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The effect of inflammation on drug metabolism: a focus on pediatrics

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Inflammation is associated with downregulation of the expression and activity of cytochrome P450 enzymes (CYP450) involved in hepatic drug metabolism. Elevated plasma drug levels and increased toxicity might be the consequences of this downregulation. Few clinical studies have investigated these consequences of inflammation in children, who are prescribed many off-label or unlicensed drugs. This review describes the impact of inflammation on CYP450 drug metabolism and drug effect in children, with the consequent implications for drug studies and clinical therapy in this group.

Introduction

Pharmacokinetic and pharmacodynamic studies in children are scarce. Knowledge of the behavior of drugs in these patients is limited, and is based mainly on information derived from studies in adult healthy volunteers and patients. There are important differences in pathophysiology and disease spectrum between children and adults, as well as developmental changes that might affect the pharmacokinetics and pharmacodynamics of a drug. Therefore, adult data on the disposition and effect of drugs cannot generally be extrapolated to children, as reviewed by Kearns *et al.* [1].

In critically ill children, extrapolation is even more problematic, because drug disposition and effect might be influenced by a range of other factors. Pediatric intensive care patients are frequently exposed to poly-pharmacy, and more than 70% of drugs prescribed are either unlicensed or off-label [2]. Both factors could impose an increased risk of drug therapy failure or adverse drug reactions on these patients. Critical illness is associated with renal failure, hepatic dysfunction and cardiac failure, all leading to altered drug clearance [3].

A relatively unrecognized factor that can greatly affect the disposition of drugs is the underlying inflammation. Inflammation is common in several disease states in children, such as critical illness, autoimmune diseases and cancer. Numerous animal and limited human studies have shown that inflammation is associated with the downregulation of several drug-metabolizing enzymes, especially the cytochrome P450 (CYP) enzymes, as reviewed by several authors [4–8]. Given that CYP is the major enzyme system involved in drug metabolism, changes in the expression or activity of these enzymes could have a significant impact on the clearance and clinical effect of drugs [9]. Although understanding the effect of inflammation on drug disposition and effect in critically ill children and children with other inflammatory disease states could be of considerable clinical relevance, data are scarce. The purpose of this review is to summarize the effect of inflammation on CYP450-mediated drug metabolism, and drug effect in children with inflammatory disease.

Hepatic drug metabolism in children and the inflammatory response

The CYP450 enzyme family consists of several subfamilies and these enzymes are the most abundant drug-metabolizing enzymes in humans. CYP3A is the most prominent subfamily in terms of number of substrates and proportion of total CYP in the liver, and it metabolizes more than half of all therapeutic drugs [10]. Many of the drugs used in children are also metabolized by this enzyme, such as analgesics (e.g. fentanyl and lidocaine), benzodiazepines (e.g. midazolam and diazepam), macrolide antibiotics, antiarrhythmics (e.g. nifedipine, verapamil and propanolol), prokinetics (e.g. domperidone and cisapride) and anticancer drugs [10].

Changes in CYP activity could have a significant impact on drug metabolism. In children, most CYP enzymes show an increase in activity after birth [1]. Furthermore, CYP enzyme activity might change as a result of the concomitant administration of other drugs, genetic polymorphisms and concomitant diseases.

The inflammatory response, which occurs in many diseases, has also been associated with decreased CYP enzyme activity. The

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release of proinflammatory cytokines, especially interleukins (IL-1, IL-6 and IL-8), tumor necrosis factor (TNF-α) and interferon gamma (IFN-γ), induce the production of acute phase proteins by the liver (e.g. fibrinogen, α1-acid glycoprotein and C-reactive protein) and decrease the synthesis of normal export proteins (e.g. albumin and transferrin). The proinflammatory cytokines involved in the acute phase response can also alter drug-metabolizing enzyme capabilities.

The effect of inflammation on drug metabolism

Animal studies

The effect of inflammation on CYP expression and activity has been extensively studied in animals and has been described in several reviews [4–6,11,12]. These studies showed a downregulation of expression and activity of CYP450 enzymes after the administration of endotoxins [lipopolysaccharide (LPS)] and cytokines (TNF-α, IL-1, IL-6 and IFN-γ) [13]. The most affected CYPs belong to the CYP1A, 2A, 2C, 2E and 3A subfamilies. The inflammatory response to viruses, bacteria and parasites also negatively alters CYP expression and function [11]. Similarly, the inflammatory response to infection, injury or autoimmune disease negatively impact drug biotransformation in animals [14]. Consequently, the downregulation of CYP activity by inflammation leads to decreased drug clearance and elevated plasma drug levels. In LPS-treated rats, a reduced clearance is observed for several drugs, such as midazolam, chlorzoxazone, telithromycin and antipyrine [12,15]. In addition, propranolol plasma concentrations are markedly elevated in inflammatory conditions in rats [16].

Given that a homology of proteins between human and rat CYP isoenzymes is reported, it could be expected that human drug metabolism is also affected by inflammation. However, the extrapolation of animal data to humans is hampered by interspecies differences in CYP450 enzymes and their regulation [13].

In vitro *studies in human hepatocytes*

In vitro studies with primary cultured human hepatocytes have served as a model for the *in vivo* effects of cytokines on CYP activity [13]. Recently, Aitken *et al.* reported that expression of CYP3A4 and CYP2C8 was downregulated by all cytokines studied [IL-1, IL-6, TNF-α, IFN-γ and transforming growth factor-β (TGF-β)], whereas CYP2C18 expression was unaffected. Expression of CYP2C9 and CYP2C19 was affected by IL-6 and TGF-β, but not by TNF-α, IFN-γ and IL-1. CYP2B6 expression was only decreased after administration of IL-6 and IFN-γ [17]. This study confirmed that inflammatory cytokines differentially regulate human CYP expression.

In addition to downregulation of expression, it was recently shown that IL-6 also mediates repression of CYP3A4 protein levels and enzymatic activity [18]. Given that different diseases have different cytokine profiles and time courses, the influence of inflammation on human drug metabolism might be disease and drug specific.

The effect of inflammation on human pharmacokinetics

Adults

During the past 40 years, several clinical studies in adults have reported alterations in drug metabolism and the pharmacokinetics of drugs in the presence of inflammation. These studies have been reviewed previously [4–8,11]. Table 1 provides a summary of all the clinical studies we identified as looking at the effect of inflammation on drug metabolism.

Reduced activity is reported for CYP3A, CYP1A2, CYP2C9, CYP2C19 and, recently, for CYP2D6 in patients with an acute infection or inflammatory disease. This cytokine-mediated decrease in drug metabolism can be up to 70%. Therefore, the clinical concern is that patients with an inflammatory disease will have an increased exposure to drugs because of a decreased clearance, and thereby an increased risk of adverse drug effects. Additionally, as inflammation can also affect the expression and activity of important drug transporters, the uptake and clearance of drugs can be further affected [19]. For instance, a recent study in patients with HIV showed that not only overall CYP3A activity, but also P-glycoprotein activity was lower in these patients compared with healthy volunteers [20].

Furthermore, other factors that are influenced by inflammation, such as protein binding, capillary permeability, cardiac output and liver blood flow, also have the potential to influence pharmacokinetics and pharmacodynamics [21]. All together, these changes could have important consequences in terms of the pharmacokinetic and pharmacodynamic disposition of drugs in adults.

Critically ill adults

In 1987, it was reported that drug metabolism is altered in critically ill patients. In patients with septic shock, a reduced clearance of midazolam was found. This altered clearance was due to a reduced capability to form the 1-OH metabolite, but was reversible after improvement of the clinical condition [22]. The reduced clearance of midazolam could be the result of reduced liver perfusion, as suggested by the authors but, given that midazolam is a medium-clearance drug, it is likely that reduced CYP3A activity is also a factor of influence.

During the past few years, additional studies have suggested a reduced CYP activity in critically ill patients with sepsis. The clearance of theophylline (CYP1A2) is reduced in patients with sepsis and multiple organ failure [23]. The formation of MEGX from lidocaine, formed by CYP3A4, is decreased in patients with sepsis and this was not influenced by acute changes in hepatosplanchnic blood flow after dopamine infusion [24]. In addition, plasma levels of atorvastatin, metabolized by CYP3A4, are high in patients with sepsis [25]. It is likely that cytokines have an important role in the suppression of CYP activity in these patients. This is further supported by the results of Novotny *et al.*, who found a significant decrease in overall CYP450 activity, measured by the aminopyrine breath test, in patients with sepsis and this reduction was inversely correlated with TNF-α serum levels [26]. In addition, mephenytoin and chlorzoxazone (CYP2C19 and CYP2E1, respectively) metabolism was depressed in severely injured patients, who also display an intense inflammatory response [27].

Children

In children, studies on the effect of inflammation on the pharmacokinetics of drugs are scarce. In 1978, a reduced clearance of theophylline was described in asthmatic children suffering from a viral upper respiratory tract infection caused by influenza A or adenovirus [28]. In 2000, Yamaguchi *et al.* showed that children

TABLE 1

Studies on the effect of inflammation on drug metabolism in adults

Inflammation mechanism	CYP activity	Measurement	Effect	Correlated with:	Refs
Healthy subjects					
LPS	Overall CYP	Antipyrine, theophylline and hexobarbital	↓22–35%	TNF-α, IL-6	[54,55]
	CYP2E1	Chlorzoxazone	↔	-	[56]
IL-10	CYP3A	Midazolam	↓12%	IL-10	[57]
	CYP2C9	Tolbutamide	↔		
	CYP1A2	Caffeine	↔		
	CYP2D6	Dextromethorphan	↔		
Influenza vaccination	CYP3A4	Erythromycin breath test	↓4%	IFN-γ	[58]
Inflammatory diseases					
Elective surgery	CYP3A4	Erythromycin breath test	↓20–60%	IL-6	[59]
Allogeneic bone marrow transplantation	CYP3A4	Cyclosporine	↓	IL-6, CRP	[60]
HIV	CYP3A	Midazolam	↓18%	TNF-α	[61]
	CYP2D6	Dextromethorphan	↓90%		
	CYP3A	Midazolam	↓50%	NA	[20]
	CYP2D6	Dextromethorphan	↔		
Hepatitis C with *Helicobacter pylori* infection	CYP3A4	Lidocaine (MEGX test)	↓60–70%	NA	[62]
Rheumatoid arthritis	CYP3A4, CYP1A2	Verapamil	↓	IL-6	[63]
Infection in schizophrenia patients	CYP1A2	Clozapine	↓	NA	[64]
Congestive heart failure	CYP1A2	Caffeine	↓	IL-6, TNF-α	[65]
	CYP2C9	Mephenytoin	↓		
	CYP2E1	Chlorzoxazone	↔		
Cancer					
Cancer with acute phase response	CYP3A	Erythromycin breath test	↓30%	CRP, IL-6	[66]
Advanced solid tumors	CYP3A	Erythromycin breath test	↓	α1-acid glycoprotein	[67]
Advanced cancer	CYP3A	Midazolam	↓	Ferritin	[68]
	CYP2C19	Omeprazole	↓	NA	[69]
	CYP2C19	Omeprazole	↓	–	[70]
Cancer	CYP2C9	Tolbutamide	↔	–	[71]

who have raised serum concentrations of C-reactive protein (>0.5 mg/dl) and fever (>37.5 °C) had a reduced clearance of theophylline. Although cytokines were not determined in this study, this suggests that the *in vivo* activity of CYP1A2 was suppressed by cytokines released in the process of acute illness [29].

Critically ill children

To the best of our knowledge, only two studies have specifically looked at the effect of inflammation on drug metabolism in children with an inflammatory response. In critically ill children, one study focused on CYP activity in the presence of critical illness and inflammation. Antipyrine metabolism, as global marker of CYP activity, was studied in 51 children with sepsis and six critically ill children without sepsis. Children with sepsis had a two-time reduction in antipyrine clearance compared with controls (0.38 ± 0.28 vs 0.74 ± 0.31 ml/kg/min, $P < 0.05$) and children with multiple organ failure had a four-time reduction in clearance compared with controls (0.22 ± 0.15 vs 0.74 ± 0.31 ml/kg/min, $P < 0.05$). The clearance of antipyrine was inversely correlated to circulating IL-6 concentration and to the number of failing organs [30]. Recently, the pharmacokinetics of intravenous pantoprazole in pediatric intensive care patients was described. The authors showed that the systemic inflammatory response was a significant covariate affecting the clearance of pantoprazole, a CYP2C19 and a CYP3A4 probe. The presence of the systemic inflammatory response in these children was associated with a 62.3% decrease in pantoprazole clearance [31]. Both studies illustrate the potentially dramatic effects of inflammation on drug metabolism in critically ill children.

Supporting evidence from pharmacokinetic studies in children

As presented above, only a few studies have specifically looked at the effect of inflammation on drug metabolism in children. Additional information can be inferred from individual pharmacokinetic and pharmacodynamic studies, comparing (relatively) healthy children with those with inflammatory disease.

Midazolam

Midazolam is one of the most widely used drugs in pediatric intensive care for sedation. It undergoes extensive metabolism by the CYP3A subfamily to form a major hydroxylated metabolite (1-OH midazolam) and is an acknowledged *in vivo* CYP3A probe.

In children, the pharmacokinetics of midazolam has been described in several studies (Table 2). Looking at these studies, there are remarkable differences in midazolam clearances between the different populations. In critically ill neonates, the clearance of midazolam appears to be low (1.2–2.0 ml/kg/min), presumably as a

TABLE 2

Pharmacokinetic studies of midazolam in children

Age (average)	**Patients**	***n***	**Reason for administration**	**Dose/route**	**Clearance (ml/kg/min) (SD and/or range)**	**Refs**
Neonates (gestational age)						
26–34 weeks	Moderately ill neonates	24	Before stressful procedure	Single dose iv; 0.1 mg/kg	1.8 (0.7–6.7)	[32]
26–42 weeks	Critically ill neonates	187	Sedation during mechanical ventilation	Continuous infusion; mean 69 mcg/kg/h	1.17 (0.22)	[33]
34–41 weeks	Critically ill neonates	10	Sedative therapy	Single dose iv; 0.2 mg/kg	2.03 (1.24)	[34]
29–41 weeks	Critically ill neonates	15	Sedation during mechanical ventilation	Continuous infusion; 0.06 mg/kg/h	1.7 (1.8; 0.6–2.7)	[35]
Children						
3.2–24.7 months (median 11.1 m)	Non-ventilated infants after craniofacial surgery	24	Sedative therapy	Continuous infusion; start dose 0.05 mg/kg/h	16.7	[36]
1.75–4 years (mean 2.5 y)	Healthy children scheduled for minor genitourinary operations	6	Study, after induction of anesthesia	Single dose iv; 0.2 mg/kg	13.3 (4.28)	[37]
7–39 months (mean 27 m)	Children with severe malaria and convulsions	12	Convulsions	Single dose iv; 0.3 mg/kg	14.4 (9.2–19.7)	[38]
6 months to 16 years	Children scheduled for minor procedures	21	Sedative premedication	Single dose iv; 0.15 mg/kg	11.33 ± 6.33 (6 m–2 y)	[39]
					10.0 ± 3.83 (2–12 y)	
					9.33 ± 3.83 (12–16 y)	
3–10 years (mean 5.5 y)	Children with minor inguinal area surgery	8	Study, after induction of anesthesia	Single dose iv; 0.15 mg/kg	9.11 (1.21)	[40]
5–9 years (mean 6.5 y)	Healthy children undergoing circumcision	12	During induction of anesthesia	Single dose iv; 0.5 mg/kg	15.4 (3.2)	[41]
8–17 years (median 13.5 y)	Children undergoing esophagogastroduodenoscopy	20	Sedation during endoscopy	Single dose iv; 0.1 mg/kg	10.0 (5.0)	[42]
Critically ill children						
26 days to 5 years (17 infants ≤1 y)	Critically ill children	24	Sedation during mechanical ventilation	Continuous infusion; 0.05–0.5 mg/kg/h	5.8 (3.8)	[43]
3 months–8 years	Children undergoing cardiac surgery					[44]
Group A: 5.2 (2.5 y)	Closed heart surgery	17	During (Group A) or after (Group B and C) surgery for study	Single dose iv; 0.3 mg/kg	11.98 (6.68)	
Group B: 4.7 (2.6 y)	Cardiopulmonary bypass				8.53 (1.82)	
Group C: 1.3 (0.4 y)	Cardiopulmonary bypass with circulatory arrest				9.07 (3.35)	
1 month to 13 years	Critically ill children	38	Sedation during mechanical ventilation	Continuous infusion	3.1 (≤12 months)	[45]
					2.3 (1–2 years)	
					13.0 (>3 years)	
2 days to 17 years	Critically ill children	21	Conscious sedation	Continuous infusion; 0.05–0.4 mg/kg/h	5.0 (3.9)	[46]

TABLE 3

Pharmacokinetic studies of omeprazole and antipyrine in children

Age (mean)	Patients	*n*	Dose (route)	Clearance (L/kg/h) (SD)	Refs
Omeprazole					
4.5–27 months	Children with esophagitis or an ulcer	9	Once a day (iv)	0.53 (0.29)	[48]
0.3–19 years	Heterogeneous group of children with an acute gastrointestinal disease	13	Twice a day (iv)	0.23 (0.32)	[49]
Antipyrine					
2–16 years (5.3 years)	Children with acute lymphocytic leukemia before and after remission-induction therapy	14	Single dose (iv)	Before remission: 0.65 (0.30) After remission: 0.95 (0.29)	[51]
2.3–17.8 years (7.8 years)	Children with acute lymphocytic leukemia in complete remission	50	Single dose (iv)	0.91	[72]
14.6–20.2 years (cystic fibrosis)	Patients with cystic fibrosis and patients with cancer treated only with surgery and radiation	14	Single dose (iv)	0.9 (0.1)	[73]
7.2–19.4 years (cancer)		12		0.7 (0.09)	

result of immature CYP3A4/5 enzyme activity [32–35]. In relatively healthy non-ventilated children, aged 3 months to 17 years, midazolam clearance is higher and ranges from 10 to 16 ml/kg/min [36–42]. By contrast, in critically ill ventilated children, aged 2 days to 17 years, the reported clearance of midazolam appears to be lower than in non-ventilated children (2.3–9.1 ml/kg/min) [43–46]. The overall average clearance, from the studies reported, is approximately 12 ml/kg/min in healthy children and approximately 7 ml/kg/min in critically ill children. Hence, the clearance of midazolam appears to be considerably lower in critically ill children compared with healthy children of the same age.

Children in the reported studies had diagnoses associated with inflammation (post-cardiac surgery, airway infections and systemic infections). It is therefore reasonable to postulate inflammation as a factor contributing to the decreased midazolam clearance in critically ill children. This observation is supported by a study in critically ill children undergoing cardiac surgery. The authors showed a tendency to a reduced clearance in children who had undergone cardiopulmonary bypass compared with children with cardiac surgery without cardiopulmonary bypass [44]. Given that cardiopulmonary bypass triggers an inflammatory response [47], it supports inflammation as a covariate in midazolam clearance in children.

Unfortunately, although a logical next step, none of these studies evaluated the pharmacodynamic consequences of the altered midazolam clearance in critically ill children compared with healthy children.

Omeprazole

Omeprazole, an acid pump inhibitor, is frequently used to treat gastroesophageal reflux in children and infants. Omeprazole is primarily metabolized in humans by CYP2C19 and, to a minor extent, by CYP3A.

In children, only a few data are available on the clearance of omeprazole (Table 3). Two studies have examined the pharmacokinetic parameters of intravenous omeprazole. Faure *et al.* found a median omeprazole clearance of 0.53 L/kg/h in children requiring intravenous omeprazole for esophagitis or an ulcer [48]. Jacqz-Agrain *et al.* studied the pharmacokinetics of omeprazole in a heterogeneous group of children who needed omeprazole for an acute gastrointestinal disease. They found a median omeprazole clearance of 0.23 L/kg/h [49]. In this study, systemic clearance was variable between individuals. When looking at the individual clearances, the lowest clearances were reported for patients with a disease that is most likely to be accompanied by an inflammatory response (e.g. Crohn's disease, leukemia, renal and liver transplantation). Inflammation could therefore also have a role in the reduced clearance. However, with only two studies available, one can only speculate on the role of inflammation as a reason for the observed difference in omeprazole clearance. If omeprazole clearance is reduced in critically ill children, it would be expected that low doses are needed to reach adequate acid-suppression. By contrast, in a large proportion of critically ill pediatric patients, acid suppression was inadequate with 'therapeutic' doses of oral omeprazole (up to 1.6 mg/kg/d). An important limitation of this study is the lack of omeprazole plasma concentrations to link exposure with (lack of) effect [50].

Antipyrine

Antipyrine has served as a good probe drug for overall CYP activity. Antipyrine clearance is a useful method for evaluating drug-metabolizing capacity. In children, a few studies using antipyrine as a probe have been performed (Table 3). Average antipyrine clearance reported in these studies was 0.9 ml/kg/min.

Interestingly, Relling *et al.* have demonstrated that there is an improvement in antipyrine clearance in children with acute lymphocytic leukemia (ALL) from before to after remission (0.65 to 0.95 ml/kg/min, $P = 0.007$) [51]. The authors hypothesize that eradication of hepatic leukemic infiltration by ALL remission therapy resulted in an improvement in the microsomal metabolism of antipyrine. Interestingly, α1-acid glycoprotein concentrations significantly decreased after induction therapy (211 vs 128 mg/dl, $P < 0.001$). Given that α1-acid glycoprotein is an acute phase protein, this indicates that an inflammatory response is present in patients with ALL. This is also reported by other authors [52]. This observation suggests a relationship between inflammation and reduced drug metabolism in children with cancer, as also reported in adult cancer patients [4]. We speculate that, after

therapy, when the inflammatory response diminishes, α1-acid glycoprotein concentrations decrease and antipyrine clearance increases.

The effect of inflammation on pharmacodynamics

Both clinical and preclinical studies suggest that the inflammatory response alters the pharmacokinetics of CYP450-metabolized drugs. Reduced clearance with consequent increased drug concentrations might expose the patient to increased effect and toxicity. However, data supporting these pharmacodynamic consequences of inflammation-mediated reduced clearance are currently limited.

For some drugs, it is shown that an increased exposure consequent to inflammation leads to increased toxicity (e.g. docetaxel) [4]. However, for other drugs, this pharmacokinetic–pharmacodynamic relationship is less clear. Inflammation might also downregulate receptors (e.g. cardiovascular receptors), leading to a reduced drug effect despite increased plasma drug concentrations, as reviewed elsewhere [4,21].

Little is known about the clinical implications of these changes in the exposure–response relationship during inflammation. Clinical studies are lacking, and data from children relating to the pharmacokinetic–pharmacodynamic relationship in inflammation are absent.

Inflammation and the impact on drug development and therapy

In vitro and *in vivo* adult studies have so far shown that CYP enzymes, which catalyze the metabolism of most drugs currently in use, are differentially downregulated by proinflammatory cytokines. By contrast, consequent high drug concentrations might not necessarily lead to higher efficacy or toxicity, as pharmacodynamics can change concomitantly. Preliminary studies described here have demonstrated that the inflammatory response in children with inflammatory diseases also appears to be associated with marked reduced hepatic drug metabolism, although pharmacodynamic data are lacking. Therefore, extrapolation of data from healthy adults and children to a pediatric population with inflammatory disease cannot be done automatically. The differential effect of inflammation on pharmacokinetics and pharmacodynamics could further complicate extrapolation. Increased drug concentrations, owing to reduced clearance, could result in toxic levels (Fig. 1b), but could also result in therapeutic, subtherapeutic or toxic levels owing to changed pharmacodynamics (Fig. 1c–e).

Consequently, the design of pharmacokinetic and pharmacodynamic studies and, ultimately, of dose regimens for CYP-metabolized drugs must capture inflammation as a covariate to ensure adequate characterization of the disposition of drugs and the

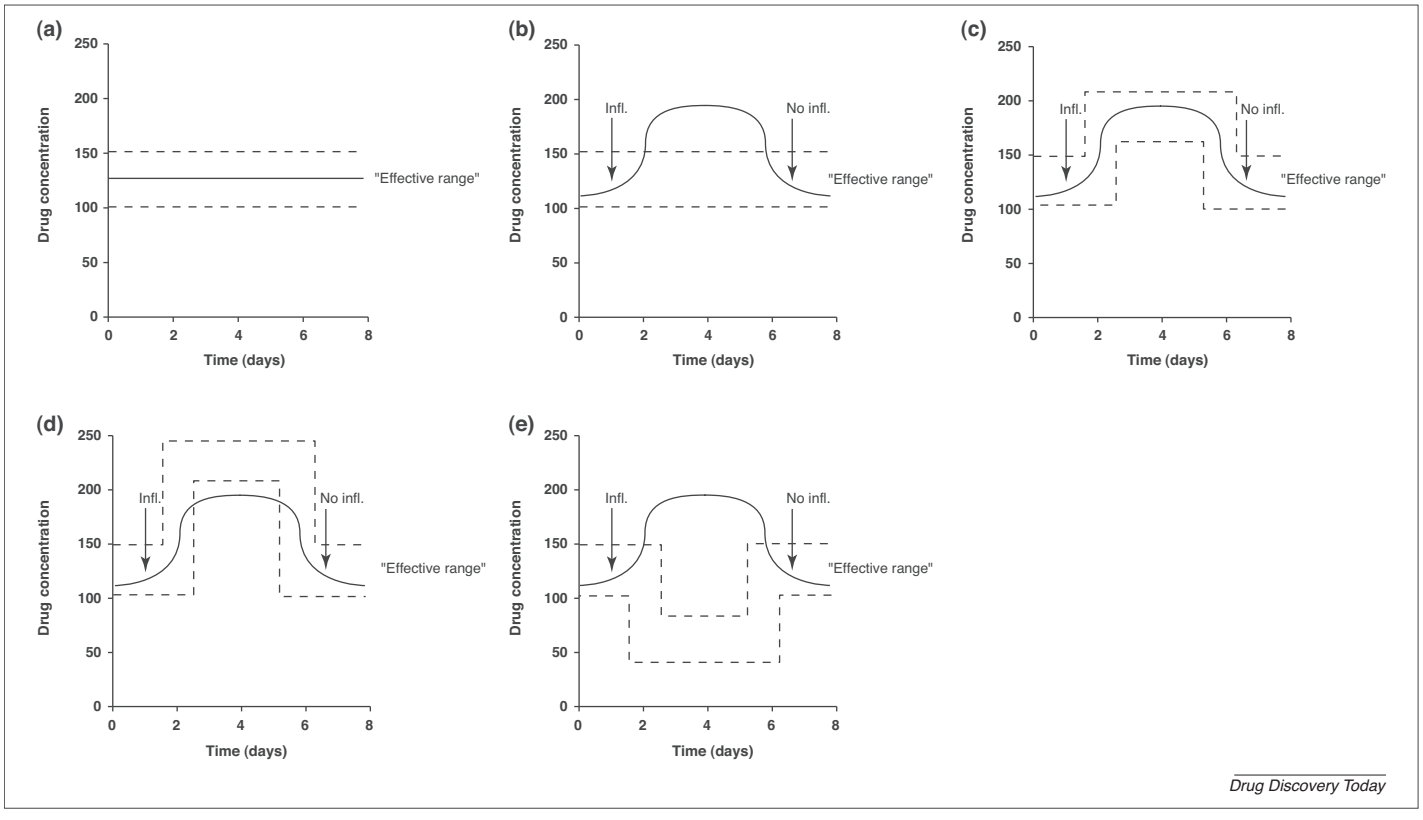

FIG. 1

Possible pharmacokinetic–pharmacodynamic relationships during inflammatory diseases. The solid black line represents the estimated plasma drug concentration, whereas the dotted lines represent the effective range of the drug (pharmacodynamic window). **(a)** Patient without inflammation on a stable drug regimen with a therapeutic drug concentration. **(b)** Patient with acute inflammatory disease only affecting pharmacokinetics, resulting in toxic plasma drug concentrations. **(c)–(e)** Patient with acute inflammatory disease affecting both pharmacokinetics and pharmacodynamics, resulting in **(c)** altered effect concentration with therapeutic drug concentrations; **(d)** altered effect concentration with sub-therapeutic drug concentrations; and **(e)** altered effect concentration with toxic drug concentrations. *Abbreviations*: Infl., inflammation; No infl., no inflammation.

translation of this information into the provision of safe drug therapy for children.

Until the relationship between exposure and response is better characterized, we need to dose carefully for safe and effective drug therapy in children. Nevertheless, a standard dose decrease in children with inflammatory disease could be considered for drugs that are easily titrated to effect (i.e. sedative drugs). Close monitoring of the effect of drugs and adequate dose adjustments are needed, also when the inflammatory response resolves because it is unclear whether, and in what time period, the activity of drug-metabolizing enzymes will normalize when inflammation diminishes [21].

Future directions

There are therefore several crucial information gaps with regard to the overall impact of inflammation on drug metabolism and drug effect, not only in children but also in adults. First, more pharmacokinetic studies are needed to understand how drug disposition is regulated in inflammatory diseases. In children, clinical drug studies must be designed, using minimal sample strategies and population pharmacokinetic modeling, to increase knowledge on drug disposition in this population [53]. Pharmacokinetic studies alone will not suffice. It is imperative that the pharmacodynamic consequences of inflammation are also studied. These studies in children will be challenging, as they need to incorporate not only inflammation as covariate, but also disease- and age-related changes. Important age-related changes in pharmacokinetics and pharmacodynamics occur during childhood. It is of paramount importance that children over the whole age range are studied, as the interplay of developmental changes and inflammation-related variation has yet to be determined.

In addition, there is a need to identify the most appropriate way to assess inflammatory status in children. During the inflammatory response, multiple cytokines are increased and the exact cytokine pattern responsible for the downregulation in CYP activity is still not known [5]. Given that a correlation between loss of drug clearance and IL-6 is described *in vitro*, in animals and in humans, IL-6 appears to have an important role in this loss. Although the time course of changes in IL-6 levels during different diseases in humans is poorly known, IL-6 might be a good biomarker to use to assess inflammation. Alternatively, measurement of acute-phase proteins, such as C-reactive protein or α1-acid glycoprotein, or a combination of several markers, could be useful in predicting the net effect of inflammation on drug pharmacokinetics [4]. If a reliable biomarker of inflammation is available, with a time course fast enough to correlate with increase or reduction of inflammation, yet slow enough to be measured once daily, this biomarker could be measured along with drug concentrations and drug effect to characterize the pharmacokinetic–pharmacodynamic relationship in inflammatory diseases [9].

Finally, in addition to well-designed pharmacokinetic–pharmacodynamic studies, individual cases of increased toxicity, adverse effects or lack of efficacy of drug therapy in children with inflammation should be reported in the peer-reviewed literature. Given that many pediatric patient groups are small and/or heterogeneous, large well-controlled studies on the effect of individual drugs are a logistical challenge or even impossible. Hence, reporting of individual or combined cases could aid in improving understanding of inflammation in relation to pediatric drug therapy.

Conclusion

The inflammatory response downregulates CYP expression and activity and contributes to pharmacokinetic and probably pharmacodynamic variability in children with inflammation. These changes might be of clinical significance for drug studies and drug therapy. Investigators and clinicians must consider the impact of inflammation in the context of developmental changes on drug disposition and effect in both the design of drug studies and the provision of safe therapy to pediatric patients.

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