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EFFECTS OF NAPROXEN AND LOW-DOSE ASPIRIN ON PLATELET COX-1 AND MONOCYTE COX-2 ACTIVITIES IN HUMANS

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Background. Epidemiological studies suggest that aspirin and non-aspirin nonsteroidal antiinflammatory drugs (NSAIDs) have differential effects in the reduction of the risk of cardiovascular thrombotic events in humans, presumably because non-aspirin NSAIDs cause incomplete and reversible inhibition of platelet cyclooxygenase-1 (COX-1) activity (1, 2). Recently it has been proposed that the non-aspirin NSAID naproxen, at conventional antiinflammatory doses, has a cardioprotective effect for its capacity to cause near complete inhibition of platelet function throughout dosing intervals (3).

Aims. The aims of this study were to evaluate the COX-1/COX-2 selectivity of naproxen using the human whole blood assays of COX-isozyme activity, *in vitro*; to compare the extent and the time-dependent recovery of steady-state inhibition of platelet COX-1 and monocyte COX-2 activities by low- dose aspirin and naproxen in healthy subjects.

Methods. Increasing concentrations of naproxen were incubated with whole blood samples allowed to clot for 1 hr at 37°C and with heparinized whole blood samples in the presence of lipopolysaccharide (LPS, 10 μg/ml) for 24 hr at 37°C; serum thromboxane B_2 (TXB_2) and plasma prostaglandin E_2 (PGE_2) levels were measured by specific radioimmunoassays (RIA), as indices of cyclooxygenase activity of platelet COX-1 and LPS-induced monocyte COX-2, respectively (4, 5).
Six healthy subjects received low-dose aspirin (100 mg/die) or naproxen 550 mg/b.i.d. for six consecutive days and whole blood samples were collected before dosing and at 1 or 3, 12 and 24 hr after the last administration of the two drugs for the assessment of serum TXB_2 and plasma PGE_2 levels as previously described.

Results. Naproxen inhibited LPS-monocyte COX-2 and thrombin-stimulated platelet COX-1 activities in a concentration-dependent fashion showing a COX-1/COX-2 IC_{50} ratio of 0.5.
One hr after dosing, aspirin caused an inhibition of platelet COX-1 activity of 99.2±0.5% (mean±SD) that remained stable at 12 and 24 hr (99.4±0.3 and 98.6±0.6%, respectively). Three hr after the last dose of naproxen (corresponding to the Cmax), platelet COX-1 activity was reduced by 98.23±0.38% and slowly recovered to pre-drug values. At 12 and 24 hr the inhibition of serum TXB2 was 90±1.3 ($P<0.01$ *vs.* 3 hr) and 77.5±2.4% ($P<0.01$ *vs.* 3 hr), respectively, that resulted less profound than that obtained at the same time points after aspirin ($P<0.01$, respectively). Monocyte COX-2 activity was not significantly affected by low-dose aspirin. In contrast, peak plasma concentration of naproxen caused a significant ($P<0.01$) reduction of inducible PGE_2 biosynthesis by 83.4±9.0% that slowly recovered to pre-drug values. At 12 and 24 hr after dosing, LPS-induced PGE_2 production was reduced by 70±18 and 58±23%, respectively.

Conclusions. A conventional dose of naproxen caused a more profound suppression of platelet COX-1 than monocyte COX-2 activity, *ex vivo*. At steady-state, naproxen and low-dose aspirin caused an almost complete suppression of platelet COX-1. However, aspirin, but not naproxen, caused >95% inhibition of platelet COX-1 activity throughout the dosing interval, that has been proposed to be a necessary requirement to produce clinically detectable cardiovascular protection via the suppression of TXA_2-dependent platelet activation (6). Only a head-to-head comparison of the two drugs in randomized clinical trials will clarify whether naproxen shares the same cardioprotective effects of aspirin.

References

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