ABSTRACT:

The market withdrawals of rofecoxib (Vioxx) and valdecoxib (Bextra) have focused considerable attention on the side effect profiles of cyclooxygenase (COX) inhibitors. As a result, attempts will be made to identify risk factors in the hope that physicians might be able to ensure patient safety. At first glance, CYP2C9 genotype might be considered a risk factor because many COX inhibitors are CYP2C9 substrates in vitro. This observation has led some to hypothesize that a reduction in clearance, in subjects expressing the CYP2C9*3/*3 genotype, will lead to increased exposure and a greater risk of cardiovascular or gastrointestinal side effects. For any drug, however, one has to consider all clearance pathways. Therefore, a number of COX inhibitors were surveyed and it was determined that CYP2C9 plays a relatively minor role in the overall clearance (≤20% of the dose) of sulindac, naproxen, ketoprofen, diclofenac, rofecoxib, and etoricoxib. CYP2C9 genotype would have no clinically meaningful impact on the pharmacokinetics of these drugs. In contrast, CYP2C9 genotype is expected to impact the clearance of ibuprofen, indomethacin, flurbiprofen, celecoxib, valdecoxib, lornoxicam, tenoxicam, meloxicam, and piroxicam. However, even when CYP2C9 is a major determinant of clearance, it is necessary to consider CYP2C8 genotype (e.g., ibuprofen) and, possibly, CYP3A4 activity (e.g., celecoxib, valdecoxib, and meloxicam) also.

Events surrounding the market withdrawal of rofecoxib (Vioxx), a potent and selective COX-2 inhibitor, have raised concerns about the safety of other COX-2 selective inhibitors such as etoricoxib (Arcoxia), celecoxib (Celebrex), lumiracoxib (Prexige), and valdecoxib (Bextra) (Mukherjee et al., 2002; Bing, 2003; Couzin, 2004; Davies and Jamali, 2004; Fitzgerald, 2004; Kim and Reiner, 2004; Ray et al., 2004; Scheen, 2004; Bannwarth, 2005; Berenbaum, 2005). Such concerns finally resulted in the withdrawal of valdecoxib about seven months after the withdrawal of rofecoxib (Lenzer, 2005; Young, 2005). Nonselective COX inhibitors (NSAIDs) like naproxen, diclofenac, and ibuprofen have also come under scrutiny from regulators, physicians, and patient safety advocacy groups (McGettigan and Henry, 2000; Meagher, 2003).

At the present time, it is thought that the CV and GI side effects of COX inhibitors are related to their mechanism of action. This involves the inhibition of COX, a hemoprotein that exists in two forms (COX-1 and COX-2). COX-1 is expressed constitutively in most tissues, whereas the expression of COX-2 can be induced by growth factors, cytokines, and vasoactive peptides such as endothelin. In response to cell damage, therefore, COX-2 is inducible by proinflammatory mediators and plays a role in the generation of prostaglandin E2, a major mediator of inflammatory response. On the other hand, the products of COX-1 are cytoprotective in GI epithelium, and selective inhibition of COX-2 is anticipated to reduce inflammation, and modulate pain, without the GI side effects characteristic of nonselective NSAIDs (e.g., peptic erosions, ulceration, and bleeding). As a result, it has become accepted that inhibition of COX-1 should be minimized, and the industry has focused on the design of potent and selective COX-2 inhibitors (Davies et al., 2000, 2003; Rienteau et al., 2001; Chavez...
and DeKorte, 2003; Meagher, 2003; Justice and Carruthers, 2005). However, it should be recognized that although COX-2 is inducible, its products are not always proinflammatory. Constitutive COX-2 in the vasculature generates mainly prostacyclin, which is a vasodilator and inhibitor of platelet aggregation. Therefore, inhibition of COX-2 may alter the balance of prothrombotic (versus antithrombotic) eicosanoids and predispose susceptible individuals to CV side effects (Mukherjee et al., 2002; Meagher, 2003; Davies and Jamali, 2004; Justice and Carruthers, 2005).

A complex picture is emerging and the clinical safety (both GI and CV) of COX inhibitors most likely depends on a fine balance of factors. These factors include COX-1 and COX-2 inhibitor potency, the IC50(COX) ratio (COX-2 versus COX-1), CYP/IC50(COX) ratios, PK, PD, PK-PD (dose response) for each COX form, tissue distribution of the inhibitor (relative to tissue distribution of each COX enzyme form), and therapeutic index (Riendeau et al., 2001; Meagher, 2003; Davies and Jamali, 2004; Lees et al., 2004; Justice and Carruthers, 2005). The situation is complicated further by the presence of allelic variant forms of COX-1 and COX-2, which may not only impact efficacy, but predispose individuals to different levels of risk (Halushka et al., 2003; Cipollone et al., 2004).

Factors governing systemic clearance (PK) have received particular attention. This is because the majority of marketed COX inhibitors are well absorbed, metabolized extensively, subject to relatively minimal first-pass extraction, and exhibit linear PK (\(|S|/K_m \leq 0.1\)). Consequently, exposure and \(C_v/IC50(COX)\) ratios will depend on systemic clearance. In turn, systemic clearance will be governed by alterations in CL\(_{int}\) in the liver (assuming that \(f_a\) approaches unity). CYP2C9 (CYP2C9*1) is considered important, because it has been known for some time that the enzyme plays a role in the metabolism of many NSAIDs in vitro and is thus considered a major determinant of CL\(_{int}\) (Zhao et al., 1992; Leemann et al., 1993; Miners and Birkett, 1998; Rodrigues and Rushmore, 2002). The catalytic efficiency (\(k_{cat}/K_m\) ratio) of the allelic variant forms of the enzyme (e.g., CYP2C9*2 and CYP2C9*3) is reduced because of a single amino acid substitution (Miners and Birkett, 1998; Takanashi et al., 2000; Tang et al., 2001; Rodrigues and Rushmore, 2002). Therefore, due to the high incidence of CYP2C9-related polymorphisms in some populations (e.g., the frequency of CYP2C9*1/*3 genotype is 12% in white subjects), one can hypothesize that the occurrence of side effects is increased in numerous subjects genotyped heterozygous, or homozygous, for the CYP2C9*2 or CYP2C9*3 alleles (Xie et al., 2002; Schwarz, 2003; Lee, 2004; Kircheiner and Brockmoller, 2005; Rettie and Jones, 2005). However, the picture is not so simple and the data so far are not clear.

For example, Wynne et al. (1998) hypothesized that PK might explain the risk of major GI hemorrhage with NSAIDs, with bleeders exhibiting a reduced clearance of NSAIDs compared with nonbleeders. A number of patients \((n = 50)\) hospitalized with GI bleeds while taking piroxicam, indomethacin, diclofenac, or naproxen, were evaluated. There were no significant differences in peak plasma concentration, time-to-peak plasma concentration, or AUC\(_p\), between bleeders and controls for any of the NSAIDs studied. The authors concluded that their results failed to support the hypothesis. In a separate study, Martin et al. (2001) evaluated the effect of CYP2C9 genotype on the incidence of gastric ulceration in a relatively small number of subjects \((n = 23)\) receiving indomethacin, diclofenac, naproxen, ibuprofen, piroxicam, or sulindac. Although some of the subjects were genotyped CYP2C9*1/*2 (17%) and CYP2C9*1/*3 (13%), the incidence of ulceration was not associated with genotype.

More recently, Martinez et al. (2004) were able to assess CYP2C9-genotyped subjects receiving NSAIDs that underwent “extensive” CYP2C9-dependent metabolism (e.g., celecoxib, diclofenac, ibuprofen, indomethacin, lornoxicam, piroxicam, or naproxen) and other drugs that were not considered CYP2C9 substrates (e.g., salicylates and acetaminophen). The authors conclude that the association of variant CYP2C9 alleles and the risk of acute GI bleeding shows a gene-dose effect, and that it is higher in patients receiving drugs that are metabolized mainly by CYP2C9 (odds ratio of 2.6 when compared with nonbleeding subjects). It is concluded also that CYP2C9 genotyping may identify a subgroup of individuals who are at a potentially increased risk of acute GI bleeding. Interestingly, the observed risk was related largely to the CYP2C9*2 allele, which is unexpected because decreases in the \(k_{cat}/K_m\) ratio in vitro are more pronounced with recombinant CYP2C9*3 (Rodrigues and Rushmore, 2002). Therefore, the authors hypothesized that the association of CYP2C9*2 with NSAID-related GI bleeding risk may be related to a combined effect of mutations on CYP2C8 (CYP2C8*3 allele) and CYP2C9 (CYP2C9*2 allele), and the work of Yasar et al. (2002) was cited. This raises an interesting possibility that for substrates metabolized by both CYP2C8 and CYP2C9, an impaired clearance in vivo previously attributed to the CYP2C9*2 variant could in part be related to CYP2C8*3. But how many COX inhibitors are metabolized by CYP2C9 and CYP2C8 (Totah and Rettie, 2005)?

The results of Wynne et al. (1998), Martin et al. (2001), and Martinez et al. (2004) focused on the GI side effects associated with COX inhibitors. In all three cases, however, no effort was made to evaluate CYP2C9 genotype in relation to changes in PK and COX inhibition. More importantly, existing P450 reaction phenotype and clinical ADM data for the drugs in each study were not considered.

**Kinetic Considerations**

Before considering the role of CYP2C9, it is important to note that many pathways may contribute to the overall clearance of a drug. For example, an absorbed drug may be cleared unchanged via hepatic (biliary) and renal routes. As a result, not all of the dose is eliminated, and therapeutic index may identify a subgroup of individuals who are at a potentially increased risk of acute GI bleeding. Interestingly, the observed risk was related largely to the CYP2C9*2 allele, which is unexpected because decreases in the \(k_{cat}/K_m\) ratio in vitro are more pronounced with recombinant CYP2C9*3 (Rodrigues and Rushmore, 2002). Therefore, the authors hypothesized that the association of CYP2C9*2 with NSAID-related GI bleeding risk may be related to a combined effect of mutations on CYP2C8 (CYP2C8*3 allele) and CYP2C9 (CYP2C9*2 allele), and the work of Yasar et al. (2002) was cited. This raises an interesting possibility that for substrates metabolized by both CYP2C8 and CYP2C9, an impaired clearance in vivo previously attributed to the CYP2C9*2 variant could in part be related to CYP2C8*3. But how many COX inhibitors are metabolized by CYP2C9 and CYP2C8 (Totah and Rettie, 2005)?

For the sake of discussion, the theoretical relationship (eq. 1) between the product \(f_m/f_{m,CYP}\) and the AUC\(_{p}\) difference in PM (AUC\(_{p,PM}\)) versus EM (AUC\(_{p,EM}\)) subjects is shown below (Rodrigues and Rushmore, 2002). A similar relationship is commonly used to evaluate the effect of an inhibitor on the AUC of a substrate. In this instance, however, one is comparing the AUC ratio across subjects of different phenotypes, or genotypes, and it is assumed that the dose, the fraction of the dose absorbed, and the unbound fraction in blood is the same in both EM and PM subjects. In addition, it is assumed that gut first pass is negligible, that drug elimination depends entirely on hepatic metabolism, and that the elimination process is first order (\(|S|/K_m \leq 0.1\)), and that no autoinduction occurs (not relevant following a single dose). One has to accept also that hepatic extraction is blood flow-limited (e.g., well stirred model). It is worth noting that recombinant CYP2C9*1 and CYP2C9*3 have been shown to exhibit nonhyperbolic (non-Michaelis-Menten) single \(K_m\) kinetics with substrates such as naproxen (e.g., biphasic) and piroxicam (e.g., substrate inhibition) (Tracy et al., 2002). The impact of such nonhyperbolic kinetics in vivo is not known. However, if
product formation (parent elimination) is first order, then concerns about kinetic behavior at higher substrate concentrations (≥K_m) are minimized.

\[
\frac{AUC_{po(PM)}}{AUC_{po(EM)}} = \frac{1}{\left(\frac{f_m \cdot f_{m,CYP2C9(EM)}}{CL_{int,CYP2C9(EM)}/CL_{int,CYP2C9(PM)}} + [1 - (f_m \cdot f_{m,CYP2C9(EM)})]\right)}
\]

Estimates of \(f_{m,CYP2C9(EM)}\) are based on in vitro P450 reaction phenotyping data, which encompasses inhibition studies with CYP2C9-selective inhibitors like sulfaphenazole or anti-CYP2C9 antibodies. Kinetic studies can be conducted also with human liver microsomes (genotyped tissue) and recombinant P450 proteins (Rodrigues and Rushmore, 2002). At the same time, one can attempt to use clinical ADME data (e.g., fraction of dose recovered in excreta as oxidative metabolites) to generate estimates of \(f_m\). Again one assumes that the drug is eliminated by the liver only and that non-P450 enzymes, such as FMO and AO, have been ruled out in vitro (Rodrigues and Rushmore, 2002).

EM phenotype (\(AUC_{pot,EM}\) and \(CL_{int,CYP2C9(EM)}\)) is assumed to be associated with CYP2C9*1/*1 genotype. On the other hand, subjects genotyped homozygous (CYP2C9*2/*2 or CYP2C9*3/*3) or heterozygous (CYP2C9*1/*2 or CYP2C9*1/*3) for the variant alleles are considered PMs. Overall, the magnitude of the decrease in \(CL_{int}\) will be governed by the net effect of variant gene dose, CYP2C9 concentration in the liver (\(E\)), and the effect of the point mutation on \(k_{cat}\) and \(K_m\) (\(CL_{int} = \frac{V_{max}}{K_m} = \frac{k_{cat}}{K_m}\)). For some drugs, heterozygotes (CYP2C9*1/*2 or CYP2C9*1/*3) and homozygous wild-type (CYP2C9*1/*1) subjects will be phenotypically indistinguishable (\(CL_{int,CYP2C9(EM)}/CL_{int,CYP2C9(PM)} \sim 1\)). In this instance, it is only with CYP2C9*3/*3 subjects that one observes higher \(CL_{int,CYP2C9(EM)}/CL_{int,CYP2C9(PM)}\) ratios (>1).

In reality, therefore, not all COX inhibitors are the same. CYP2C9 may play a relatively minor role in the overall clearance of one drug (\(f_m \cdot f_{m,CYP2C9(EM)} \leq 0.2\)) and a markedly decreased \(CL_{int}\) in PM (CYP2C9*2/*2 or CYP2C9*3/*3) subjects (\(CL_{int,CYP2C9(EM)}/CL_{int,CYP2C9(PM)} \sim 10\)) will lead to relatively modest \(AUC_{pot,PM}/AUC_{pot,EM}\) ratios (≤1.2) (Rodrigues and Rushmore, 2002). In contrast, CYP2C9 may play a significant role in the overall clearance of a second drug (\(f_m \cdot f_{m,CYP2C9(EM)} > 0.5\)) and the lower \(CL_{int}\) in PM (CYP2C9*2/*2 or CYP2C9*3/*3) subjects results in larger \(AUC_{pot,PM}/AUC_{pot,EM}\) ratios (>2.0).

**Nonselective COX Inhibitors**

Sulindac. Sulindac, a racemic sulfoxide, is pharmacologically inactive and undergoes both reduction to the active sulfoxide form and oxidation to the inactive sulfone. Once formed, the sulfoxide undergoes extensive oxidation back to parent (Hucker et al., 1973; Gibson et al., 1987; Hamman et al., 2000). Formation of the sulfide is catalyzed by AO and is not involved in human liver and kidney microsomes (Hamman et al., 2000). Although catalyzed by recombinant human FMOs, the enzymes responsible for (S)-sulfoxide formation in tissue microsomes have not been identified (Hamman et al., 2000). However, P450 form-selective inhibitors like sulfinphazene (CYP2C9-selective) have a minimal impact on (R)- and (S)-sulfoxide formation in human liver microsomes (Hamman et al., 2000). Therefore, existing data indicate that COX inhibition will be governed by exposure to the sulfide form and the balance of pathways leading to its formation and clearance. CYP2C9 plays a minimal role in both pathways (Table 1).

**Naproxen.** Like ketoprofen, a large fraction of a naproxen dose (60%) is recovered as the products of direct glucuronidation (Vree et al., 1993a,b). The desmethyl metabolite, formed by P450, more or less accounts for an additional 20% of the dose recovered in urine. Even if the desmethyl metabolite accounted for all of the dose recovered in bile (~20%), the contribution of P450-dependent oxidation to the overall clearance of naproxen would not exceed 40% of the dose (\(f_m \leq 0.4\)). Moreover, in vitro reaction phenotyping data indicate that naproxen O-demethylation is only partially catalyzed by CYP2C9 (≤50%) in human liver microsomes (\(f_m,CYP2C9(EM) < 1\)). Other P450s such as CYP2C8 and CYP1A2 are involved also (Miners et al., 1996; Rodrigues et al., 1996; Tracy et al., 1997). Therefore, CYP2C9 plays a relatively minor role in the overall clearance of naproxen also (\(f_m \cdot f_{m,CYP2C9(EM)} \leq 0.2\)) (Table 1).

**Diclofenac.** For naproxen, ketoprofen, and sulindac, there are no reports describing the effect of CYP2C9 genotype on PK and inhibition of COX activity. The same cannot be said for diclofenac, which was also included in the studies described by Martin et al. (2001) and Martinez et al. (2004). In fact, a number of laboratories have reported that the PK of diclofenac is not related to CYP2C9 genotype, despite extensive (\(f_m,CYP2C9(EM) \sim 0.8\)) CYP2C9-dependent 4′-hydroxylation in human liver microsomes (Rodrigues and Rushmore, 2002; Brenner et al., 2003; Kirchheiner et al., 2003a). Therefore, one can conclude that CYP2C9 plays a minor role in the overall clearance of diclofenac (\(f_m \cdot f_{m,CYP2C9(EM)} \leq 0.2\)) (Table 1). Kirchheiner et al. (2003a) showed also that CYP2C9 genotype has a minimal impact on the inhibition of COX-1 and COX-2 activity in subjects receiving diclofenac. Therefore, a number of groups have questioned the utility of diclofenac as a phenotyping agent (Rodrigues and Rushmore, 2002).

Although human ADME data with genotyped subjects are lacking, Kumar et al. (2002) have estimated that the direct glucuronidation of diclofenac to the acyl glucuronide is a more important component to clearance (~75%) than 4′-hydroxylation (\(f_m \sim 0.25\)). Their findings may explain why CYP2C9 genotype has a relatively minimal impact on the PK of diclofenac. In addition, the same authors reported that the acyl glucuronide is itself a substrate for CYP2C8, which then forms the 4′-hydroxy acyl glucuronide. If corroborated, CYP2C8 may greatly impact the in vivo estimate of \(CL_{int}\) for 4′-hydroxy diclofenac. This estimate is based on the urinary recovery of total 4′-hydroxy diclofenac (conjugated and unconjugated) and is supposedly reflective of CYP2C9 phenotype. Ultimately, the impact of CYP2C8 on the disposition of diclofenac and its metabolites will require clinical studies with suitably genotyped subjects.

**Indomethacin.** In the presence of human liver microsomes, indomethacin O-demethylation is monophasic (single \(K_m\)) and is catalyzed largely by CYP2C9 (\(f_m,CYP2C9(EM) \sim 0.9\)) (Nakajima et al., 1998). However, like naproxen, indomethacin can undergo direct glucuronidation, and human ADME data indicate that 22% of the dose is recovered as the acyl glucuronide (Duggan et al., 1972). An additional 11% and 13% of the dose is recovered as unchanged parent drug and
Metabolism of various COX inhibitors by CYP2C9

The various factors governing the contribution of CYP2C9 to the overall clearance of each COX inhibitor are considered: \( f_{\text{m}} \) fraction of total hepatic elimination due to all cytochromes P450; \( f_{\text{m(CYP2C9)}} \), fraction of total cytochrome P450 metabolism catalyzed by CYP2C9 in EM (wild type, CYP2C9*1/*1) subjects; \( f_{\text{m}} \times f_{\text{m(CYP2C9)}} \), product of \( f_{\text{m}} \) and \( f_{\text{m(CYP2C9)}} \). Values for each parameter are obtained from the references cited in the text. The effect of fluconazole and CYP2C9 genotype on the PK (AUC\(_{\text{PM}}\)) of some of the COX inhibitors has been reported (references cited in the text).

### Table 1

<table>
<thead>
<tr>
<th>COX Inhibitor</th>
<th>( f_{\text{m}} )</th>
<th>( f_{\text{m(CYP2C9)}} )</th>
<th>( f_{\text{m}} \times f_{\text{m(CYP2C9)}} )</th>
<th>Effect of CYP2C9 Genotype on PK</th>
<th>Effect of Fluconazole on AUC(_{\text{PM}}) (Fold Increase)</th>
<th>AUC(<em>{\text{PM}})/AUC(</em>{\text{EM}})^2</th>
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<tbody>
<tr>
<td>Sulindac</td>
<td>0.01</td>
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<td>Naproxen</td>
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<td>0.0002</td>
<td>-</td>
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<tr>
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<td>0.8</td>
<td>0.0024</td>
<td>Minimal effect</td>
<td>&lt;1.2</td>
<td>1.2</td>
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<td>0.9</td>
<td>0.0045</td>
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<td>-</td>
<td>1.8</td>
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<td>(S)-Ibuprofen</td>
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<tr>
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</tr>
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</table>

### Flurbiprofen

Data obtained with human liver microsomes and recombinant P450s have shown clearly that the 4'-hydroxylation of flurbiprofen is also monophasic and catalyzed almost exclusively (\( f_{\text{m(CYP2C9)}} > 0.9 \)) by CYP2C9 (Tracy et al., 1995, 1996; Yamazaki et al., 1998). The metabolism and disposition of flurbiprofen is also monophasic and catalyzed almost exclusively by CYP2C9 (Leemann et al., 1993). This has been supported to some extent by the findings of Hamman et al. (1997), who were able to conclude that both enzymes catalyze the oxidative metabolism of racemic ibuprofen is completely converted to 4'-hydroxy flurbiprofen, and the further (sequential) metabolism of 4'-hydroxy flurbiprofen to 3',4'-dihydroxy flurbiprofen and 3'-hydroxy, 4'-methoxy flurbiprofen.

### Ibuprofen

The metabolism of racemic ibuprofen is quite complex (Rudy et al., 1991; Davies, 1998). Both (S)-(−)-ibuprofen and (R)-(−)-ibuprofen are metabolized via acyl glucuronidation, 2-hydroxylation, and 3-hydroxylation (methyl hydroxylation). Once formed, 3-hydroxy ibuprofen is metabolized further to the corresponding carboxy derivative via cytosolic dehydrogenases (Hamman et al., 1997). (R)-(−)-Ibuprofen undergoes unidirectional chiral inversion, which is significant because pharmacological activity following a racemic dose is attributed largely to the (S)-(−)-enantiomer (Davies, 1998; Hao et al., 2005).

When inoculated with NADPH-fortified human liver microsomes, the oxidative metabolism of racemic ibuprofen is inhibited significantly by sulfaphenazole (87%), which suggests a major role for CYP2C9 (Leemann et al., 1993). This has been supported to some degree by the findings of Hamman et al. (1997), who were able to study the metabolism of both enantiomers. For example, the 2- and 3-hydroxylation of the (S)-(−)-enantiomer was inhibited (~70%) by sulfaphenazole in human liver microsomes (\( f_{\text{m(CYP2C9)}} \sim 0.7 \)). The reaction phenotype data for the (R)-(−)-enantiomer were less clear, because the \( k_{\text{cat}}/K_{m} \) ratios (2-hydroxylation) for recombinant CYP2C9 and CYP2C8 were similar. These data have led various groups to conclude that both enzymes catalyze the oxidative metabolism of CYP2C9*1/*1 subjects) is expected. To date, this has not been confirmed clinically, and only pharmacokinetic data with heterozygotes (CYP2C9*1/*2 and CYP2C9*1/*3) have been reported (Lee et al., 2003). In this instance, a statistically significant increase in AUC\(_{\text{PM}}\) was observed only with CYP2C9*1/*3 subjects (mean AUC\(_{\text{PM}}\)/AUC\(_{\text{EM}}\) = 1.7). Assuming a gene-dose effect, AUC\(_{\text{PM}}\)/AUC\(_{\text{EM}}\) ratios of more than 1.7 are possible in CYP2C9*3/*3 subjects. The impact of CYP2C9 genotype on COX-1 and COX-2 inhibition has not been reported. |
ibuprofen (Hamman et al., 1997; Garcia-Martin et al., 2004; Hao et al., 2005; Martinez et al., 2005). It is worth noting, however, that CYP2C8-selective chemical inhibitors and immunoinhibitory antibodies were not available when Hamman et al. (1997) conducted their study. Therefore, it is not possible to obtain estimates of f\textsubscript{\text{m,CYP2C9(EM)}} \text{ for the (R)-(-)-enantiomer. In reality, more detailed in vitro reaction phenotype data are needed with CYP2C9- and CYP2C8-selective reagents, recombiant proteins (CYP2C9 and CYP2C8 variants), and a larger number of individual genotyped (CYP2C9 and CYP2C8) human livers. This is important because the ratio of CYP2C9 to CYP2C8 can vary considerably (1.4 to >300) in different livers (Lasker et al., 1998; Lapple et al., 2003).

Human ADME data indicate that the (S)-(+) -enantiomer undergoes no detectable chiral inversion and is cleared via glucuronidation (14% of the dose), 2-hydroxylation (28% of the dose), and carboxy metabolite formation (45% of the dose) (Rudy et al., 1991; Davies, 1998). As a result, f\textsubscript{\text{m}} is high (~0.7) and CYP2C9 genotype is expected to impact the PK of (S)-(+) -ibuprofen (f\textsubscript{\text{m,CYP2C9(EM)}} \sim 0.5; AUC\text{pot(PM)}/AUC\text{pot(EM)} ratio of 1.8 for CYP2C9*3/*3 versus CYP2C9*1/*1 subjects) (Table 1). In agreement, Kircheiner et al. (2002) have shown that the AUC of (S)-(+) -ibuprofen is increased as much as 7.7-fold in subjects genotyped CYP2C9*3/*3 (CYP2C8*1/*1) versus CYP2C8*2/*2 (CYP2C8*3/*3). These results suggest that CYP2C8-dependent metabolism of (S)-(+) -ibuprofen in vitro may be underestimated and that the fraction of (S)-(+) -ibuprofen clearance via CYP2C8 and CYP2C9 is considerable (>0.8). Such large increases in (S)-(+) -ibuprofen AUC will likely have a major impact on PK-PD following a racemic dose of ibuprofen in a chronic setting.

It has been estimated that as much as 60% of the (R)-(--) -ibuprofen dose undergoes chiral inversion to the (S)-(+) -enantiomer (Davies, 1998). A further 9%, 10%, and 20% of the dose is recovered as the acyl glucuronide, 2-hydroxy, and carboxy metabolites of (R)-(--) -ibuprofen, respectively (Rudy et al., 1991; Davies, 1998). Therefore, it is estimated that f\textsubscript{\text{m}} is low (~0.3) for the (R)-(--) -enantiomer (AUC\text{pot(PM)}/AUC\text{pot(EM)} ratio of ~1.4 predicted for CYP2C9*3/*3 versus CYP2C9*1/*1 subjects). In agreement, Kircheiner et al. (2002) showed that the CYP2C9*3/*3 genotype had a relatively minimal impact on the PK of (R)-(--) -ibuprofen. In contrast, Garcia-Martin et al. (2004) have reported that the AUC of (R)-(--) -ibuprofen is increased 2.7-fold in CYP2C9*3/*3 (CYP2C8*1/*1) subjects. The difference in the results cannot be explained. In addition, both Martinez et al. (2005) and Garcia-Martin et al. (2004) have reported that CYP2C8 genotype does impact the PK of (R)-(--) -ibuprofen. For example, (R)-(--) -ibuprofen AUC is increased 1.8-fold in CYP2C9*3/*3 subjects genotyped CYP2C9*1/*2 or CYP2C9*2/*2 (Martinez et al., 2005). Larger (~8.0-fold) increases in (R)-(--) -ibuprofen AUC are observed in the CYP2C9*3/*3 (CYP2C8*1/*3) and CYP2C9*2/*2 (CYP2C8*3/*3) subjects described by Garcia-Martin et al. (2004). If the results of the latter study are corroborated, this means that the contribution of CYP2C8 and CYP2C9 to the overall elimination of (R)-(--) -ibuprofen is underestimated also and contradicts estimates of the fraction of the dose (~30%) cleared via P450 (Davies, 1998). The (R)-(--) -enantiomer is far less pharmacologically active and the impact of such large increases in AUC is not known. Overall, it appears that additional clinical data are needed with larger numbers of genotyped subjects.

**Meloxicam.** When meloxicam is incubated with human liver microsomes, 5-hydroxymethyl meloxicam is the major metabolite formed. This metabolite can be oxidized further to 5'-carboxy meloxicam in the presence of hepatocytes or the appropriate subcellular fractions. In human liver microsomes, formation of 5-hydroxymethyl meloxicam is biphasic, and the low K\text{m} (~15 \mu M) component is attributed largely to CYP2C9 (Chesne et al., 1998). By comparison, CYP3A4 is a high K\text{m} (~400 \mu M). At a low concentration of meloxicam (10 \mu M), methyl hydroxylation is inhibited by sulfinpyrazone (80%) and ketoconazole (20%), which indicates that both P450s are involved (f\textsubscript{\text{m,CYP2C9(EM)}} \sim 0.8). Depending on the meloxicam concentration used, and the ratio of CYP3A4 to CYP2C9 ratio in human liver microsomes, the contribution of CYP3A4 can be as high as 40% (f\textsubscript{\text{m,CYP2C9(EM)}} \sim 0.6).

In agreement with in vitro data, the pathway giving rise to 5'-carboxy meloxicam has been identified as major and accounts for about 70% (f\textsubscript{\text{m}} ~0.7) of the radiolabeled dose (Schmid et al., 1995). An additional 10% and ~6% of the dose is recovered as parent and ring-opened metabolite, respectively. Therefore, f\textsubscript{\text{m,CYP2C9(EM)}} is estimated to be 0.4 to 0.6 and AUC\text{pot(PM)}/AUC\text{pot(EM)} ratios of 1.6 to 2.2 (CYP2C9*3/*3 versus CYP2C9*1/*1 subjects) are anticipated (Table 1). To date, there are no reports describing the effect of CYP2C9 genotype on the PK of meloxicam.

**Lornoxicam.** Bonnabry et al. (1996) and Lida et al. (2004) have shown that the 5'-hydroxylation of lornoxicam is catalyzed by CYP2C9 in human liver microsomes (f\textsubscript{\text{m,CYP2C9(EM)}} > 0.9). Inhibition in the presence of sulfinpyrazone (~95%) is very consistent with the effect of CYP2C9*3/*3 genotype on the V\text{m,EM}/K\text{m,EM} ratio (97% decrease). In healthy male volunteers, recovery of radioactivity following a single dose of [14C]lornoxicam is good (93%) (Hitzenberger et al., 1990; Skjodt and Davies, 1998). Analysis of the urine (~40% of the dose) reveals that 5'-hydroxy lornoxicam is a major metabolite (f\textsubscript{\text{m}} ~0.4). This is considered an underestimate because there are no reports describing radiochromatographic analysis of the feces (~50% of the dose), and it is possible that additional P450 metabolites are present therein. Based on the available data, f\textsubscript{\text{m,CYP2C9(EM)}} is estimated to be 0.4 and an AUC\text{pot(PM)}/AUC\text{pot(EM)} ratio of ~1.6 (CYP2C9*3/*3 versus CYP2C9*1/*1) subjects is anticipated (Table 1). Recently, it was reported that the AUC\textsubscript{\text{m}} of lornoxicam is increased 1.9-fold in heterozygous (CYP2C9*1/*3 or CYP2C9*1/*2) subjects (Zhang et al., 2005). No CYP2C9*3/*3 subjects were included in the same study. However, it is reasonable to expect that AUC\text{pot} will be greater in CYP2C9*3/*3 subjects.

**Tenoxicam.** Tenoxicam is metabolized extensively (~95%) and about two-thirds of the dose is recovered in the urine. The remainder of the dose is eliminated via the bile (Dell et al., 1984; Gonzalez and Todd, 1987; Nilsen, 1994). 5'-Hydroxy tenoxicam (~40% of the dose) and 6-oxo tenoxicam (~30% of the dose) are considered major metabolites (Nilsen, 1994). Unfortunately, it is not known whether the 6-oxo metabolite is formed by P450, and so, estimates of f\textsubscript{\text{m}} (~0.4) based on 5'-hydroxy tenoxicam alone are considered tentative. In vitro data show clearly that the 5'-hydroxylation of tenoxicam is catalyzed by CYP2C9 (f\textsubscript{\text{m,CYP2C9(EM)}} ~0.8) and that catalytic efficiency is reduced in the presence of recombinant CYP2C9*3 (Zhao et al., 1992; Takamashi et al., 2000). Based on existing reaction phenotype and human ADME data, f\textsubscript{\text{m,CYP2C9(EM)}} is tentatively estimated to be ~0.3 and an AUC\text{pot(PM)}/AUC\text{pot(EM)} ratio ~1.4 (CYP2C9*3/*3 versus CYP2C9*1/*1 subjects) is anticipated (Table 1). If 6-oxo tenoxicam formation is catalyzed by CYP2C9 also, or if
the levels of 5'-hydroxy tenoxicam in excreta are underestimated, then AUC_{po,PM}/AUC_{po,EM} ratios of $>1.4$ are expected. This is possible because a 1.8-fold increase in AUC_{po} has been reported for CYP2C9*1/*3 subjects (Vianna-Jorge et al., 2004). Additional studies are needed to evaluate tenoxicam PK in CYP2C9*3/*3 (versus CYP2C9*1/*1) subjects. In addition, in vitro reaction phenotyping data for 6-oxy tenoxicam are needed. Interestingly, Vianna-Jorge et al. (2004) were able to demonstrate a statistically significant increase in tenoxicam AUC_{po} (1.4-fold) in CYP2C9*1/*2 subjects. To date, however, $k_{cat}/K_m$ ratios for recombinant CYP2C9*2 (versus CYP2C9*1) have not been reported.

**Piroxicam.** Like tenoxicam, piroxicam is metabolized extensively and only a minor fraction of the dose ($\leq 10\%$) is recovered unchanged (Brogdan et al., 1984; Richardson et al., 1987; Woolf and Radulovic, 1989; Ollkola et al., 1994). Although various metabolites have been identified in human excreta, 5'-hydroxy piroxicam is the major metabolite and accounts for about 60% of the dose ($f_{m,0}\approx 0.6$) (Richardson et al., 1987). When incubated with human liver microsomes, 5'-hydroxylation of piroxicam is inhibited by sulfaphenazole ($\approx 90\%$), and so CYP2C9 plays a major role in the reaction ($f_{m,CYP2C9(EM)}\approx 0.9$) (Leemann et al., 1993). In addition, the $k_{cat}/K_m$ ratio describing 5'-hydroxy piroxicam formation is decreased greatly ($>90\%$) in the presence of recombinant CYP2C9*3 (Tracy et al., 2002). Therefore, $f_{m,0}\cdot f_{m,CYP2C9(EM)}$ is estimated to be $0.54$ and an AUC_{po,PM}/AUC_{po,EM} ratio $=1.8$ (CYP2C9*1/*3 versus CYP2C9*1/*1 subjects) is anticipated (Table 1). In agreement, piroxicam AUC_{po} is increased 1.6- and 3.7-fold in CYP2C9*1/*3 and CYP2C9*3/*3 subjects, respectively. These changes in AUC_{po} are accompanied by an increase in COX-1 inhibition (56% and 90%, respectively). Like tenoxicam, increases in AUC_{po} (1.6-fold) are observed also with CYP2C9*1/*2 subjects (J. Perini, Instituto Nacional de Cancer, Universidade Federal do Rio de Janeiro, Brazil, unpublished). At the time of writing, no reports were available describing the $k_{cat}/K_m$ ratio for recombinant CYP2C9*2.

**COX-2-Selective Inhibitors (COX-2/COX-1 IC_{50} Ratio $\approx 0.1$).**

**Rofecoxib.** In vitro data obtained with different subcellular fractions indicate that metabolism of rofecoxib is complex and involves oxidation (5-hydroxylation), hydration, and reduction (Slaughter et al., 2003). The latter two reactions require cytoxin, and only the formation of 5-hydroxy rofecoxib in human liver microsomes is catalyzed by P450s (CYP3A4, $\approx 60\%$; CYP1A2, $\approx 30\%$). CYP2C9 plays a very minor role ($f_{m,CYP2C9(EM)} < 0.2$) in the formation of 5-hydroxy rofecoxib. Following the oral administration of [14C]rofecoxib, however, 5-hydroxy rofecoxib (Davies et al., 2003). Consequently, P450-dependent metabolism (5-hydroxy rofecoxib $\approx 4'$-hydroxy rofecoxib and rofecoxib-3',4'-dihydrodiol) cannot account for more than 50% of the dose ($f_{m,0}\approx 0.5$) and CYP2C9 plays a very minor role in the overall clearance of rofecoxib ($f_{m,0}\cdot f_{m,CYP2C9(EM)} \approx 0.1$) (Table 1).

**Etoricoxib.** In comparison to rofecoxib, the metabolic profile of etoricoxib is less complex and involves only P450-dependent 6'-methyl hydroxylation and 1'-N-oxidation as primary clearance pathways (Kassahun et al., 2001; Rodrigues et al., 2003). The 6'-methylhydroxy metabolite is major in human liver microsomes and is oxidized further to 6'-carboxy etoricoxib in the presence of cofactor-activated human liver cytoxin. Formation of 6'-hydroxymethyl etoricoxib is catalyzed by CYP3A4 ($\approx 60\%$), with CYP2C9 ($f_{m,CYP2C9(EM)} < 0.2$), CYP2D6, CYP1A2, and CYP2C19 each contributing about 10% (Kassahun et al., 2001). 6'-Carboxy etoricoxib has been identified as the major metabolite following the administration of oral and i.v. [14C]etoricoxib, and it can be estimated that about 75% of the dose ($f_{m,0}\approx 0.8$) is cleared via P450-dependent 6'-methyl hydroxylation (Kassahun et al., 2001; Rodrigues et al., 2003). As in the case of rofecoxib, therefore, CYP2C9 plays a relatively minor role in the overall clearance of etoricoxib ($f_{m,0}\cdot f_{m,CYP2C9(EM)} \approx 0.2$) (Table 1).

**Valdecoxib.** Following a single 50-mg oral dose of [14C]valdecoxib, only a small fraction ($\approx 4\%$) is recovered unchanged (Yuan et al., 2002). About 20% of the recovered dose represents the N-glucuronide of parent compound. The products of N-hydroxylation, methyl hydroxylation and benzyl hydroxylation, and their various (secondary) metabolites, account for the remainder of the dose ($\approx 75\%$). For valdecoxib, therefore, $f_{m,0}$ is estimated to be $\approx 0.7$. Although P450 reaction phenotyping data for valdecoxib remain unpublished, it has been reported that both CYP2C9 and CYP3A4 metabolize the drug in vitro (Chavez and DeKorte, 2003). In agreement, fluconazole and ketoconazole increase the AUC_{po} of valdecoxib 62% and 38%, respectively (Chavez and DeKorte, 2003). Such a result with fluconazole, a known CYP2C9 inhibitor, implies that CYP2C9 genotype would impact the PK of valdecoxib, although the clinical significance of such an increase in exposure is not known. Prior to withdrawal, the drug was marketed at the 10- and 20-mg dose level, and studies showed good tolerability at 40 mg. Thus, it appears that AUC_{po} increases of less than 2-fold do not require dose adjustment (Chavez and DeKorte, 2003). To date, the impact of CYP2C9 genotype on valdecoxib PK has not been reported.

**Celecoxib.** There are numerous reports describing the metabolism of celecoxib in vitro. Data indicate that methyl hydroxylation is a major pathway in human liver microsomes, and that this reaction is catalyzed largely (70% to 90%) by CYP2C9 ($f_{m,0,CYP2C9(EM)} \approx 0.7$), with CYP3A4 playing less of a role ($\approx 25\%$) (Tang et al., 2000; Sandberg et al., 2002). The results of additional studies show that the contribution of CYP2C9 (versus CYP3A4) in a bank of human liver microsomes is greatly dependent on the CYP3A4-to-CYP2C9 content ratio (Tang et al., 2001). The contribution of CYP2C9 is greater ($f_{m,0,CYP2C9(EM)} \approx 0.8$) in livers where CYP3A4 levels are lower. When the CYP3A4-to-CYP2C9 content ratio is high ($\approx 8.0$), the contribution of CYP3A4 increases to 40% ($f_{m,0,CYP3A4(EM)} \approx 0.6$).

There are two reports describing the metabolism of celecoxib after incubation with human liver microsomes of genotyped subjects and preparations of recombinant CYP2C9 (Tang et al., 2001; Sandberg et al., 2002). In both cases, it was shown that the reduction in catalytic efficiency was greater for recombinant CYP2C9*3 ($\approx 70\%$) than for CYP2C9*2 ($\approx 35\%$). The report of Sandberg et al. (2002) included livers from a larger set of organ donors, and it was demonstrated that the rate of celecoxib hydroxylation was decreased ($\approx 50\%$) in livers genotyped CYP2C9*1/*3 (versus CYP2C9*1/*1). In contrast, celecoxib hydroxylation was impacted minimally in livers genotyped CYP2C9*1/*2. The same study also included one liver genotyped CYP2C9*3/*3 ($\approx 80\%$ decrease in activity) and four livers genotyped CYP2C9*2/*2 ($\approx 36\%$ decrease in activity).

Once formed, methyl hydroxy celecoxib is oxidized further to the corresponding carboxylic acid metabolite via cytosolic alcohol dehydrogenase. Therefore, the metabolic profile of celecoxib is relatively simple (Sandberg et al., 2002). This is borne out in human subjects receiving a single oral dose of [14C]celecoxib, where the overall recovery of the dose is good ($\approx 95\%$) (Paulson et al., 2000). In such subjects, up to 86% of the dose is recovered as methyl hydroxy celecoxib and carboxy celecoxib ($f_{m,0} \approx 0.9$). CYP2C9, therefore, is predicted to play a major role in the overall clearance of celecoxib.
At the time of writing, three reports described the PK of celecoxib in adult (CYP2C9-genotyped) subjects. Two reported PK for a single dose of celecoxib (Tang et al., 2001; Kirchheiner et al., 2003b), whereas the third described steady-state pharmacokinetic parameters following twice daily doses of celecoxib (200 mg) for 15 days (Brenner et al., 2003). It is clear from all three reports that CYP2C9*1/*2 genotype has a minimal impact on celecoxib PK. In agreement with Brenner et al. (2003), Kirchheiner et al. (2003b) showed that the AUC<sub>oo</sub> of celecoxib in CYP2C9*2/*2 subjects is not statistically different from those of individuals genotyped CYP2C9*1/*1. In all three studies, the AUC<sub>oo</sub> in CYP2C9*1/*3 subjects was ~2.0-fold higher (versus CYP2C9*1/*1) subjects. However, it is important to note that such an increased AUC<sub>oo</sub> was observed in only two of the four CYP2C9*1/*3 subjects included in the study conducted by Brenner et al. (2003). Interestingly, one CYP2C9*3/*3 individual was included in the same study and no difference in AUC<sub>oo</sub> (versus CYP2C9*1/*1) was observed. This does not agree with the observations of Tang et al. (2001) and Kirchheiner et al. (2003b), who reported a 2.2-fold (n = 1 subject) and 3.3-fold (n = 3 subjects) higher AUC<sub>oo</sub> in their respective CYP2C9*3/*3 subjects. The results of Brenner et al. (2003) are also difficult to reconcile in light of the fact that the AUC<sub>oo</sub> of single-dose celecoxib is increased (~2.3-fold) following fluconazole (Davies et al., 2000). More recently, Stempak et al. (2005) reported that the AUC<sub>oo</sub> of a single celecoxib dose (250 mg/m<sup>2</sup> dose, equivalent to 400 mg) was ~10-fold higher in a pediatric patient genotyped CYP2C9*3/*3 (versus two CYP2C9*1/*1 patients). A similar result was obtained at steady state following a b.i.d. regimen at the same dose level.

Although ketocnazole has no effect on the AUC<sub>oo</sub> of celecoxib (Davies et al., 2000), it is possible that higher CYP3A4 activity may have compensated and negated the impact of CYP2C9*3/*3 genotype in some of the individuals reported by Brenner et al. (2003). Alternatively, it is possible that, upon multiple dosing (e.g., 200 mg b.i.d.), celecoxib might behave as an inducer of CYP3A4 and CYP2C9 in CYP2C9*3/*3 subjects (maximal plasma concentrations of total celecoxib at steady state are projected to be close to 15 µM in these subjects). At least in vitro, celecoxib (15–15 µM) has been shown to transactivate the human pregnancy X receptor and induce CYP3A4 expression in immortalized human hepatocytes (Fa2N-4 cells) (Michael Sinz, Bristol-Myers Squibb, personal communication). Therefore, induction of CYP3A4 in the gut and liver during celecoxib first pass is a possibility.

Additional studies are needed, and it will be necessary to evaluate the effect of CYP2C9 genotype and CYP3A4 activity on celecoxib PK, and COX inhibition, following multiple doses of the drug. This is important because dose adjustment has been recommended for subjects receiving fluconazole and other CYP2C9 inhibitors (http://www.fda.gov/medwatch/preview/fulltext/2005/200998s017blb.pdf). Unfortunately, in the absence of widespread CYP2C9 genotyping, it will not be possible to adjust the dose of celecoxib prospectively.

Lumiracoxib. It has been reported that lumiracoxib is “extensively” metabolized by CYP2C9 in vitro, although the P450 reaction phenotype has not been published (Mangold et al., 2004). Despite metabolism by CYP2C9 in vitro, fluconazole has a relatively minimal effect on the PK of lumiracoxib (~1.2-fold increase in AUC<sub>oo</sub>/EM) and additional “compensatory” metabolic pathways have been proposed. However, such pathways are not apparent (Mangold et al., 2004; Scott et al., 2004). For example, only a minor fraction of a [14C]lumiracoxib dose (<10%) is recovered unchanged, or in the form of lumiracoxib acyl glucuronide. In fact, the majority of the dose (CYP2C9*1/*1 subjects) is recovered as the products of oxidation on the 5-methyl group and dihaloaromatic ring (Mangold et al., 2004). Despite the minimal effect of fluconazole, the impact of CYP2C9 genotype on lumiracoxib PK needs to be determined.

Conclusions

Because most COX inhibitors (NSAIDs) are metabolized by CYP2C9 in vitro, CYP2C9 genotype may be considered by some to be a clinically relevant risk factor. The variant forms of CYP2C9 (e.g., CYP2C9*3) are less catalytically efficient, and one could hypothesize that systemic exposure, and the risk of side effects, is elevated in subjects expressing one or more variant alleles. In addition, variant allele frequency is high in white populations (~15%), and some may advocate the widespread genotyping of patients receiving COX inhibitors. Regrettably, the reports of Wynne et al. (1998), Martin et al. (2001), and Martinez et al. (2004), and the present discussion illustrate the complexity of the situation. It is estimated that CYP2C9 genotype is irrelevant for nearly half of the 16 COX inhibitors surveyed. This includes at least two of the COX-2-selective inhibitors described (rofecoxib and etoricoxib), three of the six drugs reported by Martin et al. (2001), and two of the seven “extensive” CYP2C9 substrates reported by Martinez et al. (2004). When it comes to CYP2C9 genotype, and its impact on PK, it is clear that not all COX inhibitors are the same.

Even when CYP2C9 involvement is major, one has to critically evaluate each COX inhibitor on an individual basis and take into account the available data related to all clearance mechanisms (e.g., renal clearance, direct conjugation, non-P450 oxidation, and metabolism by other P450s). This is important for currently marketed COX inhibitors such as ibuprofen and celecoxib, where additional P450 forms have been implicated in clearance and literature reports appear contradictory (Kirchheiner et al., 2002, 2003b; Brenner et al., 2003; García-Martin et al., 2004). Other considerations, such as the size of the clinical dataset and the dosing regimen, are important also. Most of the clinical examples cited herein describe studies with limited numbers of genotyped subjects receiving a single dose of drug. Therefore, additional studies using larger numbers of genotyped (COX, CYP2C9, and CYP2C8) and phenotyped (CYP2C9, CYP2C8, and CYP3A4) patients on chronic therapy are warranted. It is only with long-term study of such patients that one can assess critically the impact of CYP2C9 genotype on PK, PD, and the side effect profile.

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