Effects of nabumetone compared with naproxen on platelet aggregation in patients with rheumatoid arthritis

Ellen A J Knijff-Dutmer, Alexander Martens, Mart A F J vd Laar

Abstract

Objective—To test the hypothesis that nabumetone (a partially selective cyclo-oxygenase-(COX)-2 inhibitor) has less effect on platelet aggregation than naproxen (a non-selective COX-inhibitor) in patients with rheumatoid arthritis (RA).

Methods—A crossover study in 10 RA patients was performed, using either nabumetone or naproxen for two weeks, and, after a washout period of two weeks, the other drug during another two weeks. Platelet aggregation studies were performed and bleeding time was assessed before and after each treatment period.

Results—Maximum platelet aggregation induced by epinephrine and by collagen was significantly more reduced after the use of naproxen than of nabumetone; secondary aggregation induced by ADP and epinephrine disappeared more often by naproxen than by nabumetone. Bleeding times were not influenced.

Conclusion—COX dependent platelet aggregation in RA patients seems to be more inhibited by naproxen than by nabumetone. This may be relevant for patients requiring non-steroidal anti-inflammatory drug treatment but who have an increased risk of bleeding as well.

In the treatment of rheumatoid arthritis (RA) non-steroidal anti-inflammatory drugs (NSAIDs) play a prominent part. Through inhibition of the enzyme cyclo-oxygenase (COX) they block prostaglandin production at inflammatory sites, reducing swelling, pain, and fever. However, COX in various organs is also inhibited, causing undesired side effects as gastrointestinal damage, renal failure, and inhibited platelet aggregation.

Recently two isoforms of COX were discovered: the “physiological” or basic COX-1 (in stomach, kidney and platelets) and the “inflammatory” or inducible COX-2. It has been suggested widely that NSAIDs that selectively inhibit COX-2 have fewer side effects.

Platelet aggregation is induced by thromboxane, a prostaglandin produced by COX-1. Little is known about the effect of COX-2 selective NSAIDs on platelets. Two studies indicate minimal influence on platelet aggregation in healthy volunteers by nabumetone, a partially COX-2 selective NSAID, as compared with naproxen, a non-selective NSAID. The absence of a relevant effect on platelet aggregation in these studies may result from the use of relatively low doses (1000 mg nabumetone vs 500 mg naproxen), smaller than commonly used in RA. Therefore we have designed a study to compare the influence on platelet aggregation of regular doses of nabumetone and of naproxen in patients with RA.

Methods

Patients

During a regular visit to the rheumatological outpatient clinic, patients between 18 and 80 years old, fulfilling the ACR criteria for RA, were asked to participate in the study. Exclusion criteria were impaired renal function (creatinine clearance <75 ml/min as calculated by the Cockcroft formula), thrombocytopenia and the use of aspirin. Approval of the local ethical committee was obtained and all patients gave informed consent. From the medical record a recent erythrocyte sedimentation rate (ESR) and present medication were retrieved.

Medication

In a six week crossover design naproxen and nabumetone were given in the first and last two weeks. Two weeks before the start of the study and during the two week interval between these treatments no NSAIDs were given; if necessary, they were replaced by acetaminophen. The patients were randomised to start with naproxen 500 mg twice daily or nabumetone 1000 mg twice daily. In the last two week period the other drug was given. Disease modifying anti-rheumatic drugs (DMARDs) and/or prednisone (less than or equal to 10 mg daily) were continued in stable doses. The use of acetaminophen as rescue medication for pain was permitted.

Laboratory tests

Before entering the study the following tests were performed: serum creatinine, platelet count, bleeding time, prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet aggregation tests. Testing at two weeks, four weeks, and six weeks included bleeding time and platelet aggregation tests.

Samples

Blood was obtained by venapuncture and collected in 5 ml siliconised vacutainer tubes. Platelet rich plasma (PRP) was obtained by centrifugation of the blood at 180 g for 10 minutes; platelet poor plasma (PPP) by centrifugation of the blood at 1200 g for 15 minutes.
Table 1  Results of platelet aggregation tests after the use of nabumetone compared with naproxen

<table>
<thead>
<tr>
<th>Aggregation test</th>
<th>After nabumetone</th>
<th>After naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (%)</td>
<td>mean change (%)</td>
</tr>
<tr>
<td>Adenosine diphosphate 5.0 µM</td>
<td>77 +2 —</td>
<td>70.5 −4 —</td>
</tr>
<tr>
<td>Adenosine diphosphate 2.5 µM</td>
<td>49.5 −3.5 —</td>
<td>48 −2.5 —</td>
</tr>
<tr>
<td>Adenosine diphosphate 1.0 µM</td>
<td>17 −3.125 2/10</td>
<td>18 −1.875 2/10</td>
</tr>
<tr>
<td>Collagen 4.0 µg/ml</td>
<td>89 +10.5 —</td>
<td>81 +2.5 —</td>
</tr>
<tr>
<td>Collagen 1.0 µg/ml</td>
<td>70 +20 2/10</td>
<td>36.6 −11.875 3/10</td>
</tr>
<tr>
<td>Epinephrine 5.0 µM</td>
<td>65.5 −8.88 1/10</td>
<td>55 −24.44 1/10</td>
</tr>
<tr>
<td>Collagen 1.0 µg/ml</td>
<td>70 +20 2/10</td>
<td>36.6 −11.875 3/10</td>
</tr>
<tr>
<td>Epinephrine 1.0 µM</td>
<td>89.5 +10.5 —</td>
<td>87.5 +10 —</td>
</tr>
<tr>
<td>Ristocetin 1.2 mg/ml</td>
<td>87.5 +3.5 —</td>
<td>80.5 −3.5 —</td>
</tr>
</tbody>
</table>

AGGREGATION STUDIES
Platelet aggregation studies in PRP were performed according to Born’s method at 37 °C with constant rate of stirring at 1000 rpm in the lumi-aggrego-meter using PPP as reference. During the experiments the optical density was continuously recorded. After a stable baseline was observed for two minutes 25 µl of an aggregation inducing agent was added to 475 µl PRP. The following concentrations of aggregation inducing agents were used: 4.0 µg/ml; 1.0 µg/ml collagen, 5.0 µM; 1.0 µM adenosine diphosphatase (ADP), 1.5 mg/ml; 1.2 mg/ml ristocetin. The variation between repeated measurements of platelet aggregation in PRP was within 5%.

ROUTINE CLOTTING ASSAYS
The aPTT and the PT were performed on an AMAX CS190 coagulometer. Reagents were used according to the instructions of the manufacturer. Platelet counts were performed on a Technicon H-2 automatic cellcounter. The bleeding time was performed as described by Ivy.11

RESULTS
Ten patients entered the study, five men and five women. The mean ESR was 24.3 mm 1st h (2–53). Nine patients used a DMARD during the study: sulphasalazine (1), intramuscular gold (3), methotrexate (2), hydroxychloroquine (3). Three patients used a stable dose of prednisolone (2.5–10 mg/day). Although baseline data of two patients were incomplete because of technical problems with the aggregometer, no relevant differences between the groups were present at baseline. No significant changes in bleeding time were noted after using either naproxen (mean (SD)) (−0.12 (1.02) min) or nabumetone (−0.19 (0.89 min)).

Table 1 shows the results of the platelet aggregation tests. Platelet aggregation induced by collagen 1.0 µg/ml was negatively influenced by the use of naproxen but not by the use of nabumetone (fig 1). A decrease in platelet aggregation responses to epinephrine (both concentrations) was seen, after both NSAIDs. Platelet aggregation induced by epinephrine 5.0 µM was significantly more impaired after the use of naproxen than after the use of nabumetone (fig 1). Moreover, a disappearance of secondary aggregation was observed when induced by epinephrine (both concentrations), more often after the use of naproxen than of nabumetone (fig 2). Responses of platelet aggregation to ristocetin and ADP were not significantly changed in either group, though secondary aggregation with ADP 1.0 µM was diminished both after the use of naproxen and of nabumetone (fig 2).

Discussion
Treatment of RA with NSAIDs is limited by the toxicity of these drugs. The major side effect is gastrointestinal ulceration, probably aggravated by an increased bleeding tendency resulting from the inhibitory effects of NSAIDs on platelet aggregation. There is hope that selective COX-2 inhibiting NSAIDs have not only less gastrointestinal toxicity but also less inhibition of platelet aggregation. In this study we determined bleeding time and performed aggregation tests in vitro to compare the effects of a non-selective (naproxen) with a partially selective COX-inhibitor (nabumetone).

Bleeding time tests depend not only on platelet aggregation but also on technical and clinical variables. They do not adequately reflect the presence or absence of a bleeding tendency.12 Therefore bleeding time was not chosen as the primary outcome measure. The NSAIDs used in our study did not change bleeding time tests. This finding is in accordance with other studies that showed at most a slightly prolonged bleeding time, but always within normal limits, after the use of NSAIDs.7 13

STATISTICAL ANALYSIS
The primary outcome measure was the difference in platelet aggregation before and after the use of nabumetone compared with naproxen. The two groups were compared by means of the Mann-Whitney-Wilcoxon rank test.

Figure 1  Difference in thrombocyte aggregation, as measured by epinephrine 5.0 µM and collagen 1.0 µg/ml.

Figure 2  Frequency of normal secondary aggregation.
COX inhibitors cause impaired platelet aggregation after induction with epinephrine or collagen. Moreover, they inhibit secondary aggregation after induction with epinephrine or ADP. In contrast, platelet aggregation induced with ristocetin is mostly dependent on “von Willebrand” factor.4

In accordance with the findings of Nunn et al in healthy volunteers5 using low doses of NSAIDs, the results of our study show a significant difference in platelet aggregation, when induced with collagen 1.0 µg/ml, after the use of naproxen compared to nabumetone. Al Balla et al,7 studying the effect of nabumetone on platelet aggregation in healthy subjects, could not demonstrate significant differences in platelet aggregation induced by higher concentrations of collagen. It is well known that raising the concentration of collagen can compensate reduction in platelet aggregation by COX inhibitors.4 15

In our study, induction by epinephrine 5.0 µM of platelet aggregation was significantly more impaired by the use of naproxen than by nabumetone. This concurs with the in vitro study of Jeremy et al8 in which platelet aggregation induced by epinephrine was more inhibited when PRP from healthy volunteers was incubated with indomethacin or naproxen than with nabumetone. Al Balla, who studied the effect of nabumetone, did not demonstrate an effect on maximum aggregation, using higher concentrations of epinephrine.7

We observed inhibition of secondary aggregation (induced by epinephrine or ADP) after the use of both NSAIDs, though naproxen did so more profoundly. Maximum aggregation induced by ADP was not changed, as described before by other authors.7 14

As expected, platelet aggregation induced by ristocetin was not changed by the use of either NSAID.14

Thus, platelet aggregation tests that require the presence and functioning of COX (maximum aggregation after induction with epinephrine or low doses of collagen; secondary aggregation after induction with ADP or epinephrine) were less influenced by nabumetone than by naproxen. Although we did not observe a change in bleeding time, changed platelet function may play a part in patients with an increased risk of bleeding. In these patients the use of COX-2 selective NSAIDs may be preferred.

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