British Journal of Oral and Maxillofacial Surgery (1990) **28**, 89–91

BRITISH JOURNAL OF ORAL & MAXILLOFACIAL SURGERY

0266–4356X/90/0028–0089/$10.00

Local benefit of prostaglandin E2 in radiochemotherapy-induced oral mucositis

M. Matejka, A. Nell, G. Kment, A. Schein, M. Leukauf, H. Porteder, G. Mailath, H. Sinzinger

Basic Research Division, University Department of Dentistry; Department of Maxillofacial Surgery; 2nd Department of Oto-Laryngology; University of Vienna and Atherosclerosis Research Group, Vienna

SUMMARY. **In 15 patients suffering from maxillofacial cancer with radiochemotherapy-induced oral mucositis the local application of prostaglandin E2 (PGE2) tablets, 0.5 mg four times a day at a 4-h interval was performed. Plasma determination of the bicyclo-prostaglandin E2 metabolite showed no significant amount of the locally applied substance in the circulation. It is claimed that for this particular indication, PGE2 is a potent locally acting compound without affecting circulating levels.**

INTRODUCTION

Cancer chemotherapy in general as well as for the maxillofacial area is associated with a variety of side-effects, including the development of stomatitis which is very uncomfortable for the patient. Data on the occurrence of these side-effects varies between 40 and 80% depending on the type and duration, as well as the dosage of the cytostatics (Fig.).

It has been established that one of the mechanisms, which leads to mucositis or stomatitis, is interference by the cytostatics of DNA synthesis. The epithelium of the oral mucosa has a high rate of DNA synthesis and a short turnover time of approximately 5 days. Therefore, disruption of DNA synthesis has a strong effect on cell growth and prevents the normal replacement of the mucosa, followed by atrophy and ulceration of the mucous membrane (Dreizen, 1978).

In addition to this cause, we also regard a change in the bacterial flora as an additional factor in the development of mucositis. Dreizen has already observed a change in the oral flora at initial presentation of advanced tumours (Dreizen *et al.*, 1974). According to Allan (1976) this is on the one hand due to the primary disease and on the other, due to antibiotic treatment of patients receiving cytostatic agents. Dreizen (1978) noted that the bacterial spectrum shifted from the predominantly gram-positive organisms to the gram-negative during chemotherapy. In their findings, Main *et al.* (1984) pointed out the connection between mucositis, direct cytostatic damage of the mucosa and immunosuppression induced by chemotherapy, complicated by xerostomia and secondary infection.

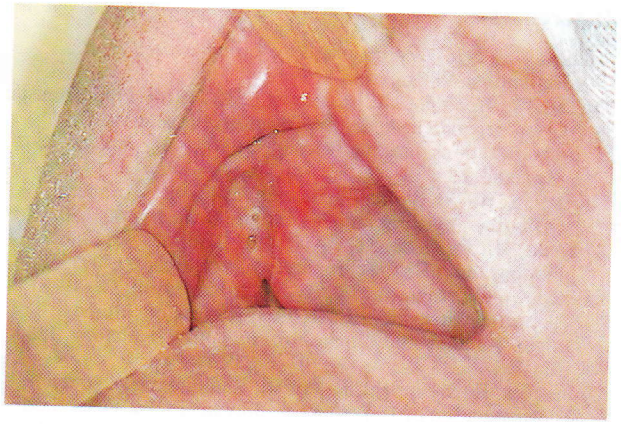

Fig. – Stomatitis occurring during chemotherapy with Methotrexate and Bleomycin

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

Prostaglandins (PGs) have been well known for decades as cytoprotective compounds especially in the gastrointestinal tract (Johansson & Bergström, 1982). They are potent locally acting compounds rather than circulating substances; topical application without systemic effects being a preferable therapeutic concept. In stomatitis in malignant disease a beneficial effect of locally administered PGE2 has been reported (Kührer *et al.*, 1986; Sinzinger *et al.*, 1989). Patients benefit significantly from this treatment and it is therefore the goal of this investigation to examine, whether locally applied PGE2 is absorbed into the blood stream to a significant extent.

MATERIAL AND METHODS

In 15 patients (13 male, 2 female; age range 45–79 yrs) with maxillofacial cancer and radiochemotherapy-induced oral mucositis a topical application of pros-

taglandin (PGE2) was performed. PGE2 tablets (0.5 mg; The Upjohn Company, Kalamazoo, Michigan, USA) were administered four times daily at 4-h intervals. Blood sampling for determination of plasma levels, was undertaken before administration of the first tablet (sample 1) and then at 1 h (sample 2) and 3 h (sample 3) following, as well as after 6 h (sample 4) and 8–10 h (sample 5). Two further samples were taken the next morning before therapy (sample 6) as well as in the early afternoon (sample 7).

Five ml blood samples were each drawn from a non-occluded ante-cubital vein using a 1.2 mm diameter needle. Precooled (4°C) 2% sodium ethylene diamine tetra-acetic acid (EDTA) was used as anticoagulant and lysinacetylsalicylic acid (1 mg/1 ml blood) was used for cyclooxygenase blockade. Plasma was obtained by centrifugation (1500g, 4°C, 10 minutes) and stored at −70°C for less than 2 weeks until radioimmunoassay. Prostaglandin E2 is rapidly metabolized to 15-keto-13,14-dihydro-PGE2, which undergoes subsequent chemical reactions in the blood, leading to 15-keto-13,14-dihydro-PGA2, which is partly covalently bound to albumin. By incubation of plasma samples at pH 10 to 11, all metabolites of PGE2 are converted into the same non-reactive stable compound 11-deoxy-13,14-dihydro-15keto-11,16-cyclo-PGE2, that is: bicyclo-PGE2 (Granström & Kindahl, 1980). Antibodies raised against this stable bicyclic derivative were used to perform a radio-immunoassay (RIA) in unextracted samples (the antibody <6> was kindly placed at our disposal by Professor Bernhard A. Peskar, Department of Pharmacology, Ruhr-University of Bochum, FRG). This approach circumvented the hazards of direct measurement of a metabolite that is chemically unstable. The assay was performed using the double antibody technique as described earlier (Punzengruber *et al.*, 1986). Standard curves were prepared with unextracted prostaglandin-free plasma to correct for nonspecific protein binding (sensitivity 10 pg/ml, blank water displacement 1%, maximum binding at 70 pg/ml; the cross reactivity to the corresponding bicyclo-PGE1m amounted to 25%, to other prostaglandins less than 1%). The intra-assay coefficient of variation was 4.1% and the inter-assay coefficient of variation was 7.3%.

Statistical analysis

The values are given as x ± SD; calculation for significance was done by means of analysis of variance.

RESULTS

PGE2 plasma levels

The pretherapeutic values of bicyclo-PGE2 amount to 33.5 pg/ml. With reference to different time intervals after the local application of 0.5 mg PGE2 no apparent differences in plasma levels of the bicyclo-PGE2 were monitored. (Table 1.)

Table 1 – Bicyclo-PGE2 values before and between different time intervals after local PGE2-application

sample	bicyclo-PGE2m	n.
1	33.5 ± 2.9	15
2	32.1 ± 4.1	15
3	32.4 ± 3.1	13
4	33.4 ± 3.2	12
5	32.7 ± 2.5	15
6	33.3 ± 2.9	14
7	34.7 ± 5.7	15

x ± SD n. = number of patients

Clinical results

An inflammatory reaction in the vicinity of the tumour could be detected in only five patients treated with topically PGE2. Bullous or desquamating inflammatory lesions in the whole oral cavity were not observed in any patient.

DISCUSSION

Prostaglandins are claimed to act as potent locally acting substances rather than as circulating hormones. They are used with clinical benefit in the gastrointestinal tract (Johansson & Bergström, 1982), and for ischemic ulcers of the lower leg (Eriksson *et al.*, 1986; 1988).

Our findings support this claim indicating that although rather high amounts of PGE2 are locally administered, no significant absorption takes place. The reported excellent clinical results, with no interruption of radiochemotherapy caused by painful bullous or desquamating inflammatory lesions of the oral cavity, demonstrate that the PGE2-treatment at a local level is a very promising and clinically effective therapeutic approach without interfering with any other biological system and therefore, without any potential side effects.

References

Allan, J. C. (1976). *Infection and the Compromised Host.* Baltimore: Williams and Wilkins.

Dreizen, S., Booley, G. P. & Brown, L. R. (1974). Opportunistic Gram-negative bacillary infections in leukaemia and manifestations during myelosupression. *Postgraduate Medicine*, **55**, 133.

Dreizen, S. (1978). Stomatotoxic manifestations of cancer chemotherapy. *Journal of Prosthetic Dentistry*, **40**, 650.

Eriksson, G., Johansson, C., Aly, A. & Topical, A. (1986). Prostaglandin E2 for chronic leg ulcers. *Lancet* **i**, 905.

Eriksson, G., Torngren, M., Aly, A. & Johansson, C. (1988). Topical prostaglandin E2 in the treatment of chronic ulcers—a pilot study. *British Journal of Dermatology*, **118**, 531.

Granström, E. & Kindahl, R. (1980). Radioimmunologic determination of 15-keto-13,14-dihydro-PGE2. A method for its stable degradation product: 11-deoxy-13,14-dihydro-15-keto-11β16E-cycloprostaglandin E2. In: Samuelson, B., Ramwell, P. & Paoletti, R. (eds) *Advances in Prostaglandin*

and Thromboxane Research, Volume 6, pp 181, New York: Raven Press.

Johansson, C. & Bergström, S. (1982). Prostaglandins and protection of gastroduodenal mucosa. *Scandinavian Journal of Gastroenterology*, **77**, 21.

Kührer, I., Kuzmits, R., Linkesch, W. & Ludwig, H. (1986). Topical PGE2 enhances healing of chemotherapy associated in mucosal lesions. *Lancet* **i**, 622.

Main, B. E., Calman, K. C., Ferguson, M. M., Kaye, S. B., McFarlane, T. W., Mairs, R. S., Samaranayake, L. P., Willox, Y. & Welsh, Y. (1984). The effect of cytotoxic therapy on saliva and oral flora. *Journal of Oral Surgery*, **58**, 545.

Peskar, B. M., Guenter, B., Steffen, C. A., Kröner, E. E. & Peskar, B. A. (1980). Antibodies against hydration product of 15-keto-13,14-dihydro-prostaglandin E2. *FEBS letters* **115**, 123.

Punzengruber, C., Stanek, B., Sinzinger, H. & Silberbauer, K. (1986). Bicyclo-prostaglandin E2 metabolite in congestive heart failure and relation to vasoconstrictor neurohumoral principles. *American Journal of Cardiology*, **57**, 619.

Sinzinger, H., Porteder, H., Matejka, M. & Peskar, B. (1989). Prostaglandins in irradiation-induced mucositis. *Lancet* **i**, 556.

The Authors

M. Matejka MD, DMD
Andrea Nell
Angelika Schein
G. Mailath
Basic Research Division
University Department of Dentistry
University of Vienna
M. Leukauf
H. Porteder
Department of Maxillofacial Surgery
University of Vienna
G. Kment
Second Department of Oto-Laryngology
University of Vienna
H. Sinzinger
Atherosclerosis Research Group Vienna

Correspondence and requests for offprints to M. Matejka, Basic Research Division, University of Vienna, Dental School, Währingerstr. 25a A-1090 Vienna, Austria

Paper received 6 April 1989
Accepted 15 May 1989