a reduced adhesion time was seen when the tablet was fixed on the cheek, initially comparable miconazole nitrate salivary levels were obtained as seen in comatose intubated patients. This might indicate that the salivary flow played a less important role and was an important factor only in non-active patients.

It can be concluded that the gingiva is the application site of choice in active patients, even if a decrease in salivary flow is seen.

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