HUMAN PHARMACOLOGY OF NAPROXEN SODIUM

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Background and Aims. The traditional nonsteroidal anti-inflammatory drug (NSAID) naproxen – with a balanced inhibitory effect on cyclooxygenase (COX)-1 and COX-2 and a long pharmacokinetic half-life (>12 h) – may confers a small cardiovascular benefit by its administration at high doses (i.e. 500 mg BID), continuously and regularly. This is plausible with the profound and sustained inhibition of platelet COX-1 *ex vivo*, detected in some, but not all, individuals. However, the prematurely terminated placebo-controlled trial Alzheimer's Disease Anti-Inflammatory Prevention Trial - for a signal of increased incidence of heart attacks and strokes - in healthy elderly patients taking naproxen sodium 220 mg BID led some to speculate that the modest cardioprotection detected with naproxen 500mg BID might be dissipated at lower doses. To address this issue we compared the variability in degree and recovery from steady-state inhibition of COX-1 and COX-2 *ex vivo* and *in vivo* and platelet aggregation by naproxen sodium 220 mg BID *versus* 440 mg BID and low-dose aspirin in healthy subjects.

Methods. Six healthy subjects received consecutively naproxen sodium 220 mg BID, 440 mg BID and aspirin (100 mg daily) for 6 days, separated by washout periods of two weeks. COX-1 and COX-2 inhibition was determined using *ex vivo* and *in vivo* indices of enzymatic activity. Arachidonic acid (AA)-induced platelet aggregation was also studied.

Results. The maximal inhibition of platelet COX-1 (95.9±5.1 and 99.2±0.4%) and AA-induced platelet aggregation (92±3.5 and 93.7±1.5%) obtained at 2 h after dosing with naproxen sodium 220 and 440 mg BID, respectively, was indistinguishable from aspirin but at 12 and 24 h after dosing, we detected marked variability which was higher with naproxen sodium 220 mg BID than 440 mg BID. Assessment of the ratio of inhibition of urinary 11-dehydro-TXB2 (mostly COX-1derived) *versus* 2,3-dinor-6-keto-PGF1α (mostly COX-2 derived) showed that the treatments caused a more profound inhibition of TXA2 than prostacyclin biosynthesis *in vivo* throughout dosing interval.

Conclusion. Neither of the 2 naproxen doses mimed the persistent and complete inhibition of platelet COX-1 activity obtained by aspirin but marked heterogeneity was mitigated by the higher dose of the drug. However, the coincident suppression of COX-isozymes detected both *ex vivo* and *in vivo* by naproxen sodium 220 mg BID throughout dosing interval seems implausible with a cardiovascular hazard.