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Impact of Drug Treatment at Neonatal Ages on Variability of Drug Metabolism and Drug-drug Interactions in Adult Life

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Abstract

Purpose of review—As the number of patients taking more than one medication concurrently continues to increase, predicting and preventing drug-drug interactions (DDIs) is now more important than ever. Administration of one drug can cause changes in the expression and activity of drug metabolizing enzymes (DMEs) and alter the efficacy or toxicity of other medications that are substrates for these enzymes, resulting in a DDI. In today's medical practice, potential DDIs are evaluated based on the current medications a patient is taking with little regard to drugs the patient has been exposed to in the past. The purpose of this review is to discuss potential impacts of drug treatment at neonatal ages on the variability of drug metabolism and DDIs in adult life.

Recent findings—Existing evidence from the last thirty years has shown that exposure to certain xenobiotics during neonatal life has the potential to persistently alter DME expression through adult life. With recent advancements in the understanding of epigenetic regulation on gene expression, this phenomenon is resurfacing in the scientific community in hopes of defining possible mechanisms. Exposure to compounds that have the ability to bind nuclear receptors and trigger epigenetic modifications at neonatal and pediatric ages may have long-term, if not permanent, consequences on gene expression and DME activity.

Summary—The information summarized in this review should challenge the way current healthcare providers assess DDI potential and may offer an explanation to the significant interindividual variability in drug metabolism that is observed among patients.

Keywords

drug-drug interactions; neonatal drug treatment; cytochrome P450; drug metabolism; precision medicine

Introduction

With the trend of polypharmacy continuing to increase, especially in geriatric populations and patients with chronic disease, the prevalence of clinical drug-drug interactions (DDIs)

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Conflict of Interest

The authors declare that they have no conflict of interest.

has become a significant clinical issue [1]. By definition, a DDI occurs when the activity or safety of one drug is altered by the concurrent administration of another drug. These alterations can include a decrease in therapeutic efficacy of one or both drugs, or unintended adverse events due to increased toxicity [2]. Harmful adverse events caused by DDIs account for almost 3% of all hospital admissions [3], leading to increased healthcare costs and in extreme cases, death. Predicting the potential for compounds to cause interactions is a critical step in the drug development pipeline, as significant interactions may not be discovered until a drug has already reached the market [4]. A complete understanding of the mechanisms, by which DDIs arise, is fundamental to prevent their occurrence clinically. However, the large number of patients experiencing these interactions today indicates the current medical practices for avoiding DDIs has room for improvement [5].

The safety and efficacy of a drug is largely dependent on its pharmacokinetic profile within the body. DDIs classified as pharmacokinetic in origin arise when one drug interferes with the absorption, distribution, metabolism, or excretion of another drug taken at the same time [6]. As 75% of drug metabolism occurs through the metabolism by cytochrome P450 (P450) monooxygenase enzymes in the liver, intestine, and kidney, compounds that alter the levels of these enzymes are involved in a majority of DDIs [7]. Some P450s are expressed at constitutive levels, while others, such as those involved in drug metabolism, are highly inducible, allowing for increased clearance rates. Certain medications, foods, and environmental compounds are able to increase the expression of P450s in a time- and dose-dependent manner, termed induction [8]. Inducers elevate the rate of metabolism for other drugs that are substrates for the same enzymes, decreasing plasma concentrations of the parent compounds, while simultaneously increasing metabolite concentrations beyond expected levels. Compounds that inhibit P450 activity produce the opposite effects by reducing rates of metabolism.

Medications that inhibit or induce P450 activity are well documented and several databases exist to aid physicians in avoiding DDIs when prescribing new therapies to patients. The patient's current medication regimen is evaluated for interaction potential while drugs the patient has taken in the past or as an infant are usually disregarded. However, recent discoveries in the establishment and regulation of P450 expression during growth may challenge current clinicians to reconsider how DDI risk is evaluated. This review explores past and current studies that have demonstrated long-term alterations in drug metabolism resulting from neonatal exposure to various xenobiotics. We suggest that exposure to certain compounds early in a patient's life may permanently alter P450 expression in the liver, and a patient's unique medication history after birth can be useful in assessing clinical DDI risks and improving precision medicine.

The Molecular Mechanisms of DDIs through Induction of P450s

The P450 enzymes responsible for the metabolism of xenobiotic compounds are expressed at relatively low basal levels in the liver in the absence of their substrates. Upon exposure to drugs, toxins, and other exogenous chemicals, expression of these enzymes can be temporarily increased or induced, elevating P450-mediated metabolizing rates. The CYP1A, CYP2B, CYP2C, CYP2E, and CYP3A subfamilies play significant roles in clinical drug

metabolism and are all capable of being induced upon exposure to various xenobiotics [9]. Induction of P450 activity most often occurs at the transcriptional level, increasing the rate, by which P450 genes are transcribed into mRNA and ultimately translated into enzymatic proteins. The elevated rate of P450-mediated metabolism is dose-dependent and reversible, as induction ceases and P450 expression returns to normal once the inducer is removed and fully excreted [10].

The process of induction is initiated by the activation of specific nuclear receptors via the binding of their various endogenous or exogenous ligands. Specific nuclear receptors regulate the expression of different P450 isoforms as well as other hepatic Phase II enzymes and transporters involved in xenobiotic metabolism, steroid synthesis, and detoxification. The pregnane X receptor (PXR) and the constitutive androstane receptor (CAR) are particularly relevant to drug metabolism, acting as xenobiotic sensors to regulate the induction of CYP3A, CYP2B, and CYP2C subfamilies [11–14]. Upon direct or indirect binding of their ligands, these nuclear receptors translocate from the cytoplasm to the nucleus, where they facilitate the recruitment of chromatin remodelers and coactivators to promote the transcription of P450 genes [15].

Co-administration of compounds that activate PXR or CAR with drugs that are substrates of P450 enzymes is a common cause of clinical DDIs [16]. Phenobarbital, a first-generation antiepileptic drug used to treat seizures, is implicated in numerous DDIs and is also a potent activator of human CAR [17]. Its ability to decrease the efficacy of other medications metabolized by P450s is evidenced by the occurrence of unplanned pregnancies in women prescribed oral contraceptives alongside phenobarbital, as elevated CYP3A4-mediated metabolism reduces plasma concentrations of the active contraceptives [18, 19]. Additionally, patients undergoing treatment for tuberculosis with rifampicin, a potent PXR activator, experience hepatotoxicity with co-administration of acetaminophen due to elevated production of reactive metabolites by P450s [20]. The activation of CAR or PXR by drug administration is implicated in numerous DDIs and could lead to decreased therapeutic efficacy or potentially serious adverse side effects.

Neonatal Exposure to Xenobiotics Alters P450 Expression and Drug Metabolism in Adult

The effects of enzyme induction on P450 expression in the liver of adults is known to be temporary, with P450 activity returning to basal levels once the inducing drug is discontinued. The length of time required for P450 levels to return to normal is also dependent on the drug's half-life within the body [7]. Many infants are administered drugs or exposed to chemicals that cause P450 induction. Hospitalized pediatric patients are often administered numerous medications concurrently, and 41% are exposed to a potential significant DDI [21]. However, whether the effects of induction are reversible at a neonatal age is an area of drug metabolism that is largely unexplored, especially in humans. Newborn patients were once viewed as small adults in terms of selecting pharmacotherapies and dosing strategies. However, we now know that pediatric patients, especially neonates, exhibit distinct hepatic drug metabolism activity from adults due to differences in P450 expression

during development [22, 23]. The mechanisms regulating pediatric gene expression and induction may differ from adults as well.

Beginning as early as 1981, numerous studies have documented the effects of early life exposure to specific drugs, nutritive compounds, and environmental toxicants on metabolic and detoxification processes in the adult liver in animal models. Initial evidence of this phenomenon was first observed in the enzymatic activities of hepatic microsomes prepared from livers of adult rats exposed to various compounds during the first five days of life. Neonatal treatment with phenobarbital, methadone, and testosterone permanently altered hepatic monooxygenase capability and increased P450 activity, suggesting that the P450-dependent monooxygenase metabolic system of the liver may be subject to permanent alterations at an early age [24–27].

With the discovery of different P450 isoforms, subsequent studies throughout the 1990s validated these observations by focusing on alterations in expression and activity of specific P450s after neonatal exposure to exogenous compounds. Adult male rats treated with diethylstilbestrol, a synthetic estrogen, at the neonatal age showed significant elevation in specifically CYP2C6 hepatic protein level, while rats administered phenobarbital show specific increases in CYP2C7 and CYP2B hepatic protein levels, indicating these drugs have the ability to alter the expression of certain P450 isoforms, rather than drug metabolism activity as a whole [28–30]. Phenobarbital has been the most commonly utilized drug to observe this phenomenon, and the persistent induction of CYP3A, 2B, 2C in rats and mice following early life exposure has been demonstrated numerous times [27, 28, 30–35]. Neonatal administration of lindane, an organochlorine used for lice treatment, to rats also produced an increase in the expression of CYP2B protein, along with CYP1A, later in life [36], indicating different compounds may set certain P450 levels through similar mechanisms early in life. Additionally, neonatal treatment with tamoxifen, an estrogen receptor modulator, produced elevated levels of CYP2A1 protein in adult male rat livers [37]. These examples demonstrate that different drugs selectively induce specific P450s and may do so through different mechanisms that all cause persistent enzyme induction.

Investigators have also considered whether the process of induction itself may be altered at the neonatal age and change the induction sensitivity of P450 genes at later ages. Phenobarbital administered to neonatal rats caused an over-exaggerated induction of CYP2B, CYP2C6, and CYP3A expression and activity when the same rats were re-challenged with a dose of phenobarbital at an adult age [38, 33]. Neonatal treatment with lindane also produced a similar over-induction of CYP1A and CYP2B expression in adult rats following phenobarbital administration [36]. This indicates that the “inducibility” of P450 enzymes is also able to be permanently manipulated by xenobiotic exposure at an early age, and may cause over-induction of particular P450 isoforms after drug treatment later in life.

In contrast to long-term inductive effects, several studies have also demonstrated persistently diminished levels of P450 activity following neonatal xenobiotic exposure. Exposing neonatal male rats to diethylbisterol significantly decreased hepatic expression of CYP3A in adults, in contrast to the elevated CYP1A and CYP2B expression mentioned earlier [28].

Neonatal tamoxifen administration, while causing persistent induction of CYP2A1 in adult male rats, interestingly caused the downregulation of CYP3A9 in adult female rats [37, 39]. However, this may highlight the intrinsic differences in P450 expression between males and females due to hormonal influences [40, 41, 39]. Although CYP8B1 is involved in cholesterol metabolism rather than drug metabolism, it is worth mentioning that neonatal treatment with the glucocorticoid dexamethasone resulted in persistent downregulation of the gene CYP8B1 and altered hepatic lipid secretion in adult rats [42]. P450 inhibition usually takes place at the protein level and would not be subject to transcriptional alteration as seen in enzyme induction. A summary of the studies that demonstrate long-term alterations in P450s following neonatal drug exposure can be found in Table 1.

The liver is not the only organ that utilizes P450 enzymes for drug metabolism and detoxification. Studies investigating the effects of xenobiotic exposure on persistent P450 expression alterations in the brain have shown similar long-lasting consequences. Prenatal exposure of lindane in rats caused persistently upregulated cerebral CYP1A and CYP2B enzymes, causing an increased incidence of convulsions when adults were re-challenged with the drug [36]. In another example, transient postnatal fluoxetine treatment to rats for 16 days decreased the amount of CYP4A protein present in the brain at the adult age, reducing arachidonic acid metabolite levels that require CYP4A activity [43, 44]. Interestingly, fluoxetine, a selective serotonin reuptake inhibitor, is a potent inhibitor of CYP2D6, CYP2B6, and CYP2C in the liver, however there are no studies to date that examine the effect of fluoxetine treatment on long-term hepatic P450 expression [45].

The doses of xenobiotics administered at the neonatal age appear to play a considerable role in determining whether alterations in P450 activity will persist long-term. In our own study, mice treated with less than 100 mg/kg of phenobarbital at the neonatal age do not display persistent induction of CYP2B10, CYP2C29, or CYP3A11 through adult life. Only neonatal mice that were administered a dose of phenobarbital greater than this exhibited the persistent elevation of these P450 enzymes in their livers throughout life [35]. Our study also demonstrated that age is another key factor for persistent induction of P450 expression in adult mouse liver. There is a sensitive age window early in life that allows induction of P450 expression to persist after drug treatment. If drug treatment occurred beyond this window, the persistent induction was no longer evident [35].

Neonatal Xenobiotic Exposure and Long-Term Epigenetic Alterations

The mechanisms involved in producing persistent alterations in P450 drug metabolism are just beginning to be elucidated. Since the induction of P450 expression occurs via increasing the rate of gene transcription, the role of nuclear receptors and epigenetic memory in this phenomenon is worth investigating. Epigenetic modifications give rise to differential gene expression without an underlying change to DNA sequences. After activation by their ligands, nuclear receptors recruit various co-regulatory complexes to regions of the gene that result in upregulation of its transcription. This occurs through the restructuring of chromatin, which allows the binding of additional transcription factors and co-activators, or through the modifications of histones [46]. Histone modifications, including acetylation and methylation, produce a histone code that is interpreted by effector molecules that can

promote or inhibit the transcription of a gene [47]. The resulting alterations to chromatin structure and gene expression following nuclear receptor activation can be transient and short-lived, or they can become permanently altered and act as a cellular memory for gene expression [48].

Following birth, organs continue to develop and exhibit plasticity, especially when responding to environmental factors. Various studies demonstrate permanent changes in chromatin structure and histone modifications in different tissues following postnatal exposure to specific xenobiotics and the activation of nuclear receptors. Rats exposed to bisphenol A, an endocrine disrupter found in plastic that binds and activates the nuclear estrogen receptor (ER), during their first five days of life exhibited markedly upregulated expression of the secretoglobin gene in the prostate at day 70. The increased expression correlated with persisting increased enrichment of histone H3K9 acetylation and DNA hypomethylation upstream of the gene's transcription start site [49, 50]. The adult enzymatic activity of P450s in the liver may also be regulated by epigenetic modifications that are able to be permanently adjusted and established early in life.

Connections between the chemical activation of a nuclear receptor at the neonatal age and permanent alterations in histone modifications and P450 expression in the liver have been established [51]. Administering diethylbisterol, an ER activator, causes downregulation of the enzyme, Enhancer of zeste homolog 2 (Ezh2), the catalyst for the addition of methyl groups to histones, in the livers of adult mice, altering the expression of several P450s [52]. In another study, the chemical TCPOBOP was administered to neonatal mice to selectively activate CAR, which lead to the persistent induction of CYP2B10 and CYP2C37 through adult life. Additionally, CAR activation also caused a permanent increase of histone H3K4 methylation and decrease of H3K9 methylation within the *Cyp2b10* gene, which correlates with increased gene transcription rates [51]. These observations indicate that activation of nuclear receptors at a neonatal age may produce a modified epigenetic memory that persists into adult life, which favors the induction of 450 expression. While TCPOBOP is a compound that specifically and directly activates murine CAR unlike phenobarbital, perhaps a similar mechanism occurs in humans, in which phenobarbital activates CAR, causing persistent induction of P450 enzymes.

Evidence that neonatal xenobiotic exposure can directly alter expression levels of the nuclear receptors themselves also exists. In one study, neonatal exposure of mice to diethylbisterol, which binds and activates the ER, caused decreased mRNA expression of CAR and PXR in adulthood via the activity of small heterodimer protein (SHP), a transcriptional inhibitor and target of ER activation. This leads to the downregulated expression of CYP3A11, CYP2B10, CYP7A1, and CYP8A1 observed in the adult mice [52]. Most recently, a study also examined the effects of neonatal activation of CAR, as well as PXR, on whole genome mRNA expression at the adult age in mice, with a focus on DMEs [53]. TCPOBOP was chosen once again to activate CAR, while pregnenolone 16 α -carbonitrile (PCN) was selected as an activator of PXR. Neonatal treatment with TCPOBOP resulted in persisting upregulation of major metabolizing enzymes CYP2B10 and CYP2C29 along with several other drug processing genes, while CYP4A enzymes were persistently downregulated. Neonatal treatment with PCN also produced persistent overexpression of CYP2B10,

CYP2B13, CYP2C55, and CYP2A enzymes and downregulation of CYP4A enzymes, suggesting there might be some overlap in nuclear receptor signaling and induction [53]. The peroxisome proliferator-activated receptor alpha (PPAR α), another hepatic nuclear receptor involved in lipid metabolism, regulates the human and murine CYP4A expression and was also downregulated later in life following neonatal activation of PXR or CAR. In adult mice, PPAR α upregulates CYP4a expression by binding to DNA regulatory elements in these genes [54, 55], however this study found that early life PXR and CAR activation diminished the binding of PPAR α to these regions in adult mice [53]. This suggests that PXR and CAR activation at the neonatal stage may also have an impact on the long-term expression of other nuclear receptors and cofactors involved in hepatic functions.

Future Directions

Phenobarbital appears to be the prototypical clinically relevant drug administered to neonatal animals to elicit the persistent upregulation of drug metabolizing P450s in the literature. And while phenobarbital is an indirect activator of both human and murine CAR, the nuclear receptor is activated by different drugs and compounds in each species, with only a few that are common [56]. To ensure that this concept is not restricted to the neonatal administration of specifically phenobarbital to rodents, additional inducers should be investigated for their potential to cause persistent P450 up- or downregulation via different nuclear receptors. While the use of phenobarbital in pediatric patients is not as common as it was in the past, infants are still regularly exposed to other drugs that cause enzyme induction for prevalent indications, including HIV, seizures, and tuberculosis (Table 2). It is also possible for inducing medications taken by a breastfeeding mother to pass through breastmilk to her infant. Although neonatal drug exposure is the focus of this review, many foods and environmental toxins such as cigarette smoke, pesticides, Brussels sprouts, genistein, and bisphenol A also cause P450 induction and are prevalent in our surroundings [57].

Although the studies discussed in this review utilize animal models to exhibit the lasting consequences of early life xenobiotic exposure on drug metabolism, work still needs to be done to prove the concept in humans. However, two studies do allude to early life environmental factors, such as diet and formula feeding versus breastfeeding, impacting the normal maturation of human P450 expression in the liver [58, 59]. Formula-fed infants demonstrate an accelerated ability to metabolize caffeine, which is primarily catalyzed by CYP1A2, when compared to breastfed infants at six months of age [59]. This observation may be due to the presence of compounds in infant formula with the ability to activate the nuclear aryl hydrocarbon receptor (AhR), which is responsible for the induction of CYP1A2 expression in adults. However, whether an infant formula-based diet can cause long-term alterations in P450-mediated drug metabolizing activity through adulthood still needs to be investigated with longer epidemiological studies. It is imperative that future works identify additional factors and confirm neonatal xenobiotic exposure as a factor contributing to the interindividual variability of P450 expression seen in adult human populations.

Conclusion

In many instances, a drug that is efficacious for one patient might not work as well as expected for another patient. One patient may experience adverse side effects while another patient will not, even when taking the same dose of the same drug. This can occur when a patient is only taking a single drug, which would exclude a causative DDI conventionally. Significant variation in basal expression levels for major drug metabolizing P450s are observed among all patients, including 40-fold variation in CYP3A, 100-fold variation in CYP2D6, 60-fold variation in CYP2B6, and 50-fold variation in CYP2C9 [60, 61]. And this variation contributes to inconsistent responses patients have to medications. The variability in drug response that is so prevalent among patient populations can be attributed to a few factors, such as age, gender, diet, and genetics, which all play a role in determining the expression level of DMEs. Polymorphisms in P450 genes have been identified and are currently used to make dose adjustments for certain medications, such as for CYP2C19 polymorphisms and clopidogrel, but genetic factors simply cannot account for the vast variability in drug metabolism observed among patients [62, 63]. With the evidence that neonatal xenobiotic exposure may influence basal expression of these P450 enzymes in adult life, a patient's drug history could be an important piece of information collected by healthcare providers before prescribing new medications to ensure a more predictable drug response. Tailoring doses and selecting appropriate drug cocktails is an important aspect of personalized medicine [63], and considering a patient's unique drug history may further aid in avoiding treatment failure and unnecessary adverse side effects.

The National Institutes of Health (NIH) recently announced a new initiative focused on improving our understanding of the effects of environmental exposures on child health and development called the Environmental Influences on Child Health and Outcomes (ECHO) program. The goal of ECHO is to utilize longitudinal human cohort studies to investigate the lasting effects of chemical, biological, social, and natural exposures on child development and health outcomes such as obesity (www.nih.gov/echo). Recognizing that early childhood exposure has lasting consequences into adulthood is a critical step in improving healthcare and patient outcomes. Neonatal drug exposure is only one factor that can be used to assess interindividual variability in precision medicine. Considering this among multiple other aspects of a patient's health history is key to predicting drug response and overall health outcomes.

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Summary of studies which demonstrate long-term alterations in hepatic P450 expression, activity, and/or induction following neonatal administration of specific drugs

Table 1

Species	Drug administered	P450s Permanently Altered	Expression ↑ or ↓	Level of Quantification	Reference
Rat (male)	Phenobarbital	2B	↑	Protein	[28]
Rat (male)	Diethylstilbestrol	2C6	↑	Protein	
Rat (male)	Diethylstilbestrol	3A2	↓	Protein	
Rat	Phenobarbital	2C7	↑	RNA, protein, activity	[30]
Rat	Phenobarbital	2C6, 3A1, 3A2	↑	RNA, protein	[33]
Rat	Phenobarbital	2C7, 2C6, 2B1, 2B2, 3A1, 3A2	↑	RNA, protein, activity	[34]
Rat	Phenobarbital	2B1, 2B2	↑	RNA, protein, activity	[38]
Mouse	Phenobarbital	2B10, 2C29, 3A11	↑	RNA, protein, activity	[35]
Rat	Lindane	2B1, 2B2, 1A1, 1A2	↑	RNA, protein	[36]
Rat (male)	Tamoxifen	2A1	↑	Protein, activity	[37]
Rat (female)	Tamoxifen	3A9	↓	RNA	
Rat (male)	Tamoxifen	2C11	↓	Protein, activity	
Rat	17β-estradiol	3A	↑	Activity	[39]

Table 2

Inducers administered to pediatric patients.

Class	Drug	Indication	P450s Induced	Nuclear Receptors Activated	Reference
Corticosteroid	Dexamethasone	Lung maturation in preterm newborns	3A4	PXR, GCR	[64, 65]
	Carbamazepine	Infant seizures, manic-depression	1A2, 2C9, 3A4	CAR	[66–68]
Antiepileptic	Phenytoin	Infant seizures	3A4, 2B6, 2C	CAR	[69, 70]
	Griseofulvin	Ringworm, tinea capitis	3A4	PXR	[71, 72]
Antifungal	Rifabutin	Tuberculosis	3A4	PXR	[73]
	Rifampicin	Staph infection, tuberculosis	3A4	PXR	[74, 75]
Antibacterial	Nelfinavir	HIV	1A2, 2B6, 2C9, 3A4	PXR	[76, 77]
	Nevirapine	HIV	2B6, 3A4		[78, 79]
	Efavirenz	HIV	3A4	PXR	[80]

GCR = glucocorticoid receptor