REVIEW

Impairment of aspirin antiplatelet effects by non-opioid analgesic medication

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Abstract

Aspirin is the mainstay in prophylaxis of cardiovascular diseases. Impaired aspirin antiplatelet effects are associated with enhanced incidence of cardiovascular events. Comedication with non-opioid analgesic drugs has been described to interfere with aspirin, resulting in impaired aspirin antiplatelet effects. Additionally, non-opioid analgesic medication has been shown to enhance the risk of cardiovascular events and death. Pain is very frequent and many patients rely on analgesic drugs to control pain. Therefore effective analgesic options without increased risk of cardiovascular events are desirable. This review focuses on commonly used non-opioid analgesics, interactions with aspirin medication and impact on cardiovascular risk.

Key words: Non-steroidal anti-inflammatory drug; Drug-drug interaction; Pharmacodynamic; Dipyrone; Aspirin; Paracetamol; Metamizole

Core tip: Aspirin is the mainstay in prophylaxis of cardiovascular diseases. Impaired aspirin antiplatelet effects are associated with enhanced incidence of cardiovascular events. Comedication with non-opioid analgesic drugs has been described to interfere with aspirin, resulting in impaired aspirin antiplatelet effects. Additionally, non-opioid analgesic medication has been shown to enhance the risk of cardiovascular events and death. Pain is very frequent and many patients rely on analgesic drugs to control pain. Therefore effective analgesic options without increased risk of cardiovascular events are desirable. This review focuses on commonly used non-opioid analgesics, interactions with aspirin medication and impact on cardiovascular risk.

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INTRODUCTION

Approximately 20% of European adults suffer of acute or chronic pain and rely on analgesic drugs[1,2]. The incidence of pain and usage of non-opioid analgesics is even higher in patients with cardiovascular diseases. Forty percent of patients with coronary artery disease reported intake of non-opioid analgesic drugs[3]. This is not surprising, as the incidence of pain correlates with increasing age[4] and cardiovascular diseases are morbidities of middle to older age patients[5].

Aspirin (acetylsalicylic acid; ASA) is essential secondary prevention of cardio-and cerebrovascular events[6]. It inhibits cyclooxygenase (COX)-1 by irreversible acetylating serine 530 near the active site. This hampers conversion of arachidonic acid to thromboxane (TX) A2 for the life span of the affected platelet[7]. Aspirin has been shown to reduce the incidence of death, myocardial infarction and stroke[8-10]. However, during the last decade substantial inter-individual variation in pharmacodynamic response to aspirin has been described. This is called high on-treatment platelet reactivity (HTPR) (formerly known as "aspirin resistance"). Patients with HTPR have an increased incidence of death, myocardial infarction and stroke[11]. Many potential mechanisms including non-compliance[12,13], impaired absorption[14], genetic polymorphisms[15] increased turnover rate, enteric coating of aspirin[16,17] and COX-1 independent pathways may cause this HTPR[18]. Besides that, non-opioid analgesic medication may impair aspirin antiplatelet effects. In contrast to above mentioned internal factors, this drug-drug interaction is avoidable. Therefore special attention should be paid to this interaction leading to impaired aspirin antiplatelet effects. This review focuses on (1) mechanisms-; (2) laboratory-; and (3) clinical evidence of the aspirin drug-drug interaction with commonly used non-opioid analgesics.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs in the world[19]. They are available on prescription as well as over the counter. In the United States, 70 million NSAID prescriptions- and 30 billion over the counter sales per year were registered[20]. Approximately 83% of United States - American adults use NSAID to relief pain at least once a year, 29% once a week and 15% daily[21]. In Australia, 55% of people consume NSAIDs at least once per month[22].

The term "NSAID" subsumes a variety of drugs with different chemical structures, pharmacokinetics, pharmacodynamics and mechanism of action but similar effects[23]. The main common feature is prevention of prostaglandin formation by inhibition of COX isoforms. This results in desirable anti-inflammatory and analgesic effects due to COX-2 inhibition in inflamed tissues[24]. On the other hand, inhibition of COX-1 in the gastric mucosa impairs maintenance of the mucosal barrier. This results in an increased risk of gastrointestinal events[25]. Additionally NSAIDs may worsen renal function[26] and affect platelets[27]. Based on the above mentioned differences in pharmacokinetics and pharmacodynamics between different NSAIDs, a considerable variability in analgesic as well as anti-inflammatory and antiplatelet effects is not surprising[23,27]. NSAIDs may also impair cardiovascular prognosis[28,29], possibly by inhibition of prostaglandin synthesis in the vasculature resulting in an increase in blood pressure and disturbed endothelial control of thrombogenesis. This aspect must not be confounded with the pharmacodynamic interaction of non-opioid analgesics with aspirin, which is discussed here. However, it is possible that this interaction contributes to the overall cardiovascular risk of NSAIDs. In the following, we will discuss the most commonly used NSAIDs with respect to their potential to interfere with platelet inhibition by low dose aspirin.

Ibuprofen

Ibuprofen was the first propionic acid derivative NSAID. Worldwide more than 100 million patients consumed ibuprofen and it is available in more than 100 countries[30]. Ibuprofen forms hydrogen bonds to arginine 120 and tyrosine 355 near the active site of the COX[27]. *In-vitro* analysis revealed, that ibuprofen inhibits platelet aggregation of human platelets[27]. In healthy individuals, ibuprofen intake led to inhibition of thromboxane formation[31] and platelet aggregation *ex-vivo*. As ibuprofen inhibited COX transiently, platelet function returned to normal within 4 to 6 h[32]. *In-vitro* coincubation with aspirin completely abrogated platelet inhibition and thromboxane formation by aspirin. This has been shown *ex-vivo* in healthy individuals as well with multiple studies demonstrating hampered aspirin antiplatelet effects in ibuprofen co-treated healthy subjects[33-37]. Catella-Lawson *et al*[33] reported that controlled order of intake with single dose ibuprofen (400 mg) two hours after aspirin intake preserves aspirin antiplatelet effects in healthy individuals. However ibuprofen medication three times per day inhibits aspirin antiplatelet effects independently of the above mentioned order of intake. This finding may be consistent even in lower doses of ibuprofen (150 mg)[36]. None of patients on aspirin for secondary prophylaxis of a cerebrovascular event with ibuprofen co-treatment had adequate aspirin induced inhibition of platelet aggregation. Additionally, 72% of patients experienced recurrent ischemic events. After termination of analgesic medication, aspirin antiplatelet effects restored[32]. In patients with cardiovascular diseases, different studies detected increased incidence of death and recurrent myocardial infarction in aspirin and ibuprofen comedicated patients[38-40]. This finding was confirmed in two meta-analyses, investigating the risk of death

and cardiovascular events in patients at increased risk of vascular disease on ibuprofen medication[29,41].

Naproxen

Naproxen is a propionic acid derivative NSAID like ibuprofen. However, its' pharmacokinetics are different. Plasma half-life of ibuprofen is about two hours, whereas the plasma half-life of naproxen is approximately 12 h[42]. Naproxen forms hydrogen bonds to tyrosine 385 and serine 530 in the active site of COX[27]. This leads to dose-dependent, reversible inhibition of platelet activation *in-vitro*. However, increasing concentrations of arachidonic acid can overcome this COX-inhibition. Additionally, ASA administration after pre-incubation with naproxen prevents ASA antiplatelet effects[43]. In healthy individuals, naproxen co-treatment with aspirin impairs aspirin antiplatelet effects as well[32,35,37]. This effect was consistent in over the counter doses as well as prescription doses[44]. However, data of clinical studies are contradictory. Some studies described an increased incidence of cardiovascular events in naproxen treated patients[32,45]. However others described a beneficial effect on the incidence of adverse events[39,40,46,47]. Two meta-analyses described no significant increase of vascular events and death in naproxen medicated patients[29,41]. The reasons for these inconstant results are unclear. Naproxen inhibits aspirin antiplatelet effects in-vitro similar to ibuprofen[27]. However, Capone *et al*[48] described permanent functionally relevant inhibition of *ex-vivo* platelet function in healthy individuals with 500 mg naproxen twice a day. Therefore, most probably the increased plasma half-life and therefore longer lasting reversible inhibition of platelets by naproxen may be responsible for the protective, respectively less harmful effects of naproxen in patients with cardiovascular diseases. The importance of naproxen's potential to interfere with the antiplatelet action of aspirin is presently not clear. Different authors recommended preferring the use of naproxen in patients with increased cardiovascular risk[49,50].

Diclofenac

Diclofenac is a heteroaryl acetic acid NSAID. It is commonly prescribed to alleviate acute and chronic pain[51]. Like other NSAIDs, diclofenac inhibits COX enzymes (COX-2 > COX-1). There may be additional mechanisms of action inducing its anti-inflammatory, antipyretic and analgesic effects, which are not completely understood. Besides affection of arachidonic acid uptake and release, activation of nitric oxide-cGMP antinociceptive pathway, inhibition of thromboxane prostanoid receptor and lipoxygenase enzymes, it may also inhibit peroxisome proliferator activated receptor gamma, block acid-sensing ion channels, alter interleukin-6 production and inhibit substrate P and N-methyl-D-aspartate receptor hyperalgesia[51].

In-vitro incubation of human platelets with diclofenac inhibited thromboxane formation and platelet aggregation[27]. This was reproducible *ex-vivo* after diclofenac treatment of healthy volunteers[31,52]. Additionally, platelet function was inhibited after diclofenac - treatment in patients[53,54]. However, there seems to be no interaction with aspirin treatment. ASA antiplatelet effects including inhibition of thromboxane formation were preserved *in-vitro* after pre-incubation with diclofenac[27]. Additionally, diclofenac treatment in healthy individuals on aspirin revealed sufficient pharmacodynamic response to aspirin as well[33,34]. This may be explained by molecular docking analyses. Diclofenac did not form any hydrogen bond interactions in the hydrophobic active channel of COX. Therefore it appears not to interfere with the ASA induced acetylation of serine 530, preserving aspirin antiplatelet effects despite of diclofenac co-treatment[27].

In aspirin and analgesic co-treated patients with coronary artery disease, MacDonald *et al*[38] described improved outcome of diclofenac co-treated patients in comparison to ibuprofen comedicated patients. In contrast, in a study including 83667 patients after myocardial infarction, diclofenac co-treatment was associated with the highest risk of recurrent myocardial infarction and death during 90 d[39] as well as in one- and five year follow-up[40]. These findings were confirmed in two meta-analysis investigating death and cardiovascular events in patients with analgesic medication. Both reported an increased risk in diclofenac treated patients as well[29,41].

COX-2 INHIBITORS

Anti-inflammatory and analgesic effects of COX-inhibitors are largely mediated by prevention of COX-2 induced prostaglandin formation in inflamed tissues[24]. Impairment of the gastric mucosal barrier resulting in increased incidence of gastrointestinal events, and affection of platelets are mostly caused by COX-1 inhibition[25,27]. Therefore, during the 90's NSAIDs with COX-2 selectivity were developed[55].

Conflicting data has been reported regarding impairment of aspirin antiplatelet effects by COX-2 inhibitors. Despite COX-2 selectivity, celecoxib was shown to form a hydrogen bond in the hydrophobic channel of COX-1 with tyrosine 355[27]. This goes in line with *in-vitro* experiments, demonstrating inhibition of thromboxane formation and platelet aggregation by celecoxib incubation. In ASA and celecoxib co-incubated platelets, ASA antiplatelet effects were inhibited[27]. Celecoxib administration in dogs interfered with the ability of aspirin to inhibit platelet aggregation[56]. In contrast, no impact on platelet function was observed in healthy individuals on celecoxib treatment[35]. Additionally, different groups reported that COX-2 inhibiting co-treatment in aspirin treated healthy individuals did not impair the pharmacodynamic response to aspirin[33,35,37,57]. Regardless, multiple studies reported increased risk of cardiovascular

events and death in patients receiving COX-2 inhibitors independently of concomitant aspirin intake[28,58-60].

PARACETAMOL (ACETAMINOPHEN)

Paracetamol is an aniline derivative. It is one of the most widely used antipyretic and analgesic drugs worldwide, especially as the risk of gastrointestinal bleeding events are lower in comparison to NSAIDs[61]. It is available over the counter in many countries[62]. However, in supra-therapeutic doses depletion of endogenous glutathione occurs, resulting in paracetamol metabolism shunting to toxic pathways causing severe, even fatal, hepatotoxicity[63,64]. To date, the mechanisms of analgesia by paracetamol remain unclear despite of extensive investigations[65]. A plethora of mechanisms have been postulated including activation of the endocannabinoid pathway[66,67], inhibition of the nitric oxide synthase[68,69], and indirect activation of descending serotonergic pathways[70-72]. Additionally, inhibition of cyclooxygenases in a direct-[73-75], or indirect (by converting to their oxidized, inactive form[76]) way has been described. Current opinion suggests that paracetamol performs its analgesic actions by multiple mechanisms predominantly in the central nervous system[65].

In-vitro addition of paracetamol to human platelets was reported to inhibit collagen, epinephrine and arachidonic acid induced platelet aggregation and TX formation[77]. Accordingly, in healthy individuals a reduced arachidonic acid-induced TX formation one hour after single dose of paracetamol was shown. However an effect on platelet aggregation was observed in only one of five investigated individuals[77]. Munsterhjelm *et al*[78] detected an inhibition of platelet aggregation in healthy individuals 10 min after ingestion of paracetamol. Already 90 min after intake of paracetamol, platelet aggregation was restored. Additionally, a combination of paracetamol and diclofenac exhibits an additive effect on platelet inhibition. In comparison to diclofenac treatment in healthy individuals alone, addition of paracetamol preserves inhibition of platelet aggregation and TX formation 90 min after intake. Nevertheless, platelet function normalized after 24 h[52]. In patients, a single dose of paracetamol reduced arachidonic acid induced TX formation, but did not inhibit platelet aggregation in patients[54]. Molecular modelling and docking analyses revealed that paracetamol forms only one single hydrogen-bond to arginine 120 in the hydrophobic channel of COX-1[27]. No aspirin interaction resulting in inhibition of aspirin antiplatelet effects was seen, suggesting that one hydrogen-bond might not be sufficient to induce impairment of aspirin antiplatelet effects[27]. These findings were supported by the results of Catella-Lawson *et al*[33] and Rao *et al*[79], both did not observe altered aspirin antiplatelet effects in presence of paracetamol, either. However an increased incidence of first cardiovascular event in patients with frequent use of paracetamol was observed[80]. Potential reasons

for this observation may be a dose dependent risk of renal insufficiency of paracetamol[81] which is a predictor of cardiovascular events[82]. Secondly, an increased blood pressure in patients with paracetamol usage has been described[83-86]. Also, an impairment of endothelial function by depletion of glutathione is thinkable to induce this enhanced risk of cardiovascular events[87].

DIPYRONE (METAMIZOLE)

Dipyrone is a pyrazolinone analgesic with favorable analgesic, spasmolytic and antipyretic effects. Gastrointestinal complications are rare in comparison to NSAIDs like ibuprofen or diclofenac[88]. Due to the risk of agranulocytosis, it has been withdrawn in many countries including the United States. Nevertheless, it is extensively used in Central- and South America and freely available over the counter in Mexico. Therefore despite of the withdrawal by the Food and Drug Administration, there is a wide spread use in the United States as well[89]. Moreover, it is freely available and the most used analgesic in Eastern European countries like Bulgaria[90]. Guidelines of the European Society of Cardiology do not recommend the use of NSAIDs in patients with cardiovascular diseases[91,92]. This may be one of the reasons why dipyrone daily doses tripled during the last decade in European countries like Germany[93]. The exact mechanism of its analgesic effects is complex and not completely understood, yet. Besides COX inhibition, an activation of opioidergic- and cannabinoid system in combination with inhibition of central COX-3 appears to contribute to its analgesic effects. Comedication with opioids causes superadditive analgesic effects. It inhibits both prostaglandin dependent and - independent pathways of fever and exhibits its spasmolytic effects by inhibition of intracellular calcium release[94]. Dipyrone inhibits all COX isoforms. It reversibly binds near the active site of COX, forming hydrogen bonds to tyrosin 385 and serine 530[27]. Dipyrone sterically hinders aspirin access to the active site and serine 530 of COX-1. Plasma half-life of dipyrone is about 2.5 h. Therefore it is 7.5 fold longer available than aspirin with a plasma half-life of only 20 min[95]. *In-vitro* experiments revealed that dipyrone active metabolite impairs ASA induced inhibition of microsomal platelet COX. The active metabolite of dipyrone in therapeutically relevant (low micromolar) concentrations showed little inhibition of platelet aggregation and TX formation. However, it prevented ASA dependent inhibition of platelet aggregation and thromboxane formation caused by arachidonic acid as well as collagen. The effect was reproducible in terms of microsomal platelet COX activity and p-selectin expression as well[96]. Increasing ASA concentrations *in-vitro* overcame this effect[97]. Additionally, previous incubation with ASA before addition of dipyrone preserves ASA antiplatelet effects[98].

In healthy individuals, aspirin intake sufficiently inhibits platelet aggregation, seven days of additional

Substance	Platelet inhibition	Aspirin interaction	Benefits	Risks
Aspirin	Irreversible	-	Analgesic, antipyretic, anti-inflammatory Reduction of cardiovascular events and death	Bleeding events
Ibuprofen	Reversible (half-life 1-4 h)	Yes	Analgesic, antipyretic, anti-inflammatory	Death Cardiovascular events Bleeding events
Naproxen	Reversible (half-life 12-24 h)	Yes	Analgesic, antipyretic, anti-inflammatory Reduction of cardiovascular events (?)	Bleeding events
Diclofenac	Reversible (half-life 1-2 h)	No	Analgesic, antipyretic, anti-inflammatory	Death Cardiovascular events Bleeding events
Celecoxib	Reversible (half-life 8-13 h)	Yes	Analgesic, antipyretic, anti-inflammatory Less gastrointestinal events	Death Cardiovascular events
Paracetamol	Reversible (half-life 1-4 h)	No	Analgesic, antipyretic Less gastrointestinal events	Cardiovascular events
Dipyrone	Reversible (half-life 2-4 h)	Yes	Analgesic, antipyretic, anti-inflammatory Less gastrointestinal events	Risk of death and cardiovascular events not investigated

Table 1 Risk and benefits of non-opioid analgesics
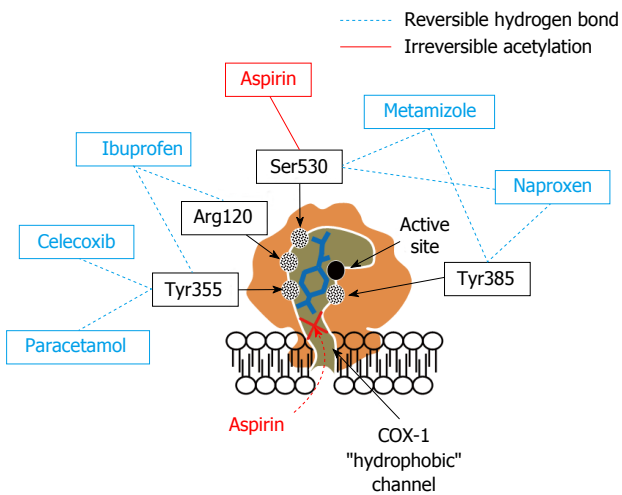
Figure 1 Graphical abstract. Non-opioid analgesics form reversible hydrogen bonds near the active centrum of cyclooxygenase (COX)-1. This prevents (1) aspirin entrance to the hydrophobic channel; (2) irreversible acetylation of Ser530; and (3) platelet inhibition for the remainder of the platelets life-span.

dipyrone intake completely blunts aspirin antiplatelet effects. This effect was reversible within three days of continued aspirin administration after termination of dipyrone intake. However, multiple daily doses of dipyrone were not tested[97]. Interestingly, Börgermann *et al*[99] reported that there was no impaired pharmacodynamic response to aspirin in dipyrone treated healthy individuals. However the duration of aspirin and dipyrone co-treatment was only two days. As aspirin antiplatelet effects are irreversible and persist for the remainder of the affected platelets life-span, it is not surprising, that no relevant differences were observed after two days of additional dipyrone treatment. A partial inhibition of aspirin antiplatelet effects has been described after four days of concomitant intake and complete inhibition after seven days[100]. Furthermore, it has been shown that aspirin intake prior to dipyrone preserves aspirin antiplatelet effects, whereas dipyrone intake

prior to aspirin completely blunts aspirin antiplatelet effects measured by platelet aggregation in healthy individuals[97].

In patients with coronary artery disease, residual platelet reactivity despite of aspirin was detected in 50% of dipyrone comedicated patients[101]. Residual platelet TX formation in patients with coronary artery disease correlated with the concentration of dipyrone metabolites. Additionally, in dipyrone treated patients after cardiac surgery, the incidence of HTPR to aspirin nearly tripled postoperatively[99]. The impact of this *in-vitro* and *ex-vivo* effects on clinical outcome has not been investigated yet.

CONCLUSION

The optimal analgesic regimen in patients with pain is challenging. Considering laboratory and clinical data, naproxen and paracetamol seem to display the most favourable benefit/risk ratio. However, increased incidence of adverse events has been described with these analgesics as well. Alternatively, aspirin would be a possible alternative to relieve pain and inhibit platelet function. Yet it is well known, that analgesic doses of aspirin increase the risk of gastrointestinal complications (Figure 1 and Table 1). If medication with non-opioid analgesics is considered indispensable, a strict order of intake, with aspirin medication at least two hours prior to analgesic medication is advisable. However, the optimal analgesic and antiplatelet regimen in patients with increased risk of cardiovascular disease is still unknown and requires further investigation.

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