Dose-Dependent Inhibition of Platelet Cyclooxygenase-1 and Monocyte Cyclooxygenase-2 by Meloxicam in Healthy Subjects\textsuperscript{1}

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ABSTRACT

We evaluated whether therapeutic blood levels of meloxicam are associated with selective inhibition of monocyte cyclooxygenase (COX)-2 in vitro and ex vivo. Concentration-response curves for the inhibition of monocyte COX-2 and platelet COX-1 were obtained in vitro after the incubation of meloxicam with whole blood samples. Moreover, 11 healthy volunteers received placebo or 7.5 or 15 mg/day meloxicam, each treatment for 7 consecutive days, according to a randomized, double-blind, crossover design. Before dosing and 24 h after the seventh dose of each regimen, heparinized whole blood samples were incubated with lipopolysaccharide (10 mg/ml) for 24 h at 37°C, and prostaglandin E\textsubscript{2} was measured in plasma as an index of monocyte COX-2 activity. The production of thromboxane B\textsubscript{2} in whole blood allowed to clot at 37°C for 60 min was assessed as an index of platelet COX-1 activity. The administration of placebo did not significantly affect plasma prostaglandin E\textsubscript{2} (21.3 ± 7.5 versus 19.1 ± 4 ng/ml, mean ± S.D., n = 11) or serum thromboxane B\textsubscript{2} (426 ± 167 versus 425 ± 150 ng/ml) levels. In contrast, the administration of 7.5 and 15 mg of meloxicam caused dose-dependent reductions in monocyte COX-2 activity by 51% and 70%, respectively, and in platelet COX-1 activity by 25% and 35%, respectively. Although the IC\textsubscript{50} value of meloxicam for inhibition of COX-1 was 10-fold higher than the IC\textsubscript{50} value of COX-2 in vitro, this biochemical selectivity was inadequate to clearly separate the effects of meloxicam on the two isozymes after oral dosing as a function of the daily dose and interindividual variation in steady-state plasma levels.

The adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the upper gastrointestinal tract of humans have been documented for nearly 50 years (Douthwaite and Lintott, 1938). The gastroduodenal complications range from dyspepsia to fatal upper gastrointestinal tract bleeding and perforation (Allison et al., 1992).

In 1971, Vane proposed that the inhibition of prostaglandin (PG) formation by NSAIDs is the basis for their therapeutic actions as well as for their side effects. This theory has gained general acceptance.

The key enzyme in the synthesis of prostanoids is prostaglandin endoperoxide synthase (PGHS), which is endowed with two distinct catalytic activities: a cyclooxygenase (COX) activity converts arachidonic acid (AA) to the endoperoxide PGG\textsubscript{2} and a peroxidase activity converts PGG\textsubscript{2} to PGH\textsubscript{2} (Smith et al., 1996). PGH\textsubscript{2} is further metabolized by specific synthases and isomerases to various prostanoids.

Except for aspirin that inhibits prostaglandin biosynthesis by irreversible blockade of the COX channel of PGHS, the other NSAIDs, such as ibuprofen and indomethacin, produce reversible or time-dependent irreversible COX inhibition by competing with the substrate, AA, for a common binding site (Smith et al., 1996). Recent epidemiological studies have shown that comparable therapeutic doses of NSAIDs are associated with a similar risk of serious gastrointestinal bleeding complications (Langman et al., 1994; Henry et al., 1996). The discovery of two isoforms of PGHS (reviewed by Smith et al., 1996), a constitutive PGHS-1 or COX-1 present in almost all cell types, and a form induced in a more restricted cell-specific fashion by mitogenic and inflammatory stimuli, PGHS-2 or COX-2, has led to the suggestion that the anti-inflammatory action of NSAIDs is due to inhibition of COX-2, whereas the toxic effects on the stomach and bleeding complications are due to inhibition of COX-1 (reviewed by Vane, 1994).

Because COX-1 and COX-2 are structurally distinct proteins with only 60% homology (Smith et al., 1996), the development of drugs that selectively inhibit the activity of COX-2 might lead to a new generation of anti-inflammatory drugs

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ABBREVIATIONS: PGHS, prostaglandin endoperoxide synthase; COX, cyclooxygenase; LPS, lipopolysaccharide; AA, arachidonic acid; PGE\textsubscript{2}, prostaglandin E\textsubscript{2}; TXB\textsubscript{2}, thromboxane B\textsubscript{2}; NSAID, nonsteroidal anti-inflammatory drug.
with improved gastrointestinal safety (Vane, 1994). A number of compounds have been described that selectively inhibit COX-2 versus COX-1; these include substances that were initially selected for development by drug companies based on an improved pharmacological profile in animal models and were later shown to preferentially inhibit COX-2, as well as newly designed specific COX-2 inhibitors. The former group of compounds includes meloxicam and nimesulide.

Meloxicam, a NSAID derived from enolic acid, has shown anti-inflammatory activity in a rat model of adjuvant arthritis at doses 20-fold lower than those causing ulcerogenic effects (Engelhardt et al., 1995). In vitro, meloxicam was 5 to 300-fold more potent in inhibiting COX-2 than COX-1 (Churchill et al., 1996; Engelhardt et al., 1996; Patrignani et al., 1997; Riendeau et al., 1997; Pairet et al., 1998). However, major limitations in expressing the degree of biochemical selectivity based on COX-1/COX-2 IC50 ratios obtained in vitro are related to variable results obtained with different assay methods, on the one hand, and to the lack of information on the actual extent of COX-1 inhibition achieved at therapeutic plasma levels of the inhibitor, on the other hand.

The induction of COX-2 in circulating monocytes in response to lipopolysaccharide (LPS) is a relatively simple model that is suitable for evaluating the extent of COX-2 inhibition both in vitro (Patrignani et al., 1994, 1997; Panara et al. 1995) and ex vivo after oral dosing of NSAIDs in humans (Patrignani et al., 1994; Cipollone et al., 1995; Panara et al., 1997). Thus, the aim of our study was to test the biochemical selectivity of meloxicam toward monocyte COX-2 versus platelet COX-1 in vitro as well as ex vivo after the oral administration of two therapeutic doses (7.5 and 15 mg/day for 7 days) versus placebo in healthy subjects.

Materials and Methods

In Vitro Study. The effects of meloxicam on platelet COX-1 and monocyte COX-2 activities of whole blood were assessed by incubating increasing concentrations of meloxicam with peripheral whole blood samples drawn from four healthy volunteers (two female and two male subjects; age range, 25–42 years).

Ex Vivo Study. Fourteen healthy volunteers who gave their informed consent were screened for the inclusion and exclusion criteria of the study. One volunteer was excluded due to abnormal laboratory values, and another volunteer dropped out because of an adverse event (the onset of influenza) that required antibiotic treatment. Twelve healthy volunteers (seven female and five male subjects; age range, 20–41 years) were included in the study. One subject completed the treatments but was excluded from the final evaluation of the results because naproxen was detected in his plasma samples and he subsequently admitted taking the nonstudy drug.

Placebo and 7.5 and 15 mg of meloxicam were administered over 6 weeks according to a randomized, double-blind, crossover design. Each treatment was administered for 7 days. After completion of each treatment period, there was a wash-out period of 7 days. Peripheral venous blood samples were drawn before starting the treatment and 24 h after the seventh dose of each regimen for the assessment of whole blood PGE2 and TXB2 production and the measurement of meloxicam plasma levels.

COX-2 Assay. Aliquots of peripheral blood samples (1 ml) containing 10 IU of sodium heparin were incubated in both the absence and the presence of LPS (10 μg/ml) for 24 h at 37°C as described in detail elsewhere (Patrignani et al., 1994). Plasma was separated by centrifugation (10 min at 3000 rpm) and kept at −80°C until assayed for PGE2.

COX-1 Assay. Peripheral blood samples were drawn from the same subjects, and 1-ml aliquots of whole blood were immediately transferred into glass tubes and allowed to clot at 37°C for 60 min. Serum was separated by centrifugation (10 min at 3000 rpm) and kept at −30°C until assayed for TXB2, as previously described (Patrignani et al., 1980; Patrignani et al., 1982).

Effects of Meloxicam on Monocyte COX-2 Activity and Platelet COX-1 Activity In Vitro. Meloxicam was dissolved in dimethyl sulfoxide (10–10,000 μg/ml), and 2-μl aliquots of the solutions were transferred directly by means of a pipette into test tubes to give final concentrations of 0.02 to 20 μg/ml. Heparinized 1-ml whole blood samples were drawn from healthy volunteers who received pretreatment with 300 mg of aspirin 48 h before sampling to suppress the activity of platelet COX-1. These samples were incubated at 37°C for 24 h with increasing concentrations of meloxicam in the presence of 10 μg/ml LPS, and PGE2 levels were assayed in plasma as an index of monocyte COX-2 activity. Meloxicam was also incubated with 1-ml whole blood samples (drawn from the same donors when they had not taken any NSAIDs during the 2 weeks before the study) that were allowed to clot for 1 h at 37°C, and serum TXB2 levels were measured as a reflection of platelet COX-1 activity.

Analyses of PGE2 and TXB2. PGE2 and TXB2 were measured by previously described and validated radioimmunoassays (Ciabattioni et al., 1979; Patrono et al., 1980; Patrignani et al., 1982). Unextracted plasma and serum samples were diluted in the standard diluent of the assay (0.02 M phosphate buffer, pH 7.4) and assayed in a volume of 1.5 ml at a final dilution of 1:50 to 1:20,000. The least detectable concentration was 1 to 2 pg/ml for both prostanoids.

Plasma Meloxicam Concentrations. Plasma concentrations of meloxicam were determined by HPLC as described previously (Turck et al., 1997).

Reagents. [3H]PGE2 and [3H]TXB2 (200–250 Ci/mmole) were from Du Pont de Nemours GmbH (Bad Homburg, Germany). Authentic PGE2 and TXB2 were from Cayman Chemical Co. (Ann Arbor, MI). Anti-PGE2 and anti-TXB2 sera were obtained in our laboratory, and their characteristics have been described previously (Ciabattioni et al., 1979; Patrono et al., 1980). Heparin, LPS derived from Escherichia coli 026:B6, acetylsalicylic acid, and dimethyl sulfoxide were purchased from Sigma Chemical Co. (St. Louis, MO).

Statistical Analysis. Statistical comparisons were made by ANOVA, and significant differences between treatments were determined by Student-Newman-Keuls test. Having excluded a carry-over effect (by comparing the inhibition of COX-1 and COX-2 activities and meloxicam plasma levels measured after a 1-week treatment with 7.5 mg of meloxicam given first with measurements obtained when 7.5 mg of meloxicam was given after the 15-mg dose or placebo), the data were combined regardless of the treatment sequence. The post-treatment measurements were compared with the baseline measurements and values of p < .05 were considered statistically significant. The sigmoidal dose-response curves were analyzed with ALLFIT, a basic computer program for simultaneous curve-fitting based on a four-parameter logistic equation (De Lean et al., 1978).

Results

We measured PGE2 production in heparinized whole blood samples, incubated with LPS for 24 h, as a reflection of the inducible COX activity of monocyte COX-2 (Patrignani et al., 1994). Plasma immunoreactive PGE2 averaged 21.3 ± 7.5 ng/ml (mean ± S.D., n = 11) in samples obtained before treatment. Moreover, we measured TXB2 production during whole blood clotting as a reflection of the constitutive COX activity of platelet COX-1 (Patrignani et al., 1980; Patrignani et al., 1982). Serum immunoreactive TXB2 averaged 426 ± 167 ng/ml (mean ± S.D., n = 11) at baseline. We also assessed the intrasubject variability of these indexes of COX-1 and COX-2 activity on three different occasions over a 14- to 42-day
period. The intrasubject coefficients of variation averaged 16 ± 9% and 23 ± 11% for repeated measurements of serum TXB₂ and plasma PGE₂₂, respectively.

Of the 12 healthy volunteers who entered a randomized, double-blind, three-period crossover trial of placebo and 7.5 and 15 mg/day meloxicam, 11 complied with the protocol for efficacy analysis. As shown in Fig. 1, the administration of placebo did not affect PGE₂ or TXB₂ production to any statistically significant extent (PGE₂₂, 19.1 ± 4 ng/ml; TXB₂, 425 ± 150 ng/ml). The administration of 7.5 and 15 mg/day meloxicam caused a statistically significant (p < .01) dose-dependent reduction in both monocyte COX-2 activity by 51% and 70%, respectively, and in platelet COX-1 activity by 25% and 35%, respectively. However, the inhibition of monocyte COX-2 activity was significantly (p = .025 and .002, respectively) higher than that of platelet COX-1 activity at both dose levels.

Plasma concentrations of meloxicam measured 24 h after the oral administration of 7.5 and 15 mg of meloxicam for 7 days averaged 0.69 ± 0.38 and 1.48 ± 0.84 μg/ml, respectively (mean ± S.D., n = 11, p < .01). To explore the meloxicam concentration-response relationship for inhibition of COX isozyme activity, plasma drug concentrations were corrected for the individual hematocrit values. As shown in Fig. 2, the relationship between meloxicam concentrations added in vitro and percentage inhibition of COX activities fitted sigmoidal dose-response curves. Using ALLFIT, we determined IC₅₀ values for monocyte COX-2 and platelet COX-1 inhibition in vitro of 0.17 ± 0.09 and 1.94 ± 0.58 μg/ml (mean ± S.E.M., n = 4), respectively, that were different from each other in a statistically significant fashion (p = .024). When individual drug levels and corresponding COX isozyme inhibition measured ex vivo are fitted onto these sigmoidal dose-response curves obtained in vitro, it becomes apparent that there is a substantial degree of overlapping of COX-2 and COX-1 inhibition within an approximately 10-fold range of steady-state trough meloxicam plasma levels. However, although individual ex vivo measurements of COX-2 inhibition tended to distribute fairly evenly on both sides of the COX-2 concentration-response curve obtained in vitro, measurements of COX-1 inhibition were unevenly distributed to the left of the COX-1 concentration-response curve. Four subjects, in the 7.5 mg meloxicam phase, and two of the same four subjects, in the 15 mg meloxicam phase of the study, failed to show any detectable inhibition of COX activities, despite drug plasma levels in the therapeutic range.

Discussion

A variety of methods have been developed to study the effects of NSAIDs on the COX activity of PGHS isozymes in vitro. Thus, inhibition of COX-1 and COX-2 has been evaluated in purified enzyme systems (Mitchell et al., 1993), microsomal membranes from cells transfected with the murine (Meade et al., 1993) or human isozymes (Laneuville et al., 1994), cultured cells selectively expressing COX-1 and COX-2 as well as in cultured intact cells, such as bovine aortic endothelial cells and endotoxin-activated macrophages (Mitchell et al., 1993). The affinity of many COX inhibitors
for COX-1 decreases in the presence of micromolar concentrations of exogenous arachidonate, whereas the affinity for COX-2 is unaffected by changes in substrate concentration (Swinney et al., 1997). This results in dramatic differences in COX-1/COX-2 selectivity of NSAIDs as a function of the arachidonate concentration employed. Therefore, measuring eicosanoid production in intact cells that selectively express COX-1 or COX-2 and utilizing arachidonate released from endogenous lipid stores is considered to be a more reliable screening method than measuring instantaneous inhibition of isozyme activity in a recombinant system utilizing exogenous substrate (Meade et al., 1993; Laneuville et al., 1994).

We described a relatively simple model of human COX-2 expression in LPS-stimulated whole blood (Patrignani et al., 1994). This method is suitable for evaluating the extent of COX-2 inhibition both in vitro and ex vivo, after oral dosing of NSAIDs in humans. We demonstrated that LPS dose-dependently stimulated blood cells to produce easily detectable amounts of PGE\textsubscript{2} in a time-dependent fashion that correlated with the accumulation of a protein doublet of approximately 72 kDa in monocytes but not in other blood cells (Patrignani et al., 1994). In contrast, the constitutive level of expression of COX-1 in unstimulated monocytes was not affected by the incubation with LPS up to 24 h (Patrignani et al., 1994). Dexamethasone, an inhibitor of COX-2 expression in monocytes/macrophages (O’Banion et al., 1992), as well as several highly selective COX-2 inhibitors, largely suppressed PGE\textsubscript{2} production in response to LPS (Patrignani et al., 1994, 1997; Panara et al., 1995). For the assessment of COX-1/COX-2 selectivity, this whole blood assay of COX-2 activity was integrated with a previously described whole blood assay for platelet COX activity (Patrignani et al., 1980; Patrignani et al., 1982). The latter has been extensively used for characterizing the time and dose dependence of platelet COX inhibition by aspirin in humans (Patrignani et al., 1982; Patrignani et al., 1985). This methodological approach has allowed the characterization of the biochemical selectivity of recently approved NSAIDs, including nabumetone (Patrignani et al., 1994; Cipollone et al., 1995) and nimesulide (Panara et al., 1998). Interestingly, the inhibitory effects of a large number of NSAIDs on human gastric PGE\textsubscript{2} synthesis correlated with COX-1 inhibitory potency in whole blood (Cryer and Feldman, 1998).

Meloxicam is a novel NSAID derived from enolic acid. The drug shows prolonged and almost complete absorption after oral dosing and is >99.5% bound to plasma proteins (Turck et al., 1996). Meloxicam is metabolized to four biologically inactive main metabolites, which are excreted in both urine and feces (Turck et al., 1996). The elimination half-life of meloxicam is approximately 20 h, and steady-state plasma concentrations are achieved within 3 to 5 days (Turck et al., 1996).

In rats, meloxicam inhibited the hind paw swelling to adjuvant injection with an ID\textsubscript{50} value that was approximately 20-fold lower than the ED\textsubscript{50} value for its ulcerogenic effect on the stomach (Engelhardt et al., 1995). In vitro, in different assays performed in the presence of exogenous arachidonate, meloxicam showed variable COX-1/COX-2 IC\textsubscript{50} ratios that ranged from 3, in guinea pig macrophages (Engelhardt et al., 1996), to 300, in Chinese hamster ovary cells stably transfected with human COX-1 and COX-2 (Rienteau et al., 1997).

In the present study, we set out to reassess the biochemical selectivity of meloxicam in vitro, to evaluate the dose dependence and selectivity of monocyte COX-2 inhibition associated with two commonly used therapeutic regimens of meloxicam, and to relate the extent of COX inhibition to steady-state plasma levels of the drug administered to healthy volunteers.

When evaluated in vitro, the IC\textsubscript{50} value for meloxicam for platelet COX-1 inhibition was 1 order of magnitude higher than the corresponding IC\textsubscript{50} value for monocyte COX-2. However, this modest degree of biochemical selectivity was inadequate to clearly separate the effects of meloxicam on the two isozymes after oral dosing in healthy subjects as a function of the daily dose and interindividual variation in steady-state trough levels of the drug (Fig. 2). There is no obvious explanation for the consistently higher level of inhibition of platelet COX-1 detected ex vivo than that predicted by the in vitro concentration-response relationship. Because we did not perform this type of assessment after single oral dosing, we cannot exclude some degree of cumulative inhibition of platelet COX-1 by meloxicam on repeated daily dosing. The present findings underscore the limitations of assessing the biochemical selectivity of COX-2 inhibitors based on COX-1/COX-2 IC\textsubscript{50} ratios obtained in vitro and emphasize the need to evaluate the actual extent of COX-1 inhibition achieved throughout the therapeutic range of plasma inhibitor concentrations after oral dosing in humans.

Thus, 24 h after the seventh daily administration of 7.5 and 15 mg of meloxicam, both platelet COX-1 and monocyte COX-2 activities were inhibited in a dose-dependent fashion. However, the inhibition of monocyte COX-2 activity was significantly higher than that of platelet COX-1 activity at both dose levels. Serum TXB\textsubscript{2} was only marginally, although significantly, reduced by the administration of 7.5 mg of meloxicam. This 25% reduction in COX-1 activity was slightly higher than the intraindividual coefficient of variation of this biochemical index based on repeated measurements of serum TXB\textsubscript{2} over a 2- to 6-week period. In contrast, Stichtenoth et al. (1997) reported that the administration of 7.5 mg of meloxicam to healthy subjects for 6 days did not significantly affect platelet aggregation and TXB\textsubscript{2} production in platelet-rich plasma in response to 1 mM AA. This discrepancy is likely due to a reduction in the affinity of meloxicam for the COX-1 active site in the presence of very high concentrations of exogenous AA. Moreover, it should be emphasized that assessment of platelet COX-1 and monocyte COX-2 inhibition at meloxicam trough levels will underestimate maximal inhibition of the enzymes at C\textsubscript{max} when plasma levels of the drug are approximately 2.4-fold higher.

Information about the gastrointestinal safety of meloxicam and other NSAIDs in clinical use has been obtained from a multinational meloxicam clinical trial program conducted in rheumatoid arthritis (RA), osteoarthritis (OA), and other rheumatic diseases (Distel et al., 1996; Dequeker et al., 1998; Hawkey et al., 1998). In double-blind studies in RA and OA, 7.5 and 15 mg of meloxicam caused significantly (p < .05) less gastrointestinal adverse events (serious and nonserious) than 20 mg of piroxicam, 100 mg of slow-release diclofenac and 750 to 1000 mg of naproxen. Although both 7.5 and 15 mg/day regimens of meloxicam showed a detectable advantage over other NSAIDs in their gastrointestinal safety profile, there was a trend toward a dose-effect relationship with
respect to gastrointestinal side effects (Distel et al., 1996) that needs to be confirmed in larger studies. It should be emphasized that none of the published studies had the statistical power to detect realistic differences in the risk of the most serious upper gastrointestinal bleeding complications between meloxicam and other NSAIDs, given the very low incidence of such complications.

Factors other than COX-1/COX-2 selectivity, such as the daily dose and pharmacokinetic profile, are likely to represent the major determinants of the occurrence of serious adverse events associated with the administration of NSAIDs with relatively narrow biochemical selectivity (COX-1/COX-2 ratios falling within a range of 0.5–20). Recent epidemiological observations are consistent with this hypothesis by reporting a very similar relative risk of serious gastrointestinal bleeding complications associated with nimesulide (COX-1/COX-2 IC₅₀ ratio = 18; Panara et al., 1998) as with conventional NSAIDs (Garcia Rodriguez et al., 1998).

We conclude that meloxicam is a more potent inhibitor of monocyte COX-2 than platelet COX-1 activity; however, the extent of COX-1 sparing is largely a function of the daily dose and interindividual variability in drug levels. Whether this modest degree of biochemical selectivity is responsible for an improved gastrointestinal safety profile remains to be determined in population-based observational studies with hospitalization due to upper gastrointestinal bleeding as the primary outcome measure.

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