Acta Derm Venereol (Stockh) 1990; 70: 46–88

SHORT REPORTS

Tetracycline Does Not Affect the Trauma- and Leukotriene B_4-induced Intraepidermal Accumulation of Polymorphonuclear Leukocytes

A. CHANG, P. STEEGMANS and P. C. M. van de KERKHOF

Department of Dermatology, University Hospital, Nijmegen, The Netherlands

The transepidermal migration of polymorphonuclear leukocytes is a well established target for antipsoriatic therapies. Tetracycline, although inhibiting the movement of PMN, is not an effective treatment for psoriasis. In contrast to the inhibition of PMN chemotactic response to serum and bacterial products, the leukotriene B_4-induced and trauma-induced intraepidermal accumulation of PMN was unaffected by tetracycline. ***Key word: Elastase.***

(Accepted July 31, 1989.)

Acta Derm Venereol (Stockh) 1990; 70: 46–48.

A. Chang, Department of Dermatology, University Hospital Nijmegen, Philips van Leydenlaan 25, 6525 EX Nijmegen, The Netherlands.

The intraepidermal accumulation of polymorphonuclear leukocytes (PMN) is one of the earliest and perhaps most characteristic constituents of the psoriatic lesion (1). In order to study the interference of drugs with the dynamics of this process 2 experimental models are available. The intraepidermal accumulation of PMN following sellotape stripping is the response to a standardized endogenous release of mediators of inflammation (2). The intraepidermal accumulation of PMN following epicutaneous application of leukotriene B_4 (LTB_4) is another reproducible model, in which a standardized exogeneous stimulus is given (3, 4). Etretinate, acitretin, methotrexate, phototherapy, photochemotherapy, dithranol and topical corticosteroids—although strikingly different therapeutical approaches—share 2 characteristics: a well established antipsoriatic effect clinically and a profound inhibition of intraepidermal accumulation of PMN in these models (4–10).

Tetracyclines have been reported to interfere with PMN functions *in vitro* and *in vivo* (11–14). Surprisingly, these drugs are not part of the repertoire of antipsoriatic therapies. However, as far as we know, the LTB_4-induced PMN accumulation has never been reported to be inhibited by tetracyclines. In the present investigation the interference of an oral course of tetracycline with the trauma- and LTB_4-induced intraepidermal accumulation of PMN was studied.

MATERIALS AND METHODS

Nine subjects without signs or previous history of skin diseases participated in the study. The group consisted of 2 females and 7 males, aged between 22 and 35 years. No subject had received any medication for at least 3 months prior to the study. Prior consent of the medical ethics committee was obtained for these experiments. The volunteers received an oral course of tetracycline in doses of 250 mg four times a day for 10 consecutive days. One day before initiation of the therapy, and on the 3rd and 10th day of the treatment, LTB_4 was applied and sellotape stripping was carried out.

LTB_4 was purchased from Paesel GmbH Frankfurt, Germany. Aliquots of 10 ng LTB_4 in ethanol were applied in 10 µl droplets through glass cylinders (diameter 5.5 mm) on the upper back skin and ethanol was evaporated under a stream of nitrogen (3, 4). Application sites were marked with eosin and covered with impermeable dressings (Silverpatch, Van der Bend, Brielle, The Netherlands). At the same time circular areas (diameter 15 mm) were stripped on areas at least 10 cm from the LTB_4 sites by repeated applications of sellotape. Removal of the stratum corneum was considered complete when the whole area appeared to be glistening (30–40 applications). Biopsies were taken from the stripped areas and from the LTB_4-treated sites 8 h and 24 h after these challenges, respectively. No anaesthetic agent was employed. All specimens were cut freehand, using a razorblade in conjunction with a metal guard. The biopsies (fresh weight 2–3 mg, approximately 3 mm diameter and 0.2 mm thick) were processed for elastase measurement.

Analytical procedures were as described previously (2, 15). In brief, the biopsies were rinsed thoroughly in phosphate buffered saline, homogenized in buffer containing cetrimide and centrifuged. Elastase activity of the supernatant was determined by measuring the fluorescence of 4-methyl-7-aminocoumarin, released from the substrate MeOSuc-Ala-Ala-Pro-Val-N-methylcoumarin; endogenous inhibition was corrected for by the inclusion of an internal standard of elastase (equivalent to 500 PMN). The density of infiltrating PMN per 10 µg skin was calculated using the value of 0.66 pmol 4-methyl-7-aminocoumarin released per hour per PMN (2).

Statistical evaluation was performed using the Wilcoxon rank test for paired samples.

RESULTS

Tetracycline in dosages of 1 g a day were well tolerated by all the subjects. Only one of them had experienced a mild gastrointestinal discomfort on days 9 and 10 of the treatment period.

PMN accumulations 8 h following sellotape strip-

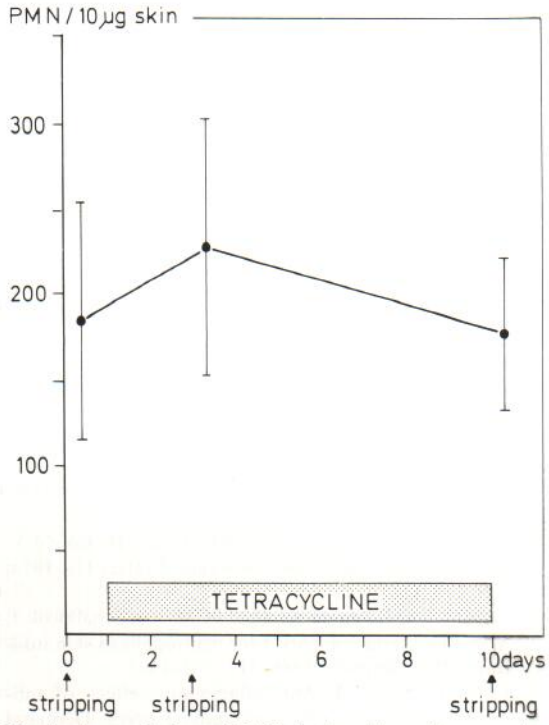

Fig. 1. Accumulation of PMN, induced by sellotape stripping at different time intervals before and during treatment with tetracycline. Bars represent mean ± SEM.

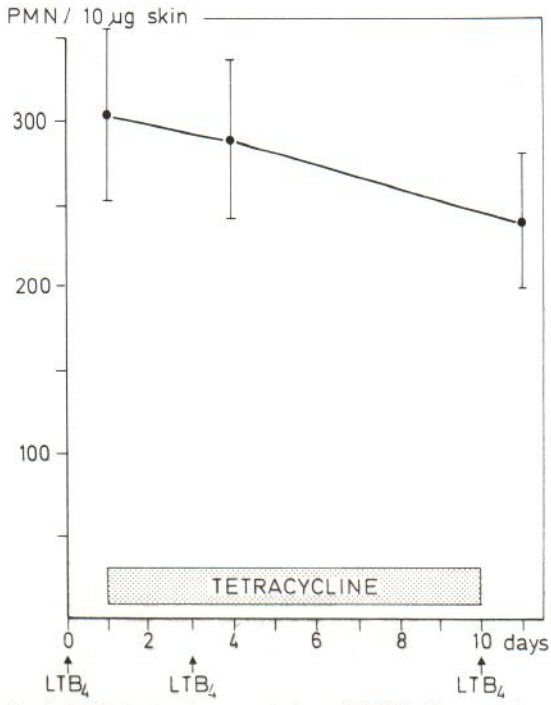

Fig. 2. LTB_4-induced accumulation of PMN before and during treatment with tetracycline. Bars represent mean ± SEM.

ping and 24 h following the application of LTB_4 before and during treatment with tetracycline are shown in Figs. 1 and 2. Both trauma- and LTB_4-induced PMN accumulations were unaffected by tetracycline ($p > 0.05$). The percentage inhibition of a standard preparation of elastase by all the skin biopsies examined was $13 \pm 1.5\%$ (mean ± SEM) and no statistically significant difference could be shown from the inhibitory activity of $12 \pm 4.0\%$ reported for normal unchallenged skin (15) ($p > 0.05$).

DISCUSSION

The present investigation clearly shows that an oral course of tetracycline in a dosage of 1 g a day does not inhibit the trauma- or LTB_4-induced intraepidermal accumulation of PMN.

The chemotactic response of PMN to human serum, C_{5a}, bacterial endotoxins and A_2 influenza virus has been shown to be inhibited by tetracycline (11–14). To the best of our knowledge, no data are available in the literature regarding a possible interference of this drug with the chemotactic response of PMN to inflammatory eicosanoids.

The molecular basis of the interference of tetracycline with PMN chemotaxis is not clear. It has been suggested that the interference is not at the level of the PMN themselves but comprises an inhibition of the generation of chemotactic factors and binding to chemoattractants (11). However, a more recent study indicates that a direct interference with the PMN movement occurs as well (13).

In contrast to the observations in the present study tetracycline has been reported to inhibit the potassium iodide-induced intrafollicular micropustule formation (16). An explanation of this discrepancy might be a different bioavailability in these models. Tetracyclines have been reported to occur in relatively high concentrations in the follicular epithelium (17). However, using skin chambers with serum complement and bacterial culture supernatants as chemoattractants, tetracycline inhibited the PMN chemotaxis (18). Combining the present study with these observations using skin chambers it seems feasible that tetracycline does not affect the chemotactic response of the whole repertoire of chemoattractants.

A selective interference of tetracycline with PMN chemotaxis is in line with the available data on the

role of PMN as a target for antipsoriatic therapies. Although some authors suggest an effect of tetracycline in pustular psoriasis (19, 20) this drug has by no means an established reputation as treatment for this disease. The negative effect of tetracycline on the LTB_4- and trauma-induced PMN accumulation is compatible with the essentially negative clinical results of tetracycline in psoriasis.

REFERENCES

1. Stadler R, Schaumberg-Lever G, Orfanos CE. Histology. In: Mier PD, van de Kerkhof PCM, eds. Textbook of psoriasis. Edinburgh: Churchill Livingstone, 1986: 40–54.
2. Chang A, de Jongh GJ, Mier PD, van de Kerkhof PCM. Enzymatic quantification of polymorphonuclear leukocytes in normal and psoriatic skin following standardized injury. Clin Exp Dermatol 1988; 13: 62–66.
3. Camp R, Russell Jones R, Brain S, Woollard P, Greaves M. Production of intraepidermal microabscesses by topical application of leukotriene B_4. J Invest Dermatol 1984; 82: 202–204.
4. Kerkhof van de PCM, Bauer FW, Maassen-de Grood RM. Methotrexate inhibits the leukotriene B_4 induced intraepidermal accumulation of polymorphonuclear leukocytes. Br J Dermatol 1985; 113: 251a–255a.
5. Lammers AM, van de Kerkhof PCM, Mier PD. Reduction of leukotriene B_4-induced intra-epidermal accumulation of polymorphonuclear leukocytes by methotrexate in psoriasis. Br J Dermatol 1987; 116: 667–671.
6. Lammers AM, van de Kerkhof PCM. Etretinate modulates the leukotriene B_4 induced intra-epidermal accumulation of polymorphonuclear leukocytes. Br J Dermatol 1987; 117: 297–300.
7. Kerkhof van de PCM, Chang A, van Dooren-Greebe, Geiger JM, Happle R. Intra-epidermal accumulation of polymorphonuclear leukocytes in persistent palmoplantar pustulosis during treatment with acitretin. Acta Derm Venereol (Stockh) 1988; 68: 449–503.
8. Chang A, Alkemade JAC, van de Kerkhof PCM. PUVA and UVB inhibit the intra-epidermal accumulation of polymorphonuclear leukocytes. Br J Dermatol 1988; 119: 281–287.
9. Chang A, Alkemade H, van de Kerkhof PCM. Dithranol modulates the leukotriene B_4-induced intraepidermal accumulation of polymorphonuclear leukocytes. J Invest Dermatol 1989; 92: 806–808.
10. Chang A, van de Kerkhof PCM. Topical application of clobetasol-17-propionate inhibits the intraepidermal accumulation of polymorphonuclear leukocytes. Acta Derm Venereol (Stockh) 1988; 68: 57–60.
11. Majeski JA, Alexander JW. Evaluation of tetracycline in the neutrophil chemotactic response. J Lab Clin Med 1977; 90: 259–265.
12. Esterly NB, Furey NL, Flanagan LE. The effect of antimicrobial agents on leukocyte chemotaxis. J Invest Dermatol 1978; 70: 51–55.
13. Esterly NB, Koransky JS, Furey NL, Trevisan M. Neutrophil chemotaxis in patients with acne receiving oral tetracycline therapy. Arch Dermatol 1984; 120: 1308–1313.
14. Martin RR, Warr GA, Couch RB, Yeager H, Knight V. Effects of tetracycline on leukotaxis. J Infect Dis 1974; 129: 110–116.
15. Lammers AM, van de Kerkhof PCM, van Schalkwijk J, Mier PD. Elastase a marker for neutrophils in skin infiltrates. Br J Dermatol 1986; 115: 181–186.
16. Plewig G, Schöpf E. Anti-inflammatory effects of antimicrobial agents: an in vivo study. J Invest Dermatol 1975; 65: 532–536.
17. Marks R, Davies MJ. The distribution in the skin of systemically administered tetracycline. Br J Dermatol 1969; 81: 448–451.
18. Elewski BE, Lamb BAJ, Sams WM, Gammon WR. In vivo suppression of neutrophil chemotaxis by systemically and topically administered tetracycline. J Am Acad Dermatol 1983; 8: 807–812.
19. Thomsen K, Østerbye P. Pustulosis palmaris et plantaris. Br J Dermatol 1973; 89: 293–296.
20. McFadyen T, Lyell A. Successful treatment of generalized pustular psoriasis (von Zumbusch) by systemic antibiotics controlled by blood culture. Br J Dermatol 1971; 85: 274–276.