The effect of flurbiprofen and tiaprofenic acid on serum cytokine levels of patients with osteoarthrosis

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ABSTRACT – 39 patients with active knee osteoarthrosis, chosen according to ACR criteria, were assigned to receive flurbiprofen (n 12, 2 × 100 mg), tiaprofenic acid (n 14, 2 × 300 mg) and placebo (n 13) in a 3-week, placebo-controlled study. All patients completed the study, and both medications were found to be effective: improvement occurred in the clinical signs. These drugs reduced the TNF-α levels. Flurbiprofen especially affected the IL-6 levels. Our findings indicate that NSAIDs may be effective in the etiopathogenesis of osteoarthrosis.

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The role of inflammation in the pathogenesis of osteoarthrosis (OA) is debated. Synovial inflammation adjacent to cartilage (Lindblad and Hedfors 1987), definite synovial hyperplasia and a dense mononuclear infiltrate, indistinguishable from findings in rheumatoid arthritis (Haraoui et al. 1991), have been reported. Thus, there seems to be an inflammatory component at least in some patients during certain phases of the disease (Creamer and Hochberg 1997). This may contribute to cartilage loss by means of inflammatory cytokines leading to release of matrix proteinases, prostaglandins and plasminogen activators (Belcher et al. 1996). Therefore, appropriate treatment of OA should reduce the inflammatory response and maintain a satisfactory clinical response. We compared the effects of two drugs commonly used in the management of OA on cytokine levels and clinical improvement.

Patients and methods

39 previously untreated patients with clinically and radiographically active OA of the knee according to ACR criteria (Altman et al. 1986), were included in the study. Patients having clinically significant laboratory abnormalities, a history or presence of hepatic, renal or hematopoietic disorders, inflammatory or infectious disease were excluded. The study consisted of a 3-week, placebo-controlled study. Patients in the study were randomized to treatment with flurbiprofen (n 12), tiaprofenic acid (n 14), and placebo (n 13).

Flurbiprofen was give in a doses of 100 mg twice daily and tiaprofenic acid in a dose of 300 mg twice daily. The patients were seen weekly, assessed clinically and with laboratory findings at the end of the third week. Clinical parameters of pain at rest and pain on motion were evaluated with the visual analog scale. Duration of morning stiffness was recorded in minutes. Interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α) were measured before and after the study in the 3 groups. Serum samples were stored in polypropylene tubes at 70 °C for analyses of these cytokines. IL-1β (Cat. No. 1042, Immunotech) IL-6 (Cat. No. 1120, Boehringer Mannheim), and TNF-α (Cat. No. 1121-Immunotech) were measured with a "sandwich" enzyme immunoassay (ELISA).

The study was approved by the Ethics Committee of Cerrahpasa Medical Faculty, and every patient gave informed consent.

Table 1. Demographic features (SD)

	Placebo n 13	Flurbiprofen n 12	Tiaprofenic n 14
Sex, M/F	6/7	6/6	7/7
Age	58 (9.7)	57 (15)	62 (9.4)
Height, m	1.68 (0.13)	1.55 (0.07)	1.61 (0.007)
Weight, kg	74 (13)	72 (10)	73 (9.9)
BMI, kg/m^2	26 (4.3)	30 (4.1)	28 (3.0)
Duration of disease, yr	4.7 (3.5)	5.0 (4.3)	5.6 (3.3)

BMI body mass index

Statistics

The calculated power of the trial was 82%. The results were assessed with analysis of variance (ANOVA) for multigroup comparisons. Scheffe's post hoc test was employed. $P < 0.05$ was regarded as significant.

Results

The mean age, sex, height, weight, blood pressure, pulse and duration of the disease of the patients in the 3 groups were similar (Table 1).

Efficacy

Pain at rest. With flurbiprofen, the pretreatment score of 4.5 (SD 3.6) decreased to 1.5 (1.9). Tiaprofenic acid and placebo reduced pain from 3.5 (3.2) to 1.6 (1.7) and from 3.0 (2.2) to 2.5 (2.1), respectively. The changes observed in the flurbiprofen and tiaprofenic acid groups were statistically significant, compared to that in placebo group.

Pain on motion. With flurbiprofen, the pretreatment score of 8.3 (1.8) decreased to 7.3 (2.2). Tiaprofenic acid also fell, from 8.3 (1.8) to 3.4 (1.7) ($p < 0.001$). The score of 6.4 (1.5) fell to 5.1 (2.7) after placebo. Only changes in the tiaprofenic acid group were statistically significant.

Morning stiffness. Flurbiprofen reduced morning stiffness from 13.1 (9.6) min. to 3.8 (6.9) min. Tiaprofenic acid likewise reduced stiffness from 17 (12.5) min. to 3.8 (6.9) min. The placebo was also associated with a reduction from 21 (11.1) min. to 15.0 (11.3) min. Only changes in the tiaprofenic acid group were statistically significant compared to that in placebo group.

Table 2. IL-1 levels (95% CI) before and after the treatment

	Before	After
Flurbiprofen	4.69 (4.20–5.12)	3.99 (3.58–4.40)
Tiaprofenic acid	3.63 (3.22–4.03)	3.18 (2.95–3.40)
Placebo	3.74 (3.25–4.23)	3.58 (3.38–3.75)

Changes observed in both flurbiprofen and tiaprofenic acid groups were statistically significant compared to the placebo group

Table 3. IL-6 levels (95% CI) before and after the treatment

	Before	After
Flurbiprofen	14.0 (13.2–14.8)	10.8 (9.92–11.7)
Tiaprofenic acid	10.9 (10.3–11.6)	8.23 (7.32–8.74)
Placebo	15.7 (14.6–16.8)	14.4 (13.4–15.3)

Changes observed in both flurbiprofen and tiaprofenic acid groups were statistically significant compared to the placebo group

Table 4. TNF-α levels (95% CI) before and after the treatment

	Before	After
Flurbiprofen	4.81 (4.41–5.21)	3.99 (3.62–4.36)
Tiaprofenic acid	3.97 (3.59–4.36)	3.74 (3.46–4.03)
Placebo	4.34 (3.88–4.80)	4.18 (3.86–4.49)

Changes observed in both flurbiprofen and tiaprofenic acid groups were statistically significant compared to the placebo group

Cytokine levels

Tiaprofenic acid, flurbiprofen and placebo ruduced the levels of IL-1β, IL-6 and TNF-α. The changes in the flurbiprofen and tiaprofenic acid groups were statistically significant compared to that in the placebo group (Tables 2–4).

Side effects

The medications were well tolerated. Side effects were experienced by 3 patients taking flurbiprofen and 4 patients taking tiaprofenic acid. They were mostly mild gastrointestinal symptoms. No patient had to discontinue the medication.

Discussion

We found both flurbiprofen and tiaprofenic acid were effective in the treatment of OA, and they also reduced the cytokine levels. The management of OA consists mainly of controlling the symptoms, but as yet there are no disease-modifying OA drugs. Pharmacological and non-pharmacological therapies of lower limb OA have been recommended in guidelines as a pyramid-like approach to add layers in a stepwise fashion (Scott 1993, Hochberg et al. 1995, Creamer and Hochberg 1997). Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended after failure of full doses of paracetamol given for a reasonable time using the minimum effective dose.

Evidence of an inflammatory component in OA has provided a better understanding of its pathogenesis and also new insights concerning its treatment. It is now well established that cytokines play key roles in many inflammatory processes (Dayer and Fenner 1992, Holt et al. 1992). IL-1 in human OA synovium and cartilage was found to increase significantly the catabolism of proteoglycan macromolecules and stimulate the metalloproteinase activity in human OA cartilage explants (Pelletier and Martel-Pelletier 1989). When stimulated by cytokines, such as IL-1, chondrocytes from cartilage affected by OA and human articular chondrocytes release inflammatory mediators including nitric oxide (Amin et al. 1995). In an animal model of OA, intraarticular administration of IL-1 receptor antagonist reduced the expression of collagenase and the subsequent development of OA (Caron et al. 1996). Gonzalez et al. (1994) have shown that IL-1 production was significantly reduced by 180 days of treatment with NSAID in patients having knee OA. Although the same treatment reduced TNF-α level in only a few patients with basal high TNF-α production, its level tended to increase in persistent low TNF-α producing patients. One NSAID (diclofenac) reduced the IL-6 level, but its reduction in all treated patients was significantly correlated with a worsening of the clinical condition (Gonzalez et al. 1994).

It is possible that some of our patients became betterh spontaneously, since placebo also led to some significant changes. Spontaneous clinical improvement or response to the treatment when the cytokine levels fell may support the association of cytokines with OA. Patients taking NSAIDs showed more marked changes in clinical parameters and cytokine levels. Patients taking placebo had somewhat better clinical results at the end of the study, but they still had considerable pain and morning stiffness.

Therefore, although there is no agreement about the relation between cytokine levels and disease activity, cytokine antagonists or drugs attenuating cytokine levels may provide better repair of structural and biochemical abnormalities of OA.

In our study, two NSAIDs improved clinical parameters of OA and reduced cytokine levels. Tiaprofenic acid reduced IL-1 and IL-6 levels more significantly. Unlike the results of a previous study (Gonzalez et al. 1994), the reduction in IL-6 level was also associated with an improvement in clinical condition. We conclude that current data show an inflammatory component in OA, and NSAIDs not only relieve symptoms, but repair structural and biochemical abnormalities. They may therefore be first-line agents in the so-called "pyramid approach" to the management of OA.

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