Clinical Pharmacokinetics (2021) 60:1537–1555
https://doi.org/10.1007/s40262-021-01064-4

SYSTEMATIC REVIEW

Impact of Inflammation on Cytochromes P450 Activity in Pediatrics: A Systematic Review

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Accepted: 26 July 2021 / Published online: 31 August 2021

Abstract

Background and Objective Cytochromes P450 (CYP) are the major enzymes involved in hepatic metabolism of drugs. Personalization of treatment in pediatrics is a major challenge, as it must not only take into account genetic, environmental, and physiological factors but also ontogeny. Published data in adults show that inflammation had an isoform-specific impact on CYP activities and we aimed to evaluate this impact in the pediatric population.

Methods Articles listed in PubMed through 7 January, 2021 that studied the impact of inflammation on CYP activities in pediatrics were included in this systematic review. Sources of inflammation, victim drugs (CYP involved), effect of drug–disease interactions, number and age of subjects, and study design were extracted.

Results Twenty-seven studies and case reports were included. The impact of inflammation on CYP activities appeared to be age dependent and isoform-specific, with some drug–disease interactions having significant pharmacokinetic and clinical impact. For example, midazolam clearance decreases by 70%, while immunosuppressant and theophylline concentrations increase three-fold and two-fold with intensive care unit admission and infection. Cytochrome P450 activity appears to return to baseline level when the disease is resolved.

Conclusions Studies that have assessed the impact of inflammation on CYP activity are lacking in pediatrics, yet it is a major factor to consider to improve drug efficacy or safety. The scarce current data show that the impact of inflammation is isoform and age dependent. An effort must be made to improve the understanding of the impact of inflammation on CYP activities in children to better individualize treatment.

1 Introduction

Inflammation is a universal protective reaction to endogenous or exogenous aggression that involves all tissues and both innate and adaptive immunity. It is known to induce changes in the concentrations of many plasma proteins and in several behavioral, physiological, and biochemical mechanisms [1]. Inflammation is complex and well orchestrated, as certain triggered mechanisms initiate, amplify, or sustain the process with many cell types and molecules [1]. Cytokines, and in particular interleukin-6, are the main stimulators of these acute changes [1]. Published data in adults indicate that inflammation has an impact on cytochromes P450 (CYP) activity, the major enzymes involved in drug metabolism, in an isoform-specific manner, and as a result of pre-transcriptional and post-transcriptional mechanisms that are cytokine specific [2–7]. Indeed, CYP activity is influenced by the interaction of genetic, environmental, and physiological factors through a wide variety of ligand-activated transcription factors and mediators regulating hepatic CYP content [6, 8]. Understanding the impact of inflammation on CYP activity is important to understand in order to personalize drug use, as many diseases such as infection, cancer, diabetes mellitus, autoimmune disease, surgery, or trauma are associated with inflammation [1, 9, 10].

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Key Points

The impact of inflammation on cytochrome P450 activities appears to be age dependent in the study population.

The impact of inflammation on cytochrome P450 activities appears to be isoform-specific.

Data that have evaluated the impact of inflammation on cytochrome P450 activities in pediatrics are lacking, as they frequently are in this particular population.

Children are not exempt from inflammation and inflammatory diseases, but data are scarce on the impact of inflammation on CYP activities and drug metabolism in the pediatric population [11]. It is well known that pediatric clinical trials are often lacking and less than half of labelled drugs have pediatric data [12]. Moral, ethical, and legal issues prevent rigorous scientific investigations in the pediatric population, and infant dosing regimens are often extrapolated based on data available only in the adult population [13]. However, children differ from adults in terms of height and weight but also in physiological perspectives because of an ontogeny [12]. The maturation and development of organs and enzyme systems influence the pharmacokinetics (PK) and pharmacodynamics of drugs, which may lead to potential variation in the efficacy and safety of drugs [13]. Ontogeny processes are complex and non-linear, making the pediatric population very heterogeneous and as such, the developmental course of all processes contributing to drug disposition cannot be described by a single uniform pattern [14, 15]. However, differences in drug-metabolizing enzyme activity appear to be the main determinants of the overall pharmacokinetic differences observed between adults and children [16]. Cytochrome P450s are mostly present at birth but are immature [15]. The development of enzyme activity over time is isoform-specific and is rapidly improving in the first weeks/years of life [12, 15]. Although data are still sporadic and sometimes contradictory, it is generally recognized that CYP1A2 has the slowest developmental pattern [17–19]. CYP2C19 and CYP3A4 likely have an intermediate pattern, with an adult's activity reached at the end of infancy [17–19]. In contrast, CYP2B6, CYP2C9, and CYP2D6 activity increases rapidly during the first months of life and early infancy [17–19]. As with adults, the use of effective and safe therapy in children requires a good understanding of the inter-individual and intra-individual variability due to their growth and maturation, and ontogeny should be taken into account when selecting a drug dosage in children [15, 17, 20]. Many efforts have been made in recent decades to predict age-related alterations in the PK of drugs in children [14]. Modeling approaches, such as physiology-based PK, are increasingly used in order to obtain pediatric data including both growth and maturation processes (intrinsic characteristics) and drug-specific parameters (extrinsic parameters) [16, 21]. They allow for safe and effective pediatric study designs and successful prediction of PK in the pediatric population [21]. Knowledge of the impact of disease and inflammation on CYP activity and drug PK appears to be an additional important element to consider. The aim of this systemic review was thus to evaluate the impact of inflammation on CYP activity in the pediatric population.

2 Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement requirements and the PICOS framework were used to manage and to develop the current literature search, respectively [22]. The PICOS framework we used was as follows: participants: children with source of inflammation; intervention: victim drugs and CYP concerned; comparison: healthy children or before the onset of inflammation or receiving treatment for inflammation; outcomes: effect of the interaction between inflammation and CYP activity; design of the studies: clinical trials and case reports/series.

2.1 Database and Search Strategy

PubMed via MEDLINE, the database of biomedical publications, was used to carry out the literature search for studies and case reports/series until 7 January, 2021. We also completed our literature search with a manual search of references for potentially relevant articles. We used the keywords "Inflammation", "cytochrome P450", "cytochromes P450", and "CYP450".

2.2 Study Selection

The following eligibility criteria were applied to select only pertinent publications from the literature search. Randomized controlled trials, non-randomized studies, and observational studies were the types of studies selected in our literature search, as well as case reports and series. Studies had to be published in English as full-text articles or congress abstracts, from database inception until 7 January, 2021. Studies participants had to be under 18 years of age, including healthy subjects and patients who suffered from inflammatory conditions caused by a disease, treatment, or a medical or surgical procedure. The outcomes of interest were the effect of potential (suggested or provided) inflammation on the metabolic ratios of CYP isoforms and the pharmacokinetic/pharmacodynamic and safety profiles of CYP substrates.

The screening of publications was done in several steps. First, the titles of the articles were read to make an initial selection. Then, the abstract and full text were read successively to filter out potentially relevant articles according to the predefined eligibility criteria. The remaining articles were categorized into literature reviews, in vitro, animals, in silico, and human studies. Studies concerning adults were then removed, retaining only those publications that concerned pediatrics (defined as under 18 years of age). Finally, they were classified as studies or case reports/series. A similar process was applied to the additional articles found by a manual search. The study selection method was summarized in a flowchart created according to the PRISMA statement requirements (Fig. 1) [22].

2.3 Data Extraction and Management

The reference management software Zotero (Version 5.0.85, © 2006-2018 Contributors) was used to collect and export highlighted articles and then, to remove duplicates. Data from the included articles were extracted and synthetized, and the extracted data were classified according to age group, namely pediatrics (under 18 years) and adults (over 18 years). The authors extracted the data according to the PICOS framework previously discussed. As a reminder, these included study design, sample size, source of inflammation and comparators, victim drugs and CYP involved in their mechanism, and outcomes of interests (effect of drug–disease interactions). A check of the metabolite pathway of the victim drug was performed to confirm whether it was a CYP substrate and which CYP was involved. The Summary of Product Characteristics, the Lexi-Interact drug interaction checker, and the Geneva table of CYP substrates, inhibitors, and inducers were used to perform this verification process [23, 24].

3 Results

3.1 Identification and Selection of the Studies

The first step of the PubMed research led to a total of 2283 articles, and of these articles, 523 remained after screening by title and abstract. By cross-referencing and handsearching the reference list of relevant articles, 366 additional articles were added, resulting in 889 articles. Next, 128 records were not available in full text and 224 were not translated into English or considered irrelevant, leading to the deletion of 352 records. The remaining 537 articles were categorized into review articles ($n = 55$), in vitro ($n = 77$), or in-silico ($n = 8$) studies and studies conducted in animals ($n = 152$) or humans ($n = 245$). Only publications involving humans were included in the current systematic review and were classified as including adults ($n = 218$) or children ($n = 27$). Articles and case reports concerning the adult population are the subject of another systematic review. Finally, 27 articles conducted in pediatrics were included and classified as studies ($n = 19$) and case reports/series ($n = 8$) for analysis. These results are summarized in Fig. 1.

3.2 Synthetized Findings

Table 1 summarizes the cases of drug–disease interactions presented in the 27 eligible publications. The drug–disease interactions found in the selected publications were organized by victim drug and CYP involved in their metabolism. The most cited inflammation perpetrator was infection and the two most studied CYPs were CYP1A2 and CYP3A because many were receiving theophylline or immunosuppressants.

4 Discussion

Understanding the PK and the pharmacodynamics of drugs is the key element to accurately determining the safest and most effective dose of a prescribed drug in pediatrics [17]. In children, in addition to environmental, genetic, and individual factors, such as comorbidities and medications, the influence of ontogeny must be considered and complicates prediction of the response to a treatment [17, 20]. However, because of the lack of specific studies, pediatric data are almost exclusively extrapolated from adult studies [15].

One of the covariates known to contribute to dynamic changes in CYP activity in adults is inflammation [2–6]. Little is known about the effect of inflammation on CYP activity in pediatrics and, to our knowledge, there is only one review on the subject [11]. Very few studies have been published in almost 10 years. The consequences of inflammation on CYP activities appear to be different between adults and children and confirms the impossibility of simply extrapolating the adult data, as shown in the different studies included in this review.

4.1 CYP3A4

CYP3A4 was the most studied CYP in children, in particular, the impact of inflammation on tacrolimus and cyclosporin A (CyA) pharmacokinetic parameters was assessed. Tacrolimus and CyA blood concentrations increased after a diarrheal episode due to a bacterial or viral infection [38–41]. Despite a probable effect of diarrhea on absorption, the authors concluded that intestinal inflammation suppressed the activity of CYP3A [38]. Similarly, in adults, several studies and case reports have focused on the impact of hepatitis C infection on tacrolimus and CyA

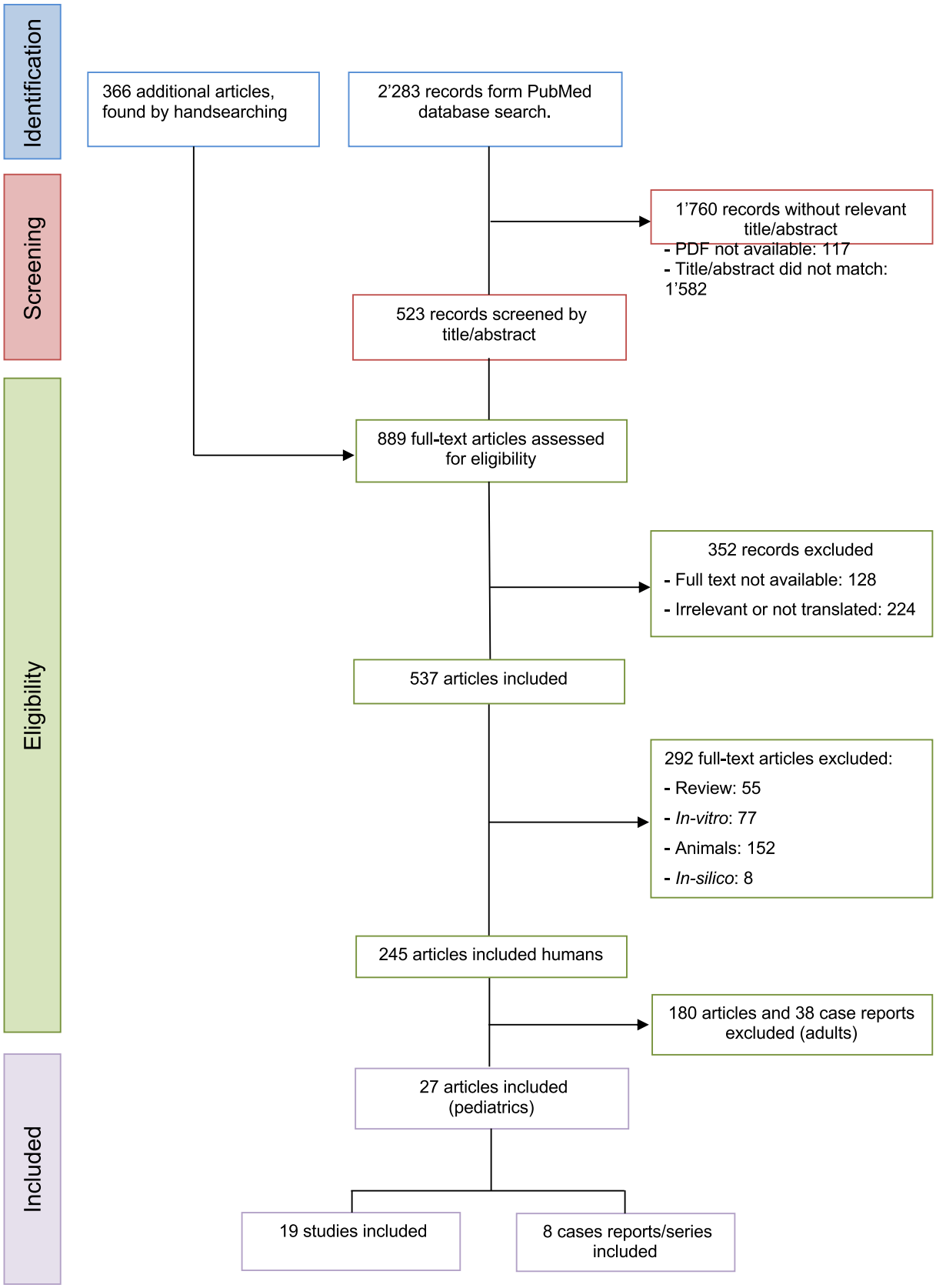

Fig. 1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flowchart of the studies selection process

Table 1 Impact of difference sources of inflammation on CYPs activities

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Upper respiratory tract infection	Theophylline (CYP1A2)	9–15 years ($n = 10$)	Mean plasma half-life was significantly longer during serologically proven infection compared with 1 month after illness (419.8 vs 249.9 min, p = not shown) [$n = 6$] Plasma half-life did not change during febrile illness without seroconversion ($p > 0.1$) [$n = 4$]	Transaminases were in the normal range and creatinine clearance did not change. No CYP modulators were introduced but there was no mention of potential usual treatment	[25] Cohort study
Bronchiolitis	Theophylline (CYP1A2)	3 weeks to 6.5 months ($n = 12$)	Mean clearance was lower in children with infection than previously published in patients of comparable age without any viral infection (p = not shown)	One child had cystic fibrosis and one had gastroesophageal reflux. No concomitant use of a CYP1A2 modulator	[26] Cohort study
Respiratory syncytial virus infection	Theophylline (CYP1A2)	6–48 months ($n = 29$ infection and 29 controls)	Clearance was not significantly different between both groups (1.32 ± 0.14 and 1.25 ± 0.05 mL/kg/min, respectively)	No mention of concomitant treatment, or even organ laboratory values to monitor organ dysfunction	[27] Case-control study
Flu-like symptoms	Theophylline (CYP1A2)	Age between 3 and 11.5 years ($n = 11$)	Clearance was reduced compared with previous determination of steady-state concentrations, but this reduction was not significant (p = not shown), but ten children had symptoms of theophylline toxicity Six had an influenza B titer and four were negative for serologic findings, and the mean difference in serum theophylline concentration between pre-infection and post-infection was 20 µg/mL and 14.2 µg/mL, respectively, for positive patients but this was not significant	Exclusion criteria were: increased dosage of theophylline, use of concomitant antibiotics, and symptoms of flu-like illness within the prior 2 weeks	[28] Cohort study
Febrile illness	Theophylline (CYP1A2)	11 and 7 years ($n = 2$, sex unknown)	Elevated serum theophylline concentrations (> 20 µg/mL) after febrile illness, adverse drug effects characteristic of inappropriate theophylline dosing	–	[28] Case report

Table 1 (continued)

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Respiratory syncytial virus infection	Theophylline (CYP1A2)	3–6 months ($n = 3$, sex unknown)	Clearance was lower in the seropositive children as compared with the other 2 (p = not shown)	–	[29] Case report
Influenza vaccination	Theophylline (CYP1A2)	15 years ($n = 1$, female)	The patient was usually known to metabolize theophylline rapidly Levels increased to a peak 5 h after vaccination and slowly returned to normal levels over the next 24 h	No CYP modulators	[30] Case report
Acute asthma exacerbation	Aminophylline (CYP1A2)	1–15 years ($n = 52$)	Patients with lower C72h/C24h ratios had a significantly higher number of patients with a CRP level > 0.5 mg/dL or fever > 37.5 °C Patients with a lower ratio had reduced CYP1A2 activity on admission because of higher CRP and fever levels and their catabolizing capacity improved during treatment	No other medication that affects theophylline metabolism such as anticonvulsants, rifampin, macrolide, or quinolone antibiotics was administered within the week prior to and during the study	[31] Cohort study
Malaria	Caffeine (CYP1A2)	7–9.9 years ($n = 5$ controls) 3–9 years ($n = 5$ malaria)	$t_{1/2}$ and oral clearance of caffeine were respectively longer and lower in children with malaria than in healthy volunteers (9.2 ± 3.5 h vs 3.7 ± 1.8 h, $p < 0.01$ and 1.6 ± 1.0 vs 4.4 ± 1.9 mL/min/kg, $p < 0.05$) Metabolic ratio was five to ten times lower in children suffering from malaria than in controls of the various timepoints	Four of five children with the diagnosis of malaria were treated with chloroquine and one was receiving artemether. There were no CYP1A2 modulators	[32] Case-control study

Table 1 (continued)

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Intensive care unit	Midazolam (CYP3A)	2 days to 17 years ($n = 18$ intensive care) 3–10 years ($n = 56$ controls)	Clearance and elimination $t_{1/2}$ determined during and after continuous infusion in intensive care patients were 5.0 ± 3.9 mL/kg/min and 5.5 ± 3.5 h, respectively Total body clearance and plasma elimination $t_{1/2}$ in controls were 9.11 mL/kg/min and 1.17 h, respectively	None of the patients received midazolam > 12 h before study or treatment that altered the PK of midazolam, but 2 patients received such a drug after inclusion. Three patients were considered as outliers (severe renal and hepatic failure and erythromycin intake). Pharmacokinetic variations could also be explained by variations in body composition (volume of distribution)	[33] and [34] Case-control study
Critically ill children	Midazolam (CYP3A)	2 days to 17 years ($n = 21$)	Clearance was significantly lower in children with multiple organ failure ($p = 0.035$) than in those without No correlation was found between CRP and clearance ($r = -0.27$, $p = 0.30$) No correlation between clearance corrected for body weight and the administered dose ($r = -0.41$, $p = 0.06$)	It was a pilot study. No mention of concomitant treatment or laboratory values. Alternative explanation could be the altered level of protein binding. Inflammation may alter drug PK and PD differently as decreased clearance is seemingly unrelated to decreased dose requirements	[35] Cohort study
Intensive care unit	Midazolam (CYP3A)	1 day to 7 years [median = 5.1 months] ($n = 83$)	Higher CRP concentration was associated with lower clearance CRP of 300 mg/L was associated with a 65.4% lower clearance than a CRP of 10 mg/L	The clearance of midazolam decreased with an increasing number of organ failures. 14 patients received a CYP3A inhibitor, but this had no effect on midazolam clearance. CYP3A polymorphisms, albumin, creatinine, and alanine aminotransferase levels were tested as covariates, but neither improved the model nor explained variability in clearance or volume of distribution. Inflammation and organ failure resulted in a better description of the data	[36] Cohort study

Table 1 (continued)

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Acute lymphoblastic leukemia	Lorazepam (CYP3A)	Mean age = 5.3 years (n = 14)	Mean increase of 52% (p = 0.016) in systemic clearance between the pre-induction and the post-induction therapy phase All patients were in remission in the post-induction therapy phase, and an effect of induction therapy was not expected, as clearance was measured 46 (35–96) days after	Clinical factors such as total bilirubin, SGOT, PT time, WBC count at diagnosis, age, and liver size at diagnosis were not predictive for the changes seen in model substrate clearance before and after induction. No influence of fever, induction therapy, or concurrent drug therapy. Changes in protein binding cannot account for the improvement in clearance of lorazepam, as lorazepam free clearance increased before and after remission	[37] Cohort study
Diarrheal episode caused by bacterial infection	Cyclosporin A (CYP3A4)	1.8 years (n = 1, boy)	Elevated C/D ratio from 2.0 to 2.9 to 6.3 during a diarrheal episode Increased C/D ratio to 6.3, then dropped below 4 after diarrhea remission Inflammation in the intestine caused by bacterial infections suppressed the activity of CYP3A and led to an increase of the C/D ratio of CyA	No CYP modulators and no change in laboratory values	[38] Case report
Diarrheal episode caused by rotavirus	Tacrolimus (CYP3A4)	2.4 years (n = 1, girl)	C/D ratio elevated from 5.4 to 5.7 to 11.3 during a diarrheal episode Upon remission of diarrhea, tacrolimus concentration decreased Inflammation of the intestine caused by viral infections suppressed the activity of CYP3A and led to an increase of the C/D ratio of tacrolimus	No CYP modulators and no change in laboratory values	[38] Case report

Table 1 (continued)

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Diarrheal episode caused by rotavirus	Tacrolimus (CYP3A4)	Age and sex unknown ($n = 1$)	Increase in tacrolimus trough concentration from 9 ± 1.5 to 60 µg/L (despite drug withdrawal) after diarrheal episodes	No CYP modulators, weight loss, or hepatic dysfunction. Decreased GI transit time might be a potential mechanism for increasing tacrolimus concentrations. The expression on the small and large intestinal epithelium of P-gp could be of clinical importance. The destruction of villous epithelial cells may be an important determinant	[39] Case report
Diarrheal episode caused by rotavirus	Tacrolimus (CYP3A4)	7 years ($n = 1$, boy)	Increase in tacrolimus trough concentration from 9.5 ± 0.7 to 20.9 µg/L, despite tapering the dose, after a diarrheal episode	No CYP modulators, weight loss, or hepatic dysfunction. Decreased GI transit time might be a potential mechanism for increasing tacrolimus concentrations. The expression, on the small and large intestinal epithelium of P-gp could be of clinical importance. The destruction of villous epithelial cells may be also an important determinant	[39] Case report
Gastroenteritis	Tacrolimus (CYP3A4)	9 years ($n = 1$, girl)	Trough concentration was higher than usual at 27.6 ng/mL	Authors suggest that it is the combined effect of altered gut motility and hepatic metabolism. Laboratory values were in the normal limits. No change in concomitant treatment but loss of weight (no change in diet)	[40] Case report

Table 1 (continued)

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Shigella infection	Tacrolimus (CYP3A4)	8 years ($n = 1$, girl)	Usual blood concentrations was 8.2 mg/mL, but it increased to more than 30 ng/mL on admission because of fever (39–40 °C), diarrhea, and abdominal cramps that had started a week earlier Over the next 2 weeks, tacrolimus blood concentrations ranged between 16.5 and 22.0 ng/mL despite reductions in tacrolimus dose After the diarrhea resolved, tacrolimus blood concentration returned to baseline	Liver function was stable, but Shigella infection facilitates the invasion, rupture, and permeability of the intestinal epithelium. No dehydration or diet changes	[41] Case report
Flu-like symptoms	Sirolimus (CYP3A)	8 and 13 years ($n = 2$ boys)	Higher than expected concentrations were observed in patients with flu-like symptoms and, therefore, an infectious state with fever	No CYP modulators during treatment and time lapse between the onset of fever and decrease in clearance	[42] Case report
Treatment with basiliximab	Cyclosporin (CYP3A)	Mean age = 7.5 years ($n = 24$ basiliximab) Mean age = 9.7 years ($n = 15$ controls)	Dose required during the first 10 days was lower in the basiliximab group than in controls, while the trough concentration was higher At days 28–50, the concentration decreased despite any change in dose	–	[43] Case-control study
Unspecified source of inflammation (150 < CRP > 150 mg/L)	Voriconazole (CYP3A4 and CYP2C19)	< 12 years [median = 4 years] ($n = 11$) > 12 years [median = 15 years] ($n = 16$)	All groups received the same doses, based on mg/kg body weight Patients aged older than 12 years with CRP levels > 150 mg/L had significantly higher trough concentrations of voriconazole CRP > 150 mg/L downregulated CYP2C19 and 3A4 in children aged > 12 years	Exclusion criteria were concomitant use of CYP modulators and relatively low/high dosage to avoid bias due to extreme dosing. Patients' characteristics (underlying disease, trough concentration, and CRP value) were similar between both groups	[44] Cohort study

Table 1 (continued)

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Aspergilloses	Voriconazole (CYP2C19 and 3A)	9 months to 18 years ($n = 10$)	8 patients had hematological malignancy and 2 had cystic fibrosis Median trough concentrations in patients < and > than 12 years were 0.53 and 0.79 mg/L, respectively CRP had no significant impact on trough concentrations of voriconazole	Impact of age, sex, weight, survival, route of administration, co-treatment (omeprazole, phenytoin, and CyA), registered biochemical parameters, and total daily dose on voriconazole trough concentrations was examined. None of these factors had a significant impact ($p > 0.5$)	[45] Cohort study
Hepatitis A	Coumarin (CYP2A6)	6–10 years ($n = 11$ hepatitis A) 6–13 years ($n = 10$ controls)	Mean reduction of 72% ($p < 0.0001$) in total urine excretion of 7-hydroxycoumarin compared with healthy controls	ASAT, ALAT, and GGT were below normal range in patients with hepatitis A. Creatinine was in normal range. Unknown concomitant treatments	[46] Case-control study
Gastroenteritis	Oxatomide (CYP2D6 and 3A4)	3 years ($n = 1$, boy)	Anti-H_1 toxicity (abdominal pain, pallor, slurred speech followed by serious long-lasting impairment of consciousness) after oxatomide, despite not having any of the following CYPs polymorphisms: CYP2D6*3, *4, *5, and *6 or CYP3A4*1B CRP value of 0.47 mg/dL (physiologic range < 0.25 mg/dL) was found	No other drug treatment and no history of recent trauma, seizure, and neurologic disorder	[47] Case reports
Febrile illness	Anticonvulsants (CYP1A2, 2C9, 2C19, 2E1, and 3A)[a]	6 months to 7 years [mean = 10 years] ($n = 111$)	55 episodes of febrile illness in 39 children during the study period 12 illnesses were associated with significant increases or decreases in serum levels 7 children experienced toxic clinical symptoms and one had increased seizures during illness	27/55 and 49/55 were treated with antibiotics and acetaminophen, respectively. Authors conclude that mechanisms of anticonvulsant level changes appeared to include interaction with antibiotics, antipyretics, or viral illness. However, investigators may have missed some illnesses	[48] Cohort study

Table 1 (continued)

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Fever	Antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18, and 3A4)[a]	5 months to 5 years ($n = 6$)	The saliva clearance of antipyrine was reduced by approximatively 50% during fever compared with the afebrile period ($p < 0.02$) The half-life during fever was almost doubled ($p < 0.01$)	Concomitant treatments (erythromycin in case 2 and cotrimoxazole in case 3) but the clearance was reduced during fever in all children by 8–64%	[49] Cohort study
Suspected sepsis	Antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18, and 3A4)[a]	1–18 years [median = 4 years] ($n = 51$ suspected sepsis and 6 controls)	Metabolism was lower in the children with suspected sepsis than in the 6 children in the control group Metabolism was much lower in patients with multiple organ failure, and the antipyrine elimination half-life increased with increasing IL-6 and nitrate plus nitrite levels	Patients were assigned 1 point for each organ failure. Univariate analysis revealed an association between reduced antipyrine metabolism and liver, respiratory, and hematological failure ($p < 0.05$). Patients were excluded if they received any exogenous NO source. Concomitant use of CYP modulators was recorded. There were 38 positive cultures	[50] Case-control study
Acute lymphoblastic leukemia	Antipyrine (CYP1A2, 2B6, 2C8, 2C9, 2C18, and 3A4)[a]	Mean age = 5.3 years ($n = 14$)	Mean increase of 67% ($p = 0.007$) in systemic clearance between the pre-induction and the post-induction therapy phase All patients were in remission in the post-induction therapy phase, and an effect of induction therapy was not expected, as clearance was measured 46 (35–96) days after	Clinical factors such as total bilirubin, SGOT, PT time, and WBC count at diagnosis, age, and liver size at diagnosis were not predictive for the changes seen in model substrate clearance before and after induction. No influence of fever, induction therapy received, or concurrent drug therapy	[37] Cohort study
Crohn's disease	–	7–15 years ($n = 19$ Crohn's disease and 19 controls)	Higher CYP3A4 and CYP3A5 expression levels detected in Crohn's disease biopsies compared with normal biopsies Crohn's disease group biopsies came from non-inflamed duodenal biopsies	All included patients were not receiving known modulators of CYP3A and had no digestive complications, but a tissue expression discrepancy should be taken into consideration	[51] Case-control study

Table 1 (continued)

Inflammation characterized by	Victim drugs (CYPs concerned)	Age and number of subjects	Potential effect of interaction	Relevant comments	References and design
Crohn's disease	–	7–17 years ($n = 18$ Crohn's disease and 12 controls)	PXR expression was decreased in the inflamed terminal ileum compared with the non-inflamed duodenum ($p < 0.001$) but this was not observed in the control group ($p = 0.52$) CYP3A4 expression followed the same line ($p = 0.014$ and $p = 0.61$, respectively) Expression of PXR/CYP3A4 was inversely correlated with IL-8 and inflamed tissue	Use of non-inflamed duodenal tissue from each subject as a negative control for that subject eliminates inter-individual genetic variability as a confounding factor. No difference in PXR expression was observed between the terminal ileus and the duodenum in age-matched and sex-matched controls, the observed decrease in the CD terminal ileus cannot be attributed to the biopsy-site location	[52] Case-control study

ALAT alanine aminotransferase, *ASAT* aspartate aminotransferase, *C/D* concentration/dose, *CRP* C-reactive protein, *CyA* cyclosporin A, *CYP* cytochrome P450s, *GI* gastrointestinal, *GGT* gamma-glutamyl transferase, *h* hours, *IL* interleukin, *min* minutes, *NO* nitric oxide, *PD* pharmacodynamics, *P-gp* P-glycoprotein, *PK* pharmacokinetics, *PT* Prothrombin Time, *SGOT* Serum Glutamic-Oxaloacetic Transaminase, $t_{1/2}$ half-life, *WBC* white blood cell

[a]Definitive conclusion cannot be drawn because of the number of CYP isoforms that contribute to the metabolism of the drug

pharmacokinetic parameters. Indeed, the plasma concentrations of tacrolimus and CyA were higher, and doses lower, in patients with hepatitis C infection as compared with patients without hepatitis C infection [53–55]. Inversely, treatment of hepatitis C resulted in decreased tacrolimus and CyA concentrations and/or increased required doses [56–60]. Thus, the treatment of the infection allowed a return to baseline CYP3A activity, probably because the subsequent inflammation disappeared.

Basiliximab is another example where inflammation downregulated CYP3A activity similarly in children and adults. Indeed, concentrations of tacrolimus and CyA increased during the first days of basiliximab treatment both in adults and children [43, 61]. Moreover, concentrations decreased spontaneously after 30 days of basiliximab treatment, despite any dose modification [43, 61]. The authors suggested that the impact of basiliximab on drug metabolism was due to interleukin-2 [61]. The similar effects observed in adults and children could be explained by the intermediate developmental pattern of CYP3A4, as adult CYP3A activity is reached at the end of infancy and children were aged older than 2 years [17–19].

Regarding critically ill patients, CYP3A4 has been shown to be downregulated in adults and the decrease of CYP34 activity was correlated with the severity of organ failure [62, 63]. The same results were observed in pediatric intensive care unit patients. Metabolism of midazolam decreased with the severity of intensive care unit-induced inflammation as a consequence of CYP3A4 downregulation [33–36]. However, it is possible that mechanisms other than CYP regulation could also be responsible for the drug's pharmacokinetic alterations during inflammatory states, such as changes in plasma protein binding and renal excretion [64]. A study indeed showed that proinflammatory cytokines trigger an acute-phase response that could increase the unbound fraction of drugs [65]. In diabetic adults, the lack of differences in CyA daily doses, but the lower production of its metabolites, could be the consequences of variations in protein binding [66]. No other studies assessing CYPs other than CYP3A could be found in the literature. Those studies should be performed, as data in adults have shown that CYPs are regulated in an isoform-specific manner in critically ill patients [67].

In children with Crohn's disease, both CYP3A4 and CYP3A5 were upregulated, which is inconsistent with the previous observation of downregulation of CYP3A4 associated with higher C-reactive protein (CRP) levels, but could be explained by the fact that the biopsies were from non-inflamed tissue [51]. In another study in children of the same age range, the expression of the nuclear hormone receptor PXR was decreased in inflamed tissues and, thus, CYP3A4 expression also decreased [52]. Further studies in children with inflammatory bowel disease should be initiated to

understand these discrepancies, as well as in vitro studies to understand the underlying mechanisms. In adults, verapamil (CYP3A4, 1A2, 2C8, 2C9, and 2C18 substrate) and propranolol (CYP2D6 substrate) concentrations were significantly higher in patients with active Crohn's disease than in healthy volunteers or patients in remission [68, 69]. The authors suggested that the reduced clearance could be attributed to CYP downregulation, but increased bioavailability due to downregulation of P-glycoprotein could not be ruled out [68]. However, a possible impact of the decrease in CYP content due to Crohn's disease should be kept in mind.

4.2 CYP1A2

In adults, the impact of inflammation on CYP1A2 activity has been well studied for two substrates (i.e., theophylline and clozapine) and a decrease in their clearances has been observed, as well as symptoms of clozapine toxicity [70–78]. In pediatrics, theophylline was the only studied substrate of CYP1A2, except one study with caffeine [32]. Theophylline has been a commonly used drug for asthma for over 50 years, but its narrow therapeutic index has made it disappear from current asthma guidelines [79, 80].

In line with what is found in adults, our literature review showed that infection may decrease CYP1A2 activity in children [25, 26, 28–30, 32]. However, a study conducted in children aged 6–48 months ($n = 58$), showed that infection had no impact on theophylline clearance [27]. CYP1A2 has the slowest developmental pattern and a large heterogeneity in the impact of inflammation on its activity is expected, with increasing intensity as age advances [17–19]. Further investigations are needed to determine whether CYP1A2 is affected by inflammation in children.

4.3 Other CYPs

Antipyrine is an older drug metabolized by several CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C18, and 3A4) and which has been widely used to investigate hepatic drug metabolism because it is almost completely absorbed from the intestine, has negligible plasma protein binding, a low hepatic extraction ratio, and is metabolized almost entirely by the liver [81]. In children, clearance of antipyrine appeared to be reduced during fever or suspected sepsis [49, 50]. Moreover, the inhibition of metabolism was proportional to disease severity and interleukin-6 levels, and a return to baseline levels was observed with cancer resolution [37, 50]. Inflammation is present at all stages of cancer, with an apparent link between certain immune-mediated diseases or infection and cancer, such as inflammatory bowel disease or *Helicobacter pylori* that are associated with colorectal and gastric cancer, respectively [82]. CYP3A and CYP2C19 are two well-studied isoforms in cancer, and several studies have found impaired activity of these CYPs in adult patients with cancer [83–90]. Only one study has been conducted in children (mean age 5.3 years) with acute lymphoblastic leukemia, and CYPs also appear to be altered during the acute phase [37]. Further studies are needed in pediatric oncology and in different age groups because chemotherapeutic and antimicrobial agents for prophylaxis are CYP substrates. In adults, the downregulation of antipyrine metabolism was also observed during infection, diabetes, or interferon treatment [91–94].

Anticonvulsants studied in children during inflammation were carbamazepine (CYP1A2, CYP2C9, and CYP3A substrate), phenytoin (CYP2C9 and CYP2C19), valproate (CYP2C9), phenobarbital (CYP2C9 and CYP2C19), and ethosuximide (CYP2E1 and CYP3A) [48]. Only seven children out of 39 with a febrile illness experienced toxic clinical symptoms and one had increased seizures during the illness [48]. The authors conclude that nearly a quarter of patients with febrile illnesses experienced significant changes in drug concentrations, with 9% developing clinical toxicity [48]. They suspected direct inhibition by antibiotics and plasma protein displacement by antibiotics and antipyretics, in addition to inhibition of CYP activity by viral infection [48]. In adults, the effect of inflammation was mostly studied with phenytoin with an increased risk of toxicity. For instance, a 52-year-old woman had toxic phenytoin concentrations with associated symptoms during the influenza illness and urinary excretion of the metabolite of mephenytoin among patients with liver disease or multiply injured was significantly lower than healthy controls [67, 95, 96].

Voriconazole is mainly metabolized by CYP2C19 and CYP3A [97]. In adults, a cohort study found that the level of CRP was positively associated with the concentration/dose (C/D) ratio or through concentration of voriconazole and was negatively associated with the metabolic ratio expressed by [N-oxide voriconazole]/[voriconazole] [98–101]. Moreover, an elevated level of CRP was a risk factor for voriconazole overdose [102]. This could be explained by CYP2C19 and/or CYP3A downregulation due to inflammation, represented by elevated levels of CRP. In children, this association is less pronounced, as a significant association between CRP levels >150 mg/L and higher voriconazole through concentrations was only observed in patients aged older than 12 years [44]. Moreover, another study conducted in children did not find an association between trough concentrations of voriconazole and CRP, but the cohort was very small and no distinction was made between older and younger children [45]. Possible explanations for this difference in association between CRP and CYP downregulation observed in children aged younger and older than 12 years are that the PK of voriconazole appears to be linear before 12 years of age and non-linear after [44]. The bioavailability of voriconazole indeed decreases (and clearance increases) in pediatric

patients compared with adults, resulting in less saturation of PK processes and, thus, linear kinetics [12, 45]. This implies that first-pass metabolism is higher in the pediatric population and it was suggested that CYP-mediated clearance is higher in children under 12 years of age and thus that downregulation by inflammation had less impact on voriconazole metabolism [44]. However, CYP2C19 and CYP3A4 activity reaches that of an adult at the end of infancy and inflammation is expected to further inhibit CYP activity because there are more CYPs to downregulate [17–19]. One possible explanation is that enzymes other than CYPs are responsible for voriconazole clearance and that they are more expressed in children and less impacted by inflammation. Voriconazole is also metabolized by flavin-containing monooxygenase 3, and the contribution of flavin-containing monooxygenase 3 and CYP2C19 has been shown to be five-fold and three-fold higher in children than in adults, respectively [45, 103]. It is important to consider these non-CYP phase I drug-metabolizing enzymes because approximatively 25% of metabolically eliminated drugs are first subjected to non-CYP-mediated biotransformation [14]. Moreover, it seems that flavin-containing monooxygenase 3 and CYP2C19 have higher catalytic activity in children than in adults [45, 103]. Another hypothesis is that the CYP2C19 contribution to CYP3A is more affected by inflammation. We have indeed previously demonstrated in adults that CYP3A was more impacted by inflammation than CYP2C19 [104].

4.4 CYP Genotype

The CYP genotype is an additional factor to be considered, as cytokines may not have the same impact on CYP activities depending on the basal genetic activity of CYPs. In adults, the different impact of inflammation on CYP2C19 and CYP2C9 depending on the genotypes has already been demonstrated [105, 106].

In children, the same conclusions can be drawn as oxotamide toxicity was observed in 3-year-old children who were not carriers of CYP2D6 or CYP3A4 main allelic variants at the time of the study, meaning that the reduced clearance is not caused by the manifestation of CYP2D6*3, *4, *5, and *6 or CYP3A*1B [47]. It is therefore conceivable that the release of pro-inflammatory molecules such as CRP decreased CYP2D6 and/or CYP3A activities, eventually leading to an increase in the oxatomide plasmatic concentration [47].

4.5 Limitations

Our systematic review has some limitations, which suggest a cautious approach to these results. First, the manual search was performed in a single database and for published articles only, which cannot rule out publication bias and the potential for omissions. Furthermore, the studies found and selected were poorly comparable to each other, owing to the heterogeneity of their overall methodology. Finally, the observed PK and clinical impact are neither robust nor generalizable because of the diversity of the sources and severity of inflammation.

5 Conclusions

In recent years, numerous clinical studies and case reports evaluated in adults have reported a modification in CYP activities and pharmacokinetic parameters of drugs in the presence of inflammation. The latter being an important factor contributing to variation in CYP activities between and within individuals. This may have a clinical impact, as CYPs play an essential role in the bioactivation or elimination of many therapeutic agents. Current data suggest that inflammation has an isoform-specific and intensity-specific impact, i.e., CYP3A and CYP2C19 activities are downregulated and CYP2D6 activity does not change during inflammation, whereas the impact on CYP1A2, CYP2B6, and CYP2C9 remains unclear and needs further investigations. Some studies have even shown that CYP activity returns to baseline after the improvement of the disease. There is significant heterogeneity in inflammatory markers, depending on the disease involved and its degree of severity.

To our knowledge, no study has evaluated inflammation-induced CYP phenoconversion in children using a cocktail approach. In addition to the moral, ethical, and legal difficulties of conducting studies in children, a cocktail approach is further complicated by the multitude of probes administered. The development of endogenous markers of CYP metabolism could help overcome these obstacles and may have interesting opportunities to develop personalized medicine in the pediatric field. Indeed, in children, the proportion of the drug cleared by the metabolism of CYPs, the patient's genotype, and concomitant medications, but also ontogeny must also be taken into account. Inflammation has a different impact on CYP activity depending on age as the proportion of CYP changes depending on the isoform and extrapolation from adult data cannot be done automatically. Despite all this evidence, much remains to be done to know the impact of inflammation on CYPs activity in the pediatric population. Indeed, this review highlights that, beyond the fact that few studies have been conducted in pediatrics, almost no studies have been conducted in neonatal to early infancy, although this is the period when developmental changes are most important. Moreover, many diseases with underlying inflammation have not yet been studied and the few existing studies do not focus on CYPs other than CYP3A and CYP1A2.

Declarations

Funding Open Access funding provided by Université de Genève.

Conflict of Interest/Competing Interests The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The data that support the findings of this study are available from all contributing authors and upon reasonable request.

Code Availability Not applicable.

Authors' Contributions CL participated in the manuscript conceptualization, experimental design, writing, data analysis, and overall manuscript review. FR, CFS, and VR participated in the manuscript conceptualization, experimental design, data analysis, supervision, and overall manuscript review. JAD participated in the supervision and overall manuscript review.

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