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REVIEW: PHARMACOLOGY

EFFECT OF ASPIRIN ON HEMOSTASIS: SYNERGISM OR ANTAGONISM WITH NON STEROIDAL ANTI-INFLAMMATORY AGENTS

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ABSTRACT

Aspirin and the other non steroidal anti-inflammatory drugs (NSAIDs) are among the most often prescribed medicines. Co-administration of aspirin and NSAIDs is also common especially among patients suffering from arthritis and cardiovascular disease. An interaction between aspirin and NSAIDs could affect both the antiplatelet effect of aspirin and the safety of these agents in case of co-administration. For example, co-administration of aspirin with another NSAID could produce a pharmacodynamic interaction with subsequent enhancement or inhibition of antiplatelet effect of aspirin. On the other hand, such a pharmacodynamic interaction could result in increased incidence of gastrointestinal and non gastrointestinal haemorrhage. This review aimed to summarize available data on the possible pharmacodynamic interaction between aspirin and NSAIDs and the clinical consequences of such an interaction. Databases were searched electronically for relevant trials. Identified data were quite limited. Theoretically at the molecular level, a competitive interaction between aspirin and NSAIDs could be anticipated in case of prior administration of a NSAID. However, in vitro data indicate that concurrent administration of aspirin and diclofenac potentiates the inhibition of platelet aggregation. Yet, in vivo studies have failed to prove competitive interaction between aspirin and diclofenac in platelet aggregation, or suggest minimal effect of diclofenac on platelet aggregation, when administered concurrently with aspirin. Retrospective studies based on prescription databases have suggested that ibuprofen counteracts the antiplatelet effect of aspirin. There is limited evidence on how NSAIDs affect platelet aggregation in vivo when they are given together with aspirin according to a regular clinical schedule e.g. a morning dose of aspirin and repeated doses of NSAIDs during the day. Existing data suggest an interaction between aspirin and NSAIDs on haemostasis. However, there is controversy regarding the direction of this interaction, i..e. synergism or antagonism. Since, co-administration of aspirin and NSAIDs is quite common in people with comorbidities, further research is needed to clarify the clinical significance of this interaction.

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Keywords: *aspirin; NSAIDs; pharmacodynamic interaction; antiplatelet action; adverse drug events*

[I] INTRODUCTION

Aspirin and the other non steroidal anti-inflammatory drugs (NSAIDs) are among the most often prescribed medicines. Co-administration of aspirin and NSAIDs is also common especially among patients suffering from arthritis and cardiovascular disease. Daily doses of 75-125 mg of aspirin are recommended for individuals at high risk for cardiovascular disease. When drugs with similar pharmacologic effects are administered concurrently, an additive or synergistic interaction is usually seen. An antagonistic interaction is also possible, but not common. On the other hand the combined use of two or more drugs, each of which has toxic effects on the same organ can greatly increase the possibility of such an organ damage. An interaction between aspirin and NSAIDs could affect both the antiplatelet effect of aspirin and the safety of these agents in case of co-administration.

For example, co-administration of aspirin with another NSAID could produce a pharmacodynamic interaction with subsequent enhancement or inhibition of antiplatelet effect of

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aspirin [1]. On the other hand, such a pharmacodynamic interaction could result in increased incidence of gastrointestinal and non gastrointestinal haemorrhage [1]. The possibility, mechanisms and clinical significance of such an interaction have not been fully investigated. This study aimed to review the possible pharmacodynamic interaction between aspirin and NSAIDs and the clinical consequences of such an interaction.

[II] CO-ADMINISTRATION OF NSAIDS AND LOW DOSE ASPIRIN

Data were quite limited. A few randomized controlled trials were identified and all of them included a small number of healthy volunteers. Catella-Lawson *et al*.[2] performed a randomized cross over study with single doses of aspirin and ibuprofen and a parallel group study with multiple doses of aspirin and ibuprofen. Serum thromboxane B2 levels (an index of cyclo-oxygenase I activity in platelets) and platelet aggregation were maximally inhibited 24 hours after aspirin in the patients who took aspirin before any dose of any single drug, as well as in those who took rofecoxib or acetaminophen before aspirin. In contrast, in subjects who took 400 mg of ibuprofen two hours before taking 81 mg of aspirin, thromboxane B2 formation was inhibited by only 53% on day 7. The authors concluded that co-administration of NSAIDs with aspirin may interfere with the irreversible antiplatelet function of aspirin resulting thus in attenuation of the antiplatelet effect [2].

Another RCT, that included eleven healthy volunteers, investigated the influence of co-administration of aspirin with diclophenac, naproxen and acetaminophen on platelet aggregation. They demonstrated, that co-administration of aspirin with NSAIDs may interfere with platelet aggregation at the beginning of the treatment, with naproxen having an additional anti-aggregatory effect to that brought by a single dose of 100 mg aspirin and with diclofenac decreasing the antiagregatory effect of aspirin. The effect was lost after 4 days and the authors concluded that a regular daily administration of NSAID does not have an effect on platelet aggregation [3]. Capone *et al*.[4] investigated the pharmacodynamic interaction of naproxen with low dose aspirin in four healthy volunteers, who received aspirin (100mg per day) for six days and then the combination of aspirin and naproxen for further six days, aspirin two hours before naproxen (500 mg twice daily) . Following a washout period of 14 days, naproxen was given before aspirin for further six days. Ex vivo markers of platelet function were measured. Co-administration of naproxen did not significantly alter the antiplatelet action of aspirin.

On the contrary, in the study of Gladding *et al*.[5], ibuprofen, indomethacin, naproxen and tiaprofenic acid blocked the antiplatelet effect of aspirin. Gengo *et al*.[6] investigated the interaction of ibuprofen and low dose aspirin in healthy volunteers and the interaction of ibuprofen or naproxen with aspirin in a confirmatory study of 28 patients taking low dose aspirin for stroke prevention. The data of both studies suggested that ibuprofen prevented the irreversible inhibition of platelet aggregation produced by low dose aspirin. However, it seems that the type of interaction between aspirin and NSAIDs may differ among different NSAIDs. Thus, in vivo studies have failed to prove competitive interaction between aspirin and diclofenac in platelet aggregation, or suggest minimal effect of diclofenac on platelet aggregation, when administered concurrently with aspirin [7,8]. Observational studies have conflicting results. Retrospective studies suggest that ibuprofen counteracts the antiplatelet effect of aspirin [9,10]. However, the strength of evidence is limited, since data came from prescription databases.

[III] MECHANISM OF PHARMACODYNAMIC INTERACTION

The most predicted hematological adverse reaction of aspirin and NSAIDs is due to inhibition of cyclo-oxygenase I. COX-I catalyzes the transformation of membrane bound arachidonic acid to thromboxane A2, a platelet agonist with resultant reduced platelet adhesiveness and prolongation of bleeding time. According to crystallographic data, aspirin inhibits cyclo-oxygenase by irreversible acetylation of a serine residue in vicinity with the catalytic site of the enzyme, while NSAIDs bind to the same hydrophobic channel of COX I in the vicinity of aspirin [11,12].

Because the ability of aspirin to acetylate a critical serine residue at the apex of the COX channel is dependent on its initial binding to arginine-120, a common docking site for all NSAIDs, the stronger binding affinity of nonaspirin NSAIDs might preclude aspirin from permanently modifying platelet COX-1. Thus, theoretically in molecular level, a competitive interaction between aspirin and NSAIDs could be anticipated in case of prior administration of a NSAID. On the other hand, highly selective COX-2 inhibitors (coxibs) are less likely to interfere with the antiplatelet effect of aspirin than conventional NSAIDs because of their limited interaction with platelet COX-1.

However, in cellular and organism level, synergistic or even additive effect between aspirin that irreversibly blocks COXI activity and diclofenac that reversibly blocks COXI activity could be anticipated. First of all, low doses of aspirin are associated with high inhibition of COXI as demonstrated by almost total inhibition of serum thromboxane [13]. However, there is residual platelet reactivity in patients treated with aspirin, the antiplatelet action of aspirin seems to be dose-related, implying thus, that aspirin as an antiplatelet might affect other targets besides COXI [14]. For example, reactive oxygen species seem to play a significant role in the regulation

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of platelet activation [15]. Aspirin has been shown to modulate reactive oxygen species through its pro-oxidant or antioxidant actions [16]. Additionally, aspirin has been shown to enhance fibrinolysis and suppress plasma coagulation, although the clinical significance of these is not determined. There is limited evidence on how NSAIDs affect platelet aggregation in vivo when they are given together with aspirin according to a regular clinical schedule e.g. a morning dose of aspirin and repeated doses of NSAIDs during the day.

[IV] NSAIDS AND ANTIPLATELET ACTION

The antiplatelet action of NSAIDs is a matter of controversy. It has been demonstrated that NSAIDs have in vitro antiplatelet action. However, in *ex vivo* studies, there is extensive variability on the extent and duration of the effects of NSAIDs on platelet aggregation and on bleeding times. The antiplatelet effects of long acting NSAIDs like piroxicam persist for several days after the drug is stopped. Platelet aggregation is inhibited within 2 hours after a single dose of ibuprofen, but the effect is lost within 12 hours. High dosages of ibuprofen cause slight but significant prolongations of bleeding time for several hours while lower doses (e.g. 200 mg three times daily) may not affect the bleeding time. In general, most NSAIDs cause transient dose dependent prolongations of bleeding time, without exceeding the upper limit of normal range for bleeding time [17].

The clinical significance of the antiplatelet action of NSAIDs is not determined [18-20]. Clinical trials have suggested cardioprotective effect of naproxen, flurbiprofen and diclofenac due to antiplatelet action [21-24]. However, other papers imply that NSAIDs do not have an antiplatelet action, since: first, the relation between the inhibition of platelet cyclo-oxygenase I dependent thromboxane A2 generation and the inhibition of thromboxane dependent platelet function is non linear and second, NSAIDs inhibit platelet cyclo-oxygenase I, but the inhibition lasts for only a part of the dosing interval. It has been proposed that platelet COX-I has to be almost completely (>95%) and continuously inhibited ex vivo throughout the dosing intervals to translate to a detectable cardiovascular protection. However, an antiplatelet action has been proposed for naproxen. It has been suggested that naproxen inhibits platelet cyclo-oxygenase I for the whole duration of the dosing interval. Ex vivo studies have shown that naproxen at therapeutic doses of 500 mg twice daily gets into the functionally relevant range of inhibition of platelet COX I activity (>95%), at the end of the dosing interval in some subjects [25]. Additionally, NSAIDs might affect platelet function in a cyclo-oxygenase independent mechanism. A recent paper suggests antagonism of thromboxane receptors as a novel mechanism of action of diclofenac [26]. Therefore, it could be proposed that COXI independent mechanisms might contribute to the pharmacodynamic interaction between aspirin and diclofenac on hemostasis.

[V] CLINICAL SIGNIFICANCE OF NSAIDs-ASPIRIN INTERACTION

The possible interaction of aspirin and NSAIDs on antiplatelet action is clinically significant not only in cardioprotection but also in aspirin and NSAIDs induced haemorrhage. If co-administration of aspirin and NSAIDs enhances antiplatelet action of aspirin alone, increased frequency of gastrenteric and non gastrenteric hemorrhage is expected. Indeed, intracerebral hemorrhage is the most serious spontaneous hemorrhage caused by aspirin. It seems that patients prescribed non aspirin NSAIDs are not at an overall increased risk of being hospitalized for intracerebral hemorrhage. However, existing data are quite scarce, and there is no estimation about the risk in case of co-administration of aspirin and NSAIDs [27].

[VI] CONCLUSION

Existing data suggest an interaction between aspirin and NSAIDs on haemostasis. However, there is controversy regarding the direction of this interaction, i..e. synergism or antagonism. Since, co-administration of aspirin and NSAIDs is quite common in people with comorbidities, further research is needed to clarify the clinical significance of this interaction.

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