Letter to the Editor

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Letter by Iannuccelli et al Regarding Article, “Paracetamol, Ibuprofen, and Recurrent Major Cardiovascular and Major Bleeding Events in 19120 Patients With Recent Ischemic Stroke”

To the Editor:

We read with a great interest the recent article published in Stroke by Gonzalez-Valcarcel et al1 on the association between paracetamol and ibuprofen use with major cardiovascular events or major bleeding in patients. The authors accomplished a huge task analyzing a cohort of 19,120 patients with recent ischemic stroke or transient ischemic attack of mainly atherothrombotic origin. They observed that patients who used paracetamol daily have a higher risk of major cardiovascular events; patients who used ibuprofen seems not to have a significant increase in the risk of major cardiovascular events, but the results become consistent when only patients randomized to aspirin, and not to terutroban, were taken into account. Overall, the strength of these associations for both paracetamol and ibuprofen was low, making possible that other undetected confounding factors explained these weak associations.

The reasons of those results are still unknown; we suggest considering the multidrug resistance protein-4 (MRP4) as a key player in those events.

Such an idea follows our demonstration that human megakaryocytes have an adaptive response to aspirin, leading to the upregulation of platelet MRP4. We demonstrated that aspirin induces platelets MRP4 overexpression through the activation of the nuclear receptor peroxisome proliferator-activated receptor α (PPARα) in megakaryocytes. Those events lead to a progressive reduction in platelet sensitivity to aspirin in long-term–treated patients. Aspirin effects are reduced in patients undergoing coronary artery bypass grafting because of platelet MRP4 overexpression because aspirin is an MRP4 substrate.2 A reduction of aspirin-dependent platelet inhibition over time was also previously evidenced by FitzGerald et al.3 Aspirin-treated healthy volunteers (either at high [1300 mg/die] or low [100 mg/die] concentrations) showed reduced platelet aggregation in the early weeks of treatment, whereas platelet aggregation returned to baseline after 7 to 8 weeks. Moreover, we recently described that both cyclooxygenase (COX)-1 and COX-2 inhibitors induced MRP4 overexpression after in vitro and in vivo treatment.4 Megakaryoblastic cell line (Dami cells) treated with celecoxib, diclofenac, and naproxen showed a significant increase in MRP4 expression compared with the mock culture. In patients with osteoarthritis (considered regular NSAIDs users) platelets presented a higher expression of MRP4 and an increase in platelet functionality compared with the control population.

Later, it has been demonstrated in MRP4-deficient mice that hemostasis and thrombosis were both defective with a prolonged bleeding time and delayed clot formation. The specific MRP4 platelet involvement in in vivo hemostasis was further confirmed using platelet-depleted wild-type mice transfused with MRP4-deficient platelets.5 Because platelets with MRP4 overexpression are hyperresponsive, we hypothesized that this mechanism could be also involved in the prothrombotic effect of NSAIDs. For this reason, we believe that the association of aspirin and COX-1 or COX-2 inhibitors has to be restricted to an occasionally and mandatory need for a short period.

Disclosures

None.

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