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Cytochrome P450-mediated drug interactions in COVID-19 patients: Current findings and possible mechanisms

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ABSTRACT

At the end of 2019, the entire world has witnessed the birth of a new member of coronavirus family in Wuhan, China. Ever since, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has swiftly invaded every corner on the planet. By the end of April 2020, almost 3.5 million cases have been reported worldwide, with a death toll of about 250,000 deaths. It is currently well-recognized that patient’s immune response plays a pivotal role in the pathogenesis of Coronavirus Disease 2019 (COVID-19). This inflammatory element was evidenced by its elevated mediators that, in severe cases, reach their peak in a cytokine storm. Together with the reported markers of liver injury, such hyperinflammatory state may trigger significant derangements in hepatic cytochrome P450 metabolic machinery, and subsequent modulation of drug clearance that may result in unexpected therapeutic/toxic response. We hypothesize that COVID-19 patients are potentially vulnerable to a significant disease-drug interaction, and therefore, suitable dosing guidelines with therapeutic drug monitoring should be implemented to assure optimal clinical outcomes.

Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease that was first reported as pneumonia of ambiguous etiology in a cluster of patients in the Chinese city of Wuhan by the end of December 2019 [1]. The causative organism was identified several days later as a novel coronavirus (2019-nCoV). Later, its name was changed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as it was found to be genetically related to the coronavirus responsible for the SARS outbreak of 2003 [2]. The infection broke out of China to spread to every continent around the world and was declared as an emerging pandemic by WHO in March 2020 [3]. Full-length genome sequences have revealed that SARS-CoV-2 is 96% identical to a bat coronavirus, thus providing a clue about its original reservoir host [4].

Human-to-human transmission of SARS-CoV-2 is evident and, as a respiratory infectious disease, COVID-19 primarily spreads with close contact through respiratory droplets and secretions. Controlling the disease is based mainly on directing the public towards reducing the transmission [5]. The disease is contagious, but people are reacting differently upon exposure to the virus. The virus may get eliminated by immune system and the infection can pass unnoticed. However, after an asymptomatic incubation period of up to 14 days, infected persons may develop mild flu-like symptoms, including fever, dry cough, fatigue, and shortness of breath [6]. Other reported manifestations include upper respiratory symptoms as sneezing, runny nose and sore throat, in addition to gastrointestinal symptoms as nausea, vomiting and diarrhea [7]. Anosmia or ageusia have been also reported as characteristic signs of infection [8]. While most cases develop mild symptoms, some may progress rapidly to a more severe stage that necessitates admission to an intensive care unit and probably mechanical ventilation [9]. The complications of this critical stage include severe pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ failure, and ultimately death [10].

In the absence of a proven therapy for COVID-19, scientists are currently endeavoring to find an effective drug capable of eradicating this infection. Several agents are currently under extensive laboratory and clinical investigations. Some of these agents are investigational new drugs while the others are repurposed drugs which are already approved for other ailments [11]. When it comes to medications, pharmacokinetics should be strongly considered especially when dealing with such critical illnesses. Drug metabolism is a highly important aspect of its pharmacokinetics that may significantly influence its clearance and, eventually, its efficacy and/or toxicity. Cytochromes P450 (CYPs) are a superfamily of heme-containing monoxygenase enzymes that have been identified in all kingdoms of life [12]. They represent the major enzyme family involved in the oxidative biotransformation of...
most drugs and other lipophilic xenobiotics [13]. In mammals, these enzymes are found primarily in microsomes of the liver, the dominant metabolizing organ, in addition to other extrahepatic tissues [14].

In humans, there are 57 functional members in CYP families, most of which have specific endogenous functions including the metabolism of arachidonic acid, cholesterol, bile-acids, steroid hormones, vitamin D, and others [15]. The biotransformation of the majority of hepatically cleared drugs and other foreign chemicals involves members belonging to the CYP1, CYP2, and CYP3 families. Pathways involving CYP3A4/5, CYP2C9, CYP2C19 and CYP2D6 are the most common, and responsible for about 80% of the phase I oxidation system reactions [16,17]. Through their profound contribution to xenobiotic biotransformation, CYPs can significantly modulate the overall body exposure to a drug. The metabolic activity of the CYPs may result in decreasing efficacy and/or toxicity of a drug by enhancing the clearance of its active form. For another drug, such metabolic activity may lead to increased efficacy or toxicity by activating its inert prodrug or generating toxic metabolites, respectively. Understanding CYP activity in relation to the target drug is crucial in predicting its behavior inside the body and the consequences of its exposure [18].

Statement of the hypothesis

We hypothesize a pharmacokinetic disease-drug interaction in which hepatic CYPs metabolizing capacity, and eventually drug response, is altered in COVID-19 patients. Based on the conclusions drawn from the currently rapidly evolving knowledge about COVID-19, our hypothesis is built on the potential modulation of CYPs activity by the inflammatory environment provoked by SARS-CoV-2 infection, as well as the pathologic involvement of the liver which harbors the majority of the drug metabolizing enzymes (DMEs). Patient characteristics are also believed to increase the likelihood of the incidence of such interaction.

Supporting evidence for the hypothesis

Susceptibility of CYPs to the immune response in COVID-19

CYPs alteration in the state of inflammation

Systemic inflammation and immune response represent a substantial element in many acute and chronic diseases which is strongly implicated in altering drug pharmacokinetics through, mainly, modulating the expression and activity of DMEs. As a main contributor to the metabolic biotransformation of most drugs, CYPs are widely involved in such disease-drug interactions [19]. Regulation of CYPs has been linked to inflammation in several disease states such as infectious diseases (including viral infections), cancer, type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease, in addition to age-related disorders such as normal aging, metabolic disorders, and neurodegenerative diseases [20].

Alterations in hepatic CYPs expression and activity are caused by the mediators produced during the inflammation process which are mainly cytokines [21]. Cytokines are a broad category of small cell signaling proteins responsible for keeping homeostasis of the immune system and its components. The immune response is driven by a complex interplay between pro- and anti-inflammatory signals mediated by different cytokines [22]. It has been reported that different CYPs are regulated differently, that is, multiple cytokines may participate in regulating single enzymes, while a subset of enzymes can be regulated by individual cytokines. This fact about specificity of regulation is highly important when considering drug interactions because drug pharmacokinetics will ultimately vary depending on disease type and its released cytokines, as well as the administered drug and its involved metabolizing enzymes [23,24].

Since the 1990s, cytokine-induced changes in hepatic CYPs activity have been described using hepatocyte cultures from different mammals including rats [25], rabbits [26], pigs [27], and humans [28,29]. A strong evidence has been also provided through in vivo studies in mice [30], rats [31], and humans [32]. Some studies have also demonstrated the suppression of hepatic CYPs by inflammatory mediators [33–36]. Interleukin 1 (IL-1) [37–39], interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon gamma (IFN-γ) [40–42] are the most predominant proinflammatory cytokines that have exhibited suppression of CYPs expression and activity, in addition to other cytokines such as interleukin 2 (IL-2) [43,44] and interleukin 10 (IL-10) [45].

El-Kadi et al have assessed the effect of serum from humans with an acute upper respiratory tract viral infection on CYPs-mediated theophylline metabolism using hepatocytes from rabbits with turpentine-induced acute inflammatory reaction. Theophylline is metabolized by several CYPs isoforms (including CYP1A1, CYP1A2, and CYP3A) yielding different metabolites. Serum treatment resulted in reducing the formation of all theophylline metabolites as well as the amount of total CYPs, indicating a significant down-regulation of these metabolizing enzymes [46]. In a later study using the same experimental model, the down-regulatory effect was mainly attributed to IL-6, interleukin 1β (IL-1β), and IFN-γ [42]. CYPs down-regulation was also proven to be subsequent to the reduction of their activity. Additionally, the inflammatory mediators in human serum provoked varying degrees of suppression to different CYPs with the CYP3A being more vulnerable than CYP1A to such effect [47]. For decades, IL-6 has been recognized as the major inflammatory element that provokes a significant repressive effect on the expression and activity of different CYPs. Human recombinant interleukin 6 (rhIL-6) has shown concentration-dependent blocking of phenobarbital-mediated induction of CYP2B1/2 mRNA and activity in rat hepatocytes [48]. In Fischer 344 rats, rhIL-6 resulted in reducing different CYPs activities with variable degrees [49]. The mRNA levels of CYP1A1, CYP1A2, and CYP3A3 were markedly suppressed in three human hepatoma cell lines (HepG2, HepG2F, and Hep3F3) because of rhIL-6 treatment [50]. Acute-phase inflammatory reaction provoked by turpentine or purified bacterial lipopolysaccharide (LPS) administration to male rats resulted in significant suppression of hepatic CYP2C11 [51], an effect that was later confirmed to be transcriptional, involving CYP2C11 promoter sequences, using rhIL-6 treatment [52,53].

IL-6-knockout (IL-6−/−) mouse was adopted in several studies as a model to assess the extent of IL-6 contribution to the suppression of different CYP isoenzymes during inflammatory response generated by various stimuli. In turpentine-induced inflammation, the inhibitory effect observed in wild-type (WT) mice on CYP1A2, CYP2A5, and CYP3A11 mRNAs was revoked in IL-6-deficient mice [54]. Induction of immune response by Bacillus Calmette-Guérin (BCG) has led to down-regulation of transcriptional expression of both CYP3A11 and CYP2C29, but only CYP3A11 in IL-1α/β-knockout mice and TNF-α-knockout mice, respectively. However, tuberculosis vaccine had non significant effect on these enzymes in IL-6-knockout mice [55]. In a disease model, Citrobacter rodentium infection was used to elicit inflammatory response in IL-6−/− mice, where CYP3A11 mRNA suppression seen in WT mice was abolished [56]. The mentioned studies have shown that the role of IL-6 is usually critical and can’t be played by another cytokine or mediator, however, sometimes IL-6−/− mice may react similarly as WT mice, i.e. show down-regulation too, for certain CYPs in certain inflammation models. This can be explained by the functional redundancy existing among the released cytokines which, sometimes, may replace IL-6 [54–56]. Interestingly, sometimes the suppression of CYPs may happen only in IL-6−/− mice, but not WT mice, thus indicating that IL-6 may have an opposing signal with inductive effect [56,57].

Several studies have evaluated the impact of IL-6 triggered by malignancies. In an interesting study by Charles et al, the hepatic levels of both human CYP3A4 as well as its murine orthologue CYP3A11 were simultaneously assessed in a tumor-derived inflammation model using transgenic mice loaded with genetic constructs containing the upstream
regulatory elements of the human CYP3A4 gene linked to the lacZ reporter gene. The tumor generated a systemic inflammatory response with high levels of circulating IL-6 resulting in down-regulation of CYP3A11 orthologue at mRNA, protein, and activity levels as well as CYP3A4 transgene product which was assessed through measuring β-galactosidase enzyme activity [58,59]. Different tumor types have also demonstrated a significant suppressive effect on hepatic CYP3A11 with an accompanying increase in IL-6, and such effect was progressively promoted by tumor growth [60]. The pivotal role of IL-6 in cancer-mediated repression of hepatic CYP3A has been further demonstrated by attenuation of such effect via Anti-IL-6 monoclonal antibody treatment [61], or interleukin-6 receptor blocking [62]. Anti-IL-6 antibody intervention was also tested in IL-6-treated primary human hepatocytes. The inhibitory effect of IL-6 affected CYP1A1, CYP1A2, CYP2B6, and CYP3A4; and it was also capable of overriding CYP1A2 and CYP3A4 induction mediated by omeprazole and rifampicin, respectively. Anti-IL-6 antibody partially abrogated enzyme activity suppression [63].

The basis of cytokine-induced down-regulation of CYPs activity is not fully elucidated; however, the associated decrease in their respective mRNAs strongly suggests a transcriptional mechanism involving a number of transcriptional factors [64,65]. Nuclear factor kappa B (NF-κB), a pivotal regulatory transcription factor in the inflammatory and immune response, has been shown to regulate gene expression of many hepatic CYP enzymes in humans, rats, and mice [66,67]. The aryl hydrocarbon receptor (AhR) is a gene battery that regulates a group of DMEs including CYP1A1, CYP1A2, and CYP1B1. Both NF-κB and AhR have a mutual inhibitory effect thus repressing each other’s functions [68,69]. For instance, pyrrolidone dithiocarbamate (PDTC), an inhibitor of NF-κB signal, has demonstrated partial blocking of the inflammatory reduction in CYP1A2 activity [70,71]. The reported inhibitory effect of NF-κB activators on the pregnane X receptor (PXR) and its target genes (most notably of which is CYP3A4) on one hand, and enhanced PXR activity by inhibiting NF-κB on the other hand, indicates how inflammatory stimuli can manipulate hepatic CYPs expression [72-74]. Activation of NF-κB results in repressing glucocorticoid receptor (GR), thus down-regulating constitutive androstane receptor (CAR) expression and its associated genes such as CYP2B, CYP2C, and CYP3A [75]. Other studies have shown that NF-κB can interfere with CYPs expression, such as CYP2C11 and CYP2E1, by binding directly to their respective genes [38,76].

Immunopathological aspects of COVID-19

The immune system plays a crucial role in resolving COVID-19 infection, but it also can go out of control and contribute to its progression. After invading the alveolar cells, the host body starts mounting an immune response during the incubation period and the mild stage to exterminate the virus and hamper disease progression to the severe stage. However, if body defenses are impaired, the suboptimal antiviral immune reaction will allow viral proliferation resulting in lung damage and dissemination to other angiotensin-converting enzyme 2 (ACE2)-expressing cells such as enterocytes [77-79]. The initial containment of the infection by innate immune response generates a strong local inflammatory reaction with a myriad of inflammatory cytokines. Upon failure of this attempt, the highly specific adaptive immune cells are summoned, by systemically disseminated cytokines, to augment the immune response and clear the increasing viral load [80]. If coordinated recruitment of innate and adaptive immunity fails to effectively control the pathogen, more immune cells will get activated, with subsequent release of more cytokines, in a positive feedback loop of pathogenic inflammation. This state of systemic inflammation is called cytokine storm syndrome (CSS) and it has been reported in severe cases as an important cause of ARDS and multiple organ failure [81]. At this point, the immune system is doing more harm than good to the body and becoming a major cause of lung damage and subsequent mortality, thus suppressing such hyperinflammation is strongly recommended together with symptomatic treatment [82,83]. It is noteworthy that the immune system starts its response upon viral exposure and continues to reinforce it till, in most cases, it effectively diminishes viral burden. Premature halting of immune response may delay virus clearance and perpetuate the infection, therefore the use of immunosuppressants should be the last resort and only for severe cases with profound inflammatory lung injury [84].

It has been reported that a wide range of proinflammatory cytokines are elevated in peripheral blood of COVID-19 patients such as interferon gamma (IFN-γ), tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage colony-stimulating factor (MCSF), and interleukins IL-1, IL-6, and IL-12; and many more [7,85]. Interfering with these inflammatory mediators can modulate the amplified immune response that ends up with lung damage. Interleukin-6 is one of the important targets for anti-cytokine therapy as it is believed to be a key player in the process and its elevation is associated with poor prognosis [86-88]. Tocilizumab is a monoclonal antibody against the interleukin-6 receptor (IL-6R) approved for the treatment of rheumatoid arthritis. It has been reported that a single dose of tocilizumab significantly improved the clinical outcomes in COVID-19 patients [89,90]. Sarilumab is another IL-6R antagonist which is also approved for treating rheumatoid arthritis and is currently assessed for its efficacy against COVID-19 [11].

Impact of COVID-19 on the hepatic metabolizing efficiency

Different organs, such as lung, kidney, and intestine, contribute to drug biotransformation in the body; however, the liver is generally regarded as the major metabolizing organ responsible for drug clearance [91]. Through several enzyme systems, the most prominent of which is CYPs, the liver can drive numerous metabolic reactions. Acute as well as chronic insults to the liver will eventually hamper its metabolic machinery resulting ultimately in inefficient drug clearance [92,93]. Regardless of the cause, it is believed that the severity of liver disease is correlated to the extent of metabolism alteration [94,95].

Lungs represent the hot spot for the pathogenesis of COVID-19, however, potential involvement of other organs, such as the liver, has been also reported [96,97]. The hepatic involvement can be tied to the incidence of other extrapulmonary, or more specifically gastrointestinal, manifestations [98,99], and it has been reported in COVID-19 patient with or without underlying liver disease [100]. Reported findings of hepatic dysfunction in COVID-19 cases include elevated aminotransferases [101] and bilirubin [102], hypoalbuminemia [6], in addition to microvesicular steatosis with mild lobular activity [77]. It is worth mentioning that hepatic impairment has been also associated with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) [103], which is highly homologous to SARS-CoV-2 [104], as well as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [105].

The exact mechanism behind liver function deterioration is not fully understood, however, it has been proposed that SARS-CoV-2 causes direct liver injury. Viral hepato-tropism can be attributed to the relatively high expression of its cellular entry gate, i.e. ACE2, in cholangiocytes, rather than hepatocytes, rendering them vulnerable to viral attack [106,107]. This assumption is supported by the increase in circulating levels of serum gamma-glutamyl transferase (GGT) in COVID-19 patients [108]. Hepatic abnormalities can be also a secondary effect induced after initiating disease management by consumption of hepatotoxic antipyretic agents (e.g. acetaminophen), antiviral medications (e.g. oseltamivir and lopinavir), antibiotics, and steroids [109,110]. Despite the absence of viral antigens in the liver, the overwhelming systemic inflammatory reaction elicited by SARS-CoV-2 can be also a major cause of multiple organ dysfunction including liver damage as seen in other respiratory viral infections [111-113].
Drug outcome alteration in a vulnerable patient population

CYPs have been implicated in mediating clinically relevant drug interactions in several disease states [114]. Such metabolic interactions have been regarded as a major reason behind revising and updating safety profiles of pharmaceutical products [115]. Disease-drug interactions are commonly observed in inflammatory conditions with drugs whose clearance is predominantly CYPs-mediated [116]. Examples of such conditions include rheumatoid arthritis [117], hepatitis [118], Crohn’s disease [119], acquired immunodeficiency syndrome (AIDS) [120], influenza [121], congestive heart failure [122], and cancer [123].

As a central inflammatory regulator, agents interfering with IL-6 actions have led to regaining the inhibited CYPs activity, thus normalizing drug disposition pattern. Blocking IL-6 receptor by the monoclonal antibodies; tocilizumab [124] and sarilumab [125] in rheumatoid arthritis patients co-administering simvastatin has reversed CYP3A4 activity suppression as demonstrated by a clinically significant decrease in simvastatin exposure. Halting IL-6 signaling by direct binding with the monoclonal antibody sirukumab has also proven effective in rheumatoid arthritis patients who received a CYPs probe cocktail consisting of midazolam (CYP3A), omeprazole (CYP2C19), and warfarin (CYP2C9). Area under the plasma concentration–time curve (AUC) for probe substrates was reduced after sirukumab administration indicating that the activity of their respective metabolizing enzymes was recovered [126]. As an attempt to predict the risk of such interactions, physiologically based pharmacokinetic (PBPK) models were developed to assess the impact of anti-IL-6 agents on the metabolism of concomitant medications [127–129].

The immune response, with IL-6 in the core of its network of mediators, is a hallmark of COVID-19 pathogenesis. Based on the aforementioned examples, it is strongly postulated that CYPs metabolic activity will be inevitably altered, mostly down-regulated, during the course of SARS-CoV-2 infection in a similar manner, resulting in a clearance-related pharmacokinetic interaction with the administered drugs. Additionally, liver involvement in COVID-19 may further complicate the picture. In May 2020, the investigational antiviral agent, remdesivir, has received U.S. food and drug administration (FDA) emergency use authorization for the treatment of COVID-19. According to its manufacturer, remdesivir undergoes extensive metabolism by CYPs especially CYP3A4 [130]. Moreover, other potential candidates for treating COVID-19 such as chloroquine [131] and colchicine [132] are also heptatically metabolized, so understanding the nature of such interaction is highly essential as it can influence the therapeutic/toxic response of patients to the agents intended for managing the disease [133,134]. Full attention should be paid when anti-cytokine therapy comes into play. In this case, partial or complete regain of normal metabolic status can be achieved as a result of the immunomodulatory effect.

In case of co-administration of multiple drugs, the risk of drug interactions increases, however, a more complex disease-drug-drug interaction is expected in COVID-19. SARS-CoV-2 infection has resulted in high rates of hospitalization and intensive care unit (ICU) admission [135,136]. This can be regarded as a major clinical concern especially when considering that critically ill patients are more predisposed to drug interactions, and that CYPs are involved in the metabolism of commonly prescribed drugs in the ICUs [137]. Moreover, demographic analysis of COVID-19 patients has revealed that older people with comorbidities are the most affected group [98,138] who also represent the potential candidates for advancing to severe stages and inevitable ICU admission [85]. Medical comorbidities in elderly patients warrant concomitant drug therapies, thus rendering them the most vulnerable group for both drug-drug and disease-drug interactions [139,140]. Therefore, the utmost level of caution is required to deliver the optimal dose for these patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Appendix A. Supplementary data

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