EFFECTS OF ROFECOXIB AND DICLOFENAC ON PROSTAGLANDIN E_2 LEVELS IN LPS-STIMULATED MONOCYTES AND IN SYNOVIAL FLUID OF PATIENTS WITH RHEUMATOID ARTHRITIS

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Background. Rofecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has been approved for treatment pain and inflammation in osteoarthritis (OA) and rheumatoid arthritis (RA) (1). COX-1 sparing in gastrointestinal (GI) tract and platelets may have been involved in the statistically significant reduction in the rate of confirmed clinical GI events by rofecoxib as compared with naproxen in RA patients (2). The administration of single doses (up to 1,000 mg) of rofecoxib to healthy subjects shows no evidence of any detectable change in platelet COX-1 activity (3). However, no information are available on the biochemical COX-2 selectivity of therapeutic doses of rofecoxib administered chronically to RA patients.

Aims. We have compared the COX-1/COX-2 selectivity of rofecoxib (50 mg daily for 7 days) vs. diclofenac (50 mg tid), a conventional NSAID, in patients with RA, using the human whole blood assays of COX-isozyme activity (4, 5). The contribution of COX-isozyme activity to synovial fluid prostaglandin(PG) E_2 levels was evaluated by comparing the inhibitory effects of the two drugs. Finally, we studied the potential pharmacodynamic interaction between glucocorticoids and rofecoxib, usually co-administered in this setting, on the inhibition of COX-2 activity *in vitro*, *ex vivo* and *in vivo*.

Methods. Twenty-five patients (21 females and 4 males; aged 56.1±15.6 years) with RA were recruited in 4 different academic Rheumatology Centers (2 in the US and 2 in Italy) and the protocol of the study was approved by the respective Ethical Committees. On day 1, blood and synovial fluid samples were collected from the selected patients; then, patients were randomized to rofecoxib 50 mg/day (n=9), diclofenac 50 mg/tid (n=8), or placebo (n=8) for 7 days in a double-blind randomized fashion. PGE_2, in lipopolysaccharide(LPS)-stimulated (10 and 100 μg/ml, for 24 h at 37°C) heparinized whole blood samples and synovial fluid, and thromboxane(TX) B_2, in whole blood allowed to clot at 37°C for 60 min, were measured by radioimmunoassays.

Results. Rofecoxib and diclofenac, but not placebo, caused a similar suppression (~90%) of monocyte COX-2 activity *ex vivo*, at 10 and 100 μg/ml of LPS. Diclofenac (n=8), but not rofecoxib (n=9) or placebo (n=8), affected platelet COX-1 activity (56%, P=0.0305, *vs.* pre-drug values). Synovial fluid PGE_2 was decreased by 11 (P=0.8053), 70 (P=0.1071) and 78.9% (P=0.0315), in placebo, rofecoxib and diclofenac arms, respectively. Glucocorticoids did not affect the extent of inhibition of monocyte COX-2 activity by rofecoxib *in vitro*, *ex vivo* and *in vivo*.

Conclusions. Rofecoxib 50 mg is a specific COX-2 inhibitor in RA patients. This effect is largely independent on the level of COX-2 expression, as modulated by LPS or glucocorticoids. The higher interpatient variability in the reduction of synovial PGE_2 levels by rofecoxib than diclofenac may suggest the contribution of COX-1 activity and/or differences in the distribution between the two drugs.

References

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