High on treatment platelet reactivity against aspirin by non-steroidal anti-inflammatory drugs – pharmacological mechanisms and clinical relevance

Thomas Hohlfeld; Aaruni Saxena; Karsten Schröer
Institut für Pharmakologie und Klinische Pharmakologie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

Summary
Inhibition of platelet function by aspirin results from irreversible inhibition of platelet cyclooxygenase (COX)-1. While sufficient inhibition is obtained at antiplatelet doses (75–325 mg/day) in most (≥95%) treated patients, the antiplatelet effect of aspirin and subsequent cardiovascular risk reduction is much less in clinical settings and disease-dependent. Several reasons for this “high on treatment platelet reactivity” are known. This paper reviews the evidence for an interaction between aspirin and other COX inhibitors, namely non-steroidal anti-inflammatory drugs (NSAIDs). Numerous experimental studies demonstrated a pharmacodynamic interaction between aspirin and NSAIDs. This likely occurs within the hydrophobic substrate channel of platelet COX-1 and might be explained by molecular competition between inhibitor drugs and substrate (arachidonic acid) at overlapping binding sites. This interaction is found with some compounds, notably ibuprofen and dipyrone (metamizole), but not with others, such as diclofenac and acetaminophen (paracetamol). Hence, this interaction is not a class effect of NSAIDs and/or non-steroidal analgesics but rather due to specific structural requirements which still remain to be defined. In vivo studies on healthy subjects and patients tend to confirm this type of interaction as well as large differences between NSAIDs and non-steroidal analgesics, respectively. These interactions may be clinically relevant and may increase the cardiovascular risk in long-term treatment for primary and secondary cardiovascular prevention in patients with chronic inflammation, such as rheumatoid arthritis. These patients have an elevated risk for myocardial infarctions and may require chronic antiplatelet treatment by aspirin in addition to treatment of inflammatory pain.

Keywords
Aspirin, drug-interaction, non-steroidal anti-inflammatory drugs, dipyrone, platelet function

Introduction
The usefulness of aspirin as first-line antiplatelet treatment for prevention of myocardial infarctions in patients at elevated vascular risk is well established. Nevertheless, large differences exist in efficacy among different groups of patients including those whose platelets respond less to conventional doses of this agent than others (1). Several explanations for this “high on treatment platelet reactivity” (HPR) have been discussed: (i) variable bioavailability and/or enhanced degradation of aspirin by aspirin esterases, (ii) alterations of the pharmacological target, i.e. “bypass” of cyclooxygenase (COX)-1-mediated thromboxane formation via COX-2 mediated generation of thromboxane precursors, (iii) gene polymorphisms of COX-1, (iv) residual platelet reactivity independent of COX-1, i.e. platelet stimulation by aspirin-insensitive mechanisms and (v) negative interactions with other drugs (2-5). Thus, HPR against aspirin is clearly multifactorial in nature.

Several studies suggested that HPR may clinically result in treatment failure, i.e. insufficient protection from myocardial infarction or ischaemic stroke. For example, Gum et al. examined a subset of stable cardiovascular patients with HPR (“aspirin resistance”) based on a low inhibition of arachidonic acid-induced platelet aggregation (6). These exhibited an increased risk of death, myocardial infarction or a cerebrovascular accident. Similar data have been reported by Chen et al. (7). HPR against aspirin, when present together with HPR against clopidogrel, also turned out as a strong risk factor for drug-eluting stent thrombosis during a six-month follow-up after percutaneous coronary intervention (8). Vice versa, another study reported that patients with drug eluting stent thrombosis exhibited a significantly greater rate of in vitro HPR against aspirin (9). A recent study in patients after off-pump coronary artery bypass grafting (CABG) suggested an association of impaired platelet laboratory response to aspirin (or clopidogrel) with an increased risk of saphenous vein graft occlusion (10).
While genetically fixed reasons for HPR cannot be modified, removal or treatment of acquired factors can. These include negative interactions with other drugs, such as non-aspirin non-steroidal anti-inflammatory drugs (NSAID). Ibuprofen, naproxen, diclofenac and various coxibs are among the most often prescribed drugs worldwide. Their use in individuals with chronic inflammatory diseases, who additionally require thrombosis prevention by aspirin, is highly prevalent. Co-medication of non-aspirin NSAIDs and aspirin is favoured by the fact that immune-mediated diseases, such as rheumatoid arthritis, show an elevated co-morbidity of myocardial infarction and ischaemic stroke (11-13) due to pathophysiological links between inflammation and atherosclerosis (14).

This article examines potential mechanisms which may cause this drug-drug interaction on a molecular basis, i.e. at the level of enzyme kinetics, summarises the existing experimental and clinical evidence of NSAID/aspirin interactions and gives an outlook of how to avoid this in clinical practice.

**Mechanism of acquired HPR against aspirin and NSAID/aspirin interaction**

The antiplatelet action of aspirin is due to irreversible acetylation of platelet COX-1, resulting in irreversible inhibition of platelet-dependent generation of prostaglandin endoperoxides and their subsequent conversion into thromboxane (TX) A_2. This inhibition must be apparently complete (>95%) in terms of TX-forming capacity to result in inhibition of platelet function. The reason is the all-or-nothing type of this response. At antiplatelet doses of 75-325 mg/day, sufficient inhibition is obtained in most (≥95%) of patients (3, 15). This is much more than the about 20% risk reduction of cardiovascular events in secondary prevention (1) and suggests additional factors, i.e. aspirin-insensitive pathways of platelet activation or HPR as explanations.

**COX-1 as the site of aspirin/non-aspirin-NSAID interaction**

While both aspirin and non-aspirin NSAIDs inhibit prostaglandin and TXA_2 biosynthesis, non-aspirin NSAIDs cannot replace for aspirin as antiplatelet drugs. Unlike aspirin, these are reversibly acting compounds and the degree of inhibition of platelet COX-1 is determined by their plasma half-life, for most compounds in the range of 2-4 hours (h). After platelet stimulation, the local concentration of the substrate arachidonic acid within the binding channel of COX-1 may become sufficient to displace these compounds from their binding to COX-1. This process becomes facilitated by

![](image1.png)

**Figure 1: Hydrophobic channel of COX-1 as derived from crystal structure analysis.**

A) Empty channel without ligand; B) Binding of arachidonic acid, the natural substrate; C) Putative position of salicylic acid and several non-selective NSAIDs within the hydrophobic channel; D) Acetylation of Ser530 by aspirin resulting in inhibition of enzyme activity (Figure kindly provided by P. Loll).
clearance of the compounds, i.e. their wash-out, from plasma, and the fact that the relation between the inhibition of platelet COX-1-dependent TXA₂ generation and inhibition of TXA₂-dependent platelet function is non-linear (16, 17). As a net effect, NSAIWs are unable to allow for continuous circadian inhibition of platelet COX-1 and platelet function although they do inhibit platelet function and this is likely to contribute to their haemorrhagic side effects.

The molecular mechanisms of this interaction are summarised in Figure 1. Cyclooxygenases are homodimeric peroxidase enzymes associated with the cell membrane. The biological substrate, arachidonic acid, is released from membrane phospholipids upon cell (platelet) stimulation and enters a hydrophobic substrate binding channel towards the catalytic site at the interior of the enzyme. The active enzyme converts arachidonic acid via a multistep reaction into prostaglandin H₂ which in platelets is further converted to TXA₂ by thromboxane synthase. Repeated administration of low-dose aspirin cumulatively inactivates platelet COX-1 in the anucleate platelet (18) by acetylation of a serine₃₅₀ near the catalytic site (19, 20). Arachidonic acid (Figure 1B) and non-aspirin NSAIWs, including ibuprofen, naproxen and others, are attracted by various amino acid residues in the hydrophobic channel at overlapping binding sites (Figure 1C) (21, 22). Both, acetylation by aspirin (Figure 1D) and the presence of NSAIWs (Figure 1C), hinder the access of arachidonic acid to the catalytic site at tyrosine₃₅₅.

Competitive mechanism of interaction

Despite of these pharmacokinetic interactions, one might still expect that COX-1 inhibition is synergistically amplified because both non-aspirin NSAIWs and aspirin act pharmacodynamically into the same direction. This, however, is not necessarily the case. The half-life of aspirin in blood plasma is only 15-20 minutes (min) due to rapid deacetylation to salicylate, which does not inhibit platelet COX-1. This is much shorter than the half-life of most non-aspirin NSAIWs as outlined above and might result in inactivation of aspirin prior to its binding to the COX enzyme. This is facilitated by a relatively weak initial binding affinity of aspirin within the hydrophobic channel, having a Ki of 27 mmol/l (23). Non-aspirin NSAIWs have Ki values several orders of magnitude lower (usually micromolar). If present, they will prevent the access of aspirin to the site of acetylation and ‘protect’ platelet COX-1 from permanent inactivation by aspirin as long as they are bound there in sufficient amounts. This is exemplified in Figure 2, showing the docking of a reversible inhibitor (ibuprofen) within the hydrophobic channel of COX-1. The carboxy group forms putative hydrogen bonds with the hydroxy residues of serine₅₃₀ and tyrosine₃₅₅. This probably hinders the access of aspirin towards this site.

The hypothetical competition between aspirin and non-aspirin NSAIWs has been examined by enzyme kinetic modelling. One model (24) included several steps of the catalytic mechanism of COX-1 and calculated the interaction of a reversible NSAID (celecoxib) with an irreversible inhibitor (aspirin). It was crossvali-

Figure 2: Computerised docking of the putative binding of ibuprofen in the hydrophobic channel of COX-1. The green lines indicate hydrogen bond interactions. The surrounding amino acids Ty₃₈₅, Ser₅₃₀, Ty₅₅₅, and Arg₁₂₀ are important for the docking of aspirin to the binding pocket. Ibuprofen likely consumes the space required for aspirin to locate within the COX-1 channel (Saxena et al, manuscript in preparation).

dated with in vitro experimental data on COX-1 enzyme kinetics available from the literature. The model suggested that COX-1 acetylation by aspirin was dramatically delayed in the presence of celecoxib and that this occurred already at concentrations of celecoxib which only weakly inhibit enzyme activity themselves. Unfortunately, this work was not extended to other common NSAIWs, which would be of interest because of the differences in inhibition kinetics among NSAIWs. A similar approach was used by Hong et al. (25) who examined the ibuprofen-induced inhibition of platelet aggregation based on experimental data generated with blood from healthy donors. While the methodology of model development was different, this simulation also concluded that a reversible COX-1 inhibitor (here ibuprofen) antagonises irreversible platelet inhibition by aspirin.

Further concepts of the molecular interaction between aspirin and NSAIWs

While a direct competitive aspirin/NSAID interaction has been clearly presented and models based on this achieve realistic results (see below), the mechanism(s) of interaction in reality may be more complex. A recent concept focusses on a ‘cross-talk’ between the two COX subunits (26, 27). Many NSAIWs appear to act by regulating one COX monomer, which does not contribute to catalysis. This monomer acts as a regulatory subunit controlling the activity of the partner monomer, which is catalytically active. There is evidence that only one of the two subunits of COX enzymes participates at a time in the catalytic cycle (28, 29). Hence, COX may be regarded both as a sequence homodimer and a functional heterodimer. Some NSAIWs appear to bind to the regulatory subunit and exert non-competitive inhibition of the catalytic subunit, while others interact with the catalytic subunit, inhibiting enzyme activity by a competitive mechanism (27).
Moreover, kinetic analyses distinguished different types of NSAIDs depending on whether they act in a time-dependent manner or not. The time-dependent mode of inhibition appears to be associated with a conformational change of the enzyme. With this in mind, it may be reasoned that the interaction between COX inhibitors does not necessarily result from direct ligand competition for a common binding site within the hydrophobic COX channel of the same subunit. It may (also) result from a cross-regulation between the two subunits of the dimeric COX enzyme, where binding of a non-aspirin NSAID to one monomer (the regulatory subunit) induces a conformational change. This may be transferred via amino acids located at the interface between the two monomers towards the partner monomer (catalytic subunit), which may undergo a secondary conformational change within the substrate channel. This change may subsequently slow down the rate of acetylation by aspirin. A careful analysis of the drug/drug interaction between celecoxib and aspirin based on crystallographic analyses and animal experimentation suggested such a mechanism for the interaction between aspirin and celecoxib at platelet COX-1 (30).

**Evidence for negative interactions in experimental and clinical studies**

An interaction of reversible COX inhibitors has been demonstrated in vitro decades ago, mainly in studies on the pharmacodynamic properties of NSAIDs (31-33). These early studies did not focus on the potential clinical significance of this interaction. This has now changed, after it became apparent that non-aspirin NSAIDs and coxibs unlike aspirin, might increase the cardiovascular risk and possibly interact with aspirin in a negative manner in both experimental (34) and clinical (35, 36) trials. Leading health agencies, such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), consider these interactions as ‘potentially important’ (37).

**In vitro studies**

Aspirin/NSAID interactions can be demonstrated experimentally, for example by pre-incubation of platelet suspensions with a non-aspirin NSAID followed by addition of aspirin and subsequent platelet stimulation by an agonist, such as arachidonic acid or low concentration-collagen, that act solely through generation of TXA₂. Many non-aspirin NSAIDs partially or completely prevent platelet inhibition by aspirin in such settings. ▶ Figure 3 gives an example for the interaction of aspirin and piroxicam, a reversible long acting NSAID. There was complete inhibition of aggregation and TX synthesis by aspirin (30 µmol/l) and no interaction with piroxicam at concentrations ≤0.1 µmol/l. Higher concentrations of piroxicam, however, resulted in a concentration-dependent antagonism of the inhibition by aspirin as seen from increased platelet aggregation and TX formation. Further increase of piroxicam concentrations above 30 µmol/l reduced platelet activity and thromboxane synthesis, probably due to COX-1 inhibition by piroxicam. However, these concentrations of piroxicam are above those after analgesic dosing: the peak plasma concentration of piroxicam after one single 20 mg tablet is 3-8 µmol/l (38). This shows that piroxicam has no antiplatelet effects by itself in clinical settings but might well reduce the antiplatelet effects of aspirin, and this for a long time, considering it extremely long (and variable) half-life of about 50 h. This collectively suggests a clinically important but not well appreciated drug interaction.

We have studied many NSAIDs in this setting, including ibuprofen, naproxen, diclofenac and others. A similar interaction with aspirin was found with many of them. ▶ Figure 4 shows a comparison of different NSAIDs with respect to their potential for in-

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**Figure 3: Pharmacodynamic interaction of aspirin and piroxicam in vitro.** Platelet-rich plasma from healthy volunteers (n=7) was preincubated with piroxicam and aspirin (30 µmol/l) subsequently added. Five min later, platelets were stimulated (1 mmol/l arachidonic acid) and aggregation recorded for 4 min. Aggregation (left) and thromboxane formation (right) (Immunoassay for TXB₂) were abolished by aspirin alone (open vs. blue symbols). The inhibition by aspirin was prevented in a concentration-dependent manner by preincubation with piroxicam (red symbols).
teraction with aspirin, as determined by platelet TX formation in the presence of NSAID and aspirin. For standardisation, all NSAIDs were added at their respective IC50, which were determined separately and are also given in Figure 4. They were comparable or lower than clinically reported plasma concentrations of these NSAIDs. For example, the mean \( \text{c}_{\text{max}} \) at standard analgesic doses of acetaminophen, diclofenac, ketoprofen, naproxen, ibuprofen and dipyridone were 141, 2, 10, 205, 69 and 51 \( \mu \text{mol/l} \), respectively (39-44). Hence, these NSAID/aspirin interactions can be expected also to occur clinically.

Notably, there were remarkable differences between the compounds, which cannot be explained solely by potency or COX-2 selectivity. Acetaminophen, diclofenac, and ketoprofen did not interfere with aspirin at all. Experiments are ongoing to further examine the structural requirements.

Non-aspirin NSAIDs with high COX-2 prevalence may also interfere with COX inhibition by aspirin. For example, pre-exposure of COX-1 in ram seminal vesicles (45) or cultured cell lines (46) with COX-2 selective inhibitors (DuP697, NS398) attenuated COX-1 inhibition by aspirin at nanomolar concentrations. Neither compound inhibited COX-1 activity when given alone. A similar interaction was described for indomethacin (instead of aspirin) but not for ibuprofen or naproxen. The authors explained this by interaction at different binding sites. Similar results were also reported by Ouellet et al., who suggested that less selective coxibs are more prone to interact (23). Nimesulide, a compound with moderate COX-2 selectivity, also interferes with aspirin (47). Interestingly, interactions with aspirin have also been shown for natural compounds, such as gallic acid (48).

Studies in healthy subjects

Several studies on healthy subjects have shown that NSAIDs can block or weaken the antiplatelet action of aspirin. For example, Catella-Lawson et al. have found that ibuprofen interferes with aspirin in terms of platelet aggregation and serum thromboxane formation if ibuprofen was given (i) once daily 2 h before aspirin or (ii) by multiple daily dosing (49). Another small trial reported similar effects also for naproxen (50) which was confirmed in a larger randomised trial (51). Six NSAIDs have been studied by Gladding et al. in healthy subjects in a randomised placebo controlled design (52). The authors examined capillary closure times by the PFA-100 analyser and found that the prolongation of closure time by aspirin was significantly antagonised by ibuprofen, indomethacin, naproxen and tiaprofenic acid, but not by sulindac and celecoxib. All the above studies noted that the NSAIDs interacted with aspirin at sub-inhibitory doses, which agrees with the experimental data summarised above.

A significant portion of patients (~75 %) subjected to CABG surgery may not respond to low-dose aspirin with the expected inhibition of platelet function (53). A more detailed analysis for possible pharmacological reasons of this HPR showed that blood samples from aspirin non-responders contained metabolites of a routinely administered analgesic (dipyridone or metamizol), while samples from responders did not. A subsequent in vitro study revealed that the active dipyridone metabolite, 4-methylaminoantipyrine, very effectively inhibited aspirin-induced inhibition of arachidonic acid- or collagen-induced platelet aggregation, TXA2 formation and P-selectin expression (54). Analgesic doses of dipyridone did not change platelet activity directly but prevented inhibition by aspirin. The effect was specific since dipyridone did not interfere with platelet inhibition by TXA2 receptor antagonists or inhibitors of TX - synthase. In agreement with this, others reported that HPR after CABG surgery can be transferred by plasma to previously responsive platelets (55).

Figure 4: NSAIDs largely differ in their interaction with aspirin at platelet COX-1. Platelets were pre-incubated with different non-aspirin NSAIDs, each at its respective IC50 (right, separately measured in platelets). Aspirin (30 \( \mu \text{mol/l} \)) was added for 5 min and platelets then stimulated with 1 \( \mu \text{mol/l} \) arachidonic acid. TXB2 was determined in the supernatants by immunoassay and is shown as % of control (no aspirin or NSAID). Acetaminophen, diclofenac, and ketoprofen did not prevent the antiplatelet effect of aspirin. All other NSAIDs (red bars) reduced the aspirin effect with large differences between the compounds. Bars represent mean values ± SEM (n=4-6) (Saxena et al., manuscript in preparation).

Studies in patients

Whether HPR against aspirin by NSAIDs also occurs in clinical settings is less clear, but some indications exist. For example, a small study identified 18 patients receiving aspirin for secondary stroke prevention and concomitant therapy with ibuprofen or naproxen (56). At 27 months follow-up, all patients showed
largely normal arachidonic acid and collagen-stimulated whole blood platelet aggregation, similar to drug-free controls. Then, NSAIDs were either discontinued or aspirin taken at different time schedule (see section Sequential dosing) in order to minimise an interaction. Re-testing after 2-4 weeks revealed that this had largely restored platelet inhibition by aspirin. This suggests that an appropriate modification of therapy can indeed avoid HPR. In another study on patients with osteoarthritis celecoxib did not appear to interfere with the antiplatelet effect of low-dose aspirin (57), although some experimental studies support an interaction (23, 30).

A prejudice of the above studies is that they examined laboratory parameters without proven prognostic relevance for clinical outcome. Although meta analyses (58, 59) and some studies in different clinical settings (6, 8-10, 60) suggested that HPR to aspirin may be related to worse clinical outcome, there is also recent data in patients with stable angina suggesting that HPR does not relate to clinical outcome (61).

It is still a matter of debate whether and if so which platelet function assay has (the best) predictive value for clinical outcome in aspirin-treated patients. Two principal laboratory assays are available to examine platelet inhibition by aspirin ex vivo – the measurement of platelet function (e.g. aggregation, P-selectin expression, secretion) and the determination of platelet-derived TXA2 formation. The analysis of platelet aspirin sensitivity is based on inhibition of platelet function after stimulation by a particular agonist. Such assays may not capture the full antiplatelet response to aspirin and ignore indirect effects on coagulation and anti-inflammatory processes. Assay sensitivity to antiplatelet effects of aspirin also depends on the agonist used. Arachidonic acid-induced aggregation in platelet rich plasma is probably the most aspirin-sensitive functional assay and well suitable to demonstrate the interaction between aspirin and NSAIDs in vitro (Figure 3). Collagen, ADP and thrombin are less appropriate as agonist to study aspirin effects because they stimulate platelet responses largely by thromboxane-independent pathways. Serum- or arachidonic acid-induced thromboxane formation in whole blood or platelet-rich plasma are also appropriate to examine aspirin/NSAID interaction in vitro. Whole blood assays, such as arachidonic acid-induced impedance aggregometry (e.g. Multiplate Aspi test), Verify Now and the PFA-100 assay, are available as point-of-care assays for monitoring of aspirin antiplatelet effects. These assays have not been systematically tested for their ability to detect aspirin/NSAID interactions. While normal ranges have been established here, they appear to produce divergent clinical results in patients (62). We have recently discussed the available test-
ing methods for antiplatelet effects of aspirin in more detail, including flow cytometry and analysis of urinary thromboxane metabolites (3).

The available data on clinical outcome in conjunction with HPR due to possible NSAID/aspirin interactions are also ambiguous. For example, two studies (63, 64) examined the association between NSAID and aspirin use according to the issued prescriptions in the UK General Practice Research Database. They found no indication for an adverse NSAID/aspirin interaction, but the results may have been biased by non-compliance and undocumented “over-the-counter” (OTC) use of aspirin and non-prescription analgesics, including ibuprofen and diclofenac among others.

Other trials, however, support the notion that NSAIDs may adversely interact with aspirin. For example, a case-control study with 1,055 cases of first non-fatal myocardial infarction and 4,153 controls showed that aspirin alone reduced cardiovascular events but was without favourable effect when given combined with NSAIDs (65). This applied particularly to ibuprofen and became even more evident with more frequent NSAID use. Also, the retrospective Tayside trial on 7,107 patients with established cardiovascular disease observed an about two-fold increase in all-cause and cardiovascular mortality when low-dose aspirin was taken together with ibuprofen, as opposed to aspirin alone (66). Interestingly, patients on diclofenac plus aspirin had mortality rates similar to aspirin alone.

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) randomised patients to ibuprofen, naproxen or lumiracoxib. It also included patients with high cardiovascular risk on low-dose aspirin. In a post-hoc substudy, patients on ibuprofen exhibited a higher cardiovascular event rate than those on lumiracoxib (2.14 vs. 0.25 %, p=0.038), whereas event rates were similar for naproxen vs. lumiracoxib (67). This suggests that ibuprofen, but not naproxen, reduces cardiovascular prevention by aspirin. A similar conclusion can be drawn from a post-hoc analysis of the US Physician’s Health Study (PHS), a randomised controlled trial in 22,071 healthy physicians (68), which analysed whether co-therapy of low-dose aspirin and NSAIDs modified the effect of low-dose aspirin on cardiovascular outcome during the five-year treatment period. Participants taking NSAIDs together with aspirin for >60 days/year behaved similar to aspirin non-adherent subjects, i.e. missed any protection from myocardial infarction in contrast to those who regularly took the drug (Figure 4) (69). Though the particular NSAIDs which were taken have not been identified, the data indicate that NSAID/aspirin interactions are clinically important. The overall benefit of the total population was significant and driven by individuals who regularly took aspirin (every other day) and avoided regular intake of NSAIDs.

Thus, there is evidence that ibuprofen and other - but not all - NSAIDs may counteract the antiplatelet effects of aspirin in clinical practice. More detailed information is highly desirable but might be difficult to obtain from randomised prospective trials because of ethical reasons.

Options for avoiding HPR against aspirin by NSAIDs

Since platelet inhibition by aspirin is irreversible and long-lasting, single doses of an interacting NSAID taken for acute pain relief are unlikely to interact with aspirin: In the original experiment shown in Figure 5, it took more than three days of regular co-medication of dipyrone in a conventional analgesic dose until the recovery of TXA2 formation was sufficient to allow for normal arachidonic acid-induced platelet aggregation.

Sequential dosing

A critical determinant of the interaction of NSAIDs with aspirin at platelet COX-1 is the actual NSAID plasma concentration. Since immediate release aspirin reaches cmax after about 1 h and is rapidly deacetylated to salicylic acid, NSAIDs, if necessary, should not be given within 2 h after aspirin intake. Accordingly, an appropriate time interval between NSAID and aspirin intake might restore platelet inhibition in patients with HPR against aspirin (56). It has been recommended to take a single dose of ibuprofen at least 30 min after immediate release aspirin and not less than 8 h before aspirin (37). In contrast, repeated daily dosing of short acting NSAIDs or single doses of long acting NSAIDs (e.g. piroxicam) may permanently interact with aspirin. Similar effects may also be expected for individuals with a poor metaboliser phenotype of NSAID-metabolising enzymes (e.g. CYP2C9) (70). Whether NSAIDs may also form ‘active’ metabolites causing a longer duration of interaction with aspirin is not known.

NSAID selection

An interesting aspect is that NSAIDs differ in their interaction potential with aspirin (Figure 4). Therefore, if combined therapy is required, NSAIDs should be selected that do not show this interaction. These include acetaminophen, diclofenac (49, 71) and others (52). Data on celecoxib are contradictory (30, 52, 57). Naproxen has been recommended for use in patients with cardiovascular disease taking low-dose aspirin (72), but several studies found that it impairs platelet inhibition by aspirin (50-52). The ongoing PRECISION trial (Prospective Randomised Evaluation Of Celecoxib InTEGRated Safety vs Ibuprofen Or Naproxen), which compares chronic treatment with ibuprofen, naproxen or celecoxib with respect to cardiovascular outcome in patients with arthritis at elevated cardiovascular risk, will provide more information and will be completed in 2014.

The competitive mechanism of aspirin/NSAID interactions at platelet COX-1 suggests that both, reducing the dosage of NSAIDs as well as increasing the dose of aspirin, may also overcome this interaction. In human platelets, the prevention of aspirin effect by dipyrone could be restored in the presence of dipyrone by increasing the concentration of aspirin (54). A possible explanation may be the interaction kinetics of aspirin with COX-1: aspirin, like many non-aspirin NSAIDs, initially binds reversibly to Arg(120) at the COX channel entrance before entering the acetylation site at of Ser(530) (Figure 1C) (73). During this initial reversible step aspirin...
may become displaced by other NSAIDs in a competitive manner. No clinical data appear to exist on this issue.

Change of the antiplatelet compound

A final option for prevention of aspirin/NSAID interactions is to replace aspirin by another antiplatelet agent. One alternative is clopidogrel which was comparable to or modestly better than aspirin for secondary prevention in the CAPRIE trial (74). So far, there is no clinical evidence supporting the replacement of aspirin by clopidogrel to avoid HPR by NSAIDs against aspirin. However, one should keep in mind that all patients in all clinical trials on dual antiplatelet therapy with P2Y12-ADP-receptor antagonists were on aspirin. This was not "placebo" treatment and the possible contribution of HPR to aspirin for the overall clinical outcome is unknown.

Conflicts of interest

None declared.

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