# Naproxen and paracetamol compared with naproxen only in coxarthrosis

## Increased effect of the combination in 18 patients

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**In a double-blind study of 18 patients with coxarthrosis the effect of 3 naproxen doses (0.5, 1.0, and 1.5 g daily) and 2 naproxen doses combined with paracetamol (0.5 g + 4 g daily and 1.0 g + 4 g daily) was investigated. Plasma levels of naproxen and paracetamol were measured (HPLC), and clinical assessment of pain, joint movement, activity of daily life and side-effects were performed at the end of the 5 treatment periods. A relationship was found between the 3 naproxen doses, naproxen plasma levels, pain at rest, and pain during movement.**

**The combined treatment was more effective than treatment with the same naproxen dose alone. The effect of naproxen (0.5 g daily) combined with paracetamol (4 g daily) did not differ from that obtained during treatment with higher naproxen doses only. Furthermore, the effect of the highest naproxen dose was not better than the effect of the lower naproxen dose (1.0 g daily) combined with paracetamol.**

**The main finding was that treatment with naproxen and paracetamol is more effective than treatment with higher naproxen doses alone.**

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Submitted 92-05-15. Accepted 92-10-02

The main therapeutic goal in the medical treatment of arthrosis is to relieve pain, but sometimes anti-inflammatory effects may also be required. The rationale for using NSAIDs instead of analgesics in OA is to obtain both anti-inflammatory and analgesic effects. However, knowledge of the dose-response curves for analgesic and anti-inflammatory effects during NSAID treatment is still insufficient. No human model exists for differentiating between the anti-inflammatory and the analgesic properties of NSAIDs. Paracetamol (acetaminophen) is an analgesic drug without prostaglandin-mediated effects. Studies of the combined effect of paracetamol with NSAIDs may therefore mirror the role of non-prostaglandin-mediated analgesic effects during treatment with NSAIDs. Another major problem of NSAID treatment are the frequent side-effects mainly from the central nervous system and the stomach. As these side-effects are thought to occur more frequently at higher doses, smaller doses are preferable.

The present study was undertaken to investigate the dose-effect relationship of three naproxen doses, and the effect of combined naproxen treatment with paracetamol in arthrosis.

## Patients and methods

20 patients (10 of each sex), mean age 69 (53–82) years, with unilateral coxarthrosis and pain requiring treatment with NSAIDs, were selected for the study. Excluded were patients not flaring during 7 days without treatment or with a history of serious gastrointestinal problems, known intolerance or lack of beneficial response to NSAIDs, or other concomitant diseases contraindicating NSAIDs. All the patients gave fully informed consent to take part in the study, and local Ethics Committee's approval was obtained.

2 patients were excluded, one because of surgery of the hip and one because of lack of compliance. All the patients were listed for arthroplasty within a short period. All patients had pain at rest and during movement.

### *Study design*

The patients started with a one-week wash-out period, during which they were instructed not to use NSAIDs or analgesics. For intolerable pain during the wash-out, only dextropropoxiphene (0.1 g) was allowed. Patients not experiencing aggreavation of their symptoms within seven days without NSAIDs were excluded from the study. After the wash-out period each patient was scheduled to receive different treatment regimens during each 5 consecutive 1-week

treatment periods. The treatment allocation and order were predetermined according to Latin square design, ensuring that each treatment followed each of the other treatments equally often. The treatments tested were naproxen at daily doses of 0.5, 1.0, and 1.5 g, respectively, either alone or at the two lower dose levels also in connection with 4 g a day of plain paracetamol tablets. The medications were provided double-blind in dosing devices permitting double-dummy medication. Each patient was to take 3 tablets of naproxen 0.25 g or their placebo twice daily, each morning and evening, and 2 tablets of paracetamol 1 g or their placebo twice daily. Thus, throughout the entire 5-week treatment period the patients were requested to take medication at 8 a.m. (5 tablets) and at 8 p.m. (5 tablets). The last dose of the respective treatment regimens had to be taken on the evening before scheduled reassessment. Naproxen and naproxen placebo tablets were provided by NN Pharma, paracetamol sustained release formulation and identical paracetamol placebo by Pharmacia Denmark, and the local hospital pharmacy was responsible for dispensing the medication in the dosing devices.

### *Clinical assessment and blood sampling*

At the end of each treatment period, the patients were clinically assessed and adverse effects were recorded. On the day of investigation, drug intake was postponed until after blood sampling and clinical investigation. At each visit, blood samples were taken at about 10 a.m. in the morning, i.e., about 14 hours after the last dose. All assessments in each patient were performed by the same investigator. Measurements of joint movement (extension, flexion, rotation, abduction and adduction) were performed (American Academy of Orthopedic Surgeons 1965). Pain at rest and pain during movement were graded by the patient on a 100 mm horizontal visual analogue scale (VAS). In addition, the patient was asked for a global assessement of the extent to which pain interfered with daily life. For this purpose an arbitrary 6-graded score was used. The ability to perform daily activities was also estimated (Harris 1969).

Side-effects were recorded by the patient and were asked about at each visit. They were graded as none, slight discomfort, marked discomfort or unbearable discomfort.

The blood samples were centrifuged and the serum stored at –20 °C until the end of the study when drug plasma concentrations of paracetamol and/or naproxen were assayed, processing the samples from each patient in single assay runs.

### *Drug analysis*

*Paracetamol.* Concentrated perchloric acid was added to plasma samples to remove proteins. Aliquots of the supernatant were analyzed by the HPLC system. Paracetamol was quantified by using ODS 5 μm columns (15 cm × 4.6 mm) at 25 °C, eluted with 28% methanol in distilled water, delivered at 2 mL/min. Detection was by UV absorbance at 254 nm with a retention time of 2.2 minutes.

The limit of quantification was 0.05 μg/mL and the assay was linear to at least 30 μg/mL. The mean precision between 0.5 and 25 μg/mL ranged from 1.3 to 2.8% and the mean accuracy over the same range was from –2.0 to +2.0%. Naproxen was not extracted in the supernatant and, therefore, did not compromise paracetamol quantification.

*Naproxen.* Hydrochloric acid was added to plasma. Naproxen was extracted using a column-switching system. The acidified plasma samples were extracted using a precolumn (40 × 4.6 mm), hand-packed with Pellicular (40–50 μm) ODS using water as a mobile phase, delivered at 2 mL/min. After 3 minutes, the direction of flow was switched, backflushing with 45% acetonitrile in 0.05% acetic acid at 2 mL/min. Naproxen was eluted from the precolumn directly onto the analytical column (15 cm × 4.6 mm) containing Hypersil ODS 5 mm and maintained at 50 °C. Detection was by UV absorption at 330 nm with a retention time of 3.2 minutes.

The limit of quantification was 0.1 μg/mL and assay was linear to at least 130 μg/mL. The mean precision between 1 and 120 μg/mL ranged from 1.5 to 3.6%, and the mean accuracy over the same range was from –2.4 to +2.2%. Paracetamol was eluted in the solvent front of the chromatogram and, therefore, did not compromise naproxen quantification.

### *Statistical methods*

All patients had measurable naproxen concentrations in blood and in most patients paracetamol blood levels were detected during the combined treatment, implying that compliance was adequate. Tablets counted at the end of each treatment period also indicated good compliance. As a result of the Latin square design, carry-over effects were equally distributed and did not introduce a systematic bias.

The regression coefficient between the given naproxen dose (x) and a disease activity variable (y) was calculated according to Fisher for each patient (Bradley 1968). The effect of additional paracetamol was tested by use of two-sided non-parametric tests, and $P < 0.05$ was chosen as the lowest limit of significance.

**Table 1. Clinical and correlation coefficients for 3 naproxen doses (A–D) and combined treatment (E, F) with paracetamol in 18 patients with OA**

| Case | Overall pain | | | | | | Pain at rest | | | | | | Pain during movement | | | | | | Morning stiffness | | | | | | Correl. coeff. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | A | B | C | D | E | F | A | B | C | D | E | F | A | B | C | D | E | F | G | H | I |
| 1 | 10 | 20 | 30 | 30 | 30 | 30 | 52 | 44 | 23 | 15 | 26 | 13 | 96 | 86 | 23 | 13 | 16 | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0.95 | 0.98 | 0.95 |
| 2 | 10 | 20 | 30 | 30 | 30 | 30 | 68 | 50 | 43 | 31 | 46 | 31 | 58 | 53 | 27 | 18 | 25 | 15 | 20 | 15 | 10 | 10 | 10 | 10 | 0.93 | 0.99 | 0.97 |
| 3 | 10 | 10 | 10 | 10 | 20 | 20 | 106 | 94 | 70 | 60 | 68 | 55 | 99 | 98 | 96 | 83 | 85 | 70 | 10 | 5 | 5 | 5 | 5 | 3 | 1.00 | 0.99 | 0.87 |
| 4 | 20 | 30 | 30 | 30 | 40 | 44 | 28 | 15 | 10 | 7 | 8 | 7 | 25 | 15 | 13 | 7 | 5 | 10 | 5 | 3 | 3 | 3 | 3 | 3 | 0.98 | 0.95 | 0.97 |
| 5 | 10 | 10 | 20 | 20 | 20 | 20 | 82 | 73 | 44 | 31 | 41 | 29 | 95 | 81 | 43 | 23 | 46 | 23 | 0 | 0 | 0 | 0 | 0 | 0 | 0.94 | 0.98 | 0.99 |
| 6 | 20 | 20 | 20 | 20 | 20 | 20 | 46 | 32 | 30 | 29 | 28 | 25 | 88 | 73 | 52 | 48 | 57 | 45 | 20 | 15 | 15 | 15 | 15 | 15 | 0.89 | 0.86 | 0.97 |
| 7 | 10 | 10 | 10 | 20 | 20 | 20 | 100 | 99 | 98 | 97 | 80 | 60 | 96 | 73 | 69 | 56 | 72 | 53 | 20 | 20 | 20 | 20 | 20 | 20 | 0.89 | 1.00 | 0.96 |
| 8 | 10 | 10 | 20 | 20 | 30 | 30 | 55 | 30 | 16 | 4 | 3 | 3 | 79 | 62 | 40 | 27 | 32 | 22 | 5 | 2 | 2 | 2 | 2 | 2 | 0.87 | 0.98 | 1.00 |
| 9 | 20 | 20 | 20 | 20 | 20 | 20 | 94 | 65 | 48 | 30 | 40 | 28 | 68 | 62 | 18 | 17 | 18 | 17 | 7 | 3 | 3 | 3 | 3 | 3 | 1.00 | 0.99 | 0.92 |
| 10 | 10 | 20 | 20 | 20 | 20 | 20 | 82 | 59 | 42 | 32 | 30 | 22 | 85 | 82 | 57 | 45 | 47 | 30 | 20 | 20 | 20 | 20 | 20 | 20 | 1.00 | 0.99 | 0.96 |
| 11 | 20 | 20 | 20 | 20 | 30 | 30 | 50 | 31 | 22 | 25 | 8 | 6 | 89 | 74 | 46 | 38 | 48 | 33 | 0 | 0 | 0 | 0 | 0 | 0 | 0.99 | 0.86 | 0.98 |
| 12 | 20 | 20 | 20 | 20 | 20 | 20 | 36 | 26 | 15 | 10 | 11 | 11 | 79 | 47 | 33 | 17 | 34 | 15 | 7 | 5 | 3 | 3 | 1.5 | 1.5 | 0.99 | 0.99 | 0.98 |
| 13 | 10 | 30 | 20 | 30 | 40 | 40 | 20 | 18 | 14 | 7 | 14 | 4 | 83 | 66 | 33 | 24 | 31 | 19 | 3 | 1 | 1 | 1 | 1 | 1 | 0.95 | 0.97 | 0.98 |
| 14 | 10 | 30 | 30 | 30 | 30 | 30 | 48 | 42 | 37 | 33 | 35 | 17 | 75 | 37 | 27 | 17 | 29 | 17 | 3 | 2 | 2 | 2 | 2 | 1 | 0.96 | 1.00 | 0.94 |
| 15 | 20 | 20 | 30 | 40 | 30 | 40 | 42 | 38 | 34 | 28 | 26 | 20 | 83 | 65 | 48 | 44 | 41 | 38 | 45 | 12 | 10 | 10 | 10 | 10 | 0.93 | 0.99 | 0.97 |
| 16 | 10 | 20 | 20 | 20 | 20 | 20 | 102 | 56 | 46 | 28 | 23 | 18 | 68 | 85 | 73 | 25 | 70 | 23 | 60 | 60 | 60 | 60 | 60 | 60 | 0.90 | 0.95 | 0.70 |
| 17 | 20 | 20 | 20 | 20 | 20 | 20 | 83 | 60 | 25 | 15 | 33 | 13 | 86 | 67 | 42 | 50 | 50 | 41 | 30 | 0 | 0 | 0 | 0 | 0 | 0.88 | 0.98 | 0.88 |
| 18 | 20 | 20 | 20 | 20 | 20 | 20 | 3 | 15 | 10 | 7 | 14 | 10 | 80 | 65 | 55 | 30 | 57 | 33 | 15 | 5 | 5 | 5 | 5 | 5 | 1.00 | 0.58 | 0.98 |
| Mean | 14 | 19 | 22 | 23 | 26 | 26 | 61 | 47 | 35 | 27 | 30 | 21 | 80 | 66 | 44 | 32 | 42 | 29 | 15 | 9.3 | 8.8 | 8.8 | 8.6 | 8.8 | 0.95 | 0.95 | 0.94 |
| *SD* | *5.1* | *6.6* | *6.2* | *6.9* | *7.0* | *8.2* | *30* | *25* | *22* | *22* | *20* | *16* | *17* | *20* | *21* | *19* | *21* | *16* | *16* | *14* | *14* | *14* | *14* | *14* | *0.05* | *0.10* | *0.07* |

A 0
B 0.5
C 1.0
D 1.5
E 0.5+
F 1.0+
G Naproxen conc.
H Pain at rest
I Pain on movement

## Results

No major side-effects were reported. Minor side-effects from the gastro-intestinal system were ($P$ 0.03) more often reported during treatment with higher naproxen (1 g daily), compared to treatment with the lower naproxen dose (0.5 g daily) combined with paracetamol (4 g daily). Similarly gastro-intestinal side-effects were ($P$ 0.04) less intense with a lower naproxen dose (1 g daily) and paracetamol (4 g daily) compared to treatment with naproxen (1.5 g daily) only. Sedimentation rate (ESR), C-reactive protein, hemoglobin, white blood counts and liver enzymes were all unchanged during the study.

A relationship ($P$ 0.001) between naproxen dose and pain during movement and pain at rest was observed by using the regression coefficients of each patient. From the correlation coefficients shown in Table 1 it can be seen that a positive relationship between effect and dose was observed in all patients. A similar relationship was obtained between trough naproxen plasma levels and pain during movement and pain at rest ($P$ 0.001). Overall pain was less sensitive to changes of treatment, as correlation coefficients were unchanged in all but four patients.

The ability to use stairs, sitting in a chair, putting on shoes and socks, gait, support required to walk, walking distance, and ability to use public transport were insensitive to changes in treatment during this study and thus not related to naproxen dose, naproxen concentration or paracetamol treatment.

Combined treatment with naproxen (0.5 g daily) and paracetamol (4 g daily) was more effective ($P$ 0.001) in reducing overall pain, pain during movement and pain at rest compared to treatment with only naproxen (0.5 g daily) (Table 1). Similarly, combined treatment with naproxen (1.0 g daily) and paracetamol (4 g daily) was more effective in reducing overall pain ($P$ 0.008), pain during movement ($P$ 0.001) and pain at rest ($P$ 0.001) compared to the same naproxen dose (1.0 g daily) only. The effect of combined naproxen (0.5 g daily) and paracetamol (4 g daily) on global pain, pain during movement and pain at rest did not differ from that obtained during treatment with the higher naproxen dose (1.0 g daily) only. Similarly, the combined effect of naproxen (1.0 g daily) and paracetamol (4 g daily) on global pain, pain during movement and pain at rest did not differ from that obtained during treatment with the higher naproxen dose (1.5 g daily) only.

## Discussion

One important finding in this study was that the effect of naproxen in arthrosis increases with the dose in the range from 0.5 g to 1.5 g daily. Our data also suggest

that naproxen plasma levels are similarly related to the effect, but that measurements of naproxen blood levels do not contribute further to our understanding of naproxen effects. A major goal in therapeutics is to understand the relationship between the dose given and the clinical effect. Such information regarding treatment of arthrosis has so far been lacking. This study is the first to show that the effect of naproxen increases in a dose- as well as a concentration-dependent way in arthrosis.

A common mechanism in the action of NSAIDs is inhibition of cyclo-oxygenase, which catalyzes the transformation of arachidonic acid to prostaglandin precursors (Yamamoto et al. 1980). As prostaglandins enhance inflammation, inhibition of cyclo-oxygenase can be assumed to explain the anti-inflammatory properties of NSAIDs. On the other hand, more than 90 percent suppression of prostaglandin excretion occurs at low NSAID doses (Rane et al. 1978, Tomson et al. 1981). Thus, since NSAIDs seem to have potent anti-inflammatory effects during treatment with low doses, it is surprising to find that they are frequently used at higher doses. It may be possible that their effect is only partially related to cyclo-oxygenase inhibition. In fact, no dose-dependent anti-inflammatory effect of NSAIDs has ever been demonstrated in man. Increasing evidence thus indicates that during high-dose treatment with NSAIDs only marginal increments of anti-inflammatory activity are obtained, but that toxicity is increased. These observations are supported by the results in our study. The effect of treatment with higher naproxen doses may relate more to analgesic properties than to prostaglandin inhibition. It is therefore interesting that combined treatment of arthrosis with naproxen and paracetamol was more effective than treatment with naproxen alone. The shift of the naproxen dose-response curve to the left during combined treatment with paracetamol indicates analgesic and not prostaglandin-mediated anti-inflammatory properties of higher naproxen doses, as paracetamol does not inhibit prostaglandin synthesis.

Our study implies that administration of low-dose naproxen combined with paracetamol can contribute to more effective drug therapy in arthrosis. High NSAID doses should be avoided and paracetamol or NSAIDs in low doses used as first-line treatment of OA. In patients with insufficient effect on that treatment, paracetamol should be supplemented to NSAID treatment to improve pain relief. If prescription of NSAIDs can be reduced and lower NSAID doses employed, one of the major reasons for drug toxicity will be decreased.

## Acknowledgement

The assistance of Physiotherapist Suzanne Révay is greatly appreciated.Drug analyses were performed by Winthrop Laboratories, England, and statistical analyses by Anders Odén, Ph.D.

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