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Immunological response as a source to variability in drug metabolism and transport

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Through the last decades it has become increasingly evident that disease-states involving cytokines affect the pharmacokinetics of drugs through regulation of expression and activity of drug metabolizing enzymes, and more recently also drug transporters. The clinical implication is however difficult to predict, since these effects are dependent on the degree of inflammation and may be changed when the diseases are treated. This article will give an overview of the present understanding of the effects of cytokines on cytochrome P450 enzymes and drug transporters, and highlight the importance of considering these issues in regard to increasing use of the relatively new class of drugs, namely therapeutic proteins.

Keywords: cytokines, cytochrome P450 enzymes, P-glycoprotein, therapeutic proteins

INTRODUCTION

Differences in drug response among individuals are a great challenge in order to optimize drug dosage regimen for a patient. The reason for this variability is multifactorial and include genetic, environmental, and disease related factors, which may affect both pharmacodynamics and pharmacokinetics. Understanding the factors contributing to inter-individual variability in drug response is of crucial importance both in the development of new drugs and in optimization of the use of drugs already on the market.

Factors contributing to determining the pharmacokinetic profile of a drug include drug metabolizing enzymes and drug transporting proteins. The most important drug metabolizing enzymes are the phase I enzymes belonging to the cytochrome P450 (CYP) enzyme family which metabolize many structurally different xenobiotics (drug, chemicals), as well as endobiotics (steroids, fatty acids, prostaglandins; Gonzalez, 1990). There are several CYP subfamilies, of which CYP1, CYP2, and CYP3 are mainly involved in drug metabolism, and in humans 50% of the overall elimination of commonly used drugs is performed by these subfamilies (Wilkinson, 2005). Liver, the principal organ of drug elimination, is the organ with the highest abundance of CYP enzymes, while the small intestinal mucosa has been described to be the most important extra hepatic site of biotransformation (Lin and Lu, 2001). Inter-individual variability in the expression and activity of CYP enzymes is recognized as significant contributor to variation in drug response. CYP3A4 is the most prominent CYP enzyme, mainly because it is highly expressed in organs involved in drug disposition, such as liver, gastrointestinal tract, and kidney (Shimada et al., 1994; Paine et al., 2006) and because of the broad substrate specificity. The expression of this isoenzyme displays a 30- to 60-fold variability in human liver and intestine biopsies (Thummel et al., 1994; Paine et al., 1997). The reason for inter-individual variability in the expression and activity of CYP enzymes is multifactorial, but may to some degree be explained by genetic, environmental, and disease related factors.

The most studied drug transporter is the transmembrane efflux transporter P-glycoprotein (P-gp), a human ABC-transporter encoded by the *ABCB1* gene (Higgins, 1992). P-gp was discovered in 1976 (Juliano and Ling, 1976) as an important multi-drug resistance (MDR) mechanism in cancer treatment. It is expressed and distributed in the luminal surface membrane of the enterocytes in the small intestine, renal proximal tubular cells, the bile canalicular membrane of hepatocytes, the capillary endothelial cells in the blood–brain barrier (BBB) and in different cell types involved in the immune response (Thiebaut et al., 1987; Sugawara et al., 1988; Cordon-Cardo et al., 1989; Klimecki et al., 1994). Based on its localization, the function of P-gp is suspected to be protection of the cells against various toxicants, among these therapeutically active drugs. As P-gp is abundant in the intestinal epithelium, one important function is to restrict oral bioavailability of drugs, and since the substrate specificity of P-gp is to a great deal overlapping with that of CYP3A4, the general view is that P-gp and CYP3A4 work together in restricting the intestinal bioavailability of drugs (Benet and Cummins, 2001).

Through the last decade, there has been an increasing awareness on drug transporters other than P-gp and their role in bioavailability, elimination, and tissue distribution of drugs. These include other ABC transporters such as multidrug-resistance associated proteins (MRPs), the SLC transporters [e.g., organic anion transporting polypeptides (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs)]. Similar to drug metabolizing enzymes, there is also a considerable variability in the expression and activity of drug transporters. This variability is only to a minor extent explained by genetic polymorphism and other causes, such as environmental influence (e.g., drug interactions) and disease-state also play a role.

Immunological response and the release of cytokines is part of the pathophysiology of various diseases like autoimmune diseases, infections, brain injuries, and cancer. It has been known for several decades that cytokines regulate the expression and activity of drug metabolizing enzymes and thus, may affect the pharmacokinetics of drugs. More recently it has become evident that this applies to drug transporters as well. This article will give an overview of the present understanding of the effects of cytokines on CYP enzymes and transporters involved in drug pharmacokinetics, and also point out the importance of considering these issues in regard to the increasing use of the relatively new class of drugs, namely therapeutic proteins and their involvement in drug–drug interactions.

IMMUNOLOGICAL RESPONSE AND CYP METABOLISM

Several clinical studies have reported alterations in drug pharmacokinetics in patients with inflammations, infectious diseases, and cancer as well as in critically ill patients (Aitken et al., 2006; Morgan et al., 2008; Morgan, 2009). Already in 1978 acute virus infections in asthmatic children were shown to significantly increase the terminal half-life of theophylline (Chang et al., 1978). Also during an influenza B out break asthmatic children developed a sudden decrease in theophylline clearance and were hospitalized with toxicity problems (Kraemer et al., 1982). Already in 1976 it was shown that agents causing inflammation and infection depressed hepatic CYP enzymes in rats (Renton and Mannering, 1976a,b) and thus, the decreased theophylline clearance could be explained by a down-regulation of the CYP enzyme responsible for the metabolism of theophylline (CYP1A2). Several viruses, e.g., Herpes simplex, adenovirus, and HIV, have since then been identified to depress CYP metabolism and reduce drug clearance (Anolik et al., 1982; Forsyth et al., 1982; Lee et al., 1993). Also acute hepatitis virus A infection has been shown to decrease the excretion of 7-hydroxycoumarin in children and adults, indicating a depressed CYP2A6 activity during virus infection (Pasanen et al., 1997). CYP2D6 and CYP3A4 activities have been reported to be significantly lower in patients with chronic hepatitis C compared to in healthy volunteers (Becquemont et al., 2002). Interestingly, HIV patients genotyped as CYP2D6 extensive metabolizers (EM) expressed a shift toward a poor metabolizer (PM) CYP2D6 phenotype which correlated with disease activity (O'Neil et al., 2000). Also bacterial infections cause impaired drug clearance in humans. Administration of low doses of bacterial lipopolysaccharide (LPS) to healthy volunteers has been reported to cause reduced clearance of theophylline, antipyrine, and hexobarbitone (Shedlofsky et al., 1994, 1997). In rats CYP-mediated drug metabolism is suppressed during polymicrobial sepsis, particularly in the late phase (Lee and Lee, 2005).

Several studies have reported decreased theophylline and aminopyrine clearance following influenza virus and bacillus Calmette–Guerin (BCG) vaccination in healthy volunteers (Renton et al., 1980; Kramer and McClain, 1981; Gray et al., 1983). The effect was shown to be largest in individuals with high theophylline clearance before vaccination (Meredith et al., 1985), probably those with high CYP1A2 activity. On the other hand, influenza immunization did not significantly change CYP3A4 or CYP2E1 activities, as measured by the erythromycin breath test (ERMBT) and chlorzoxazone clearance (Kim and Wilkinson, 1996; Hayney et al., 2001). However, an inverse correlation between interferon-γ (IFN-γ) production and changes in ERMBT has been reported after administration of influenza vaccine to healthy volunteers (Hayney and Muller, 2003). In this respect it is interesting to note that *in vitro* studies with hepatocytes cultured with IFN-γ showed a decreased CYP3A4 expression and activity (Donato et al., 1997). The observed discrepancies in effect of vaccines might be due to different purity of vaccines, variable vaccination protocols or differences in response on the various CYP enzymes.

Additionally altered pharmacokinetics is observed in patients with inflammatory diseases and cancer. The largest effect of inflammatory disease on the pharmacokinetics of drugs has been reported for patients with rheumatoid arthritis, which showed a three and fourfold higher systemic exposure of verapamil and simvastatin compared to healthy volunteers (Mayo et al., 2000; Zhang et al., 2009). Also in patients with advanced cancer, all genotyped as EM of CYP2C19, a reduction in omeprazole metabolism was observed, and all patients had a slower metabolic CYP2C19 phenotype compared to healthy volunteers (Williams et al., 2000). Similarly decreased CYP3A4-dependent CsA metabolism has been reported in bone marrow transplanted patients, and interestingly an association between high interleukin 6 (IL-6) plasma concentrations and increased CsA concentrations were found (Chen et al., 1994). Later, Frye et al. (2002) studied the relationship between plasma concentrations of IL-6 and tumor necrosis factor alpha (TNF-α) and CYP enzyme activities in patients with congestive heart failure. IL-6 and TNF-α concentrations were negatively correlated to the activities of CYP1A2 and CYP2C19, investigated by use of caffeine and mephenytoin as probe substrates. There was no significant relationship between the cytokine level and CYP2D6 and CYP2E1 activities in these patients (Frye et al., 2002). In this respect it is interesting to note that increased adverse events and discontinuing treatment of the CYP2C19 substrate imipramine has been reported in heart failure patients (Glassman et al., 1983).

To summarize, depression of metabolic capacity through CYP enzymes seems to be a common feature of a variety of diseases involving an immune response with the release of cytokines. The different CYP enzymes are to a variable degree affected, and increases in drug exposure from less than 50 to up to 400% have been observed. The potential effects of cytokines on the pharmacokinetics of a large number of drugs accounts for increased awareness in treating patients with diseases involving an immune response. Also, there are indications of differential effects, with larger effects on patients with initially high clearance through the enzyme in question. Thus, depression of CYP activity is a considerable factor contributing to inter-individual variability in drug exposure.

IMMUNOLOGICAL RESPONSE AND DRUG TRANSPORT

Similar to the drug metabolizing enzymes, a variety of diseases have also been shown to influence on the expression of drug transporters. P-gp is in this area by far the most extensively studied drug transporter. For example, several studies have shown intestinal P-gp to be inversely correlated with inflammatory disease activity. In a study by Ufer et al. (2009), P-pg mRNA and protein expression were decreased in patients with ulcerative colitis compared

to healthy volunteers and P-gp mRNA was inversely correlated with disease activity. Also, while expression of breast cancer resistance protein (BCRP) and P-gp in inflamed mucosa is reduced in patients with ulcerative colitis, expression of these transporters is comparable in unaffected mucosa from ulcerative colitis patients and healthy volunteers (Gutmann et al., 2008). Accordingly, a post mortem study of seropositive HIV patients showed that P-gp in brain microvascular endothelial cells was decreased compared to HIV-negative controls (Langford et al., 2004). However, this picture is more complicated as different parts of the brain were differently affected; i.e., in contrast to the aforementioned decrease of P-gp in endothelial cells, P-gp immunoreactivity was increased in astroglial cells in AIDS patients with HIV encephalitis compared to HIV encephalitis-negative patients and seronegative controls (Langford et al., 2004).

Many *in vitro* studies have examined the effect of inflammatory mediators on expression and activity of P-gp in the brain (Bauer et al., 2005; Miller et al., 2008; Roberts and Goralski, 2008). Several studies show a difference in effect after short-term versus long-term exposure to inflammatory mediators; whereas P-gp activity is initially depressed, long-term exposure to inflammatory mediators seems to upregulate P-gp expression and activity (Hartz et al., 2006; Bauer et al., 2007). Not surprisingly, the magnitude and direction of changes in drug transport activity is dependent on both the specific cytokine and model examined (as reviewed by Roberts and Goralski, 2008). This is exemplified by the diverging results of two separate rat models. Seelbach et al. (2007) reported that P-gp expression in brain microvessels increased 3 h after induction of inflammatory pain. These results were accompanied by *in situ* brain perfusion studies and antinociceptive studies that showed decreased brain uptake and decreased analgesia of morphine, a P-gp substrate (Seelbach et al., 2007). In contrast, Goralski et al. (2003) showed that LPS-induced CNS inflammation decreased P-gp expression and activity. In this study radioactive labeled digoxin was increased both in the brain and liver following intracranial ventricle administration of LPS in male rats (Goralski et al., 2003). Accordingly, P-gp mRNA in the brain and mRNA of both P-gp and OATP1B1 in liver were reduced. The diverging results of *in vitro* and animal models call for more *in vivo* studies to explore the effect of inflammatory disease on drug transport in patients. So far, altered pharmacokinetics of drugs relative to disease activity has been observed by Roberts et al. (2009). This group showed that patients with acute inflammatory brain injury obtained increased levels of the morphine metabolites morphine-3-glucuoronide and morphine-6-glucuronide with increasing IL-6, while no linkage between the P-gp substrate morphine and CSF IL-6 was observed. These data suggests an inhibition or down-regulation of drug efflux transporters specific to these metabolites other than P-gp in the BBB, possibly OATPs, as postulated by the authors (Roberts et al., 2009). Taken together, data on the effect of inflammatory mediators/disease on drug exposure in the brain are not conclusive and more *in vivo* studies are needed to explore this issue.

There is increasing evidence for differential ability of cytokines to influence on the regulation of expression and activity of drug transporters in immune cells compared to other tissue (Liptrott and Owen, 2011). While most studies suggest a depression or down-regulation of P-gp upon an inflammatory response, a recent study showed that P-gp expression on lymphocytes in patients with systemic lupus erythematosus (SLE) correlated positively with disease activity (Tsujimura and Tanaka, 2011). Up-regulation of P-gp in peripheral blood mononuclear cells has previously been shown for a variety of diseases, by far most studied in malignant diseases, where it causes the problem of MDR (Kantharidis et al., 2000; Shtil, 2002), but also in rheumatoid arthritis (Suzuki et al., 2010), HIV (Langford et al., 2004), and in solid organ transplantation (Donnenberg et al., 2001). This observation is supported by *in vitro* studies where P-gp in lymphocytes is induced by various stimuli such as IL-2 (Tsujimura et al., 2004; Liptrott et al., 2009). Up-regulation of P-gp and other drug transporters resulting is a problem in the use of drugs which are P-gp substrates and have their site of action within the immune cells, where an up-regulation of P-gp leads to reduced levels of drugs at their site of action. This applies to drugs such as antiviral agents used in HIV, immunosuppressants used in autoimmune diseases and solid organ transplantation, among others.

In vitro studies in human hepatocytes also suggest a role for proinflammatory cytokines in the regulation of a wide range of drug transporters other than P-gp, such as OATPs, MRPs, OATs, and OCTs (Le Vee et al., 2008, 2011; Vee et al., 2009). However, *in vivo* data is lacking, and more studies are needed to explore the role of immune response in the regulation of drug transporters and its effect on the pharmacokinetics of drugs.

MECHANISMS OF CYP AND TRANSPORTER REGULATION BY CYTOKINES

In response to infections and inflammatory diseases, cytokines like interferons (IFNs), interleukins (IL-1 and IL-6), and TNFα are produced and released from monocytes, macrophages, and stromal cells. The mechanisms by which they affect drug metabolism and transport is not fully understood, but in brief cytokines bind to receptors on the cell surface in target organs and activate intracellular signal systems regulating gene transcription of enzymes and transporters. Such receptors include Toll-like receptors (TLRs), which are presented on the surface of Kupffer cells in the liver and are involved in mediating inflammatory response. In patients with sepsis, TLR2 and TLR4 expression has been found to be significantly up-regulated in several organs (Cinel and Opal, 2009). It has been shown that CYP enzyme expression was regulated by a TLR4-dependent mechanism in a LPS-induced inflammation model (Ghose et al., 2008). Several animal studies have shown that individual CYP enzymes and transporters are down-regulated by cytokines at the level of gene transcription with decreases in mRNA and protein expression (Renton, 2004, 2005; Aitken et al., 2006; Morgan et al., 2008; Roberts and Goralski, 2008; Miller, 2010). The major mechanistic explanation involve the transcription factors pregnane X receptor (PXR) and constitutive androstane receptor (CAR), which both are involved in the expression of genes associated with drug metabolism and transport (Chang and Waxman, 2006).

For CYP3A4 and P-gp transcriptional activation is mediated by PXR and NF-κB (Bentires-Alj et al., 2003; Gu et al., 2006; Kojima et al., 2007). Moreover cytokines have been shown to induce the production of NF-κB, which directly disrupt binding of the

PXR–retinoid X receptor (RXR) complex to its response element, leading to suppression of CYP3A4 expression (Gu et al., 2006). Recently suppression of CYP3A4 by IL-6 was shown to occur after the decrease of PXR in human hepatocytes (Yang et al., 2010). Several additional transcription factors may be responsible for regulation of P-gp expression. Heat-shock transcription factor 1 (HSF-1) and stimulatory protein 1 (SP-1) both have binding sites within the *ABCB1* promoter (Rohlff and Glazer, 1998; Vilaboa et al., 2000), and in tumor cells P-gp expression is regulated by Y-box protein (YB-1; Ohga et al., 1998).

Studies in human hepatocytes indicate that the effect of various cytokines is gene-specific. While IL-1 down-regulated CYP2C8 and CYP3A4 mRNA expression by 75 and 95%, respectively, there was no effect on CYP2C9 or CYP2C19 (Aitken and Morgan, 2007). IL-6, on the other hand, caused a decrease in CYP2C8, CYP2C9, CYP2C19, and CYP3A4 mRNA expression. Recently IL-6 was also shown to suppress the activities of CYP3A4 and CYP1A2 in human primary hepatocytes, while anti-IL-6 monoclonal antibody partially blocked this suppression (Dickmann et al., 2011). The effects of various cytokines on individual CYP isoenzyme expression and activity investigated *in vitro* are summarized in **Table 1**. With respect to P-gp, *in vitro* studies in human hepatoma cells and human colon carcinoma (Caco-2) cells as well as *in vivo* studies in mice have shown that IL-6 and IL-2 down-regulate its expression (Piquette-Miller et al., 1998; Hartmann et al., 2001; Belliard et al., 2002; Hosten et al., 2008). On the other hand induction of P-gp by TNF-α or IL-2 has been shown in mice (Hartmann et al., 2001), human lymphocytes (Liptrott et al., 2009), and rat brain capillaries (Bauer et al., 2007). Thus, for P-gp there seems to be organ- and cytokine-specific effects. The response of cytokines on CYP protein expression correlated generally well with the effect on mRNA expression (Aitken and Morgan, 2007), while P-gp expression was strongly decreased with no change in mRNA expression in patients with inflammatory gastrointestinal disorders (Blokzijl et al., 2007).

DRUG INTERACTION WITH THERAPEUTIC PROTEINS

Therapeutic proteins are a group of drugs currently extensively used in the treatment of autoimmune diseases (e.g., rheumatoid arthritis), cancer, and HIV. These drugs include monoclonal antibodies, interferons, and other cytokines among others. Therapeutic proteins are macromolecules, and compared to small-molecule drugs there is still limited knowledge about their pharmacokinetics. For small-molecule drugs problems related to metabolism-based drug–drug interactions have gained extensive attention as a major cause of adverse drug reactions and toxicity problems in general. There are however major differences regarding clearance mechanisms for small-molecule drugs and therapeutic proteins. Proteins are mainly cleared by renal filtration or receptor-mediated clearance, and since they are not metabolized by CYP enzymes, drug–drug interactions involving CYP enzymes have been considered not to be relevant for therapeutic proteins. However, it has recently been clear that these drugs, due to altering the immunological state in patients, can affect the pharmacokinetics of a variety of other drugs by interferences with CYP-mediated metabolism and drug transport (**Table 2**).

INTERFERONS AND INTERACTIONS WITH CYP METABOLISM

Interferons (IFNs), produced by the immune system in response to infections and inflammations, have antiviral, antiproliferative, and immunoregulatory effects. INF therapy is extensively used in the treatment of chronic hepatitis C, multiple sclerosis and cancer. In addition to the effect of endogenous cytokines on drug metabolism, therapeutic use of cytokines may therefore additionally contribute to the decreased metabolic ability. Williams et al. (1987) reported already in 1987 that 1 day after a single intramuscular injection of IFN-α in five patients with chronic hepatitis B and four healthy volunteers, clearance of the CYP1A2 substrate theophylline was significantly reduced (30–80%). A 26% reduction in clearance of theophylline was also observed in patients with hepatitis C after IFN-β treatment, with a corresponding increase in terminal half-life of about 40% (Okuno et al., 1993). Additionally IFN-α administration in patients with hepatitis B has been shown to cause a minor decrease of erythromycin metabolism (15%), as determined by ERMBT (Craig et al., 1993), and patients monitored on warfarin needed a dose reduction when IFN-α-2b and IFN-β were given (Adachi et al., 1995).

Table 1 | Effects of various cytokines on individual drug metabolizing CYP enzyme expression (mRNA or protein) and activity *in vitro* (no available data for CYP2D6).

Cytokines	CYP enzymes						
	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2E1	CYP3A4
IFN-γ	⇓	⇓	⇓	⇓⇔	⇔		⇓⇔
TGF-β1	⇓	⇑⇓	⇓	⇓	⇓		⇓
TNF-α	⇓	⇑⇓	⇓	⇓⇔	⇓⇔	⇓	⇓
IL-1β	⇓	⇓	⇓	⇓⇔	⇔	⇓	⇓
IL-2		⇓					⇓
IL-4	⇓	⇑				⇑	⇑⇔
IL-6	⇓	⇓	⇓	⇓	⇓	⇓	⇓
IL-10		⇔					⇑

Two arrows indicate that studies show diverging results (Abdel-Razzak et al., 1993, 1994; Donato et al., 1997; Sunman et al., 2004; Aitken and Morgan, 2007; Liptrott et al., 2009).

Table 2 | Examples of drug interactions caused by therapeutic proteins.

Therapeutic protein	Affected drug	Effect	Reference
INTERFERONS			
INF-α	Theophylline	30–80% reduced clearance	Williams et al. (1987)
INF-β	Theophylline	26% reduced clearance	Okuno et al. (1993)
INF-α	Erythromycin	15% decreased CYP3A4 activity	Craig et al. (1993)
INF-α-2b, INF-β	Warfarin	Increased concentration	Adachi et al. (1995)
INF-α	Cyclophosphamide	60% reduced clearance 140% increased $t_{1/2}$	Hassan et al. (1999)
IFN-α-2b	Caffeine	60% decreased CYP1A2 activity	Islam et al. (2002)
IFN-α-2b	Mephenytoin	40% decreased CYP2C19 activity	Islam et al. (2002)
INTERLEUKINS			
IL-2	Erythromycin	50% decreased CYP3A4 activity	Elkahwaji et al. (1999)
MONOCLONAL ANTIBODIES			
Muromonab-CD3	Cyclosporine	Increased concentration	Vasquez and Pollak (1997)
Basiliximab	Cyclosporine	Increased concentration	Strehlau et al. (2000)
Basiliximab	Tacrolimus	60% increased concentration	Sifontis et al. (2002)
Tocilizumab	Omeprazole	30% decreased AUC	Zhang et al. (2009)
Tocilizumab	Simvastatin	60% decreased AUC	Zhang et al. (2009)
Tocilizumab	Simvastatin	40–60% decreased AUC	Schmitt et al. (2011)

In cancer patients with multiple myeloma, administration of IFN-α before treatment with cyclophosphamide caused about 60% decreased clearance and 140% increased peak concentration and half-life, accompanied by a decreased concentration of the CYP3A4 metabolite 4-hydroxycyclophosphamide, compared to when IFN-α was administered after cyclophosphamide (Hassan et al., 1999). Also a study in 17 patients with melanoma showed that the activities of CYP1A2 and CYP2C19, measured by the probe drugs caffeine and mephenytoin, were 60 and 40% reduced, respectively, after treatment with high-dose IFN-α-2b (Islam et al., 2002).

On the other hand when administered in lower doses to hepatitis C patients, IFN has been shown to induce a small, statistically non-significant increase in activity of CYP3A4 and CYP2D6 after 1 month of exposure, when administered in combination with ribavirin as antiviral therapy (Becquemont et al., 2002). It is however important to note that these patients had significantly lower pretreatment CYP3A4 and CYP2D6 activities than healthy volunteers. Recently also Gupta et al. (2011) demonstrated that weekly administration of IFN-α-2b to patients with chronic hepatitis C was associated with small increase in CYP2C8/9 and CYP2D6 activities in some individuals, while there was no effect on CYP3A4 activity and a limited inhibitory effect on CYP1A2. IFN-β treatment in patients with multiple sclerosis revealed unaltered CYP2D6 and CYP2C19 activities (Hellman et al., 2003). Several studies have been performed with administration of IFN-α-2b and IFN-α-2a and possible interaction with methadone, which is predominantly metabolized by CYP3A4. A minor increase in methadone exposure in hepatitis C patients after multiple doses of peginterferon-α-2b or peginterferon-α-2a have been reported, but the authors conclude that this may not be of any clinical relevance (Sulkowski et al., 2005; Gupta et al., 2007). However several reports indicate that IFN could cause a clinically relevant interaction when administered with drugs that are CYP substrates, but there might be different effect on the individual CYPs. At least IFN given in high doses for the treatment of cancer seems to decrease the activity of CYP3A4, CYP1A2, and CYP2C19, and it is important to be aware of possible interactions with drugs metabolized through these enzymes. However, a decreased CYP activity due to the disease-state in chronic hepatitis patients may be restored by antiviral therapy involving IFN.

INTERLEUKIN AND INTERACTIONS WITH CYP METABOLISM

Interleukins (ILs) are cytokines mainly synthesized by T lymphocytes, as well as monocytes, macrophages, and endothelial cells. They promote the development and differentiation of T, B, and hematopoietic cells. Therapeutic administration of IL-2 has shown several immunological effects, including activation of cellular immunity and production of cytokines (Winkelhake and Gauny, 1990). Recombinant IL-2 is used to treat advanced cancers (Vlasveld et al., 1992), but there is not much clinical data on the effect of IL-2 on CYP metabolism. However, high-dose administration of IL-2 to patients with liver cancer has been shown to decrease expression of CYP1A2, CYP2C, CYP2E1, and CYP3A4 by approximately 40–60%, and also the CYP1A2 and CYP3A4 activities were 62 and 50% reduced, respectively (Elkahwaji et al., 1999). Thus administration of IL-2 to cancer patients has been proposed to cause clinically important drug interactions (Lee et al., 2010).

MONOCLONAL ANTIBODIES AND INTERACTIONS WITH CYP METABOLISM

Human monoclonal antibodies are widely used for treatment of several diseases, e.g., autoimmune diseases (rheumatoid arthritis), cancer, and rejection episodes following transplantation. Since it is now recognized that cytokines induce alterations in CYP metabolism of drugs, it is also evident that cytokine modulators may have an effect on CYP-mediated drug metabolism. However, the prediction of this effect is not straightforward. Use of

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