THE EFFECTS OF ETODOLAC ON THE CLINICAL COURSE AND GASTRIC MUCOSAL PGE OF KNEE OSTEOARTHRITIS

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SUMMARY : *Several studies on the reliability and effectiveness of etodolac on the symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) have been carried out in recent years. In 25 patients with knee osteoarthritis (Group A) we used etodolac, a nonsteroidal anti inflammatory drug (NSAID). Administered twice daily (200 mgx2) for 4 weeks. The control group (Group B) received the same amount of placebo starch tablets for the same period. In spite of general recovery of the symptoms, the only statistically significant healing was observed in rest pain.*

Ten patients in the improvement etodolac group received gastric biopsy with endoscopy at the beginning and end of the therapy and the prostaglandine E-like activity (PGE) was measured. It was established that gastric PGE was not affected with the use of edodolac. This may explain Etodolac's safety for gastric mucosa.

Key Words : *Osteoarthritis, Etodolac, Prostaglandine E.*

INTRODUCTION

Etodolac, a pyranocarboxylic acid derivative is a NSAID, generally used in rheumatoid arthritis, ankylosing spondylitis and other painful rheumatic conditions (2, 4) (Fig. 1).

Etodolac inhibits the cyclooxygenase but not the lipooxygenase and in experimental animal models it was observed that it also inhibits the PGE_2 specifically responsible for skeletal involvement (3, 7).

Etodolac has a serum elimination half life of 6 hours, is well absorbed and 99 % is bound to protein. It is highly metabolized, and excreted with urine and stool. In pharmacokinetic studies it was obser-

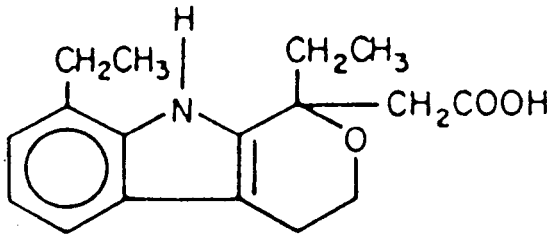

Fig - 1 : Chemical structure of Etodolac.

ved that the albumin and protein concentrations were lower, but contrarily the free Etodolac fraction was significantly higher in synovial fluid than in serum samples (3, 5, 9).

Etodolac is approved by the food and drug administration (FDA) for treatment of pain and osteoarthritis (OA) (15). According to the characteristics of the pain, doses of 200-300-400 mg, are administered twice daily or if the slow-release (SR) form is used 600 mg/24 hour, for 2-4 weeks. The ultimate dose is 1200 mg/24 hour (3, 19).

In several comparative clinical studies, besides its efficacy, Etodolac, has been suggested as a highly reliable drug as far as gastrointestinal tolerance is concerned. This is explained by its suppressive effect on gastric and duodenal prostaglandins which was observed by endoscopic evaluation (4, 10, 13, 14). This effect was lower than for other NSAIDs. We must be very careful when using etodolac in pregnancy and lactation as in the other NSAIDs and to watch out for GIS, hepatic, renal and haematopoetic pathologies (16).

In this study, our purpose was to evaluate the effects of Etodolac, a recently-used NSAID in Turkey, on the activity of gastric PGE, clinical course and patients tolerance.

MATERIALS AND METHODS

Forty patients with knee OA who had at least one of the criteria listed below in addition to knee pain at rest or on movement study. The criteria were 1. ROM limitation, 2. tenderness with palpation, 3. crepitation, 4. swelling, 5. stiffness after sleep or immobilisation.

Patients with at least 2 of the following racholegical conditions were studied: joint space narrowing, subchondral sclerosis, marginal osteophyte formation or subchondral pseudocysts.

Patients with hepatic, renal or cardiac insufficiency, history of GIS bleeding or active peptic ulcer and known NSAID intolerance were excluded. Etodolac was given to 25 out of 40 patients and the remaining 15 received placebo starch tablets. In the etodolac group, the patients received 200 mg Etodolac twice daily for 4 weeks and the control group received placebo for the same period. Before and after treatment, duration of morning stiffness, pain with movement and at rest, limitation, crepitation, swelling and duration of walking 15 m were recorded. ESR, Hb, WBC, CRP, Eosin-latex, hepatic function tests, BUN- Creatinin and other biochemical tests, urine analysis and chemical testing of stool specimens for occult blood were evaluated.

In the etodolac group 10 patients without any previous GIS complaints underwent endoscopy before and after medication.

Two biopsy specimens taken from the corpus wall and 3 from the antrum wall were frozen at -20° C and kept at -40° C. After extracting with the proper methods explained before (6), PGE like activity was established by bioassay in Gazi University Medical Faculty, Department of Pharmacology (18). Student-t test was used for statistical analysis.

RESULTS

The demographic findings of the patients in both groups are shown in Table 1. After receiving Etodolac for 4 weeks the rate of decrease in rest pain was 60 %, pain with movement was 33 %, morning stiffness 26 % (Table 2). There was no change in knee ROM and duration of 15 m walking. In the control group it was observed that the decrease in rest pain was 15 %, pain with movement 13 % and

Knee osteoarthritis	Women	Men	Total
Etodolac group	n = 18	n = 7	n = 25
Mean age (years)	58 ± 10	69 ± 10	
PGE measured	n = 8	n = 2	n = 10
Placebo group	n = 9	n = 6	n = 15
Mean age (years)	62 ± 8	60 ± 10	
PGE measured	n = 7	n = 3	n = 10

Table 1 : The number, sex and mean age of patients in Etodolac and placebo groups.

		%	t
Relief of pain at rest	Etodolac group	60	3.2 $p < 0.05$
	Placebo group	15	
Relief of pain on movement	Etodolac group	33	1.6 $p > 0.05$
	Placebo group	10	
Shortened duration of mor ning stiffness	Etodolac group	26	1 $p > 0.05$
	Placebo group	12	

Table 2 : The condition of clinical relief criteria in both groups post treatment.

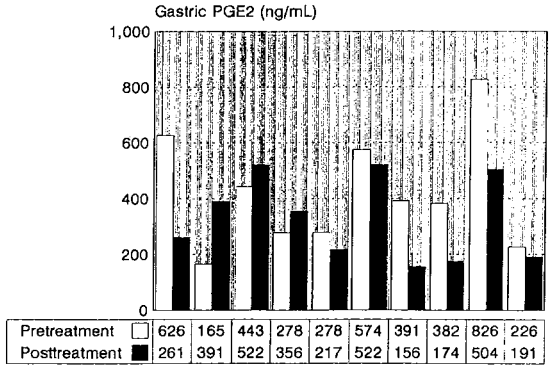

Fig - 2 : Changes of gastric PGE before and after Etodolac therapy.

morning stiffness 12 %. But comparison of the two groups showed the only statistically significant relief was in rest pain ($t=3.2$ $p < 0.05$). Improvement of morning stiffness and pain with movement were not statistically significant ($t=1.6$ $p>0.05$, $t=1$ $p>0.05$). Patients were questioned about GIS complaints but nothing significant was found. In 7 patients who had undergone endoscopy, only a small decrease in gastric PGE levels was found, which was not statistically significant (Fig. 2).

DISCUSSION

Many comparative studies have been performed to evaluate the efficacy and tolerability of Etodolac and other NSAIDs.

A study of knee OA was carried out to compare the efficacy of Etodolac, 300 mg twice daily, with that of piroxicam, 20 mg, once daily, for 8 weeks. Significant symptomatic improvement in both treatment groups was observed. However the improvement ratio was 38 % for etodolac and 35 % for piroxicam. Tolerability differences were not statistically significant (11).

Queiros et al. divided 39 RA patients into two groups; who received Etodolac, 200 mg twice daily and naproxen, 500 mg twice daily for 12 weeks (12). Pain score, joint tenderness and swelling, hand grip, duration of morning stiffness, ESR and other data showed significant improvement. Gastric and duodenal mucosal lesions were seen in 20 % of the etodolac group and 53 % of the naproxen group at endoscopy.

Some NSAIDs used in OA treatment may lead to articular cartilage damage healthy male. A study using Etodolac 200-600 mg daily, showed a significant difference between the placebo group in symptoms of OA and etodolac in vitro proteoglycan synthesis in 3-dimensional human chandrocyte cultures (1). Salom et al. in healthy male volunteers used Etodolac (400 mg/day), Etodolac (600 mg/day), Ibuprofen (2400 mg/day), Indomethacin (200 mg/day) and Naproxen (750 mg/day) for 7 days. In the etodolac groups gastrointestinal microbleeding was significantly lower than with other NSAIDs (14). It was suggested that no dose-related increase was found.

A total of 64 patients with knee OA were divided into two equal groups and received either Etodolac SR 600 mg or diclofenac SR 100 mg, for 4 weeks. After treatment, clinical improvement in rest pain and 5 other clinical parameters were detected in both groups with no significant difference between them (8), however improvement in the 2^{nd} week in the Etodolac group was more evident and rapid than in the diclofenac group.

A comparative RA study between etodolac and naproxen in therapeutic doses evaluated their effect on gastric and mucosal PGs. After 4 weeks of treatment, PG values did not change in either group, but naproxen suppressed gastric and duodenal PG, while Etodolac had no suppressive effect. It was suggested that this mucosal protective effect may be due to Etodolac's lower suppression of PGE than the other NSAIDs (17).

In our study, patients with OA of the knee treated with Etodolac 200 mg twice daily for 4 weeks revealed statistically significant improvement in rest pain compared with the controls. This is in agreement with the literature. Improvements in the other parameters were not statistically significant and can be explained by the low dosage. Tolerance was good as reported by other authors. The decrease in gastric PGE activity was not statistically significant and this result is also in agreement with the literature.

In conclusion, our opinion is that Etodolac is an effective and reliable agent in the management of OA.

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