Dipyrone (Metamizole) Can Nullify the Antiplatelet Effect of Aspirin in Patients With Coronary Artery Disease

To the Editor: In this letter we report an adverse drug interaction between aspirin and dipyrone in patients with coronary artery disease (CAD).

Dipyrone (metamizole) is a widely used nonnarcotic analgesic. Its common usage is largely due to its favorable clinical effects in conjunction with a low incidence of gastrointestinal side effects compared with other nonsteroidal anti-inflammatory drugs (NSAIDs). In Europe, dipyrone daily doses have nearly doubled since 2005. Aspirin, a unique cost-effective antiplatelet drug, is the backbone of current clinical practice for secondary prevention of cardiovascular events and is indispensable after coronary stent implantation. Aspirin inhibits cyclooxygenase (COX)-1 by acetylation serine 530 near the active site of the enzyme, thus preventing subsequent thromboxane (TX) formation and TX-tylating serine 530 near the active site of the enzyme, thus implantation. Aspirin inhibits cyclooxygenase (COX)-1 by acetytylating serine 530 near the active site of the enzyme, thus preventing subsequent thromboxane (TX) formation and TX-dependent platelet aggregation for the remainder of the platelet’s life-span. This activity may be hampered by NSAIDs, which transiently bind to COX-1, thus interfering with the binding of aspirin to COX-1. Indeed, such interactions have been demonstrated recently in vitro (1). Increased cardiovascular morbidity and mortality has been reported in patients treated with NSAIDs (2). It is not known whether non-anti-inflammatory analgesics, such as dipyrone, have similar effects that might be harmful in patients with CAD. In this study, we demonstrated that a novel drug–drug interaction between aspirin and dipyrone occurs in cardiac patients on continuous low-dose aspirin treatment.

Three subgroups of patients with CAD treated with optimal medical therapy according to current guidelines were studied. Group A consisted of 10 patients with CAD in whom aspirin had been withdrawn because of scheduled cardiac surgery (black curve/bar; 74 ± 9 years of age). Group B comprised 20 patients with CAD taking aspirin (red curve/bar; 78 ± 10 years of age). Group C included 36 patients with a comedication of aspirin/dipyrone (blue curve/bar; 77 ± 10 years of age). Seventy-five percent of patients in groups B and C were on dual antiplatelet therapy with clopidogrel; none of the patients were on oral anticoagulants (Online Table 1). In these 66 patients with CAD, platelet function was measured by arachidonic acid (AA)–induced light transmission aggregometry and TX B2 formation by immunoassay. AA was used to stimulate platelet function because it is the only compound that allows specific determination of the antiplatelet effects of aspirin in terms of inhibition of platelet-dependent TX formation (3).

In platelets from patients with CAD not treated with aspirin (group A) AA induced formation of TX and thus effective platelet aggregation. TX formation was nearly completely inhibited in patients treated with aspirin (group B). Dipyrone comedication in patients with CAD treated with aspirin (group C) restored AA-induced TX formation to levels sufficient for complete restoration of platelet aggregation (Fig. 1). In group B, aspirin induced a sufficient inhibition of platelet aggregation in every single individual (20 of 20). In contrast, we observed an impaired aspirin effect in 50% (18 of 36) of dipyrone-comededicated patients with CAD (group C). This interaction of dipyrone with the antiplatelet effects of aspirin is most likely due to reversible binding of dipyrone to platelet COX-1, resulting in steric inhibition of aspirin access to the active site of COX-1. We have postulated, via ongoing studies by docking and enzyme kinetic analyses in our laboratory, that a hydrogen bond between dipyrone and serine 530 as well as steric blockade of other amino acids like tyrosine 355 and arginine 120...
are involved in prohibiting acetylation of serine 530 by aspirin. Consequently, aspirin fails to inhibit platelet COX-1, the pharmacological target of aspirin (4).

Dipyrone comedication in patients with CAD can completely blunt the antiplatelet effects of aspirin. This unfavorable pharmacological drug interaction might result in unexpected treatment failure and implies several consequences: 1) in future pharmacological and interventional trials aiming to modify platelet function, patients comedicated with dipyrone should be carefully monitored; 2) analgesic therapy in patients with CAD with chronic pain should be reevaluated with respect to the use of NSAIDs and dipyrone; 3) the prescription of dipyrone in patients on continuous treatment with aspirin undergoing surgery has to be questioned; and 4) in particular, the use of dipyrone to alleviate acute pain in the post-operative setting of patients who have undergone coronary artery bypass graft surgery should be reconsidered carefully.

This study investigated a pharmacological aspirin-dipyrone interaction in terms of TX formation and light transmission aggregometry. Point-of-care assays like the VerifyNow assay or the multiplate analyzer were not used. To establish the clinical impact of the reported aspirin-dipyrone interaction, randomized trials with clinical endpoints are needed. (NSAIDs in Coronary Artery Disease Patients; NCT01402804).

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Please note: The study conformed to the Declaration of Helsinki and was accepted by the University of Düsseldorf Ethics Committee. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES


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