Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the conversion of arachidonic acid (AA) into cyclic endoperoxidases by the enzyme cyclooxygenase (COX). Two isoforms of COX are already known, one that is dichotomized in "mostly physiological" COX-1 and one in "mostly pathological" COX-2. The ideal situation would be to have their beneficial therapeutic properties (analgesic, anti-inflammatory and anti-pyretic) without their potential side-effects (renal and gastrointestinal toxicity and inhibition of blood clotting). Additionally, these drugs exert many other actions at the molecular level that are sometimes present with clinically recommended doses.¹

Studies comparing NSAIDs for their ability to inhibit both COX enzymes have been performed; a marked inhibition of COX-2 without any significant inhibition of COX-1 may characterize NSAIDs with an improved side-effect profile.

The withdrawal from the market of valdecoxib has raised concerns about other selective COX-2 inhibitors and non-selective COX-2 inhibitors.

The COX-2 induced by pro-inflammatory factors plays a role in prostaglandin E₂ (PGE₂) production while its constitutive form in the vasculature produces prostacyclin which inhibits platelet aggregation. Therefore, inhibition of COX-2 may predispose susceptible individuals to cardiovascular (CV) side effects with different levels of risk if the allelic variant forms of COX-1 and COX-2 are taken into account. The CYP2C29 enzyme plays a role in the in vitro metabolism of many NSAIDs and also has allelic variant forms (CYP2C29*1, CYP2C29*2, CYP2C29*3). Gastrointestinal bleeding is another side effect of NSAIDs; it has been hypothesized that there is a dose-gene effect in a gene-associated clearance reduction (CYP2C29 alleles). However, the impact of the CYP2C29 genotype on valdecoxib pharmacokinetics (PK) has not been reported.²

It is accepted that whole blood assay use thromboxane B₂ (TXB₂) production as an index of platelet COX-1 activity for endogenously formed thrombin and prostaglandin E₂ (PGE₂) production as an index of leukocyte COX-2 expression for bacterial endotoxins. Blain H et al. evaluated twenty-four healthy 21- to 25-year-old male volunteers performing analyses on whole blood submitting the material to several concentrations of NSAIDs (in vitro) to determine TXB₂ and PGE₂ levels.

The same volunteers were submitted to administration of non-selective COX-2 inhibitors and the blood (ex vivo) was evaluated as above. They found that the level of COX-1 and COX-2 inhibition achieved in vivo could not be predicted from corresponding in vitro dose-response curves.¹

Taking these facts into account, animal models of drug evaluation are very important to understand the effects of NSAIDs.

In this issue in "Evaluation of the changes on hemostatic parameters induced by valdecoxib in male wistar rats" Fronza M et al showed that administration of valdecoxib in male rats at different doses, including doses higher than therapeutically prescribed, caused alterations in the hemostatic parameters measured. Blood was collected after the 1st, 2nd, 3rd, and 4th weeks of continuous drug administration to measure drug levels, APTT (activated partial thromboplastin time), PT (prothrombin time) and platelet, fibrinogen, anti-factor Xa and anti-factor IIa activities. They found that valdecoxib produced changes in the blood coagulation parameters, specifically the APTT, PT and factor Xa activity. They also suggest that further investigation in this field is important to understand the side effects and safe use of valdecoxib.

References
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