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Local Prostaglandin E_2 in Patients with Oral Malignancies Undergoing Chemo- and Radiotherapy

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Summary

Patients undergoing chemo- and/or radiotherapy for malignancies were often found to develop annoying inflammation of the oral mucosa. As prostaglandins are known to be cytoprotective Prostaglandin E_2 was given to 10 patients who received combined radio- and chemotherapy for oral neoplasms. Patients receiving PGE_2 reported substantially less intense pain then those in the control group. Our statistically significant results indicate that topical treatment of side effects produced by combined radio- and chemotherapy of oral neoplasms with PGE_2 holds promise and is clearly superior to conventional treatment modalities.

Key words

Mucositis – Oral malignancies – PGE_2

Introduction

Patients undergoing chemo- and/or radiotherapy for oral malignancies are often found to develop inflammation of the oral mucosa as a side effect of treatment (*Berkositz* et al., 1983). In severe cases, typical extensive inflammatory infiltration of the entire oral mucosa may be compounded by desquamation of superficial mucosal tissue (ulcerative stomatitis) associated with high-grade pain, secretion of tenuous mucus, local dryness and dysphagia (*Scherer*, 1967; *Moss* et al., 1979), so that feeding becomes difficult or altogether impossible.

Conventional treatment of this special variant of ulcerative stomatitis with Xyloviscose, a local anaesthetic; Bepanthene lozenges, a disinfectant; wetting of the oral mucosa or other measures is often inadequate so that radiotherapy and chemotherapy have to be discontinued for some time.

As prostaglandins are known to be cytoprotective (*Schrör*, 1984), they are likely candidates for the treatment of this condition. Beneficial effects of PGE_2 were reported in chronic leg ulcers (*Eriksson* et al., 1986), gastric ulcers (*Cohen* and *Clark*, 1983) and cytostatic-associated mucosal lesions (*Kührer* et al., 1986). As a result, we have used cytoprotective prostaglandin E_2 (Prostin E_2®, Upjohn, Kalamazoo, Michigan, USA) locally for the prevention and treatment of stomatitis for the past 8 months. The purpose of our trial was to establish whether or not the drug can be expected to have a beneficial effect on the inflammatory process and the associated pain. In addition, we wanted to shed light on a local absorption of PGE_2, if any, by assaying patient plasma for its stable final metabolite bicyclo-PGE_2.

Material and Methods

Prostaglandin E_2 was given to 10 patients, 8 males and 2 females, aged between 33 and 83 years who had received combined radio- and chemotherapy for oral and maxillary neoplasms (Table 1). The drug* was administered throughout the radio- and chemotherapy courses for a total of 6 to 31 days. Local treatment other than prostaglandin was omitted.

The trial group of 10 patients was compared with a control group of 14 patients (11 males and 3 females) aged between 31 and 79 years who received combined radio- and chemotherapy for analogous diseases, but were not put on PGE_2.

Outcome was evaluated in terms of the extent and severity of the inflammatory mucosal reactions (visible reddening or desquamation of oral mucosa).

At 9, 13, 17 and 21 hours patients were given 1 lozenge of Prostin E_2® (Upjohn, Kalamazoo, Michigan, USA) to be sucked. If their tongues were rigid, the lozenges were deposited into the oral floor.

Blood samples for plasma level assays of bicyclo-PGE_2, the degradation product of the stable final metabolite in vitro (*Granström* et al., 1979), were obtained in 7 cases. Sampling was done immediately before and 30 and 60 minutes after the first dose as well as after 3–4 and 7–9 hours in the first 2 days. Blood was taken from the non-occluded antecubital vein. Each 9 ml sample was mixed with 1 ml of a solution consisting of 2% Na-EDTA (for anticoagulation) and 1% Aspisol® (acetylsalicylic acid; Bayer Leverkusen, FRG), (for cyclo-oxygenase inhibition) cooled to 4° C. After sedimentation for 5 minutes at 4° C samples were centrifuged for 10 minutes of 1500 g at a temperature of 4° C. The plasma was transferred to plastic tubes and stored for no more than 2 weeks at – 70° C for subsequent radioimmunoassay (RIA) (*Sinzinger* et al., 1984).

Using a specific radioimmunoassay (*Silberbauer* et al., 1983) samples were examined for the presence of 11-desoxy-13,14-dihydro-15-keto-13,11 ß-16-epsilon-bicyclo-PGE_2, the degradation product of 15-keto-13,14-dihydro-PGE_2. Double antibodies were used for separating the free and antigen-associated ligands in non-extracted plasma (*Peskar* et al., 1979). The method was based on the principle described by *Granström* et al. (1979) and modified by

* 0.5 mg PGE_2/tablet, 4 time/day

Table 1

Name	Age	Sex	Diagnosis	Site	Chemother.	Radiation	Total PGE_2	Duration of medication
K. G.	54 yrs.	f	squ. cell carc.	r. tongue base	Mitomycin C® Fluoro-Uracil®	Betatron 25 X 50 Gy	50 mg	25 days
B. G.	41 yrs.	m	squ. cell carc.	r. palatogl. fold	Mitomycin C® Fluoro-Uracil®	Betatron 25 X 50 Gy	50 mg	25 days
G. S.	63 yrs.	m	squ. cell carc.	l. subling. sulcus	Mitomycin C® Fluoro-Uracil®	Betatron 6 X 12 Gy	12 mg	6 days
B. H.	48 yrs.	f	squ. cell carc.	r. palatogl. fold + tons. reg.	Mitomycin C® Fluoro-Uracil®	Gammatron 25 X 50 Gy	50 mg	25 days
S. L.	76 yrs.	m	squ. cell carc.	r. subling. sulcus	Mitomycin C® Fluoro-Uracil®	Betatron 25 X 50 Gy	50 mg	25 days
F. F.	55 yrs.	m	squ. cell carc.	r. tongue + floor of mouth	Mitomycin C® Fluoro-Uracil®	Betatron 31 X 50 Gy	62 mg	31 days
D. A.	77 yrs.	m	squ. cell carc.	r. maxillary tuberosity	Mitomycin C® Fluoro-Uracil®	Gammatron 26 X 50 Gy	52 mg	26 days
C. J.	33 yrs.	m	squ. cell carc.	r. and l. tongue + floor of mouth	Mitomycin C® Fluoro-Uracil®	Betatron 25 + 17 X 50 + 20 Gy	34 mg	17 days
W. A.	53 yrs.	m	squ. cell carc.	tongue	Mitomycin C® Fluoro-Uracil®	Betatron 25 X 50 Gy	50 mg	25 days
H. F.	83 yrs.	m	B cell lymph.	cheek	Mitomycin C® Endoxan® Oncovin® Cis-Platin®	Gammatron 25 X 45 Gy	50 mg	25 days

us. Its sensitivity was 10 pg/ml; its antibody cross-reactivity was below 1 %. At a level of 50 pg/ml the intra-assay and inter-assay coefficients of variation were 4.9 % and 7.4 %, respectively.

Statistical analysis

Results were expressed as means (x) ± S. D. Significances were evaluated with Student's t test.

Results

In 8 of 10 patients, cytostatic and radiotherapy courses were completed as scheduled. One patient temporarily discontinued the combination treatment because of severe nausea and appreciable stomatitis with associated pain. Another patient requested to be discharged from hospital before completing the course and discontinued drug treatment of his own accord.

While the 8 patients who completed their cytostatic and radiation courses as scheduled developed treatment-related stomatitis, the severity of the condition was less pronounced than in patients not receiving PGE_2 (Figs. 1 and 2).

In 3 patients on PGE_2 the inflammatory reaction was confined to an area of a few centimetres around the tumour, in the others it involved the entire oral cavity. Bullous or desquamating inflammatory lesions of the oral mucosa were not seen in any of the PGE_2-treated patients.

By contrast, such severe lesions were encountered in 6 of the control cases (42.8 %, [Fig. 3]). While there was no definite evidence of a progression of the inflammatory process after the first 6 to 8 radiation courses in the PGE_2 group, the severity of the reaction (intense reddening, infiltration to the point of epithelial sloughing, pain, functional impairment on eating, drinking and speaking) clearly continued to increase in the controls.

Patients on PGE_2 reported substantially less intense pain than those in the control group. Of the 8 responders, 3 had almost no spontaneous pain, the others complained of slight to moderate painful sensations which did not interfere with feeding.

Bicyclo-PGE_2 plasma levels did not show any significant changes during the trial period so that there was apparently no major absorption of topically applied PGE_2 (Table 2).

Discussion and Conclusions

Results in the patients evaluated so far suggest that the treatment of side effects produced by combined radio- and chemotherapy of oral neoplasms with PGE_2 holds promise and is clearly superior to conventional treatment modali-

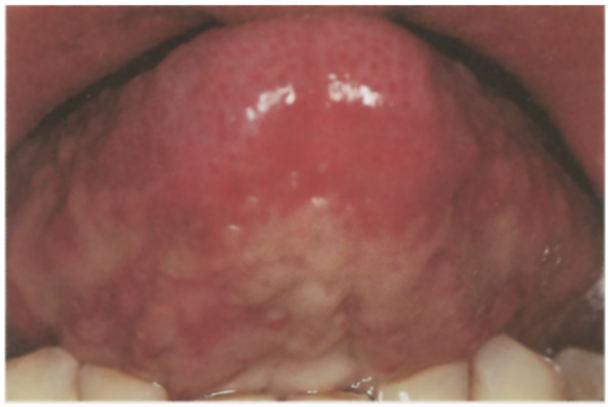

Fig. 1 Condition during radiotherapy with desquamating bullous inflammation of the oral mucosa in a patient of the control group.

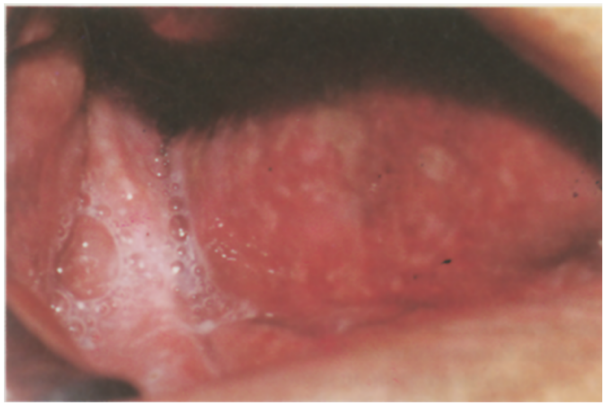

Fig. 2 Condition during radiochemotherapy (after 12th betatron course and fluorouracil and mitomycin C medication) and PGE_2 treatment (total dose, 24 mg).

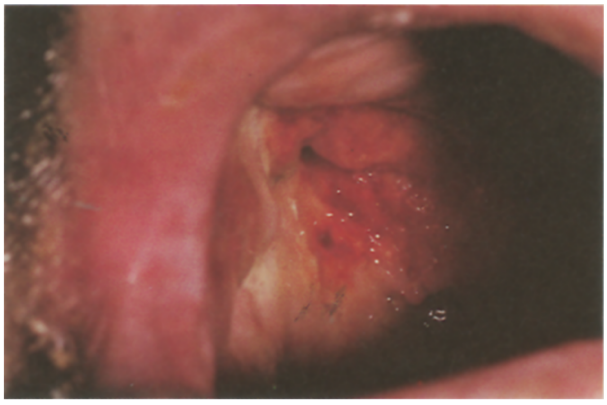

Fig. 3 Desquamating bullous inflammation of oral mucosa in a patient of the control group.

Table 2

Pretreatment	21 ± 5.3
30 minutes	24 ± 7.6
60 minutes	22 ± 6.1
3–4 hours	25 ± 5.2
7–9 hours	23 ± 7.4

$\bar{X}$ ± S. D.; bicyclo-PGE_2 in pg/ml

ties. It was of particular interest that patients with moderately severe stomatitis at best complained of mild pain, while those with mild disease reported almost no pain (*Schrör* et al., 1984; *Fantone* et al., 1985). This is in agreement with observations by *Kührer* et al. (1986) in patients undergoing cytostatic chemotherapy.

Preexisting pain attributable to the size of the mass, (stage of infiltrative growth) was largely reported to be unaffected by the treatment.

Although relatively large quantities of the drug were applied topically, there was no evidence of any relevant systemic absorption. Bicyclo-PGE_2 plasma levels did not show any changes throughout treatment. This appears to suggest that the cytoprotective action of PGE_2 is local. PGE_2 was suspected of interfering with the outflow of blood from the gastrointestinal mucosa (*Schrör*, 1984). Such an action mechanism is, however, unlikely, as the drug is apparently not absorbed systemically.

The excellent clinical results go to show that topical PGE_2 is superior to conventional modalities in the prevention and treatment of stomatitis secondary to combined radio- and chemotherapy for oral malignancies and constitutes the treatment of choice.

Acknowledgements

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