Drug disposition in diseases altering cyp450-mediated metabolism

Abstract

Drug-disease interaction should be considered in drug prescribing, as some inflammatory diseases down regulate CYP activities and thus may alter drug disposition, especially for autoimmune diseases. Many studies either in animals or humans demonstrated the effect of inflammatory mediators released during inflammation or infection on drug metabolism, circulating cytokines depress cytochrome P-450 enzymes activities which are responsible for the metabolism of many drugs. These drugs may include drugs used for the control of these diseases per se. Also, several organisms have been reported to alter P450-mediated metabolism by inoculating the organisms or their lipopolysaccharides in laboratory animals either peritoneal, intra cerebroventricularly or orally.

The mechanism of inhibition was suggested and proved in some studies to be related to inflammatory cytokines such as IL-6 and TNF-α, IL-1β and IFN-γ and C-reactive protein (CRP), another proposed mechanism involves nitric oxide (NO) production as an inhibitory intermediate released from cytokines to inhibit CYP-450 enzymes.

Start of inhibition time varies from 12hrs to 24hrs depending on cytokines release in inflammatory disease or 2-8 days in infection related to the time of release of inflammatory mediators. The percentage of inhibition varied from 40-60%.

Type of inflammatory disease and degree of inflammation will differently affect CYP metabolism. The data generated stress the importance of monitoring drug level or clinical response during episodes of infection or inflammation. Limited number of studies showing induction of CYP-450 was also discussed. Regarding human studies, similar studies were also reported to alter CYP-450 metabolism during infection episodes. To conclude, care should be taken in patients with inflammatory diseases concerning drug dose adjustment which may be required according to severity and duration of disease and depending on safety profile of the drug.

Keywords: inflammation, infection, drug disease interaction, cyp-450 metabolism, inflammatory mediators, cytokines

Abbreviations: AhR, aryl hydrocarbon receptor; Amt, nuclear translocator; CLP, cecal ligation and puncture; CVB3, coxsackievirus B3; CRP, c-reactive protein; CYP-450, cytochrome P-450; ECOD, ethoxycoumarin o-deethylase; GH, growth hormone; IMND, imipramine n-demethylase; iNOS, inducible nitric oxide synthetase; icv, intracerebroventricularly; IFN-γ, interferon γ; IL, interleukin; KC, kupffer Cells; L-NAME, nitro-l-arginine methyl ester; LPS, lipopolysaccharides; NF-KB, nuclear factor-kappa B; NO, nitric oxide; TLR, toll like receptor; TNF-α, tumor necrosis factor α; WT, wild type

Introduction

The alteration of drug metabolism under diseased conditions is of clinical importance. Many studies have looked at the depression of cytochrome P450-dependent hepatic drug metabolism during inflammatory reactions & infectious diseases.

Inflammatory diseases inhibiting cytochrome P450

Diseases inhibiting CYP450

Infectious diseases and other inflammatory diseases have been associated with down regulation of CYP activities involving a decline in cytochrome P450 enzyme activity, as well as in extra hepatic cytochrome P450s and transporters activities. These inflammatory conditions include severe trauma, degenerative diseases such as arthritis, malignancies, sepsis, in addition, a central inflammation, such as meningitis, differentially decreases the levels of hepatic CYP isozymes. These inhibitors also included antibodies with unique specificities. Effect on drug metabolism may vary; while, head injury, a non-infectious condition, decreased the level of mRNA of CYP2C11 and CYP3A without altering the levels of these proteins in rat experiments, neuro trauma increased the drug clearance and oxidative metabolism in human subjects.

Animal models or human subjects

These studies were either performed in vivo in experimental animals, reported in human, or in vitro in cultured hepatocytes. These models involved animal models of endotoxemia or cultured hepatocytes stimulated by endotoxin where CYP isoforms were dramatically decreased.

Mechanism of inhibition

Inflammatory mediators play a key role in the down regulation of CYP450. This is mediated largely through down-regulation of gene transcription by the pro-inflammatory cytokines such as IL-6 and TNF-α, in addition IL-1β and IFN-γ and C-reactive protein...
(CRP), which reach level of >10mg/L during acute-phase response, had on average a 30% decrease in CYP metabolic activity.3

During inflammation, Kupffer cells (KCs) play an important role in producing pro-inflamatory cytokines such as TNF-α and IL-1β in sepsis.4 It was suggested that CYP isoforms are significantly down regulated in sepsis and this decrease is due to the reduction of aryl hydrocarbon receptor (AhR) and nuclear translocator (Arnt), two critical transcription factors involved in the regulation of CYP1A2 mRNA. AhR and Arnt expressions were inversely correlated with pro-inflamatory cytokines in sepsis and that exposure of cells with such cytokines down regulated these transcription factors. To conclude the decreased CYP1A2 can be, in part, due to increase in pro-inflamatory cytokines such as TNF-α and IL-1β which then directly suppress CYP1A2 mRNA.5

Another proposed or additive finding was that cytokines induce inducible nitric oxide synthetase (iNOS) resulting in nitric oxide (NO) production in many cell types. Using the NO inhibitor, it was shown that cellular ligation and puncture (CLP) caused decrease in CYP1A1, CYP1A2, and CYP2E1 and was reversed by the NO inhibitors. This suggests NO might contribute to the suppression of CYP in sepsis.6 It has also been postulated that since NO binds to the heme center of CYP directly and inhibits CYP activity;5,6 decreased CYP activity in sepsis could also be due to NO-mediated post-translational modification.6

However, in other studies, they found that the inhibition of CYP450 activities by cytokines was probably not due to the production of NO, because L-NAME totally blocked NO production but had no effect on the cytokine-induced suppression of CYP450 enzyme activities.7 Specially, IL-6 was unable to induce NO synthase activity in hepatocytes.8

Regarding the human studies, Shedlofsky et al.,17 reported that endotoxin injected adult human volunteers showed decrease in metabolism of the CYP enzyme by probe drugs which included antipyrine, hexobarbital and theophylline. The degree of inhibition of drug metabolism correlated with the circulating plasma levels of IL-6 in these endotoxins injected volunteers. Harbrecht et al.18 further demonstrated that CYP activity is differentially altered in severely injured patients. In this study, twenty-three multiply injured patients admitted to a trauma critical care unit were compared with healthy volunteers. CYP metabolizing activity was measured using the probe drugs mephenytoin (CYP-2C19), chlorozaoxone (CYP-2E1), dapsone (multiple CYP enzymes) and fluibprofen (CYP-2C9). Mephenytoin metabolism was suppressed after injury and increased during post-injury recovery, whereas chlorozaoxone was suppressed to a lesser degree.9

Time of inhibition

As described by Morgan et al.,19 in rat hepatocytes, a near-maximal decrease in CYP4502C12 protein was observed within 12hrs of initiation of IL-1 treatment.2 In another study, rat hepatic CYP1A2 mRNA was significantly downregulated at 10-20hrs and its proteins decreased at 20hr safer cellular ligation and puncture (CLP), in addition, the INOS mRNA level significantly increases 24hr after CLP.6 In pig hepatocytes, effects of IL-1α and TNF-α were most pronounced after 12hr exposure, but the decrease was still significant after 24hr. IL-6 differed from IL-1α and TNF-α by inhibiting CYP450 and glucuronidation more effectively after 24hr. This time-dependent effect suggests that perhaps IL-1α and TNF-α are acting via different mechanisms, may be because IL-6 mechanism’s of inhibition was unrelated to NO production, or that IL-1α and TNF-α disappear more rapidly from the hepatocyte cultures than IL-6, allowing the hepatocytes to recover.2

While Abdel Razzak et al.,20 reported that cytokines, IL-1β, IL-6, TNFα, acting directly on human hepatocytes in primary culture, inhibited CYP isoforms after 72hrs of treatment as reported previously.1,20

Age

Further drop in CYP3A function may occur with age22 and reduced hepatic drug clearance may contribute to a greater risk of adverse events in elderly cancer patients.22 Meanwhile limited number of studies discussed the effect of infectious diseases on the metabolism of drugs, and this is what the next section and this thesis aim to present.

Infections-mediated inhibition of cytochrome P450

Like inflammatory diseases, some infections were associated with alteration of CYP-450 activities. Alteration in drug metabolism in infection was also tested in various animal models. Influenza23 and Coxsackievirus B324 have been shown to increase the toxicity of dioxin, including an increase in lethality in dioxin-exposed infected mice.25 Alteration in enzyme CYP-450 activity has also been measured after in vivo exposure of laboratory animals to a variety of immunomodulatory agents, including viruses, lipopolysaccharides and bacteria.26

Organisms

Concerning infection, the list of infections that have been reported to alter P450-mediated metabolism includes several bacteria such as Corynebacterium parvum,27 Listeria monocytogenes,27,28 Mycobacterium butyricum, Chlamydia trachomatis,27 Proteus,29 Escherichia,19 Salmonella, Bacteroides and Coxiella strains,29 Citrobacter rodentium30 and various types of Schistosoma.31 In addition, the hookworm Ancylostoma caninum,31 viruses like Coxsackievirus B3 (CVB3),32 parasites like Toxoplasma gondii, Fasciola hepatica, Trypanosoma brucei,27 and malaria infection by Plasmodium berghei,32,33 and Plasmodium falciparum,33 were also implicated.

Animal model

Studies reporting alteration of P450-mediated metabolism were performed by inoculating the organisms in laboratory animals like mice,25,27,30,32,33 or hamster,31 or lipopolysaccharides of Proteus,29 Escherichia,29 Salmonella, Bacteroides and Coxiiella strains,29 were injected in rodents.1,20 Alternatively, isolated hepatocytes were cultured in vitro with lipopolysaccharides for 24hrs where transcription factors and protein of the metabolizing enzymes were significantly decreased.9

Route of inoculation

In all these studies, organisms were injected intraperitoneal,25,27,30,33 in one of these studies they were comparing the injection of bacterial lipopolysaccharides intraperitoneal & intracerebroventricularly.
CYP isoforms and percentage of inhibition

Khatsenko et al.,27 suggested that the suppression is generalized rather than isoform specific. Also Kaca et al.,29 discussed the decrease of CYP-450 activity by Salmonella typhi by 59%; E. coli, S. typhimurium, P. mirabilis, and C. burnetii lipopolysaccharides, decrease cytochrome P-450 level. While other studies aimed to demonstrate specific CYP isoform inhibited by the previously mentioned infection. For example, Chlamydia trachomatis infection can depress CYP1A and CYP2B-mediated metabolism in the liver of the mice by 49%.27 Listeria monocytogenes causes a depression of cytochrome P450A1 and P4502D9-mediated biotransformation in mice by 40-60%.28 Coxsackievirus B3 (CVB3) infection suppresses the expression of CYP-gene expression in the liver of mice, especially for CYP2B.29 Toxoplasma gondii suppresses CYP3A-mediated drug metabolism in mice.30 The bacterial lipopolysaccharides of Escherichia coli injected intracerebroventricularly (i.c.v.) significantly decreased the total P450 contents by 30% of the levels of control rats treated with saline i.c.v., and the contents of CYP1A by 48%, 2B by 54%, 2C11 by 37% and 3A by 40%;31 while Sewer et al.,32 reported that the down-modulation of murine CYP2C29, 2E1 and 3A11 was by the Escherichia coli endotoxin.30 Plasmodium chabaudiachabaudi (non-lethal) infection52 and Plasmodium berghei depressed CYP1A and 2B in mice.33,34 it was also found that CYP2E1 activity was relatively unaltered while total-CYP content and CYP3A2 activity were depressed in P. berghei-infected.35,36 This could be compared with the action of xenobiotics that can induce specific P450 isoforms while leaving others unaffected.32

Start of inhibition post inoculation

In studies discussing the start of inhibition, they were relating the level of organisms in the blood of the infected animal to the degree of inhibition, i.e. the maximum inhibition of cytochrome P450 is at the maximum level of the infection.

This was indicated either by the time of sacrifice of the animal and liver isolation; example with CVB3 where mice were sacrificed on day 4 post-inoculation and liver was excised for assessment of inhibition,25 also in Plasmodium berghei infection, animals were sacrificed by the second or third week after infection; when parasitaemia rose to levels to or higher than 20%.35 It was also shown that non-lethal P.c.chabaudi infection modulates CYP activities in the mice liver on the day, and/or shortly before or after the day on which parasitaemia peak was recorded.33

In other studies, they were more specific about the time of maximal suppression of CYP450 in relation to the time of infection, example Chlamydia trachomatis reached maximal suppression of CYP450 at days 6-8 and fully recovered at day 11 post infection.27 Listeria monocytogenes causes a depression of cytochrome P450 after 48hrs of infection and mRNA levels returned to normal after 96hrs of infection.28 In the same line, the level of total P450 contents in the rat liver microsomes was decreased 24h after i.c.v. injection of LPS and returned to the initial value by 48h.1 Another reason for the start of inhibition and maximum inhibition of CYP450 may be related to the time of release of inflammatory mediators following an infection which will be discussed later.

Mechanism of inhibition of CYP450

Large quantities of cytokines and nitric oxide (NO) released during inflammation are implicated as the major mediators for the observed down-regulation. The role of cytokines is well established, and they are known to inhibit drug metabolism by acting at the level of gene transcription,39 this hypothesis was discussed in one study where the changes in the levels of CYP1A and CYP2D9 that are observed during L. monocytogenes infection occur at a pretranslational step and proved by the loss of CYP 2D9 mRNA after 48hr of infection. CYP 2D9 mRNA levels returned to normal after 96hr of infection as previously mentioned.38

In vivo studies discussing these issues were performed either by stimulation of host defense mechanisms against infection, by injecting cytokines as such20,22 in vivo32 or in vitro,30 or by the use of null mice for certain cytokines or cytokine receptors, which has resulted in abolishment or modification of CYP response to inflammatory stimuli, that’s why such studies support an important role for cytokines.39

Examples of cytokines are the circulating cytokines TNFα,13,40 IFNγ,12, IL-6 and IL-11,14,41 which are produced in large amounts and are the first mediators of the host response, and which have been proved to inhibit P450 content and activity.1,13,18

The suppression of the constitutive expression of different isoforms from CYP1–CYP3 families by IL6 has been documented in hepatocyte cultures of different mammals including pigs,26 rabbits,40 rats,40,45 and humans,12,28,40. There is also evidence that IL6 has significant role in rodents. Ashino et al.,40 reported that IL6 deficiency blocked the down-regulation of CYP3A11 and CYP2C29 in mice treated with Bacillus Calmette-Guerin vaccine. The turpentine-induced down-regulation of CYP1A2, CYP2A5, and CYP3A11 mRNAs observed in wild-type (WT) mice was completely abolished in IL6-deficient IL6(-/-) mice.41 The injection of rats with IL6 caused the suppression of CYP2C11 and CYP2E1 but not CYP3A2 mRNA.19

IFNγ has immunomodulatory effects on several cell types, including the activation of murine macrophages that have microbialic activity.49 Compared with WT mice, IFNγ-deficient IFNγ(-/-) mice have been reported to be significantly more susceptible to infection by Mycobacterium bovis,50 Listeria monocytogenes,50 and C. rodentium.51 The injection of rats with IFNγ resulted in the suppression of CYP3A2 mRNA, whereas the activities associated with CYP2C11 and CYP2A1 were unaffected.51 IFNγ has been reported to down-regulate the mRNA and/or activity levels of different P450 isoforms in the hepatocytes of rats,45 and humans.20,55,59 So, IL6 is not the primary or sole mediator of P450 down-regulation in all disease models.20 One study aimed to analyze different CYP isoforms activity by different cytokine, this study pooled data from different studies of peripherally injected inflammatory cytokines and showed that they differentially affected each hepatic CYP. In this study, TNF-α decreased the activities of ethoxycoumarin O-deethylation ECOD,45 pentoxysorfin O-deethylation, which is catalyzed by CYP2B1/216 and the levels of CYP1A1,37 2C11,48 and 3A2.56,59 while IL-1 or IL-6 decreased these CYPs except for CYP2B.56,57,59 IL-1 also depressed the activity and content of CYP2D.49 Interferon-γ decreased CYP3A2

but not CYP2C11. NO production was largely discussed as a cause of inhibition of CYP-mediated drug metabolism. The NO effect on drug metabolism is direct, rapid (<1h), and differential to various CYP isoforms. Although some reports suggest that P450 enzyme down-regulation occurs independently of NO, others have shown that NO plays an important role in this event.  

On the other hand, some studies discussed an indirect inhibitory effect by cytokines to CYP, while one discussed the role of growth hormone (GH) due to the fact that the combined effect of these cytokines could not explain the fact that an extremely small amount of LPS (0.01µg) significantly decreased the activity of imipramine N-demethylase IMND (CYP2C11) only. The expression of CYP2C11 but not CYP3A2 is regulated by pulsatile secretion of growth hormone (GH). Therefore, it is possible that the decrease in CYP1A, 2B, 2C11, and 3A by i.v. LPS may be attributed to changes in the levels of not only cytokines but also GH 1. The release of GH is reported to be inhibited by i.v. IL-1.  

Gu et al. suggested that NFkB activation could play a role in the down-modulation of CYPs by inflammatory and infectious diseases. Also malaria was reported to enhance Toll-like receptor (TLR)-mediated pro-inflammatory responses.  

Examples of induction of cyp450 by infections  

Seldom have the above studies showed induction of CYP450, however; it has been reported that malaria infection led to down-regulation of CYP2C11 in rats. Infection induces CYP2A5 and 2E1 in the mouse liver, while Uhl et al. found that CYP2E1 activity was relatively unaltered, which were proved also with infection of rat liver by Taenia taeniformismetacestodes. In addition, CYP2A5 is up-regulated during infections such as viral hepatitis, especially B hepatitis, trematode infections, Fasciola hepatica, and also in male hamsters infected with Opisthorchis viverrini. In addition, CYP2A6 seems to be induced in the liver of patients infected with O. viverrini. Finally, infection of rat liver by Taenia taeniformismetacestodes produced an increase in total CYP450 content and induced activity of the CYP1A1, CYP2B1 isoforms.  

Mechanism of induction was suggested to be due to liver damage, or starvation. Recent advances made by LaBella & Brandes demonstrated that histamine (which is released by mast cells under stimulation by a histamine releasing factor produced by eosinophils and neutrophils in an inflammatory reaction) could be involved in the regulation of some P450 isoforms, since histamine has been shown to bind the P450 haem moiety, regulating the catalytic activity of P450 enzymes and evidence suggests that several P450 families could be regulated this way, not only CYP3A, but also those involved with cyclophosphamide, arylalkylamine and imidazole metabolism. Furthermore, Delescluse et al. have suggested that CYP1A1 could be induced by mechanisms different to the classical AhR, but related to other nuclear receptors, like hormone receptors, which were shown to be related to histamine action on P450.  

Human studies  

Most of the previously mentioned studies were performed in animals. Regarding human studies, Hegazy et al. demonstrated that bacterial and fungal infections alter cyclosporine levels probably by inhibiting CYP-450. The probe drug was cyclosporine, and the subjects were renal transplant patients. Monitoring cyclosporine levels served to illustrate the inhibitory effect of infection (Candida or bacterial infections) on CYP-450. Cyclosporine levels significantly increased during the period of infection (P < 0.001), and then subsided down to levels not significantly different from baseline values after the infection was resolved (P=0.382). The rise in cyclosporine trough levels reached up to 200%, which exposes the renal transplant patients to increased risk of adverse drug reactions. The down-regulation of CYP-450 by infection, is in good agreement with the observation of Shedlofsky et al., who reported that adult human volunteers given endotoxin showed decrease in metabolism of the CYP enzyme probe drugs including antipyrine, hexobarbital and theophylline.  

Some observations appeared in clinical reports, concerning patients with P. falciparum malaria, where clearance rates of quinine and caffeine were slower suggesting that drug metabolism is depressed during human malaria. Viral and bacterial infections as well as influenza and BCG vaccinations decrease the clearance of exogenous substances such as theophylline and antipyrine, secondary to a decrease in activity of multiple isoforms of the cytochrome P450 (P450). “Clinical reports from the Malaria patients showed slower clearance rate of quinine and caffeine, which suggests that drug metabolism is suppressed during P. falciparum infection.” Similarly, in case of viral and bacterial infection or vaccination it is reported that the activity of multiple isoforms of the CYP-450 and also the clearance rate of theophylline and antipyrine is reduced.  

Also, human CYP2A6 seems to be induced in the liver of patients infected with Opisthorchis viverrini. In addition, the serum from humans with an acute upper respiratory viral infection and from rabbits with turpentine-induced inflammation reduces the catalytic activity of hepatic cytochrome P450. In this study, they showed that in serum from humans with a viral infection, IFN-γ, IL-6 and IL-1β contribute to the inactivation of the P450 of hepatocytes of rabbits with a turpentine-induced inflammatory reaction. The ability of IFN-γ to inactivate the P450 appears greater than that of IL-6 and IL-1β. Supporting that IFN-γ has a predominant role, the decrease in plasma levels of IFN-γ induced by an acute viral respiratory infection is associated with a reduction in the clearance of antipyrine, and administration of IFN-γ to humans down-regulates P450.  

Discussion  

From the previously discussed parts, any disease condition that causes inflammatory state and cytokines release may alter drug disposition, as documented in many examples of human conditions that stimulate host cytokine responses. These include viral, bacterial or parasitic infections, tissue injury, surgery, cancer and autoimmune conditions. Interferons, interleukins-1 and-6 and tumor necrosis factor are the central mediators. These cytokines have been traditionally viewed with respect to their ability to suppress hepatic cytochrome P450 (CYP)-mediated drug –detoxification, especially the cytochrome P450 3A family (CYP3A), which is responsible for the metabolism of almost 60% of drugs used in medicine. Such aberrant drug handling has placed patients at risk for adverse drug responses. Not to mention the low therapeutic index, CYP-metabolized drugs like theophylline. The consequences of drug-cytokine interactions also involve altered absorption, elimination and/or cellular and tissue distribution of drugs.
Drug disposition in diseases altering cyp450-mediated metabolism

Some of the above results were discussed by Khatsenko et al., 27 that Chlamydia trachomatis-induced suppression of metabolism by CYP may prolong the duration and intensity of action of drugs, such as the antibiotic erythromycin, used for the treatment of chlamydial infections. Erythromycin is a substrate for the CYP3A family of P450s, which has been shown to also be attenuated in vivo during activation of host defense. Such attenuation of drug metabolism and elimination can cause overdosing with consequent toxic effects.

Also, Shimamoto et al., 1 overviewed the alteration of drug metabolism and subsequent side effects in disease condition in the literature. For example, severe side effects of the drugs used for the patients with meningitis have been observed in clinical studies of Diamond & Bennett, 82 Dismukes et al., 13 and Salaki et al., 44 suggesting that an overdose of the drugs arose from the decreased elimination of the drugs. On the other hand, Beam & Allen 69 proved that the concentrations of some antibiotics in serum were reported to be unchanged in animals with inflamed meninges. These results were speculated by Shimamoto et al., 1 that the differential alterations of the pharmacokinetics in drugs used for meningitis are due to differential alterations in the activities of drug metabolism in the liver. Thus, careful selection of the drug dosage is needed for the treatment of central inflammation in order to prevent the occurrence of side-effects.

In addition, patients with acute-phase response like cancer and impaired drug metabolism due to cytokines release in this phase may partly explain the observation of increased toxicity of drugs especially chemotherapeutic agents such as (e.g., taxanes, vinca alkaloids, camptothecins, tamoxifen, etoposide and oxazaphosphorines) that are metabolized by the cytochrome P450 3A. 3

Finally, for hepatically metabolized drugs, approval procedures from FDA or regulatory issues should include a clear statement about monitoring the drug-blood level or signs of toxicity during infection or inflammatory conditions to guard against consequences of raised drug levels. This issue was not previously raised as studies are usually performed on either healthy volunteers or uncomplicated patients, where usually infected patients or patients suffering concomitantly from inflammatory conditions are excluded.

Conclusion

In conclusion, during the course of acute inflammation or infection, extreme care should be taken to subside inflammatory response or treat the infection while monitoring drug response (therapeutic and safety monitoring), which may pose a significant risk for aberrant drug handling and adverse drug reactions. Drug monographs of hepatically metabolized drugs should include requirements for monitoring drug level or its clinical response to guide dosage adjustments starting 24hr post inflammatory condition or infection and until the condition is resolved.

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Conflicts of interest

Author declares that there is no conflicts of interest.

References


51. Simmons CP, Goncalves NS, Ghaem–Maghami M, et al. Impaired resistance and enhanced pathology during infection with a noninvasive,


60. Fuvugalla R. Effects of Nitric Oxide on cytochrome P450–mediated drug metabolism: Texas Tech University Health Sciences Center; 2005.


