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THE BIOCHEMICAL SELECTIVITY OF NOVEL COX-2 INHIBITORS IN HUMAN WHOLE BLOOD ASSAYS OF COX-ISOZYME ACTIVITY

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Background Selective cyclooxygenase (COX)-2 inhibitors (coxibs) have been designed with the aim of developing a new class of antiinflammatory and analgesic drugs with less side-effects than conventional nonsteroidal antiinflammatory drugs (NSAIDs), particularly COX-1-dependent gastrointestinal complications (1, 2). Two coxibs, celecoxib and rofecoxib, have been approved by FDA and EMEA for the treatment of rheumatoid arthritis and/or osteoarthritis (1). The development of novel COX-2 inhibitors with improved biochemical selectivity over that of commercially available coxibs, may have two distinct potential advantages. In principle, it should lead to a clear-cut separation of COX-2- from COX-1-dependent effects, by virtue of maximizing the likelihood of exposed patients being in the 80 to 100% range of COX-2 inhibition and in the 0 to 20% range of COX-1 inhibition throughout the dosing interval. Secondly, it could diminish the probability of the COX-2 inhibitor of interfering with permanent inactivation of platelet COX-1 by low-dose aspirin, in patients requiring antiinflammatory and antiplatelet therapy (3, 4). Screening and structure-activity relationship studies have been performed in order to identify a novel wave of selective COX-2 inhibitors, such as 4-[5-methyl-3-phenylisoxazol-4-yl]-benzensulphonamide (valdecoxib), 5-chloro-2-(6-methylpyridin-3-yl)-3-(4-methylsulphonylphenyl) pyridine (etoricoxib), 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl)phenyl-2(5H)-furanone (DFU) and 3-(2-propyloxy)-(4-methylsulphonylphenyl)-(5,5-dimethyl)-furanone (DFP) (5-8). Etoricoxib and valdecoxib, derivatives of rofecoxib and celecoxib, respectively, have been approved recently in some countries. On the other hand, DFU and DFP are primarily chemical prototypes for the development of highly selective COX-2 inhibitors.

Aims We have evaluated the biochemical selectivity of novel COX-2 inhibitors, etoricoxib, valdecoxib, DFU and DFP (5-8) *vs*. rofecoxib and celecoxib, using the human whole blood assays of COX-isozyme activity, *in vitro* (9, 10).

Methods Increasing concentrations of the test compounds were incubated with whole blood samples, allowed to clot for 1 h at 37°C and with heparinized whole blood samples in the presence of lipopolysaccharide (LPS 10 μg/ml) for 24 h at 37°C. Serum TXB_2 and plasma PGE_2 levels were measured by specific RIA, as indices of the cyclooxygenase activity of platelet COX-1 and LPS-induced monocyte COX-2, respectively (9, 10).

Results Using the whole blood assays, we have shown that the new compounds, etoricoxib, DFU and DFP have higher COX-1/COX-2 IC_{50} ratios (i.e. 344, 660 and 1918, respectively) than rofecoxib (COX-1/COX-2 IC_{50} ratio: 272). The analysis of the sigmoidal concentration-response curves for inhibition of COX-2 and COX-1 by rofecoxib, etoricoxib, DFU and DFP showed that virtually complete suppression (>90%) of monocyte COX-2 activity occurred at concentrations that did not affect platelet COX-1 activity, to any statistically significant extent. Valdecoxib resulted 60-fold more potent towards

monocyte COX-2 than platelet COX-1 and showed a COX-1/COX-2 IC_{50} ratio that was 2-fold higher than that of celecoxib (i.e. 30).
Conclusion A second wave of highly selective COX-2 inhibitors with higher biochemical selectivity than the existing coxibs has been developed. Whether their administration will be associated with a detectable improved clinical efficacy and/or safety vis-à-vis celecoxib and rofecoxib remains to be established.

References

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