European Journal of Pharmacology 609 (2009) 96–99

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Cardiovascular Pharmacology

# A randomized, controlled study on the influence of acetaminophen, diclofenac, or naproxen on aspirin-induced inhibition of platelet aggregation

Katja S. Galliard-Grigioni, Walter H. Reinhart *

*Department of Internal Medicine, Kantonsspital Graubünden, CH-7000 Chur, Switzerland*

ARTICLE INFO

*Article history:*
Received 7 August 2008
Received in revised form 26 January 2009
Accepted 9 February 2009
Available online 9 March 2009

*Keywords:*
Acetaminophen
Diclofenac
Acetylsalicylic acid
NSAID
Platelet aggregation

ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAID) may interfere with aspirin (acetylsalicylic acid) and increase the risk for cardiovascular events. The clinical relevance is uncertain. The aim of this study was to analyse the influence of a co-administration of aspirin and NSAID on platelet aggregation. In a randomized, placebo controlled trial, eleven healthy volunteers were studied during 4 separate study periods of 4 days each. Individuals were treated on each occasion with 100 mg aspirin daily in combination with either 3×1 g acetaminophen, 3×50 mg diclofenac, 3×250 mg naproxen, or 3×1 placebo. Primary hemostasis was assessed with a platelet function analyser (PFA-100®), which measures the closure time (CT) of a collagen- and epinephrine-coated pore by aggregating platelets in flowing blood. Naproxen enhanced the anti-aggregatory action of aspirin after 24 h (CT rising from 104 ± 16 s at baseline to 212 ± 69 s at 24 h, $P<0.001$), which was not seen with any other drug combination. Diclofenac reduced the anti-aggregatory action of aspirin in the first two days, since the CT did not rise significantly (109 ± 19 s, 148 ± 56 s, and 168 ± 66 s at 0 h, 24 h, 48 h, respectively, $P>0.05$). Acetaminophen had no effect compared with placebo. After 4 days of treatment platelet aggregation was similarly inhibited by all combinations. We conclude that a co-administration of NSAID and aspirin may interfere with platelet inhibition at the beginning of a treatment with an increase of naproxen and a decrease of diclofenac. This effect is lost after 4 days, suggesting that a regular daily co-administration of NSAID does not have an influence on platelet inhibition by aspirin.



## 1. Introduction

Platelet aggregation is responsible for the physiological primary hemostasis after a vessel injury (Davi and Patrono, 2007). It is also the key pathophysiological event of an acute occlusion of arterosclerotic vessels after plaque rupture and thus contributes to the high morbidity and mortality of vascular diseases (Davi and Patrono, 2007). A pharmacological inhibition of platelet aggregation has been successfully applied in the last decades for prevention of vascular events such as myocardial infarction and stroke (Antithrombotic Trialists' Collaboration, 2002). Platelet aggregation can be inhibited by different mechanisms. By far the most often used way is by a single daily dose of acetylsalicylic acid (aspirin), which irreversibly acetylates a serine residue of position 529, the active site of the membrane-bound enzyme cyclo-oxygenase (COX) (Funk et al., 1991). COX catalyses the transformation of membrane-derived arachidonic acid into thromboxane $A_2$, a platelet agonist (FitzGerald, 1991). COX exists in 3 different isoforms (Chandrasekharan et al., 2002), of which platelets express only COX-1 (Patrignani et al., 1999). Platelet COX-1 has been crystallized (Picot et al., 1994) and the mode of inhibition by aspirin has been elucidated (Loll et al., 1995). The aspirin-binding site lies at the apex of a hydrophobic channel in the core of the membrane-bound COX-enzyme.

Nonsteroidal anti-inflammatory drugs (NSAID), which are also widely prescribed, bind in the same hydrophobic channel of COX in the vicinity of aspirin and may thus inhibit COX-1 activity competitively and reversibly and may interfere with the irreversible action of aspirin (Catella-Lawson et al., 2001). This phenomenon is clinically important, because a co-administration of aspirin for vascular diseases and a NSAID, e.g. for osteoarthritis, is very frequent. Acetaminophen is a weak, unspecific COX inhibitor, which acts by reducing the oxidized active form of COX to a resting stage (Ouellet and Percival, 2001).

An association exists between the consumption of NSAID or acetaminophen and cardiovascular events (Chan et al., 2006; Kearney et al., 2006; MacDonald and Wei, 2003; McGettigan and Henry, 2006). Selective COX-2-inhibitors (coxibs) have been found to have similar cardiovascular risks (Bombardier et al., 2000; Bresalier et al., 2005), which finally led to the withdrawal of rofecoxib from the market. The administration of the NSAID ibuprofen 2 h before aspirin reduces the anti-aggregatory effect of the latter, when it is given after aspirin, the action of aspirin is not influenced (Catella-Lawson et al., 2001). It is not known how NSAID affect platelet aggregation *in vivo* when they are given together with aspirin according to a regular clinical schedule, i.e. a morning dose of aspirin and repeated NSAID doses during the day (Strand, 2007). In the present study we have, therefore,

* Corresponding author. Tel.: +41 81 256 63 05; fax: +41 81 256 63 81.
*E-mail address:* walter.reinhart@ksgr.ch (W.H. Reinhart).

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doi:10.1016/j.ejphar.2009.02.042

studied combinations of aspirin with either placebo, acetaminophen, diclofenac, or naproxen. The latter two NSAID were chosen because their risk for vascular events seems to be different with an increased risk for diclofenac but not naproxen (Catella-Lawson et al., 2001).

## 2. Materials and methods

### 2.1. Study subjects

Eleven healthy subjects (3 women, 8 men) with a median age of 35 years (range 21–58 years) gave their written informed consent to the study, which had been approved by the local ethics committee before. They were not taking any drug with a potential effect on platelets one week before and during the entire period of the study. They had no personal history of bleeding or gastrointestinal disorders and no hypersensitivity to aspirin and/or NSAID. Participating women were not taking oral contraceptives and were not pregnant or breastfeeding.

### 2.2. Study design

The following study medications were purchased from the hospital pharmacy and given in a randomized, controlled way during 4 different study periods: 100 mg enteric-coated aspirin (Aspirin-Cardio®, Bayer, Zurich, Switzerland) was given every morning at 9 a.m. for 4 days during all 4 study periods, which was accompanied by either 3×1 g acetaminophen (Dafalgan®, Upsamedica, Baar, Switzerland), 3×50 mg diclofenac (Voltaren®, Novartis, Basel, Switzerland), 3×250 mg naproxen (Naproxen-Mepha®, Mepha Pharma, Aesch, Switzerland), or 3×1 placebo at 9 a.m., 3 p.m. and 9 p.m. for 4 days, respectively. Washout periods of at least 10 days were allowed between experiments.

### 2.3. Blood sampling

Blood was taken between 08.30 and 09.00 a.m. immediately before the first dose (9 a.m.), and then after 24 h, 48 h, and 96 h. Blood was drawn by atraumatic venipuncture from an antecubital vein with a 21-gauge butterfly cannula and a Vacutainer-System® (Becton Dickinson, Basel, Switzerland) under standardized stasis (40 mm Hg with a blood pressure cuff) and collected in 3.8% (0.129 M) buffered sodium citrate. All samples were kept at room temperature for 30 min to 2 h before use.

### 2.4. Platelet aggregation

Platelet aggregation was assessed with a platelet function analyser (PFA-100®, Dade Behring, Düdingen, Switzerland). In this microprocessor-controlled instrument, citrated whole blood is aspirated at high shear rates (5000–6000 $s^{-1}$) through a glass capillary (diameter 200 µm) into a membrane pore (diameter 150 µm), which is coated with 2 µg of type I collagen and 10 µg epinephrine (EPI cartridge). Platelets adhere to collagen and become activated by epinephrine, which leads to platelet aggregation. With time, aggregating platelets form an occluding plug, which stops blood flow and is measured as closure time (CT). A prolongation of CT reflects the degree of platelet inhibition (Wuillemin et al., 2002). When no occluding platelet plug forms after 300 s, the instrument stops automatically. In such cases a CT of 300 s was taken into account for statistical calculations. All measurements were done in duplicate and the mean value was calculated.

### 2.5. Statistical analysis

Statistical analysis was performed with an InStat version 3.0 (GraphPad, San Diego, CA) software program. Repeated measures analysis of variance and Tukey–Kramer multiple comparisons test were used for comparing more than two groups. Student's paired *t*-test was used for paired observations (e.g. non-responders vs responders). Results are presented as mean values ± standard deviation (S.D.). $P<0.05$ was regarded as significant.

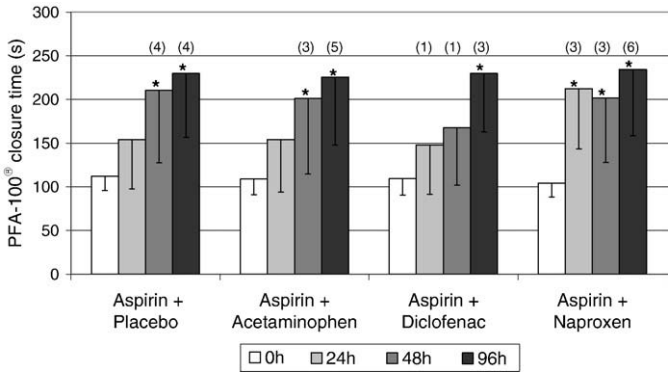


**Fig. 1.** Inhibition of platelet aggregation by 100 mg aspirin combined with either placebo (3×1), acetaminophen (3×1 g), diclofenac (3×50 mg) or naproxen (3×250 mg) given for 4 days. Platelet aggregation was measured as closure time (CT) with a PFA-100® instrument using epinephrine as a platelet activator. Mean ± S.D. are given, $n=11$. The numbers in parenthesis above the columns indicate the number of individuals with CT values > 300 s. *Denotes $P<0.001$ compared with corresponding baseline value (0 h).

## 3. Results

All volunteers completed the study according to the protocol. Three of them had decided to take pantoprazol, a proton pump inhibitor, throughout the study to prevent gastrointestinal discomfort. Five volunteers missed a drug intake at some point in time; one the third placebo on day 4, one the third placebo on day 4 and the third dose of naproxen on day 2, one the second dose of diclofenac on day 2, one the third diclofenac on day 2 and one the third acetaminophen on day 1 and 2. Their CT values after the missed dose were, however, not obviously different from the rest of the values and were included in the final statistical evaluation. No side effects were reported by the participants for any drug combination.

The results of the closure times obtained with the PFA-100® are shown in Fig. 1. Baseline values (time 0 h), i.e. before any drug administration, were normal in all participants and at the beginning of all study periods (PFA-100® reference range: 85–165 s). After 24 h, i.e. after 100 mg aspirin and 3 doses of NSAID, naproxen in combination with aspirin increased CT significantly compared with baseline ($P<0.001$), whereas combinations of aspirin with either placebo, acetaminophen, or diclofenac did not prolong CT significantly. No statistically significant difference was seen when the 4 groups were compared among each other at 24 h. After 48 h, aspirin in combination with placebo, acetaminophen, and naproxen increased CT ($P<0.001$), but aspirin combined with diclofenac did not prolong CT significantly compared with baseline. After 96 h, all combinations resulted in significant and very similar CT prolongations, indicating a comparable anti-aggregatory effect.

It is noteworthy that 5 subjects had a consistently lower response to aspirin than the other 6 subjects (CT value at 96 h for aspirin + placebo: 161 ± 45 s and 287 ± 20 s, $P<0.002$; for aspirin + acetaminophen 147 ± 16 s and 291 ± 22 s, $P<0.0001$; for aspirin + diclofenac 197 ± 75 s and 257 ± 49 s, ns; and for aspirin + naproxen 156 ± 17 s and 300 ± 0 s, $P<0.0001$).

## 4. Discussion

Our data indicate that NSAID given together with aspirin according to a routine clinical schedule, i.e. 3 doses of NSAID during the day with the morning dose at the same time as aspirin, affected platelet

inhibition in different ways. Naproxen enhanced the aspirin-induced platelet inhibition significantly after 24 h, which was not seen with other drug combinations including aspirin and placebo. Thus, naproxen had an additional anti-aggregatory effect to that brought about by a single dose of 100 mg aspirin, which is known to be insufficient to block COX activity completely (Wuillemin et al., 2002). COX is a pit-shaped enzyme, in which the arachidonic acid substrate has to gain access to the catalytic site in the core of the enzyme (Catella-Lawson et al., 2001). Aspirin irreversibly acetylates a serine residue at the apex near the catalytic site and hereby sterically hinders the enzyme activity and prevents the formation of the pro-aggregatory thromboxane $A_2$ (Catella-Lawson et al., 2001). Our data suggest that the unselective COX inhibitor naproxen also blocks the access of the arachidonic acid substrate to the catalytic site. Naproxen is the strongest COX-1-inhibitor among the NSAID (Van Hecken et al., 2000). Our experimental data are in line with epidemiological studies indicating that naproxen may have the lowest cardiovascular risk among all NSAID (McGettigan and Henry, 2006; Van Hecken et al., 2000) or even decrease it compared with selective COX-2 inhibitors (Farkouh et al., 2007). When the COX inhibition by aspirin is fully developed (after $4 \times 100$ mg in our study), naproxen had no longer an additional anti-aggregatory effect, which agrees with another *in vivo* study with a concomitant treatment with aspirin and naproxen for 6 days (Capone et al., 2005).

In contrast, diclofenac given together with aspirin impaired the anti-aggregatory effect of aspirin in the first 2 days, since the PFA closure time did not rise significantly above baseline values during this time period. Diclofenac, like the other NSAIDs, binds to COX in vicinity of the acetylication site of aspirin (Loll et al., 1996) and thus interacts competitively with aspirin at the catalytic site of COX (Livio et al., 1982; Rao et al., 1983). Because of the shorter half-life of diclofenac compared e.g. with naproxen, its COX-inhibiting action regularly disappears a few hours after drug application. This allows COX-1, which had not been acetylated by aspirin, to resume its thromboxane-$B_2$ production. This may explain why platelet aggregation measured in our study before the next application of aspirin remained lower than after aspirin combined with either placebo, acetaminophen or naproxen in the first 2 days. It is conceivable that such a mechanism may be the reason for the increased cardiovascular risk in patients using diclofenac (Kearney et al., 2006; McGettigan and Henry, 2006). After regular intake of aspirin and diclofenac over 4 days in our study, this effect was lost and platelet inhibition was similar to all other combinations. This suggests that a repetitive, long enough administration of aspirin leads to a degree of COX-1 acetylation, which is no more influenced by drugs with a weaker action on the same pathway of platelet inhibition.

Frequent acetaminophen consumption has been found to be associated with an increased cardiovascular risk (Chan et al., 2006). Acetaminophen is a very weak COX inhibitor (Ouellet and Percival, 2001). It is still a matter of debate, with which COX-isoform acetaminophen interacts. In humans acetaminophen seems to be primarily a COX-2 inhibitor rather than a COX-1 inhibitor (Lee et al., 2007). These observations are in agreement with our results showing that acetaminophen had no influence on aspirin-induced COX-1 inhibition on platelets, comparable to placebo, which is in line with another *in vivo* study (Munsterhjelm et al., 2006). From this point of view, a co-administration of aspirin and acetaminophen seems to be safe.

Our *ex-vivo* data may be applicable to daily clinical practice. The PFA-100® instrument simulates the *in vivo* situation with blood flowing through a vessel, where underlying collagen may become exposed (caused by an endothelial damage and/or plaque rupture), to which platelets adhere with the help of von Willebrand factor, become activated (by epinephrine), and aggregate. This instrument thus reflects primary hemostasis more closely than any other test and has been used to test aspirin responsiveness by several groups (Abaci et al., 2005; Blaicher et al., 2004; Feuring et al., 2005). Nevertheless, there are some limitations to our study. We investigated only a small number of healthy young volunteers treated for a short period of time and not older patients with cardiovascular disease treated with platelet inhibitors on a long-term basis. There are studies, which did not find a clinically meaningful interaction between aspirin and NSAID with regard to cardiovascular events (Cryer et al., 2005; Garcia Rodriguez et al., 2004; White et al., 2002). NSAID interact more readily with endothelial than platelet COX-1 (Mitchell et al., 2006), which suggest that endothelial cells rather than platelets may be involved in the cardiovascular risk of traditional NSAID and selective COX-2 inhibitors (Chan et al., 2006; Kearney et al., 2006; McGettigan and Henry, 2006).

Another noteworthy observation in our study was the fact that 5 of the 11 subjects had some degree of aspirin-hyporesponsiveness as measured with the PFA-100®, which was present during every single treatment period over several weeks, indicating that there are consistent interindividual differences in aspirin effectiveness. The PFA-100® has been used by others to test for aspirin resistance (Coma-Canella et al., 2005; Fuchs et al., 2006; Grundmann et al., 2003) and shorter PFA-100® closure times has been associated with an increased risk for cardiovascular (Fuchs et al., 2006) or cerebrovascular (Grundmann et al., 2003) events. A titration of the aspirin dose according to PFA-100® measurements could be an option, which should be investigated further in a prospective study.

We conclude that standard doses of traditional NSAID may have an either enhancing (naproxen) or inhibiting (diclofenac) effect on aspirin-induced platelet inhibition at the beginning of a treatment, but not during regular treatment of more than two days and may thus be negligible in daily practice. It is conceivable, however, that with an irregular intake of aspirin and NSAID, e.g. malcompliance of aspirin intake or on-demand administration of NSAID, the above mentioned effects of NSAID may play a role and should be considered by clinicians.

## Acknowledgements

This study was supported by a grant from the Bonizzi–Theler Foundation, Switzerland, a non-profit organisation not involved in any part of the study. The secretarial work of Franziska Cajochen is greatly acknowledged.

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