Dose-dependent Inhibition of Platelet Function by Acetaminophen in Healthy Volunteers

Edward Munsterhjelm, M.D.,* Nina M. Munsterhjelm, B.Pharm.Sc.;† Tomi T. Niemi, M.D., Ph.D.;‡ Olavi Ylikorkala, M.D., Ph.D.;§ Pertti J. Neuvonen, M.D., Ph.D.;|| Per H. Rosenberg, M.D., Ph.D.#

Background: Acetaminophen (paracetamol) is widely used for postoperative analgesia. Its mechanism of action is inhibition of prostaglandin synthesis in the central nervous system, and acetaminophen is traditionally not considered to influence platelet function. The authors studied the dose-dependent inhibition of platelet function by acetaminophen in healthy volunteers.

Methods: Thirteen healthy male volunteers (aged 19–26 yr) were given placebo or 15, 22.5, or 30 mg/kg acetaminophen intravenously in a double-blind, crossover study. Ten and 90 min after infusion, platelet function was assessed by photometric aggregometry and by measuring release of thromboxane B2, anaglogia by cold pressor test, and plasma acetaminophen concentrations by high-performance liquid chromatography.

Results: When triggered with 500 μM arachidonic acid, median platelet aggregation (area under the curve) was 25.7, 22.8, 4.1, or 3.6 × 10^3 area units (P < 0.001) 10 min after placebo or 15, 22.5, or 30 mg/kg acetaminophen, respectively. An increasing concentration of arachidonic acid attenuated the antiaggregatory effect. After 90 min, platelet function was recovering. Release of thromboxane B2 was also dose-dependently inhibited by acetaminophen. Although plasma concentration of acetaminophen increased linearly with the dose, no analgesic effect was detected in the cold pressor test.

Conclusions: Acetaminophen, which is a weak inhibitor of platelet cyclooxygenase 1, has a dose-dependent antiaggregatory effect. This property may become clinically significant in patients with intrinsic or drug-induced impairment of hemostasis.

CYCLOOXYGENASE (COX), the key enzyme in prostaglandin formation, is an important pharmacologic target.1 The antithrombotic effect of acetylsalicylic acid is caused by irreversible inhibition of COX-1, constitutively expressed in platelets, whereas the analgesic effect of acetaminophen with the cold pressor test as a painful stimulus.

Normal platelet function is dependent on the production of proaggregatory thromboxane A2 (TxA2) through COX-1, and acetaminophen has been shown to inhibit platelet function both in vitro6 and in high intravenous doses in vivo.7 However, oral administration of conventional doses (approximately 1 g) of acetaminophen does not alter platelet function.7,9

Acetaminophen is widely used for postoperative analgesia,9 although the optimal dose is debatable.10,11 In pediatric patients, no analgesic ceiling effect was detected when acetaminophen was administered rectally in doses up to 60 mg/kg.12 However, high doses of acetaminophen may alter platelet function through peripheral COX-1 inhibition. Because proper platelet function is essential for adequate intraoperative and postoperative hemostasis, we studied the dose-dependent effect of acetaminophen on platelet function in healthy volunteers. We also measured the analgesic effect of acetaminophen with the cold pressor test as a painful stimulus.

Materials and Methods

The protocol was approved by the Ethics Committee for Studies in Healthy Subjects and Primary Care in the Hospital District of Helsinki and Uusimaa (Helsinki, Finland) and by the National Agency for Medicines in Finland. Fifteen healthy, nonsmoking men aged between 19 and 26 yr volunteered in this double-blinded, randomized, placebo-controlled, crossover study. Written informed consent was obtained from each subject before the study. Normal plasma alanine transaminase and aspartate aminotransferase activities were a prerequisite for participation. Two volunteers withdrew their consent before completing the study. The use of acetylsalicylic acid was forbidden for 10 days and that of other drugs affecting platelet function was forbidden for 1 week before each experiment.

Experimental Procedures

Every volunteer participated in four experiments with at least a 1-week interval. After 3 h of fasting, 15, 22.5, or 30 mg/kg acetaminophen (Perfalgan®; Bristol-Myers Squibb, New York, NY) or placebo (0.9% NaCl; Braun, Kronberg, Germany) was given as a 10-min intravenous infusion through a 20-gauge cannula (Venflon; Becton Dickinson, Franklin Lakes, NJ) in a dorsal vein of the hand. The infusions were blinded and administered in random order. The code was not broken until all experiments had been performed.

* Resident, Department of Anesthesiology and Intensive Care Medicine, Helsinki University Hospital, Helsinki, Finland. † Researcher, ‡ Assistant Professor, § Professor, Department of Obstetrics and Gynecology. ‖ Professor, Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland. || Professor, Department of Obstetrics and Gynecology. # Professor, Department of Anesthesiology and Intensive Care Medicine. ¶ Professor, Department of Obstetrics and Gynecology. || Professor, Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland.

Received from the Department of Anesthesiology and Intensive Care Medicine, University of Helsinki, Helsinki, Finland. Submitted for publication February 15, 2005. Accepted for publication June 17, 2005. Supported by departmental funding and a grant from the Medical Society of Finland, Helsinki, Finland. Presented in part as a poster at the XXth Congress of the International Society on Thrombosis Hemostasis, Sydney, Australia, August 6–12, 2005.

Address reprint requests to Dr. Munsterhjelm: P.O. Box 340 (P-floor), FIN-00029 HUS, Finland. Address electronic mail to: edward.munsterhjelm@hus.fi. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.
were centrifuged at 3,000 g. The coefficient of variation was 17.7% (n = 11005).
The area under the concentration-time curve of aggregometry was recorded. Aggregation was allowed to proceed for 300 s; after that, concentrations are known to cause platelet aggregation.

Diego, CA). Based on previous experience, these concentrations were purchased from Sigma-Aldrich (St. Louis, MO) and Calbiochem (San Diego, CA).

and sensation of strong pain were recorded. There was there was at least a 50-min interval between the cold pressor test and the next blood sampling.

Cold Pressor Test. Immediately after each blood sampling, a cold pressor test was performed. The volunteer immersed his arm, halfway to the elbow, into an ice bath, and the times elapsed until first sensation of pain and sensation of strong pain were recorded. There was a 50-minute interval between the cold pressor test and the next blood sampling.

Laboratory Tests

Platelet Aggregation. Platelet aggregation was measured with a four-channel photometric aggregometer (Packs-4; Helena Laboratories, Beaumont, TX) based on the method of Born.

Platelet-rich plasma and platelet-poor plasma were prepared by centrifuging as described previously. Aggregation was induced in 270 µl platelet-rich plasma by adding 30 µl of one of the following triggers: adenosine diphosphate (ADP) to a final concentration of 1.5 or 3 µM; arachidonic acid to a final concentration of 500, 750, or 1,000 µM; or epinephrine to a final concentration of 5 µM. Reagents were purchased from Sigma-Aldrich (St. Louis, MO) and Calbiochem (San Diego, CA). Based on previous experience, these concentrations are known to cause platelet aggregation.

Aggregation was allowed to proceed for 300 s; after that, plasma for thromboxane B2 (TxB2) determination was prepared with as described previously. The area under the curve of aggregometry was recorded.

Thromboxane B2 Concentration. Thromboxane B2 is the stable metabolite of TxA2, released during aggregation. TxB2 concentrations in platelet-rich plasma triggered with 3 µM ADP or 1 nm arachidonic acid were determined with a radioimmunoassay.

The interassay coefficient of variation was 17.7% (n = 15).

Acetaminophen Concentration. Blood samples were centrifuged at 3,000g for 10 min, and plasma was stored at −20°C. Acetaminophen concentration was determined using high-performance liquid chromatography.

The limit of quantification was 0.1 mg/l, and the day-to-day coefficients of variation were 7.4% at 16.8 mg/l and 4.2% at 36.8 mg/l (n = 6).

Statistical Analysis

The sample size needed was estimated in advance as described in the statistical literature. The study was designed to discover a difference in platelet aggregation between each acetaminophen group and placebo greater than 1 SD, with a power of 80% (α error = 5%, Bonferroni correction was applied). The sample size needed was n = 11. A difference smaller than 1 SD was considered of minor clinical significance. Data distribution was tested with the Kolmogorov-Smirnov test, and nonparametric statistics were used for normally distributed data. Nonnormally distributed data are presented as medians and 25th/75th percentiles; normally distributed data are presented as mean values and 95% confidence intervals.

The difference between all groups was analyzed with the Friedman test (repeated-measures analysis of variance on ranks), and when a significant difference was encountered, each acetaminophen group was further compared with placebo using the Wilcoxon matched pairs signed rank sum test and applying the Bonferroni correction. Statistical testing was with SigmaStat for Windows Version 2.03 (SPSS Inc., Chicago, IL). Confidence intervals were calculated using the appropriate t distribution.

Results

Thirteen volunteers completed the study according to the protocol, all of whom showed normal platelet function before drug infusion. Plasma acetaminophen concentrations increased linearly with dose, and exceeded 17.0 mg/l at 10-min sampling after all doses used (table 1). Ninety minutes after infusion, plasma acetaminophen concentrations decreased, but they remained significantly above 10 mg/l after 22.5 and 30 mg/kg acetaminophen. No acetaminophen was detected before infusion in any of the volunteers.

Effect of Acetaminophen on Platelets

Acetaminophen dose-dependently inhibited platelet aggregation triggered with arachidonic acid, ADP, or...
epinephrine (table 2). Ten minutes after infusion, 15 mg/kg acetaminophen caused a significant inhibition of platelet aggregation triggered with arachidonic acid. Inhibition was most pronounced with 500 μM arachidonic acid. An increasing concentration of arachidonic acid counteracted the inhibition; with 1,000 μM arachidonic acid, it was minimal, although still statistically significant. Aggregation triggered with ADP or epinephrine was less sensitive to inhibition by acetaminophen; at 10 min, a significant inhibition was achieved only with 30 mg/kg acetaminophen. The inhibition was reversible; aggregation in response to all triggers was recovering at 90 min, reflecting the decreasing plasma concentration in response to all triggers was recovering at 90 min. Statistical tests are the Friedman test (all groups) and Wilcoxon matched pairs signed rank sum test with Bonferroni correction (each acetaminophen dose vs. placebo): *P < 0.05, †P < 0.01, ‡P < 0.005.

ADP = adenosine diphosphate.

Table 2. Platelet Aggregation Triggered with Arachidonic Acid, Adenosine Diphosphate, or Epinephrine

<table>
<thead>
<tr>
<th>Aggregation Trigger</th>
<th>Aggregation Trigger Administration</th>
<th>0 mg/kg</th>
<th>15 mg/kg</th>
<th>22.5 mg/kg</th>
<th>30 mg/kg</th>
<th>P Value (All Groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachidonic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 μM</td>
<td>Pre</td>
<td>25.5 (24.5/26.2)</td>
<td>25.4 (24.7/26.1)</td>
<td>24.9 (22.5/26.1)</td>
<td>25.7 (24.4/26.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td>25.7 (25.3/26.6)</td>
<td>22.8 (23.5/24.1)</td>
<td>4.1 (3.5/4.5)</td>
<td>3.6 (3.4/4.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>90 min</td>
<td>25.6 (25.0/26.0)</td>
<td>23.9 (3.2/24.9)</td>
<td>14.7 (3.7/24.7)</td>
<td>4.8 (3.6/23.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>750 μM</td>
<td>Pre</td>
<td>26.9 (25.4/27.0)</td>
<td>26.0 (24.9/26.3)</td>
<td>25.9 (25.0/26.4)</td>
<td>26.5 (25.5/27.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td>26.7 (26.4/27)</td>
<td>25.3 (22.0/26.0)</td>
<td>4.1 (2.8/26.0)</td>
<td>16.7 (3.3/25.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>90 min</td>
<td>25.9 (25.7/26.6)</td>
<td>25.4 (24.4/26.1)</td>
<td>25.6 (23.2/26.6)</td>
<td>24.9 (22.7/26.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>1,000 μM</td>
<td>Pre</td>
<td>26.6 (25.2/27.3)</td>
<td>25.9 (23.6/26.3)</td>
<td>26.0 (25.5/26.7)</td>
<td>26.6 (25.9/27.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td>26.5 (25.8/26.9)</td>
<td>25.5 (21.2/26.6)</td>
<td>25.9 (22.6/26.1)</td>
<td>24.5 (21.8/26.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>90 min</td>
<td>26.0 (25.7/26.8)</td>
<td>25.8 (23.9/26.8)</td>
<td>25.8 (24.4/26.7)</td>
<td>25.7 (24.7/26.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>ADP</td>
<td>1.5 μM</td>
<td>15.7 (16.4/22.1)</td>
<td>14.8 (11.2/19.0)</td>
<td>16.0 (12.3/19.0)</td>
<td>16.4 (11.0/23.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>14.6 (16.0/20.6)</td>
<td>11.1 (10.2/16.4)</td>
<td>12.2 (8.3/14.9)</td>
<td>11.6 (8.4/14.8)</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>90 min</td>
<td>17.8 (10.2/22.4)</td>
<td>13.5 (10.1/19.1)</td>
<td>13.6 (9.2/19.2)</td>
<td>13.9 (10.7/20.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>3.0 μM</td>
<td>23.7 (21.7/26.1)</td>
<td>24.1 (20.6/25.1)</td>
<td>23.8 (22.3/24.6)</td>
<td>24.5 (22.7/26.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>24.3 (22.2/26.0)</td>
<td>23.5 (20.1/24.6)</td>
<td>22.5 (20.3/23.3)</td>
<td>23.7 (19.7/24.4)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>90 min</td>
<td>24.4 (22.2/25.2)</td>
<td>23.3 (21.0/24.9)</td>
<td>23.5 (21.0/24.6)</td>
<td>22.4 (19.7/24.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>5 μM</td>
<td>Pre</td>
<td>21.1 (17.2/22.9)</td>
<td>19.5 (16.4/23.4)</td>
<td>20.4 (16.5/22.7)</td>
<td>20.6 (18.2/23.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td>19.6 (15.5/21.7)</td>
<td>14.6 (10.6/19.9)</td>
<td>13.9 (10.3/19.6)</td>
<td>12.7 (10.1/16.8)</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>90 min</td>
<td>20.9 (16.4/22.7)</td>
<td>18.3 (14.6/21.5)</td>
<td>20.1 (11.3/21.4)</td>
<td>16.9 (13.6/20.2)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Data are aggregation (area under the curve, 10^2 area units) reported as medians (25th/75th percentiles). Each volunteer (n = 13) was given placebo and 15, 22.5, and 30 mg/kg acetaminophen. Sampling was before drug administration (Pre) and 10 and 90 min after infusion. Statistical tests are the Friedman test (all groups) and Wilcoxon matched pairs signed rank sum test with Bonferroni correction (each acetaminophen dose vs. placebo): *P < 0.05, †P < 0.01, ‡P < 0.005.

ADP = adenosine diphosphate.

Thromboxane B2 release during aggregation triggered with arachidonic acid or ADP was dose-dependently inhibited by acetaminophen (table 3). Reduction of TxB2 release was significant after all doses of acetaminophen at 10 min, and reversibility of the inhibition was evident with both triggers at 90 min.

Cold Pressor Test

Pain threshold in the cold pressor test showed a large variation and was not increased by acetaminophen (fig. 1). Time until sensation of strong pain was also highly variable and not significantly influenced by acetaminophen (data not shown).

Table 3. Thromboxane B2 Release from Activated Platelets

<table>
<thead>
<tr>
<th>Aggregation Trigger</th>
<th>Time after Drug Administration</th>
<th>0 mg/kg</th>
<th>15 mg/kg</th>
<th>22.5 mg/kg</th>
<th>30 mg/kg</th>
<th>P Value (All Groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM arachidonic acid</td>
<td>Pre</td>
<td>1,201 (1,111/1,491)</td>
<td>1,227 (1,058/1,406)</td>
<td>1,060 (926/1,496)</td>
<td>1,193 (1,119/1,379)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td>1,432 (1,182/1,526)</td>
<td>1,012 (8,20/1,168)</td>
<td>748 (673/979)</td>
<td>923 (739/1,000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>90 min</td>
<td>1,262 (1,190/1,458)</td>
<td>1,301 (1,026/1,419)</td>
<td>968 (653/1,222)</td>
<td>1,181 (987/1,260)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 μM ADP</td>
<td>Pre</td>
<td>24.7 (20.9/41.1)</td>
<td>24.9 (13.7/39.5)</td>
<td>21.5 (19.3/36.1)</td>
<td>35.0 (22.2/44.5)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td>28.5 (18.1/40.0)</td>
<td>18.5 (9.5/24.2)</td>
<td>10.0 (6.3/20.8)</td>
<td>6.6 (3.2/11.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>90 min</td>
<td>30.8 (20.2/39.7)</td>
<td>22.6 (16.2/29.2)</td>
<td>15.8 (12.6/26.0)</td>
<td>12.7 (10.0/28.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are concentrations (μg/L) reported as medians (25th/75th percentiles). Each volunteer (n = 13) was given placebo and 15, 22.5, and 30 mg/kg acetaminophen. Sampling was before drug administration (Pre) and 10 and 90 min after infusion. Statistical tests are the Friedman test (all groups) and Wilcoxon matched pairs signed rank sum test with Bonferroni correction (each acetaminophen dose vs. placebo): *P < 0.05, †P < 0.01, ‡P < 0.005.

ADP = adenosine diphosphate.
ACETAMINOPHEN AND PLATELETS IN HEALTHY VOLUNTEERS

Discussion

Platelet Function

Traditionally, acetaminophen is considered not to influence platelet function in vivo. Studies on conventional doses (approximately 1 g) of oral acetaminophen have shown negative results. In the current study, however, we demonstrate that intravenous acetaminophen inhibits platelet aggregation and TxB2 release in healthy volunteers in a dose-dependent fashion. We have previously shown that propacetamol (prodrug of acetaminophen) has a clear inhibitory effect in large doses and that propacetamol augments the antiaggregatory effect of diclofenac.

When platelet aggregation was induced with arachidonic acid, acetaminophen significantly inhibited platelet function at all doses tested. Arachidonic acid is the physiologic substrate of COX, the key enzyme in prostaglandin formation. The reaction catalyzed by COX proceeds in two steps: First, arachidonic acid is converted to prostaglandin G2 in the cyclooxygenase reaction, and in the second step, the peroxidase reaction, prostaglandin G2 is converted to prostaglandin H2. In platelets, thromboxane synthase further converts prostaglandin H2 to TxA2, which initiates aggregation by binding to specific G protein–coupled receptors on the surface of the platelet.

In contrast to traditional NSAIDs, which inhibit COX by competing with arachidonic acid for entering the cyclooxygenase reaction, the mechanism by which acetaminophen inhibits COX is not known. Acetaminophen may inhibit either the cyclooxygenase or peroxidase reaction by competing with the substrate for entering the reaction or by interfering with the propagation of the reactions in the catalytic center of COX. It has been suggested that acetaminophen, like other phenolic compounds, can act as a reducing agent and quench a tyrosyl radical necessary for propagation of the cyclooxygenase reaction. In our study, the antiaggregatory effect of acetaminophen was inversely related to the concentration of arachidonic acid used as a trigger. This suggests a competition either between acetaminophen and arachidonic acid for entering the cyclooxygenase reaction or between acetaminophen and prostaglandin G2 for entering the peroxidase reaction. Previous data from vascular endothelial cells point toward the latter alternative.

When ADP or epinephrine was used to trigger aggregation, the inhibitory effect of acetaminophen was much less pronounced. In contrast to aggregation induced with arachidonic acid, no clear difference was detected when the concentration of ADP was increased. This is probably because aggregation triggered with ADP is mainly independent of COX activity and TxA2 release. ADP and epinephrine bind directly to their own receptors on the surface of the platelet. Two ADP-binding receptors, P2Y1 and P2Y12, have been isolated, whereas only one adrenergic receptor, α2A, seems to be active in platelets.

In previous studies, the conclusion was drawn that acetaminophen does not inhibit platelet function. Our results contradict this conclusion. We suggest two main reasons for this contradiction. First, ADP, epinephrine, and collagen were used to trigger aggregation in those studies. When we triggered platelet aggregation with ADP or epinephrine, only the highest dose of intravenous acetaminophen, 30 mg/kg, corresponding to a total concentration of approximately 2 g, caused a significant inhibition. Second, a lower peak plasma acetaminophen concentration is achieved with oral than with intravenous administration. Because approximately 1 g oral acetaminophen was used in the previous studies, no inhibition could have been detected under those circumstances.

Thromboxane A2, produced in platelets by COX-1 and thromboxane synthase, is unstable and decomposes rapidly into its stable metabolite TxB2. TxB2 release triggered with arachidonic acid (1 mm) or ADP (3 μM) was also dose-dependently inhibited by acetaminophen. Although significant, TxB2 release was considerably less inhibited by acetaminophen than by the traditional NSAID diclofenac in our previous study. Under similar conditions, median TxB2 release in response to ADP shortly after an intravenous infusion of diclofenac (1.1 mg/kg) was only 3.3% of preinfusion release, as compared with 24% after acetaminophen (30 mg/kg) in the current study. Our results in vivo therefore confirm previous observations in vitro showing that acetaminophen is a weaker inhibitor of COX-1 than are conventional NSAIDs.

Analgesic Effect

The plasma concentration of acetaminophen required for optimal analgesia is not known. Antipyretic properties of acetaminophen are evident in the plasma concentration range of 10–20 g/l. This concentration or higher
was observed 10 min after infusion with all doses tested, but after 90 min, plasma acetaminophen concentration remained significantly above 10 g/l only with doses higher than 15 mg/kg. Optimal analgesia may require higher concentrations than antipyresis in adults, but this topic is controversial. When acetaminophen was administered rectally in children, a linearly increasing morphine-sparing effect was achieved with doses up to 60 mg/kg. Considering that the site of action of acetaminophen is mainly in the central nervous system, a high peak plasma concentration may be important. This could explain why 1 g intravenous acetaminophen has been found more effective in relieving pain than the same dose given orally. In an experimental study using transcutaneous electrical stimulation, 2 g intravenous acetaminophen was more effective than 1 g. Whether higher doses than 1 g intravenous acetaminophen are more effective also in a clinical setting is not known.

In contrast to clinical observations, we detected no analgesic effect of acetaminophen with the cold pressor test, which provokes acute sharp pain. In a previous study, 1 g oral acetaminophen showed an analgesic effect in this pain model, but smaller doses were ineffective. Also in a previous study, we did not observe any analgesic effect in the cold pressor test using the combination of propacetamol (prodrug of acetaminophen) and diclofenac. In a recent study, acetaminophen was shown to reduce central hyperalgesia induced by electrical stimulation, further confirming the central mechanism of action of this drug. It is conceivable that the short duration of pain in the cold pressor test does not induce any central sensitization, and probably therefore no analgesic effect of acetaminophen was detected in this study.

**Clinical Implications**

Because acetaminophen inhibits TxA2 synthesis less than traditional NSAIDs, surgical bleeding attributable to acetaminophen seems unlikely. A moderate inhibition of platelet aggregation periperooperatively could rather be beneficial. Low-dose aspirin, for example, has been shown to reduce the incidence of deep-vein thrombosis in patients undergoing surgery for hip fracture, as well as the incidence of death from pulmonary embolism. The situation would be different, however, if hemostasis is impaired by, for instance, drugs or massive hemorrhage. Acetaminophen has been suspected to increase the effect of oral warfarin, as demonstrated by a rise in the International Normalized Ratio. Impaired platelet function is a possible interaction that is not detected with standard tests of hemostasis.

In conclusion, our results indicate that intravenous acetaminophen dose-dependently impairs platelet function for at least 90 min after its administration. Inhibition was clear also with the dose of 15 mg/kg, which could be considered a typical routine dose in clinical practice.

**Large patient studies are needed to determine the clinical impact of acetaminophen-induced inhibition of platelet function.**

The authors thank Hannele Yki-Jarvinen, M.D., Ph.D. (Professor of Internal Medicine, Helsinki University Hospital, Helsinki, Finland), for the use of her laboratory facilities; Anna Becker, B.Sc. (Technician, Department of Anesthesiology and Intensive Care Medicine, Helsinki University Hospital), and Miikka Köykkä, B.Sc. (Technician, Department of Anesthesiology and Intensive Care Medicine, Helsinki University Hospital), for skilled technical assistance; and our volunteers for smooth cooperation.

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Anesthesiology, V 103, No 4, Oct 2005