SESAME OIL IN INJECTABLE GOLD: TWO DRUGS IN ONE?

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SUMMARY

To investigate the potential anti-inflammatory effects of sesame oil, which is present in the injectable gold preparation Auromyose®, the synthesis of tumour necrosis factor alpha (TNF-α), prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) by in vitro stimulated blood cells was measured before, during and after 12 weeks of dietary supplementation with 18 g of sesame oil daily in 11 healthy male volunteers. Neither TNF-α, PGE2 nor LTB4 production levels showed statistically significant changes during the 12 weeks of dietary supplementation with sesame oil. These results do not suggest an anti-inflammatory effect of sesame oil as present in injectable gold preparations which are used in the treatment of rheumatoid arthritis.

KEY WORDS: Rheumatoid arthritis, Gold compounds, Sesame oil, Prostaglandin, Cytokine.

CHRYSOTHERAPY for rheumatoid arthritis (RA) [1] has been applied in many different preparations during the past 60 yr. Gold salts, such as aurothiomalate and aurothioglucose, have been given in both oily suspensions and aqueous solutions. Oily suspensions were associated with reduced toxicity [2] and enhanced efficacy as compared to aqueous solutions [3]. Since oily suspensions produced more even serum gold concentrations, it was assumed that the depot function of the oil was responsible for the favourable efficacy/toxicity balance of oily suspensions compared with aqueous solutions. However, the therapeutic response is not related to serum gold levels [4]. Therefore, the difference in efficacy between aqueous solutions and oily suspensions must have another explanation.

With the increasing evidence that dietary supplementation of particular fatty acids may have anti-inflammatory and immunomodulating effects [5], the hypothesis arose that the oil in i.m. gold injections might play a role in the enhanced efficacy of these preparations. Polyunsaturated fatty acids (PUFAs) are precursors for the synthesis of eicosanoids, which include prostaglandins, thromboxanes, prostacyclins and leukotrienes. Eicosanoids play an essential role in the inflammatory process [6, 7] and are, therefore, targets for pharmacological intervention in inflammatory joint disease.

Modulation of eicosanoid precursor fatty acids by dietary supplementation with fish oil, borage seed oil or black currant seed oil has been shown to decrease the production of prostaglandin E2 (PGE2), leukotriene B4 (LTB4) [8–13] and the inflammatory cytokines tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) [13, 14]. Furthermore, a suppressive effect of essential fatty acids on lymphocyte and synovial cell proliferation in vitro [15–18], and acute and chronic inflammation in animal models [19–21], has been observed. Clinical improvement of RA patients was reported during dietary supplementation with fish oil [8–10, 22, 23], evening primrose oil [24, 25], borage seed oil [26], blackcurrant seed oil [27] and olive oil [28].

The present pilot study was undertaken to investigate whether sesame oil, which is present in the injectable gold preparation Auromyose®, had an anti-inflammatory effect. Therefore, in healthy volunteers, the effect of dietary supplementation with sesame oil on the production of PGE2, LTB4 and TNF-α by in vitro stimulated blood cells was investigated.

SUBJECTS AND METHODS

Subjects and study design

The study was approved by the committee of medical ethics of the University Hospital Leiden. Eleven healthy male volunteers entered the study in January 1993 after giving informed consent (average age 28 yr; range 18–50). The subjects were free of disease and refrained from taking medication during the study.

For 12 weeks, the subjects added daily 18 g of sesame oil to their otherwise unchanged diets. Sesame oil was prepared by the hospital pharmacy as a 400 mg/ml emulsion containing the following substances: sesame oil, water, methylcellulose as emulsifying agent (0.8% g/v), saccharin sodium, citric acid and banana essence as flavouring agents, and benzoic acid as preservative. The volunteers had to take 45 ml of this emulsion daily. Sesame oil is known by gas chromatography to have the following fatty acid composition: < 0.5% saturated fatty acids, 7–12% palmitic acid (C16:0), 4–6% stearic acid (C18:0), 35–50% oleic acid (C18:1), 35–50% linoleic acid (C18:2) and 5–10% linolenic acid (C18:3).


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Stimulation of whole blood in vitro

Venous blood (10 ml) was drawn into heparinized tubes (Becton Dickinson, UK), which were kept at room temperature and used within 3 h. Another 4 ml of venous blood were collected in tubes containing EDTA for total and differential leucocyte counts. Heparinized samples were diluted 10-fold with RPMI 1640 (Gibco, Eggenstein, Germany), supplemented with antibiotics (100 U/ml penicillin and 100 μg/ml streptomycin; Boehringer Mannheim, Germany), and aliquotted in 24-well plates (Costar 3524, Cambridge, MA, USA).

For stimulation of TNF-α production in whole blood cultures, 10 μg/ml lipopolysaccharide (Sigma, St Louis, MO, USA) was added to the wells (final volume 1 ml/well). Thereafter, the plates were incubated for 24 h at 37°C in a humidified atmosphere with 5% CO2. After incubation, the cell-free supernatants were removed and stored at −20°C until required. For the induction of PGE2 and LTB4 production by whole blood cultures, plates were pre-incubated at 37°C, whereafter 20 μM calcium ionophore A23187 (Sigma) was added to the wells and the plates were incubated for 30 min at 37°C in a humidified atmosphere with 5% CO2. Supernatants were harvested and stored at −70°C.

Determination of TNF-α, PGE2 and LTB4

TNF-α was measured by ELISA as described previously [29]. Levels of PGE2 in the culture supernatants were determined by radioimmunoassay as described previously [30]. LTB4 was measured by a radioimmunoassay from Amersham, Hertogenbosch, The Netherlands, according to the manufacturer’s instructions.

RESULTS

All 11 healthy male volunteers completed the protocol. Their normal diets did not change during the study. The estimated mean daily energy intake was 2600 kcal. Fatty acids were responsible for 33% of this energy intake and the estimated mean daily intake of PUFAs was 15 g. Furthermore, the mean body weight of 76 kg did not increase during the dietary supplementation with sesame oil. Total and differential leucocyte counts were in the normal range in all subjects during the study. None of the volunteers reported adverse events from the sesame oil emulsion.

The mean production of TNF-α, PGE2 and LTB4 by in vitro stimulated whole blood cultures were calculated for the five study points (Table I). None of the differences between baseline and 6 or 12 weeks of dietary supplementation with sesame oil reached statistical significance. Comparison of the production at the end of 12 weeks dietary supplementation with that after 10 or 20 weeks of wash-out did not show any significant differences either. During the wash-out period, the production levels of TNF-α and PGE2 were not significantly different from their baseline production levels. LTB4 production, on the other hand, was significantly decreased after 10 weeks of wash-out as compared to baseline production (P = 0.04).

<table>
<thead>
<tr>
<th>Compound</th>
<th>12 weeks dietary supplementation with sesame oil</th>
<th>Wash-out period</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>6 weeks</td>
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<tr>
<td>TNF-α (ng/ml)</td>
<td>0.55 ± 0.06</td>
<td>0.48 ± 0.06</td>
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<tr>
<td>PGE2 (pg/100 μl)</td>
<td>280 ± 25</td>
<td>269 ± 27</td>
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<tr>
<td>LTB4 (pg/25 μl)</td>
<td>53 ± 7</td>
<td>55 ± 7</td>
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Data expressed as the mean ± s.e.m.

*P < 0.05 as compared to baseline using Wilcoxon’s signed rank test for paired samples.
DISCUSSION

The main conclusion of this pilot study is that neither TNF-α production nor eicosanoid production by in vitro stimulated whole blood cultures was significantly decreased during 12 weeks of dietary supplementation with sesame oil.

Anti-inflammatory effects in vitro and in vivo have been most consistently reported for plant seed oils containing relatively large amounts of GLA, such as evening primrose oil and blackcurrant seed oil [13, 15, 21, 24, 26, 27, 31–34]. This effect can be explained by the fact that metabolism of GLA results in increased production of PGE1, an eicosanoid with anti-inflammatory properties [5, 31, 35]. Sesame oil contains <1% GLA, which might explain the lack of a significant effect of dietary supplementation with sesame oil on the eicosanoid synthesis.

On the other hand, sesame oil is rich in PUFAs other than GLA and is known to inhibit tumour cell line growth in vitro [36, 37]. Moreover, several studies have suggested that PUFAs can modulate immune responses by acting directly on T cells [13, 16, 17]. We observed a non-significant declining trend in TNF-α production during dietary supplementation with sesame oil and a restoring trend during the wash-out period. This might suggest a direct effect of sesame oil on T lymphocytes and monocytes. Since TNF-α is a critical inflammatory mediator in RA, it is an important target for specific immunotherapy.

For this pilot study, we preferred oral administration of sesame oil in healthy volunteers. We are aware that results in healthy volunteers cannot be extrapolated to RA patients, although an earlier study has shown that the effect of another plant seed oil on cytokine and prostaglandin production by monocytes was not essentially different between RA patients and healthy volunteers [13]. Furthermore, the dosage of sesame oil in the present study was much higher than that RA patients will receive with i.m. gold injections. The diets were supplemented with 18 g of sesame oil daily, of which at least 10% will be absorbed. The usual weekly dose of i.m. gold is 50 mg of gold in 0.25 ml of injectable gold (Auromyose®) is ~225 mg. Therefore, it can be concluded that even if there is a weak effect of high-dose sesame oil on TNF-α or LTB4 production, the dose of sesame oil that is present in gold injections will probably not have an anti-inflammatory effect in RA patients. In the future, it would be interesting to investigate the efficacy of i.m. gold preparations containing GLA-rich plant seed oils or fish oil.

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