The Antiplatelet Effect of Six Non-Steroidal Anti-Inflammatory Drugs and Their Pharmacodynamic Interaction With *Aspirin* in Healthy Volunteers

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Patients with cardiovascular disease taking aspirin and some nonsteroidal anti-inflammatory drugs (NSAIDs) appear to have increased vascular events. This study was conducted to compare the ex vivo antiplatelet effects of 6 commonly used NSAIDs and to determine whether these agents antagonize the effect of aspirin. Platelet function was assessed by Platelet Function Analyzer 100 closure time in normal subjects in a randomized, blinded, multiple-crossover study. Platelet function was measured 12 hours after the administration of each NSAID. The NSAID was then given 2 hours before aspirin 300 mg, and platelet function was reassessed 24 hours later. At 12 hours after the administration of naproxen and tiaprofenic acid, closure time was significantly prolonged, whereas the other NSAIDs did not cause significant prolongations. Compared with placebo plus aspirin, closure time was significantly reduced when ibuprofen, indomethacin, naproxen, or tiaprofenic acid was given before aspirin. In conclusion, ibuprofen, indomethacin, naproxen, and tiaprofenic acid all block the antiplatelet effect of aspirin. Sulindac and celecoxib did not demonstrate any significant antiplatelet effect or reduce the antiplatelet of aspirin and, therefore, of the NSAIDs evaluated may be the drugs of choice for patients requiring aspirin and NSAIDs. **(Am J Cardiol 2008;101: 1060–1063)**

A recent meta-analysis of randomized trials found that cyclooxygenase (COX)–2-specific nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen and diclofenac, but not naproxen, were associated with increased risk for vascular events, particularly myocardial infarction.[1] Similar findings have been reported in observational and case control studies of nonspecific NSAIDs.[2] One potential mechanism of harm with NSAIDs is a pharmacodynamic interaction with aspirin by steric hindrance at the active site of COX-1, preventing irreversible platelet inhibition. This has been suggested in some,[3,4] but not all,[5] studies evaluating ibuprofen and might also occur with indomethacin[6] and naproxen.[7] Various in vitro and ex vivo tests have been used, and there are no standardized comparisons among NSAIDs.

Methods and Results

The study protocol was approved by the Northern Regional Ethics Committee of New Zealand; all subjects gave written informed consent. Hematocrit, platelet count, creatinine, and von Willebrand factor were measured at baseline. Exclusion criteria included a history of cardiovascular disease, bleeding, gastrointestinal ulceration, allergy to aspirin or NSAIDs, renal impairment, anemia, and thrombocytopenia. Subjects abstained from medications or herbal supplements that might affect platelet function during the study.

Twenty-four healthy volunteers, mostly nurses, were randomly allocated into 1 of 2 groups of 12 in a series-crossover study. Six NSAIDs were evaluated in a double-blinded fashion; those in each group took 3 NSAIDs and placebo, in random order. The NSAIDs, per dose, were naproxen 550 mg (Synflex; Roche Diagnostics GmbH, Mannheim, Germany), ibuprofen 400 mg (Brufen; Knoll Pharmaceutical Company, Mount Olive, New Jersey) celecoxib 200 mg (Celebrex; Pharmacia, Uppsala, Sweden), indomethacin 25 mg (Rheumacin 25; Pacific Pharmaceuticals Ltd., Auckland, New Zealand), tiaprofenic acid 300 mg (Surgam SA; Sanofi-Aventis, Bridgewater, New Jersey), and sulindac 200 mg (Daclin; Pacific Pharmaceuticals Ltd.). Aspirin 300 mg (Solprin; Reckitt Benckiser, Slough, United Kingdom) and placebo (Pacific Pharmaceuticals) were also administered. All were standard preparations, apart from slow-release tiaprofenic acid.

On day 1, blood was taken for platelet function testing (Platelet Function Analyzer 100 [PFA-100]; Dade Behring, Deerfield, Illinois). Each subject was then given 2 doses of an NSAID, 12 hours apart. Platelet function was measured on day 2, 12 hours after the second NSAID dose. Subjects then received the final doses of NSAIDs and, 2 hours later, soluble aspirin 300 mg. Platelet function was measured again on day 3, 24 hours after the last NSAID dose (Figure 1). The cycle was repeated after a 12-day washout period.

Ex vivo platelet function was measured using the high-shear PFA-100 epinephrine cartridge at the same time of

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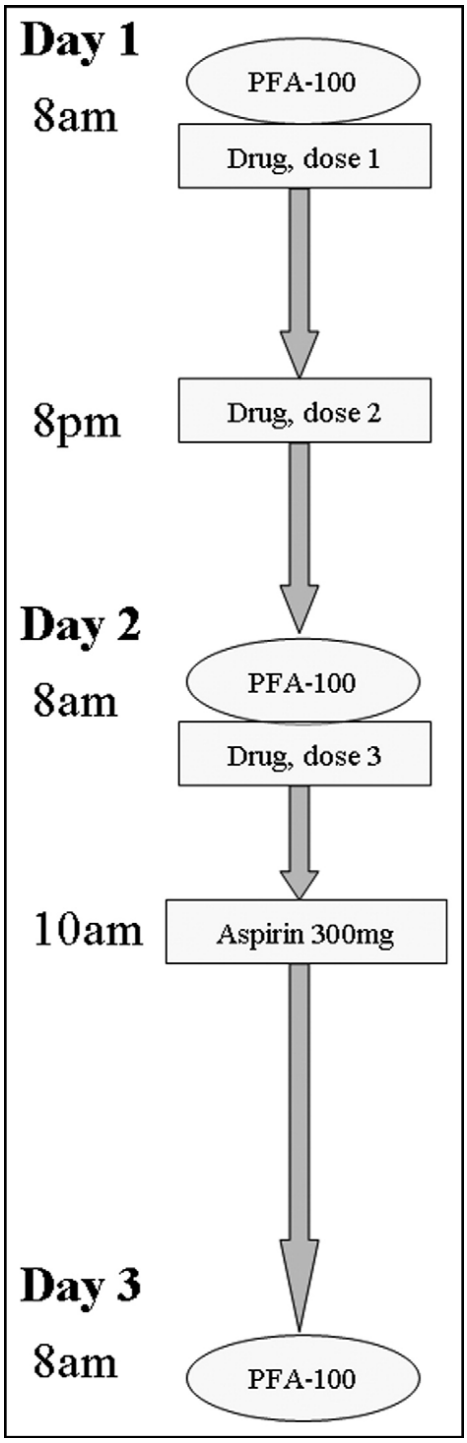

Figure 1. Study protocol.

day, at rest, in all subjects. Aspirin response was defined as a PFA-100 closure time >178 seconds, which was the weighted average threshold from 7 studies in which it was evaluated (range >142 to >196).[8–14] Aspirin nonresponse was defined as an increase of <20 seconds in PFA-100 closure time after aspirin 300 mg, compared with baseline, and partial response was defined as an increase of >20 seconds but <178 seconds after aspirin.

Because the PFA-100 has an upper threshold of 300 seconds, the data were not normally distributed. Wilcoxon's rank test was used to compare treatment groups. For group means, values >300 seconds were counted as 300 seconds. On the basis of previous studies, it was calculated that a sample size of 18 (9 in each group) would afford power >90% to detect a difference between groups of >20% in PFA-100 measurements, with a type I error rate <0.05. The study population was increased to 24 subjects to adjust for an estimated 25% aspirin nonresponse rate.

The study subjects were aged 23 to 67 years (mean 38); 14 were women. Two were replaced at the start; 1 developed ataxia with the first NSAID dose (indomethacin), and the other had poor venous access. There were 2 aspirin nonresponders and 4 partial responders; they had higher levels of von Willebrand factor than other subjects (188% ± 77% vs 90% ± 42%, $p = 0.01$). No subjects had depressed von Willebrand factor levels.

The effect of each NSAID on PFA-100 closure time is depicted in Table 1 and Figure 2. Naproxen and slow-release tiaprofenic acid significantly prolonged closure time at the end of a 12-hour dosing interval. Closure time 24 hours after an NSAID dose followed 2 hours later by aspirin was significantly reduced by ibuprofen, indomethacin, tiaprofenic acid, and naproxen, compared with placebo (Table 1 and Figure 3). Neither sulindac nor celecoxib significantly reduced closure time nor reduced the antiplatelet effect of aspirin. Comparing those NSAIDs that inhibited aspirin, day 3 closure time was lower with ibuprofen than with naproxen ($p = 0.004$).

Discussion

The nonselective NSAIDs ibuprofen, indomethacin, tiaprofenic acid, and naproxen all antagonize the antiplatelet effect of aspirin, as assessed by a high-shear ex vivo platelet function analyzer. This may in part explain findings from the primary prevention Physicians' Health Study (PHS); those taking NSAIDs for >60 days/year in addition to aspirin had a 2.8-fold increased risk for myocardial infarction.[15] Many are at risk for this pharmacodynamic interaction. In a Danish study of patients followed after first myocardial infarctions, 36% filled ≥1 prescription for an NSAID, and more took low-dose ibuprofen, which is available over the counter in Denmark.[16]

Naproxen and slow-release tiaprofenic acid may be cardioprotective if taken regularly but hazardous if taken intermittently with aspirin. Our findings are consistent with those of Capone et al,[17] who demonstrated that aspirin, naproxen twice daily, or the 2 drugs given together reduced thromboxane B_2 levels at 24 hours to a similar extent.

Ibuprofen and indomethacin did not have antiplatelet effects at the end of a 12-hour dosing interval, but submaximal doses were given in this study. These 2 drugs may be particularly hazardous when given with aspirin. The finding that ibuprofen inhibited aspirin to a greater extent than did naproxen is consistent with limited trial data. This occurs even with lower doses of ibuprofen, as used in this study. Subset analysis of patients taking aspirin in the Therapeutic Arthritis Research and Gastro-

Table 1
Platelet Function Analyzer 100 closure time (seconds; 95% confidence intervals)

Time	Placebo	Naproxen	Ibuprofen	Celecoxib	Placebo	Indomethacin	Tiaprofenic acid	Sulindac
Day 1	133 ± 37	131 ± 33	125 ± 32	123 ± 22	126 ± 31	118 ± 29	120 ± 35	127 ± 44
Day 2	126 ± 20	252 ± 73	131 ± 35	126 ± 35	128 ± 63	168 ± 72	225 ± 85	142 ± 59
Day 3	254 ± 84	204 ± 77	133 ± 28	258 ± 64	250 ± 79	164 ± 53	173 ± 61	234 ± 73
Day 2 vs day 1								
Difference	(−27, 12)	(81, 162)	(−2, 13)	(−19, 27)	(−45, 47)	(−4, 102)	(67, 144)	(−4, 38)
p value	0.42	<0.0001	0.12	0.82	0.13	0.07	<0.001	0.10
Day 3, NSAID vs placebo								
Difference	—	(−94, −1)	(−153, −73)	(−38, 69)	—	(−129, −29)	(−125, −20)	(−49, 7)
p value	—	0.04	0.001	>0.9	—	<0.001	0.007	0.38

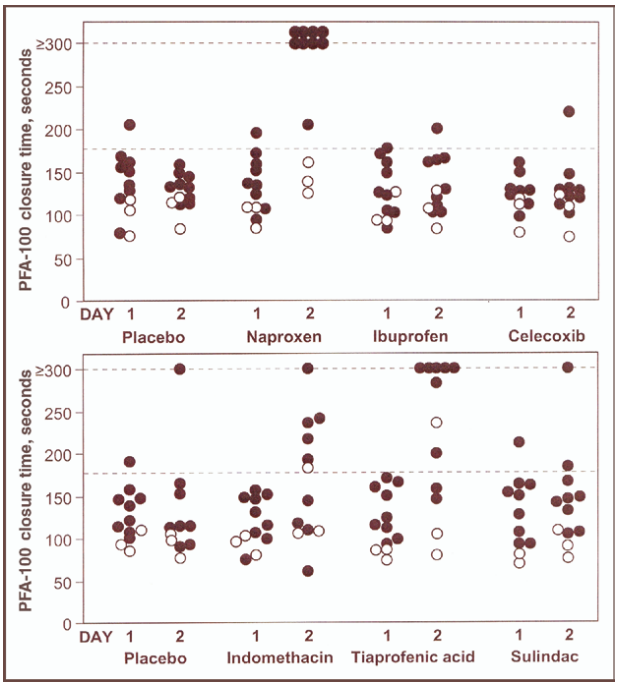

Figure 2. PFA-100 closure time at baseline (day 1) and 12 hours after NSAID administration (day 2). *Solid circles* represent aspirin responders and *open circles* aspirin partial responders and nonresponders.

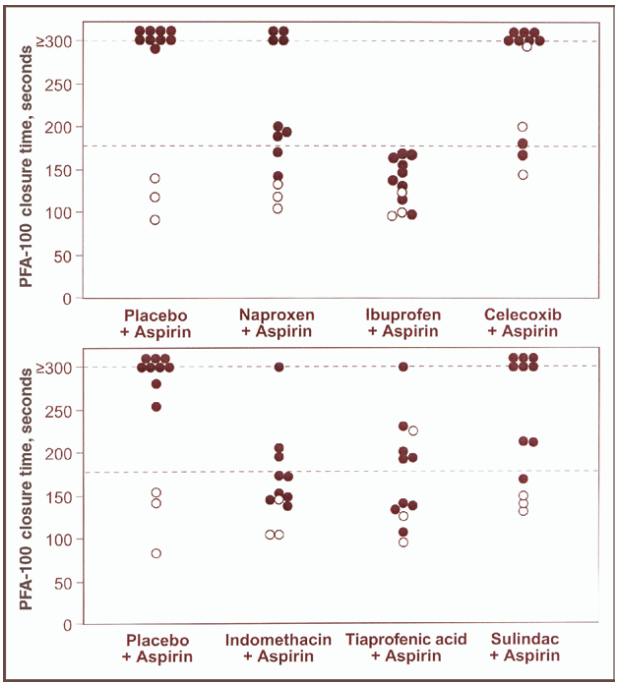

Figure 3. PFA-100 closure time on day 3, 24 hours after the last NSAID dose and 22 hours after aspirin 300 mg.

intestinal Event Trial (TARGET) study of NSAIDs for osteoarthritis found that those taking ibuprofen had more cardiovascular events than those taking naproxen.[18]

Sulindac and celecoxib had no significant effect on closure time and did not reduce the prolongation with aspirin. Of the NSAIDs evaluated, sulindac may be the drug of choice for patients requiring aspirin and an NSAID; the safety and efficacy of the combination requires evaluation in appropriate clinical trials. Despite in vitro data to the contrary,[19] celecoxib, the least COX-2-specific coxib, did not block the effect of aspirin on closure time, a finding consistent with a study of celecoxib coadministered with aspirin.[20]

How long does the gap between NSAID and aspirin administration need to be to avoid this pharmacodynamic interaction? Ibuprofen, despite a short 2.2-hour half-life, inhibited an aspirin dose taken 12 hours later.[4] Similarly, the coadministration of naproxen with aspirin antagonized the inhibition of thromboxane B_2 at 1 hour, despite naproxen alone having no measurable effect on COX-1 at that time.[17] Taken together, it appears that NSAIDs may antagonize aspirin at blood levels considerably lower than those inhibiting platelet COX-1.

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