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REVIEW

The Impact of Pharmacogenetics on Pharmacokinetics and Pharmacodynamics in Neonates and Infants: A Systematic Review

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Abstract: In neonates, pharmacogenetics has an additional layer of complexity. This is because in addition to genetic variability in genes that code for proteins relevant to clinical pharmacology, there are rapidly maturational changes in these proteins. Consequently, pharmacotherapy in neonates has unique challenges. To provide a contemporary overview on pharmacogenetics in neonates, we conducted a systematic review to identify, describe and quantify the impact of pharmacogenetics on pharmacokinetics and -dynamics in neonates and infants (PROSPERO, CRD42022302029). The search was performed in Medline, Embase, Web of Science and Cochrane, and was extended by a PubMed search on the 'top 100 Medicines' (medicine + newborn/infant + pharmacogen*) prescribed to neonates. Following study selection (including data in infants, PGx related) and quality assessment (Newcastle–Ottawa scale, Joanna Briggs Institute tool), 55/789 records were retained. Retained records relate to metabolizing enzymes involved in phase I [cytochrome P450 (CYP1A2, CYP2A6, CYP2B6, CYP2C8/C9/C18, CYP2C19, CYP2D6, CYP3A5, CYP2E1)], phase II [glutathione-S-transferases, N-acetyl transferases, UDP-glucuronosyl-transferase], transporters [ATP-binding cassette transporters, organic cation transporters], or receptor/post-receptor mechanisms [opioid related receptor and post-receptor mechanisms, tumor necrosis factor, mitogen-activated protein kinase 8, vitamin binding protein diplotypes, corticotrophin-releasing hormone receptor-1, nuclear receptor subfamily-1, vitamin K epoxide reductase complex-1, and angiotensin converting enzyme variants]. Based on the available overview, we conclude that the majority of reported pharmacogenetic studies explore and extrapolate observations already described in older populations. Researchers commonly try to quantify the impact of these polymorphisms in small datasets of neonates or infants. In a next step, pharmacogenetic studies in neonatal life should go beyond confirmation of these associations and explore the impact of pharmacogenetics as a covariate limited to maturation of neonatal life (ie, fetal malformations, breastfeeding or clinical syndromes). The challenge is to identify the specific factors, genetic and non-genetic, that contribute to the best benefit/risk balance.

Keywords: developmental pharmacology, infant, ontogeny, child development, genetic variation

Introduction

At the beginning of the second half of the 20th century, Friedrich Vogel developed the concept that genes play an important role in determining drug response and coined the term pharmacogenetics (PGx).[1] Subsequently, PGx became a powerful tool to understand variability in drug exposure, efficacy, tolerability, or toxicity. When applied to clinical care, this holds the promise to be integrated in individualization and precision medicine.[2,3] In neonates, PGx has an additional complexity next to genetic variability (ie, polymorphisms) in the genes that code for proteins responsible for drug pharmacokinetics (PK) (like metabolism, transporter) or pharmacodynamics (PD) (like receptor, target enzyme). This is because there are rapidly evolving, ontogenic changes in expression of these same proteins or processes related to maturation of renal, cardiac, intestinal function, etc.[4] Maturation (like receptor expression, receptor activity, cellular

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metabolism, enzyme activity) hereby displays collinearity with age and weight, be it with a lot of diversity in maturational patterns.[5,6]

To a certain extent, this subpopulation displays a specific "phenoconversion" setting, with a maturational, age-dependent mismatch between genotype and phenotype.[7] Using the same approach, PG holds the promise in related fields of neonatal medicine, like forensic medicine and sudden infant death syndrome.[8]

PK describes the relationship of concentration over time, PD describes the relationship between a concentration and (adverse) effects.[9] In total about 18,000 variants in 231 pharmacogenes have been determined, the majority of which are rare variants, some of which may be deleterious regarding gene function with significant consequences in PK and PD.[10] This genetic variability can affect drug absorption, distribution, metabolism, elimination, toxicity (ADMET), and effectiveness.

There are many illustrations on the integration of PGx and age-related maturation (ie ontogeny) to improve the prediction of phenotypic drug ADMET [like cytochrome P450 (CYP) C219, CYP 2D6 or N-acetyl transferase-2 (NAT2), UDP-glucuronosyltransferase 2B7 (UGT2B7), mu-opioid receptor (Opioid OPRM1), Catechol-O-methyltransferase (COMT), or P-glycoprotein (ABCB1)].[11,12] This phenotypic variability is further aggravated by interfering disease characteristics (like renal or liver failure, sepsis, growth restriction) or interventions (like co-medication, extracorporeal membrane oxygenation, whole-body cooling).

As we are not aware of a recent systematic review on this topic and to provide a contemporary overview on the current knowledge on PGx in neonatal pharmacology, we performed a systematic review to identify, describe and quantify the impact of PGx on PK and PD in neonates and infants.

Materials and Methods

This review was performed based on the PRISMA (Preferred Reporting Items for Systematic Reviews and MetaAnalysis) guideline.[13] The protocol was registered in PROSPERO on February 6th, 2022, an international prospective register of systematic reviews (CRD42022302029, review ongoing).[14]

Search Strategy

Potentially relevant publications published between January 1st, 1946 and January 1st, 2022 were identified by searching the following databases: Medline ALL (1946–present), Embase (1971–present), Web of Science Core Collection (1975–present), and Cochrane Central Register of Controlled Trials (1992–present). In addition, reference lists of relevant reviews were screened for any potentially relevant individual studies (backward snowballing). The search strategy, terms or subject headings (and related concepts, depending on the database) are provided in Supplementary File 1. Furthermore, a search was performed based on the "Top 100 medications prescribed in the NICU" (800,000 cases, 2010–2018), as recently reported by Stark et al.[15] The names of each drug were searched with the keywords "newborn or infant" and "pharmacogen*" in the PubMed database until February 22nd, 2022.

Study Selection and Data Extraction

Search results were downloaded into EndNote X9, duplicates were removed automatically and manually. One reviewer (N.Y.) verified the removal of duplicates. Two reviewers (N.Y. and K.A.) subsequently screened the reports independently by title and abstract, and then by full-text for potentially eligible studies. Discrepancies were discussed with a third reviewer (R.F.) until consensus was reached. The following data were extracted when reported in the papers retained: first author, year, country, study aim, setting, study design, study population, sample size (male/female), ethnicity or nationality, postnatal or gestational age, and impact of PGx on PK/PD in these studies. Only clinical trials and case reports were included in this systematic review. Due to a significant degree of heterogeneity between PGx and PK/PD measures, a meta-analysis was not deemed suitable.

Inclusion and Exclusion Criteria

The inclusion criteria were formulated using the PICOS (Participant, Intervention, Comparison, Outcome, and Study) design.[13] Studies were included if they met the following criteria:

Participants: the study population involved only patients <1 year, including neonates (day 1–28). For studies with a mixed population of participants, the studies were included for only infants according to the age (minimum or categorical values) of the patients. Studies in children and adults were excluded.

Intervention: since the majority of PGx findings are cohort (retrospective or prospective) studies, clinician-oriented intervention studies are not available. However, this may vary depending on the study design involved. For studies with a mixed population with ontogenetic and/or phenotypic study design, outcomes relating to the analysis of PGx and PK/PD findings were included if data could be extracted.

Comparator and outcome: data on impact of PGx variability on PK/PD parameters were included, with or without a comparator group.

Study design: Any clinical trial and case report published in English was considered for inclusion, regardless of study design.

The following types of studies were excluded: (a) papers that rather report on pre-assessment before PG implementation in children; (b) studies containing only ontogenic/phenotypic data, without PG data, or (c) non-primary clinical publications, such as conference abstracts, editorials, reviews, letters, and animal studies.

Risk of Bias and Quality Assessment

The risk of bias and quality assessment for each paper was assessed using the Newcastle–Ottawa Scale (NOS)[16] for non-randomized (case-control, cohort, and randomized controlled trials (RCTs) respectively) studies and the Joanna Briggs Institute (JBI) Critical Appraisal Tools for case reports. The risk of bias and quality assessment was primarily performed by N.Y., in consultation with K.A. and R.F. According to the NOS, a study can be awarded a maximum of one star for each numbered item within the "Selection" (4 items) and Exposure (3 items) categories. A maximum of two stars can be given for Comparability (1 item).[16] In the JBI checklist, a case report can be evaluated with 8 bias items, each of which answered as "Yes", "No", "Unclear" or "Not/Applicable". The overall appraisal is completed with one of the options: "Include", "Exclude" or "Seek further info".[17]

Results

We summarized the numbers of records screened, assessed and retained following identification via databases or registries, or by other methods (backward snowballing and top 100 list of medications prescribed in the NICU) in Figure 1 and Table 1. The flow diagram provides information on reasons for exclusion, and the extent of (dis)agreement. In total 55 reports were retained, published from 1998 onwards (2 reports before 2000, 10 between 2000–2009, 38 between 2010–2019, and already 5 reports from 2020 onwards), with a diversity of countries involved (based on the corresponding author).

Quality assessment was based on the NOS tool in 34 cohort studies (Table S1), 11 case-control studies (Table S2) and 6 randomized controlled trials (Table S3), and by the JBI critical appraisal tool for 4 case reports (Table S4). Because of the relevant number of reports retained, we post hoc decided to subdivide these findings by phase I related, phase II related, transporter related PG reports, or receptor and post receptor PGx related reports.

Phase I Related Pharmacogenetics

CYP1A2

In a dataset of 99 Chinese preterm neonates (gestational age (GA) 25–33 weeks, 201 caffeine concentrations), body weight, postmenstrual age (PMA) and serum creatinine affected caffeine clearance, while CYP1A2 polymorphism was not identified as independent covariate.[18]

CYP2A6

In a cohort of 270 children (2–72 months old) that had to undergo cardiac surgery, dexmedetomidine (3 µg/kg, intranasal) was administered for pre-sedation. In all cases, dexmedetomidine was quantified in blood samples collected one hour after administration. Comparing GG (185/257) versus T carriers (either TT or TG, 72/257) cases (CYP2A6 rs835309 genotypes), the mean concentration was 0.456 versus 0.397 ng/mL, so that T carriers had a 13% lower concentration at

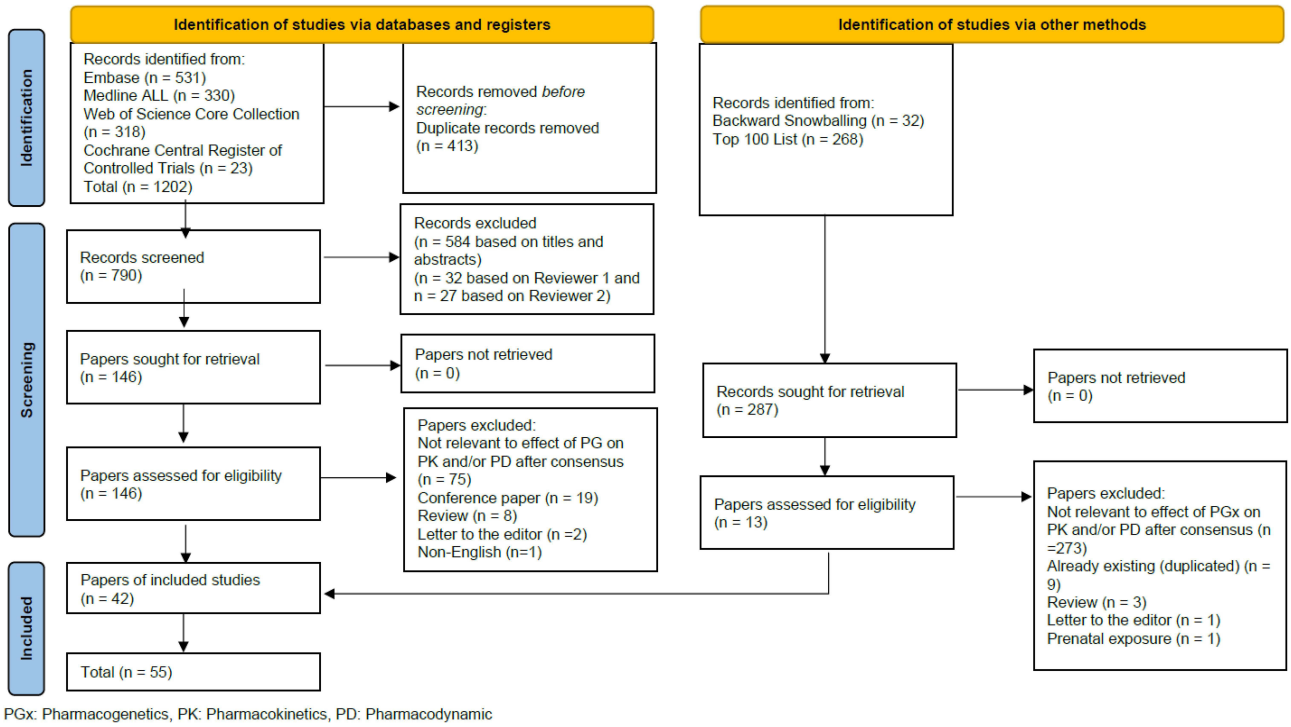

Figure 1 PRISMA flow diagram showing process of study selection for inclusion in systematic review.
Notes: PRISMA figure adapted from Moher D, Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). Creative Commons.[13]

one hour, reflecting faster clearance (p=0.025).[19] Unfortunately, no sub-analysis in infants, nor any analysis on maturational covariates were reported in this bio-analytical paper.[19]

CYP2B6

In a dataset of 25 young children (range 4–23 months), of whom 14 were infants (n = 4, ≤6 months, n = 10, 7–12 months), the median cyclophosphamide clearance was 46.6 (range 9.4–153) mL/min/m^2. Despite this marked inter-patient variability, no covariates (age, weight, CYP2B6 or CYP2C19) were identified, with only a trend for lower clearance in CYP2B6 *1/*6 (n = 7) versus *1/*1. The authors suggested that the absence of a significant difference was due to the small number.[20]

CYP2C8/C9/C18

As non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in preterm neonates to induce closure of a patent ductus arteriosus (PDA), data on the impact of CYP2C8/2C9 polymorphisms on ibuprofen and indomethacin have been reported, all with focus on pharmacodynamic outcome (ie, the need for surgical closure). Durrmeyer et al reported on the response to ibuprofen in a cohort of 86 extremely preterm neonates with a hemodynamically significant PDA. While a higher gestational age (GA) and non-Caucasian ethnicity were associated with an ibuprofen response, CYP2C polymorphisms (CYP2C8*3, CYP2C9*2, CYP2C8*3) were not.[11] On indomethacin, we retrieved two papers.[21] Besides other factors (GA, surfactant use), the presence of CYP2C9*2 (adjusted OR, 3.74) was associated with indomethacin treatment failure (defined by the need for surgical ligation, 35% of cases) in a 3-center cohort study on 144 preterm (GA 22–32 weeks) cases.[21] This paper confirmed a previously published case-control (52 non-responders versus 96 responders, <32 weeks) analysis. Besides GA, these authors identified an association between CYP2C9 rs2153628 (increased odds of response 1.92) or rs1799853, and DA response.[22]

We also retrieved a case report of phenytoin toxicity (lethargy) in a two-month-old Thai infant, associated with a CYP2C9 *1/*3 (slow metabolizer) and a CYP2C19 *1/*1 (normal metabolizer) genotype.[23]

Table 1 Description of Studies About Impact of Pharmacogenetics on Pharmacokinetics and -Dynamics in Neonates and/or Infants

Author, Year, Country	Study Aim	Setting	Study Design	Study Population	Sample Size (Male/Female)	Ethnicity or Nationality	Age (Days)	Effect on PK and/or PD
Allegaert et al 2008, Belgium[31]	Determinants of tramadol *O*-demethylation	NICU	Cohort study	Neonates and young infants	N=86 (n/a)	-	1–7 days: 45/86 8–28 days:22/86 >28 days: 19/86	PMA and CYP2D6 polymorphisms
Ansari et al 2010, Canada[43]	GST polymorphism on busulfan	HSCT Unit	Cohort study	Children	N=4/28 infants (1/3)	-	<1 years: 0.5 y 1–4 years: 2.2 y >4 years: 10.4 y	GSTM1 genotype was the best predictor of first-dose pharmacokinetic variability
Barnett et al 2021, UK[20]	PK and PGx of cyclophosphamide (CYP2B6, CYP2C19)	Multicentre (8 UK centres)	Cohort study	Children	N=14/25 infants (10/15)	-	0–6 months: 4/25 7–12 months:10/25 13–24 months: 11/25	No significant differences in cyclophosphamide clearance in patients <2 years
Blake et al 2007, USA[30]	Ontogeny of Dextromethorphan O- and N-demethylation	Multicentre (6 Pediatric Pharmacology Research Unit)	Cohort study	Healthy infants	N=193 infants (95/98)	African american (n=81) European american (n=64)	Between mean (SD), 14.4 (2.2) and 371.1 (18.2) days (Strength= repeated measurement)	A strong correlation between CYP2D6 genotype and Dextromethorphan O-demethylation
Cao et al 2018, China[64]	Association between TNF and MAPK8 polymorphisms and low response to HBV vaccines	A University Hospital	Cohort study	Infants	N=709 infants (374/335)	-	GA, mean (SD) Low responders: 39.0 (1.4) weeks High responders: 38.9 (1.4) weeks	MAPK8 polymorphisms are associated with immune response to HBV vaccinations in infants
Chen et al 2014, China[36]	Impact of CYP3A5 variants on tacrolimus disposition	LDLT Unit	Cohort study	Pediatrics	N=90 (52/38)	-	10 (4–120) months	CYP3A5 genotyping both in recipient and donor, not ABCB1 or ACE is necessary for establishing a personalized tacrolimus dosage regimen
Elens et al 2016, the Netherlands[63]	Impact of two SNPs on the response to opioid treatment (intubation setting)	NICU	Cohort study	Preterm infants 193 (185–200) days, equal to 26.4–28.6 weeks	N=34 (21/13)	-	7.17 (4.10–10.23) days	KCNJ6 −1250A and COMT^{158}Val alleles are predisposing to diminished opioid-induced pain relief
Enlund-Cerullo et al 2019, Finland[65]	GC genotype–related differences in 25OHD concentrations	Maternity Hospital	RCT	Infants	N=913 (459/454)	-	GA, mean (SD) 40.2 (1.1) weeks	Vitamin D binding protein genotype affects 25OHD concentration

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Table 1 (Continued).

Author, Year, Country	Study Aim	Setting	Study Design	Study Population	Sample Size (Male/Female)	Ethnicity or Nationality	Age (Days)	Effect on PK and/or PD
Fanta et al 2008, Finland[53]	Variations in the ABCB1, ABCC2, SLCO1B1, CYP3A4, CYP3A5, or NR1I2 genes associated with the pharmacokinetics of cyclosporine	Children's and Adolescents Hospital	Cohort study	Children and adolescents with renal transplant candidate	N=31/104 infants (66/38)	Finnish Caucasians (n=103) East African (n=1)	0.72 (0.17) months	Age-related effect of ABCB1 polymorphism on oral bioavailability
Fukudo et al 2006, Japan[35]	PopPK of tacrolimus and the effects of the MDR1 gene and the CYP3A4 and CYP3A5 on the oral clearance of tacrolimus	LDLT Unit	Retrospective observational study	Pediatric liver transplant recipients	N=130 (67/63)	-	Subpopulation PG data 1.3 (0.3–15) year	The enterocyte MDR1 mRNA level and the CYP3A5*1 allele in the graft liver contribute differently to the interindividual variability in the oral clearance of tacrolimus after living-donor liver transplantation
Gao et al 2021, China[18]	Evaluate the suitability of the current caffeine dosing regimen for the Chinese population using modelling and simulation approach.	NICU	Cohort study	Preterm newborns GA 28.3 (25–33.4) weeks	N=99 (58/41)	-	19.8 (10.8) days	CYP1A2 genotypes had no effect on caffeine clearance
Gorny et al 2010, Germany[33]	CYP2D6 ultrarapid metabolism with ritonavir	Pediatric Oncology	Case report	Infant	N=1	African	6 months	Failure of ritonavir due to CYP2D6 ultrarapid metabolism
Guan et al 2019, China[19]	Correlation between genetic polymorphisms and dexmedetomidine concentration levels	Children's Hospital	Cohort study	Pediatrics	N=260 (120/140)	-	28.82 (24.42) months aged 4–72 months	Correlation between CYP2A6 rs835309 activity and concentration of dexmedetomidine
Hahn et al 2019, USA[62]	How does OCT1 ontogeny and genetic variation influence morphine disposition in neonatal patients?	NICU	Cohort study	Neonates	N=83 (53/30)	Caucasian (n=28) African American (n=11) Asian (n=1)	14 days PMA 38.3 (24.9–57.3) months PNA 14 (1–212) days	Morphine clearance follows a developmental trajectory in parallel with ontogeny of hepatic OCT1 protein expression
Hahn et al 2020, USA[60]	The influence of MRP3 genetics on morphine clearance	Children's Hospital	Retrospective study	Neonatal and pediatric patients	N=57/142 neonates (Fig 1 and 2 of relevance)	-	PMA: 24–58 weeks	Morphine clearance showed an identical but nonsignificant decreasing trend by MRP3 genotypes

Hamberg et al 2013, Sweden[24]	Comparison of accuracy in dose prediction relative to published warfarin algorithms for children	Children's Hospital	Cohort study	Pediatrics	N=64 (33/31)	Caucasian (n=53) Asian (n=6) African (n=2)	4.3 years	The bridged PK/PD model performed prediction for warfarin maintenance dose CYP2C9, VKORC1
Hill et al 2014, UK[54]	Actinomycin D pharmacokinetics and investigate the impact of pharmacogenetic variation on the disposition	Multicentre	Cohort study	≤21 years Children with cancer	N=9/158 infants (78/80)	White British (n=140)	4.6 years	Body weight as the major determinant of actinomycin D clearance Variation in ABCB1 does not significantly impact on actinomycin D pharmacokinetics
Hronova et al 2016, Czech Republic[56]	Effect of dosing and genetic factors on sufentanil- and midazolam-induced analgosedation and withdrawal syndrome	PICU	Retrospective study	Neonates and children over 3 months of age	N=30/48 neonates (17/13)	-	PMA: 40 (37–42) weeks	SNPs in the candidate genes COMT, PXR and ABCB1 affected the dosing of analgosedative drugs
Kato et al 2011, Japan[67]	Effect of the genotype of VKORC1 on warfarin dose requirements	Children's Hospital	Cohort study	Pediatrics	N=48 (33/15)	Japanese patients	6.6 (5.8) years Range: 0.42–19.25 years	VKORC1 genotype and age were major factors affecting the relationship between the weight-normalized warfarin dose
Keller et al 2014, Argentina[45]	Evaluate the genotype and phenotype of NAT2 under isoniazid	Children's Hospital	Cohort study	Pediatrics	N=25/88 infants	Argentinian patients	4–23 months	A typical high proportion of rapid acetylators compared with other populations
Langaee et al 2021, USA[42]	Relationship between genetic variations in relevant drug disposition genes and niverapine PK parameters	Children's Hospital	Cohort study	Ghanaian children younger than 3 years old	N=53	-	1.6 (0.3–3.6) years	Genotyping for CYP2B6 rs3745274, and the NR1I2 rs6785049 G > A SNP (which encodes the transcriptional factor, pregnane X receptor), could improve prediction of nevirapine PK
Lee et al 2012, Korea[27]	Effects of CYP2C19 genetic polymorphisms on phenobarbital PK	Children's Hospital	Cohort study	Neonates and infants	N=44 (27/17) infants	-	8 days-6 months (subgroup analysis < 4 months, or 4–6 months)	Phenobarbital PK were not significantly different among the groups with different CYP2C19 genotypes
Linakis et al 2018, USA[50]	The role of genetic variability on the relevant metabolic pathways to determine which variants contribute to the variability observed in the PK profile of acetaminophen metabolites	NICU	Cohort study	Neonates	N=33 (19/14)	Non-Hispanic (n=22) Hsipanic (n=8) Declined to respond (n=3)	6 (1–26) days Extreme preterm (10), preterm (6) and term cases (17)	Pharmacogenetic effect of a sequence variations in the UGT1A9 promoter region on the metabolism of acetaminophen (glucuronide formation clearance)

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Table 1 (Continued).

Author, Year, Country	Study Aim	Setting	Study Design	Study Population	Sample Size (Male/Female)	Ethnicity or Nationality	Age (Days)	Effect on PK and/or PD
Maagdenberg et al 2018, the Netherlands[25]	Dosing algorithms for pediatric patients receiving acenocoumarol with and without genetic information	Multicentre (4 Pediatric Hospital)	Retrospective study	≤ 18 years	N=4/166 infants (84/82) N=123/175, and 86/123 with valid data on weight and height, only 2 infants included	European (n=141) Asian (n=4) African (n=4)	Clinical cohort: 8.9 (4.2–13.3) years Genetic cohort: 9.2 (4.2–14.0) years (86 and 80 cases), only 2 infants included	Genotypes of VKORC1, CYP2C9 and CYP2C18 to the algorithm increased variability in dose requirement to 61.8%.
Matic et al 2014, the Netherlands[51]	Determine whether SNPs of OPRM1 118A>G (asn40asp), COMT 472G>A (val158met) and ARRB2 8622C>T are associated with morphine rescue in placebo	NICU	RCT	(Pre)term newborns on mechanical ventilation	N=64 neonates (39/25)	Caucasian (n=53)	PNA <3 days GA, rescue morphine:28.7 (27.3–31.4) weeks No rescue morphine: 30 (29.1–32.1) weeks in the placebo group	Combined OPRM1 118A>G and COMT 472G>A genotype might serve as a predictor for the need of rescue morphine
Matic et al 2014, the Netherlands[52]	Association between UGT2B7 polymorphism −900G>A (rs7438135, also known as-842G>A) with morphine kinetics	NICU	RCT	Preterm newborns on mechanical ventilation (<37wks)	N=15 neonates (8/7)	-	0.14–7.4 days	GT2B7 −900G>A polymorphism significantly alters morphine PK (morphine, and morphine ratio's, M3G/M and M6G/M
Matic et al 2016, the Netherlands[61]	Effect of SLC22A1 (encoding the OCT1) genotype on tramadol PK	Children's Hospital	Retrospective study	Neonates and infants	N=50	Caucasian (n=45)	7.0 (2.0–27) days	Additional role of SLC22A1/OCT1 genetics in M1 exposure OCT1 is already active early after birth OCT1 allelle frequency and CYP2D6 functional genes copies <2 or ≥2
Pogliani et al 2012, Italy[57]	Relationship between renal morphine toxicity and genetic background	Children's Hospital	Case report	Premature infant	N=1	Caucasian	Newborn	Effect of impaired P-glycoprotein activity due to C3435T polymorphism in the ABCB1 gene on accumulation of morphine within urothelial cells
Roberts et al 2016, USA[59]	Determine the popPK of oral topotecan, specifically evaluating the effects of age and ABCG2 and ABCB1 on the Ka	Children's Hospital	Cohort study	Infants and very young children	N=61 (38/23)	-	2.37 (0.48–4.59) years	A possible role for the ABCG2 rs4148157 allele in the PK of oral topotecan

Schaaf et al 2005, South Africa[46]	PK of isoniazid in relation to the NAT2 genotype.	Children's Hospital	Cohort study	<13 years	N=18/64, 0–2 years	-	3.8 years	Younger children eliminate isoniazid faster than older children for each genotype (NAT2) *k* decreases with age within each genotype
Shimizu et al 2018, Japan[34]	Dihydrocodeine overdoses and PK modelling with genotyped as cytochrome P450 2D6*1/*10-*36	Children's Hospital	Case report	Neonate and 14-years old girl	N=2	Japanese patients	1 month	CYP2D6*1/*10-*36 genotype may not significantly contribute to the likelihood of dihydrocodeine overdose
Sridharan et al 2021, Kingdom of Bahrain[41]	Prevalence of SNPs in the key CYP enzymes and their effect on urinary metabolites and serum acetaminophen concentrations	Children's Hospital	Cohort study	Neonates	N=74 (38/36)	-	4 (1–20) days	A significant prevalence of SNPs in the key CYP enzymes related to acetaminophen metabolism was observed Relevant, but in essence negative study (cyp isoenzymes focused)
Uesugi et al 2006, Japan[37]	Liver transplants, CYP3A5 genotype in both recipients and donors, and the effect of the recipients' polymorphism on the concentration/ dose ratio of tacrolimus in patients after LDLT	LDLT Unit	Cohort study	General population	N=204	-	0.25–70 years	Intestinal CYP3A5, as well as hepatic CYP3A5, plays an important role in the first-pass effect of orally administered tacrolimus
Veeravigrom et al 2015, Thailand[23]	Effext of CYP2C9 and CYP2C19 on phenytoin metabolism	Neurology Unit	Case Report	Infant	N=1	-	2 months	Phenytoin toxicity resulting from CYP2C9 gene polymorphism
Ward et al 2010, USA[28]	PK profile of pantoprazole granules	Multicentre	RCT	Neonates with GERD	N=40	White (n=30) Hispanic or Latino (n=8) African American (n=6) Asian (n=1)	8.0 (1.3–19.6) weeks	Two patients with the CYP2C19 poor metabolizer genotype had a substantially higher AUC than extensive metabolizers
Xue et al 2014, China[73]	Effect of CYP3A5 genotype on optimal dosage regimen in LDLT patients	LDLT Unit	Cohort study	Pediatrics	N=64 (39/25)	Chinese recipients and donors	9–11 months	CYP3A5 genotype in both recipients and donors significantly affects tacrolimus PK after Liver transplantation
Yang et al 2011, China[74]	The role of PGx determinants in the treatment of childhood ALL	University Hospital	Retrospective study	Pediatrics	N=7/105 infants (59/46)	Chinese patients	0–1 years	Independent PGx determinants associated with treatment outcome (event free survival): ABCB1, MDR1, etc.

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Table 1 (Continued).

Author, Year, Country	Study Aim	Setting	Study Design	Study Population	Sample Size (Male/Female)	Ethnicity or Nationality	Age (Days)	Effect on PK and/or PD
Yang et al 2015, China[75]	Impact of SNPs of CYP3A5 and ABCB1 genotypes on tacrolimus PK	LDLT Unit	Retrospective study	Pediatrics	N=136 (74/62)	Chinese recipients and donors	8–10 months	CYP3A5 (R and D) and ABCB1-1236 genotyping (R), in addition to recipient age, are necessary for establishing a more accurate tacrolimus dosage regimen
Zhao et al 2018, China[29]	Effect of both age and PGx on developmental pattern of CYP2C19 in omeprazole	Children's Hospital	Cohort study	(Pre)term Neonates and young infants with GERD	N=51 (24/27)	Caucasian (n=51)	38 (7–87) days GA 31.3 (24–41 weeks)	Both CYP2C19 genotype and age contribute to the developmental PK of omeprazole and its metabolites ABCB1 PG is relevant on the absorption rate constant
Zhu et al 2012, USA[49]	İmpact of polymorphism of izoniazide PGx	Children's Hospital	RCT	Infants	N=151 (71/80)	South African	8.84 ± 8.03 (3.03–33.47) months	A different NAT2 enzyme maturation profile for each of the 3 acetylation groups, with the 70-kg body weight–normalized typical apparent clearance for the fast and intermediate acetylators increasing from 14.25 L/h and 10.88 L/h at 3 months of age to 22.84 L/h and 15.58 L/h at 24 months of age, respectively
Zielinska et al 1998, Poland[48]	Comparison of the acetylation phenotype and NAT2 coding genotype in the prediction of idiosyncratic reaction to Cotrimoxazole	Children's Hospital	Cohort study	Infants	N=20 (10/10)	-	6.35 (2–12) months	The NAT2 genotype rather than phenotype provides the basis for the detection of hypersensitivity to Cotrimoxazole
Zwaveling et al 2008, the Netherlands[76]	The contribution of genetic polymorphisms in the GST isozymes to the PK of busulfan	Multicentre HSCT	Retrospective study	Pediatrics	N=77	-	5 (0.2–23) years	Variability in PK of busulfan could not be related to polymorphisms in GST
Snowball								
Allegaert et al 2008, Belgium[31]	Impact of CYP2D6 polymorphism on IV tramadol disposition	Children's Hospital	Cohort study	(Pre)term neonates and young infants	N=57	-	6 (1–149) days	A limited m-opioid receptor-mediated analgesic effect of M1 in preterm neonates and a CYP2D6 polymorphism dependent effect
Moreau et al 2012, France[26]	The relative contributions of nongenetic and genetic factors (VKORC1, CYP2C9, and CYP4F2) on warfarin or fluindione dose requirements	Children's Hospital	Cohort study	Pediatrics	N=118 (64/54)	-	9 (3 months-18 years) years	Contribution of the VKORC1 and CYP2C9 genotypes to variations in warfarin response among children with cardiac disease

Ashton et al 2007, Australia[44]	Polymorphisms in the genes encoding phase I and II drug metabolizing enzymes associated with the risk of relapse or death	Children's Hospital	Double center Cohort study	Children with neuroblastoma	N=209 (122/87) <1 year: 86 (41%)	-	14.4 (0–13 years) months	NAT1*11 variant and the GSTM1 wild-type genotype contribute to a more favorable outcome in patients treated for neuroblastoma and are the first to demonstrate a relationship between NAT1 and GSTM1 genotypes in childhood neuroblastoma.
Gijsen et al 2011, the Netherlands[40]	Relationship between age and CYP3A5 and ABCB1 genotype and the Pediatric Risk of Mortality score on tacrolimus dose, steady-state trough concentrations, concentration/dose ratio	Children's Hospital	Cohort study	Pediatric heart transplant recipients	N=39 (25/14) <1 year: 15 (38.5%)	White (n=28) Asian (n=4) African American (n=2)	6.0 years	First 14 days after heart transplantation, younger age and CYP3A5 expressor status were independently associated with higher tacrolimus dosing requirements and concentration/dose ratio
de Wildt et al 2011, Canada[38]	The effect of these covariates on tacrolimus dose requirements in the immediate post-transplant period	Children's Hospital	Retrospective study	Pediatric liver recipients	N=42 for liver recipients	-	Liver recipients: 1.5 (0.05–14.8) years	In liver recipients, variation in tacrolimus disposition appears related to age and ABCB1 genotype
Hawwa et al 2009, UK[58]	Influence of genetic polymorphisms in ABCB1 on the incidence of nephrotoxicity and tacrolimus dosage-requirements	Children's Hospital	Cohort study	Pediatric liver transplant population	N=51 (27/24)	-	2 (0.6–16) years	ABCB1 polymorphisms in the native intestine significantly influence tacrolimus dosage-requirement in the stable phase after transplantation. In addition, ABCB1 polymorphisms may predispose them to nephrotoxicity over the first year posttransplantation
Durrmeyer et al 2010, France[11]	CYP2C8/2C9 polymorphisms may predict ibuprofen response	NICU	Cohort study	Extremely preterm infants with PDA	N=111 (60/51)	Caucasian mother (n=49) Caucasian father (n=52)	GA: 25.6–26.6 weeks	CYP2C polymorphism was not associated with PDA response to ibuprofen and this factor appears not appropriate to optimize the ductal closure rate by modulating ibuprofen dosing strategy
Zielinska et al 1999, Poland[47]	Extent to which genotype coding for N-acetyltransferase agrees with acetylation phenotype	Children's Hospital	Cohort study	Pediatrics	N=82 (57/25) <1 years: 37 (45%)	Caucasian	1 month-17 years	Disagreement between the acetylation phenotype and genotype is more often found in the group of children characterized by low AFMU/1X and that in small children only N-acetyltransferase genotype studies enable the detection of genetic acetylation defect

(*Continued*)

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Table 1 (Continued).

Author, Year, Country	Study Aim	Setting	Study Design	Study Population	Sample Size (Male/Female)	Ethnicity or Nationality	Age (Days)	Effect on PK and/or PD
Wachman et al 2013, USA[77]	SNPs in the OPRM1, ABCB1, and COMT genes are associated with length of hospital stay and the need for treatment of NAS.	Multicenter (5 tertiary care)	Cohort study	Infants	N=86 (51/35)	White (n=84)	GA ≥38 weeks: 70 (81%)	Variants in the OPRM1 and COMT genes were associated with a shorter length of hospital stay and less need for treatment
Wachman et al 2017, USA[55]	Genetic variations in thePNOC and COMT genes of opioid-exposed mother infant pair	Multicenter (5 tertiary care)	Cohort study	Infants	N=113 (41/72)	White (n=99)	GA: 39 weeks	Differences in NAS outcomes depending on PNOC and COMT SNP genotype
Top 100 List								
Lewis et al 2019, USA[66]	Candidate SNPs in corticosteroid metabolism and response genes are associated with short-term phenotypic response to systemic corticosteroids	Multicenter	RCT	Preterm infants at high risk for BPD	N=80 (46/34)	White (n=39) African American (n=38)	22.8–29.2 days	Genetic variability is associated with corticosteroid responsiveness with regard to respiratory status
Smith et al 2017, USA[22]	Association between SNPs in CYP2C9 and the closure of PDA in response to indomethacin	NICU	Retrospective study	Preterm infants with PDA	Responders N=96 (53/43) Non-responders N=52 (27/25)	White (n=123) Black (n=15)	GA: 25.3–26.9 weeks	Association between two SNPs in CYP2C9, rs2153628 and rs1799853, and indomethacin response for the treatment of PDA
Rooney et al 2019, USA[21]	Clinical and genetic factors associated with indomethacin treatment failure	Multicenter (3 NICU)	Cohort study	Preterm neonates with PDA	N=144 (75/69)	White (n=105)	7–8 days	Age, surfactant use, and CYP2C9*2 influence indomethacin treatment outcome

Related to coumarins, we retrieved 3 datasets reporting on CYP2C9 and 2C18 polymorphisms in children, be it that the number of infants included in these studies was limited. Using an adult PK/PD model bridging effort to children for warfarin, the INR response was predicted reasonable well in 64 children (age range 0.05–18.9 years, weight range 3.4–94 kg), be it with a tendency to overpredict the international normalized ratio (INR), or underpredict dose in children <2 years. It was hereby extrapolated from adult findings that CYP2C9 polymorphisms explained up to a 4.2-fold (CYP2C9 *3/*3 vs *1/*1) difference in warfarin maintenance dose.[24] Another cohort of 123 children (only 2 infants included) body surface area (BSA) and indication explained 45% of the variability in acenocoumarol dose requirement (INR targeting), while Fontan circulation was another covariate (4.3 to 3 mg/kg, 1.4 fold difference). Specific for CYP2C9*2/CYP2C9*3, the median maintenance dose displayed a 1.35 fold difference (median observed dose, 1.21 versus 1.88 mg/day), for CYP2C18 (GG versus AG) this was 1.15 fold (median observed dose, 1.62 to 1.85 mg/day).[25] Finally, in a dataset with 118 cases (age range 3 months to 18 years, 19 cases <3 years) on acenocoumarol dosing, CYP2C9 (*1/*1, *1/*x, or *x/*x:) to a certain extent (2%) showed a 1.88 fold difference in weekly median dose requirement of warfarin, ie 24.8, 22.2, or 13.13 mg/week, respectively.[26]

CYP2C19

In the previously mentioned (related to CYP2B6) cyclophosphamide study in young children, CYP2C19 polymorphisms (*1/*1, *1/*2) were neither relevant covariates.[20] Other observations relate to phenobarbital and proton pump inhibitors (pantoprazole, omeprazole) PK.[27–29] Body weight and age determined phenobarbital clearance in a cohort of 52 neonates and young infants (age range, 8 days - 6 months), while CYP2C19 (*1/*1, *1/*2, *2/*2 or *2/*3) polymorphisms were not, in contrast to similar studies in adults.[27] As part of a population PK study with oral pantoprazole (granules) in preterm infants and neonates, the mean area under the plasma concentration versus time curve (AUC) was substantially higher in 2 (2/40) cases (median PMA 37 weeks, range 33–44) with a CYP2C19 poor metabolizer profile. In these poor metabolizers (*2/*2), the AUC was 10.8 and 27 µg.h/mL (1.9- and 4.8-fold increase) respectively, while the median AUC value was 5.63 (range 1.3–27) µg.h/mL.[28] Along the same line, Zhao et al quantified the impact of CYP2C19 polymorphisms (poor, intermediate to extensive metabolizer) on the formation clearance of omeprazole to 5-hydroxy-omeprazole.[29] Compared to the extensive/ultrarapid metabolizer (*1/*1, *1/*17, *17/*17) genotype, clearance to 5-hydroxy-omeprazole is at the 44.9th and 12.5th percentile for the intermediate (*1/*2 or *2/*17) and poor metabolizer (*2/*2), respectively.

CYP2D6

For CYP2D6 polymorphism and its related CYP2D6 activity score, observations on dextromethorphan (oral) and tramadol (parenteral) have been reported.[30–32] Dextromethorphan *O*- and *N*-demethylation in the first year of life was quantified, based on paired urine metabolic ratio's following a single oral (0.3 mg/kg) dose at 0.5, 1, 2, 4, 6 and 12 months in 193 term born infants. There was a strong correlation between CYP2D6 genotype (CYP2D6 activity score) and O-demethylation (r=−0.638), with concordance from 2 weeks postnatal age onwards. The mean log urinary dextromethorphan/dextrorphan (DM/DX) metabolic ratio for a given CYP2D6 activity score (0, 0.5, 1, 2, >2) was −0.05, −1.29, −1.64, −2.05, or −2.21 respectively.[30] In 86 neonates (median PMA 39 weeks, range 25–62) exposed to continuous intravenous tramadol, the plasma and urine log tramadol/0-demethyl tramadol (M/M1) ratio were determined (R^2 0.59 and 0.64 respective) by PMA and the CYP2D6 activity score in a multiple regression model in 86 neonates (median PMA 39 weeks, range 25–62). Median urine log M/M1 values for a CYP2D6 activity score of 0, 1, 2 or 3 were 2.3, 1, 0.7 and 0.2, median plasma log M/M1 values for the same score (1, 2 or 3) were 1, 0.5 and 0.35 in this cohort. Tramadol clearance to M1 displayed a CYP2D6 activity score, with an additional maturational pattern. Clearance to M1 had a large between subject variability (111%). Size and PMA were the major contributors (52.7%), while CYP2D6 activity score contributed 6.4%.[31,32]

Two case reports on the impact of CYP2D6 polymorphism on pharmacotherapy related to lopinavir/ritonavir and dihydrocodeine were also retrieved.[33,34] The first case relates to pharmacogenomic adaptation of antiretroviral therapy (lopinavir failure) in a 6 month old African infant with a CYP2D6 ultrarapid metabolizer profile.[33] The second paper described two children, of whom one was a neonate (1 month, 3 kg) with a CYP2D6*1/*10-*36 genotype. The newborn

was exposed to dihydrocodeine-containing cough mixture (1 mg q12h dihydrocodeine phosphate, for 2 days), and subsequently displayed acute respiratory depression, followed by ventilation for 3 days.[34]

CYP3A5

Related to tacrolimus PK, we retrieved 6 reports (5 hepatic and 1 cohort on cardiac transplants). However, the number of infants in these observations were rather limited, so these data should be interpreted with caution in this specific population. Fukudo et al reported on a population PK study in 130 (including PGx in 65/130) pediatric transplant recipients (age 0.1–15 years) shortly after (<50 days) transplantation. CYP3A5*1 carrier donor liver was associated with a 2-fold higher oral clearance (CL/F) compared to CYP3A5*3/*3.[35] Chen et al also studied personalized tacrolimus dosing requirements by CYP3A5 recipient and donor polymorphisms in 90 children (median 10, range 4–120 months). The recipients with an expressor genotype required more time to achieve the tacrolimus therapeutic range during the induction phase, and needed more upward dose during late induction and the maintenance phases compared with those with CYP3A5 *3/*3. Donor CYP3A5 genotypes impacted the tacrolimus trough concentrations after liver transplantation.[36] Uesugi assessed the effect of intestinal CYP3A5 on post-liver transplant tacrolimus through levels in a population of 204 transplanted patients (age range 0.25–70 years). The tacrolimus concentration/dose (C/D) ratio was lower in recipients with the CYP3A5*1/*1 and *1/*3 genotype (CYP3A5 expressors) compared to the CYP3A5*3/*3 genotype (non-expressors). Amongst the combination of CYP3A5 genotypes between the graft liver and native intestines, CYP3A5 expressors in both graft liver and native intestine had the lowest C/D tacrolimus ratio (1.7–2.6 fold difference between *1/*1 and *3/*3, respectively) in the first 35 days after liver transplant. This indicates that intestinal CYP3A5, as well as hepatic CYP3A5 affect the first-pass effect of oral tacrolimus.[37]

With focus on the immediate (14 days) post-transplant period in kidney (48, no infants) and liver (42, including infants) recipients, de Wildt et al observed no impact of CYP3A5 expression in the hepatic transplant cases (age range 0.05–14.8 years) in liver recipients (in contrast to kidney transplants).[38] Xue et al reported-on liver recipient and donor data in 64 cases (median age 10 months, range 5–60), and analysed the impact of CYP3A5 (CYP3A5, *1 expression allele) polymorphisms on tacrolimus PK and infectious complications. The authors hereby confirmed the contribution of CYP3A5 expression (38%) to the C/D ratio, and the graft liver was a key determinant. Expressors (recipient + donor) showed a significant higher incidence of infectious complications (Odd ratio 3.86).[39] Finally, Gijsen et al reported on 39 cardiac transplant cases (median age 6 years, 15 infants) where CYP3A5 expressors (CYP3A5 *1/*1 or *1/*3) needed higher doses (+ 133%, 0.14 vs 0.06 mg/kg/12 h). Both age and CYP3A5 affected dosing, although this has not been separately analyzed in infants.[40]

Multiple CYPs

Sridharan et al evaluated the association between urinary acetaminophen metabolites (glucuronides, sulphated metabolites) and serum acetaminophen concentrations, and a set of key CYP enzyme (CYP1A2, CYP2D6, CYP2E1, CYP3A4, and CYP3A5) polymorphisms in cohort preterm neonates (GA range 23–34.5 weeks) exposed to acetaminophen because of a symptomatic PDA. Postnatal age was associated with and increased formation of urinary metabolites and decreased serum acetaminophen concentrations, while none of the CYP enzyme polymorphisms contributed to acetaminophen disposition.[41]

The relationship between genetic variations in relevant drug disposition genes and nevirapine PK parameters were explored in 53 Ghanaian children (age 3–35 months, or <10 kg) living with HIV eligible to initiate nevirapine-based antiretroviral therapy, with nevirapine minimum concentration (C_{min}), AUC_{0-12h} and CL/F as outcome variables. On CYPs, CYP2B6, CYP2A6 and CYP3A5 polymorphisms were hereby explored. CYP2B6 rs3745274 (reduced clearance) turned out to be one of the predictors of these outcome variables, although the multivariate (age, sex, co-medication, tuberculosis co-infection, and PGx) models only explained a limited portion of the variability (29–37%).[42]

Phase II Related Pharmacogenetics

Glutathione-S-Transferases (GST)

Ansari et al reported on the PK of busulfan used for myelo-ablation in 28 children (age range 0.4–19.8 years, weight range 6.2–84 kg) who underwent hematopoietic stem cell transplantation (HSCT).[43] In this cohort, GSTA1, GSTM1 and GSTP1 polymorphisms were explored as covariates of first-dose intravenous busulfan (age range 3–12 months, median dose 0.8 mg/kg). In a multivariate regression analysis, dose, age and GSTM1 genotype were the best predictors of the first-dose PK variability. Furthermore, GSTM1-null patients received a lower cumulative busulfan dose. In contrast, GSTA1 or GSTP1 gene variants were not predicting. As this review focusses on the findings in infants (n = 4, 3 GSTM1-Null cases, 1 non-Null), differences in AUC or cumulative dose were not (yet) observed. Besides some information on PK, Ashton et al assessed the influence of polymorphisms of GSTM1 and N-acetyl transferase (NAT, see below) on outcome of children (86/209 < 1 year) with neuroblastoma.[44] These authors hereby documented that the GSTM1 wild type and NAT1*11 was associated with a more favorable outcome in these patients, while GSTM1 null were more likely to relapse or die (hazard ratio 1.6, after adjusting).

N-Acetyl Transferase

We retrieved 5 different reports on the exploration of NAT-related polymorphisms in neonates and infants. PK findings were explored by Keller et al (isoniazide, NAT-2), Schaaf et al (isoniazide, NAT-2), and Zielinska et al (caffeine, NAT-2), PD finding by Ashton et al (neuroblastoma, see above, and Zielinska et al (trimethoprim-sulfamethoxazole toxicity).[45–48] Related to isoniazide PK, Keller et al used the metabolic ratio (MR, acetyl-isoniazide/isoniazide) in blood, and hereby described a positive correlation with age (r = 0.53, age range 4 months to 17 years, 25/88 cases were 4–23 months).[45] The slow genotype (no alleles) had a much lower MR compared to the rapid (two alleles) genotype (0.5 versus 1.15). Schaaf et al estimated the first order elimination rate constant (k) and AUC in 64 children (18 cases < 2 years). The k value was dependent on the age, as well as on NAT-2 allele frequency (SS = 0.254; FS = 0.51; FF = 0653 h^{-1}). Finally, Zhu et al quantified the pharmacogenetics of NAT2 enzyme maturation in perinatal HIV exposed infants receiving isoniazide, to describe the genotype-dependent enzyme maturation processes for the NAT2 enzyme. Consecutive plasma concentration-time measurements of isoniazide from 151 infants (starting at 3–4 months of age) receiving isoniazide 10 to 20 mg/kg/day orally during the course of the 24-month study were incorporated in a population analysis along with NAT2 genotype, body weight, age, and sex.[49] Apparent clearance (70 kg body weight-normalized) for fast and intermediate acetylators increasing from 14.25 L/h and 10.88 L/h at 3 months of age to 22.84 L/h and 15.58 L/h at 24 months of age, while slow acetylators displayed no changes over age (7.35 L/h).[49]

UDP-Glucuronosyl-Transferase (UGT)

For UGT-related polymorphisms, we retrieved data on acetaminophen (UGT1A9) and morphine (UGT2B7).[50,51] Linakis re-explored a previously reported parent-metabolite (glucuronidated, sulfated, and oxidative metabolites) PK model following iv acetaminophen in 33 neonates (PNA range 1–26 days). Integration of a specific UGT1A9 gene promoter region covariate (rs3832043, - 118 > ins T, T_9 > T_{10}) significantly improved model fit (reduced between-subject variability in formation clearance of acetaminophen-glucuronide). UGT1A9 T_{10} was associated with a 42% reduction in clearance to acetaminophen-glucuronide.[50]

Morphine plasma concentrations in 17 preterm neonates (range 25–32 weeks GA) collected 20 min post intubation (morphine for rapid sequence intubation) were associated with postnatal age (range 0.14–16 days) and UGT2B7 −900G>A, while the morphine-3 and morphine-6-glucuronide/morphine ratio was higher compared to −900G/G type (GG, GA, and AA, MG3/M and MG6/M: 15.3 and 4.6-fold difference).[52]

Transporter Related PG Reports

ATP-Binding Cassette Transporters

In an exploratory study on the impact of ABCB1 and ABCC2 polymorphisms on cyclosporine PK (intravenous and oral, pre-transplant) in children (104 cases, age 0.36–16.3 years, 31 infants), Fanta et al observed an age-dependent influence of ABCB1 polymorphisms.[53] BCB1 polymorphisms affected bio-availability (c.2677GG, GT or TT, 0.64, 0.52 and 0.41, 1.5-fold difference). However, this observation only to a limited extent explained the inter-patient variability (3.2-fold

variability in oral bioavailability, prehepatic extraction ratio 3.7-fold, hepatic extraction 2.4-fold), and specific in infants (31/104 cases), no PG related effects were observed.

Hill et al explored the impact of ABCB1 PGx on actinomycin PK in 117 sampled children (age range 0.3–19.8 years, 9 infants). Body weight was the dominant covariate, while pharmacogenetic variation in candidate drug transporter genes - identified from preclinical studies – had no significant impact on intravenous actinomycin disposition.[54]

With focus on neonatal abstinence syndrome (NAS) cases, Wachman et al explored the association of ABCB1 gene polymorphisms with the length of hospital stay (LOS) and the need for pharmacological treatment in 86 NAS newborns, but this association was not confirmed.[55] Similarly, a signal on the contribution of ABCB1 polymorphisms on nevirapine PK variability (cf supra) was not observed.[42] Hronova reported on the effect of ABCB1 polymorphisms in a group of 30 neonates and 18 children exposed to midazolam or sufentanil on withdrawal syndrome characteristics. Treatment duration and cumulative doses for midazolam and/or sufentanil were associated with a higher risk to develop withdrawal syndrome: While ABCB1 polymorphisms affected the dose, there was no effect on the likelihood of withdrawal syndrome.[56] We also retained one case report, describing transient bilateral hydronephrosis and obstruction related acute kidney injury secondary to bladder sphincter spasm, solved with bladder catheterization and stopping morphine exposure in a preterm (GA 34 weeks) newborn.[57] In further PGx screening, the patient turned out to be homozygous for C3435T polymorphism (ABCB1 gene), associated with impaired P-glycoprotein activity. As P-glycoprotein is also expressed in urothelial cells, the authors suggested that this polymorphism contributed to opioid-induced urinary retention.

In a dataset of 105 childhood acute lymphoblastic leukemia (ALL, 7 infants), Yang et al explored associations with 17 genetic polymorphisms in 13 targets (Taiwan ALL-93 protocol), and observed three polymorphic alleles in the multi-drug resistance 1 (MDR1) ABCB1 gene. Furthermore, they found that homozygotic MDR1 2677GG, 3435CC, and 2677G-3435C genotypes were highly associated with a significant reduction in event free survival (Hazard ratios were 6.8, 21.7, and 6.8) in those patients treated by the standard risk (SR) protocol.

Related to tacrolimus PK, we retrieved 5 reports (4 hepatic, with 1 also including data in renal transplant cases, 1 cardiac) on ABCB1 polymorphisms or haplotypes. Chen et al studied personalized tacrolimus dosing requirements by recipient and donor polymorphisms in 90 liver transplant children (median 10 months, range 4–120), including ABCB1. No effects of ABCB1 polymorphisms on dosing requirement were observed.[36] In contrast, Fukudo et al reported on a population PK study in 130 (including PGx in 65/130) pediatric liver transplant recipients (age range 0.1–15 years) shortly after (<50 days) transplantation, and observed an effect of ABCB1 mRNA expression on CL/F (+15–20%), much smaller than the 2-fold impact of CYP3A5 polymorphisms.[35] Hawwa et al assessed the tacrolimus dose and nephrotoxicity after liver transplant in 51 pediatric cases (recipient PGx, range 0.6–16 years). Trough levels in TTT haplotype and G2677>T and C3435>T were correlated to higher exposure, with a different C/D ratio from 3 years after transplant onwards (like G2677->T and C3435->T 62 versus 39, and 60 versus 33 ng/mL/mg/kg.[58] Reduction in estimated glomerular filtration rate (eGFR) was more common and more pronounced in T-T-T haplotype carriers and G2677->T or C1236->T.[58] With focus on the immediate (14 days) post-transplant period in kidney (48, no infants) and liver (42, including infants) recipients, de Wildt et al observed in liver recipients (age range 0.05–14.8 years) that homozygous cases (T-T-T haplotype) needed higher doses (+136%, 0.26 versus 0.11 mg/kg/12h).[38] In pediatric liver recipients, but not renal transplant recipients, variation in tacrolimus disposition appeared related to age and ABCB1 genotype shortly after transplantation. Using a similar approach in 39 cardiac transplant cases, Gijsen et al documented that age and CYP3A5 expression affected tacrolimus dosing, but not ABCB1 polymorphisms or disease severity (PRISM = Pediatric Risk of Mortality).

Roberts et al reported on a population PK study of oral topotecan in infants and young children with brain tumors. Based on PK observations in 61 cases (age range 0.48–4.59 years, 20/61 cases <2 years). After including BSA in the V/F and CL/F as a power model centered on the population median, the ABCG2 rs4148157 allele had a significant role in the Ka value. Patients homozygous or heterozygous for G>A demonstrated a Ka value 2-fold higher than GG, complemented with a 2-fold higher maximal concentration as well.[59]

Related to ABCC3 polymorphisms (Multidrug Resistance Protein 3), Hahn et al observed a decreasing trend on morphine clearance with MRP3 efflux transporter (rs4793665) genotypes (CC>CT>TT) (morphine clearance, standardized to 70 kg, 31.3, vs 26.39 vs 20.76 L/h, 1.5-fold difference) in a subgroup of OCT1 wild-type cases.[60]

Organic Cation Transporters

Matic et al reported that the plasma log M/M1 ratio in 50 preterm neonates and infants (27–54 weeks PMA) exposed to intravenous tramadol, was also affected by the OCT1 allele frequency, in addition to the previously mentioned CYP2D6 activity score and age, with a 1.14-fold difference between cases with ≥2 functional gene copies (n=27/50) or with <2 (n = 23/50).[31,32,61] Using a physiologically-based pharmacokinetic modelling effort in 85 neonates and young infants (PMA range 24.9–57.3 weeks), the impact of age, OCT1 ontogeny, and OCT1 allele frequency (loss of function) on morphine disposition were explored based on in vivo morphine observations. Comparing the wild, to the hetero- or homo-haplotype, there were not yet differences in morphine clearance in the 24–34 weeks group, while these differences appeared (about 2-fold differences) at 34–40 (19.3, 15.5 and 10.9) and 40–58 weeks (38.7, 30 and 20 L/h, standardized to 70 kg).[62]

Organic Anion Transporter Protein 1B1 (OATP1B1, SLCO1B1 genotype) polymorphisms were also explored in the previously mentioned cyclosporine cohort ((intravenous and oral, pre-transplant) in children (104 cases, age range 0.36–16.3 years, 31 infants), but this analysis remained negative.[53]

Receptor and Post Receptor Mechanism Reports

Opioid Related Receptor and Post Receptor Mechanisms

The relevance of the KCNJ6-1250G.A (rs6517442, c.-1787G.A, G-protein-activated inwardly rectifying potassium channel 2) and the COMT c.472G.A (rs4680, Val158Met) single-nucleotide polymorphisms were studied in preterm infants needing intubation and randomized to a premedication strategy including remifentanil (n = 17) or morphine (n = 17) by Elens et al.[63] The authors hereby documented that KCNJ6-1250A (time to response to pain therapy, delay to reach a pain free score, AA vs AG vs GG: 182, 109 and 60 minutes, 3-fold difference) and COMT 158 Val alleles (Val/val, vs Val/Met vs Met/Met: 285, 137 and 63 minutes, 4.5-fold difference) were associated with diminished opioid-induced pain relief in preterm neonates. Within the same theme, Matic et al assessed the need for rescue morphine within a randomized controlled trial in preterm (n = 64, placebo cases) neonates that required mechanical ventilation. The authors hereby aimed to determine whether single nucleotide polymorphisms (SNPs) of OPRM1 118A>G (asn40asp), COMT 472G>A (val158met) and beta-arrestin-2 (G-protein coupled receptor, ARRB2) 8622C>T were associated with morphine rescue. For OPRM1 and COMT separately, the expected risk for rescue morphine or morphine dose was not significantly increased. However, the combined OPRM1/COMT "high-risk" genotype had a higher likelihood for the need for rescue (OR: 5.12).[52]

With focus on neonatal abstinence syndrome (NAS) cases, Wachman et al explored the association of OPRM1 and COMT genes (ABCB1 discussed higher) with LOS and the need for pharmacological treatment in 86 NAS newborns.[55] OPRM1 (118A>G AG/GG shorter LOS (−8.5 days versus average 22.3 days, −38%) compared to AA genotype and were less likely to receive treatment (48% vs 72%). COMT AG/GG shorter LOS (−10.8 days versus average LOS 22.3 days, −48%) and less "advanced, ≥2 drugs" treatment (18% versus 56%) compared to AA genotype.[55]

In a subsequent study of the same researchers, the association COMT genes with NAS severity was confirmed in a replication cohort (n = 113).[55] Furthermore, infants with the PNOC (prepronociceptin, ligand of OPRM) rs4732636 A allele had a reduced need for pharmacological treatment (adjusted OR 2).[55] In the study of Hronova et al, the impact of COMT and human pregnane X receptor (PXR) (besides ABCB1, cf higher) on sufentanil and midazolam dosing were also explored, and observed that these polymorphisms affected dosing, but not the depth of analgo-sedation or withdrawal syndrome.[56]

Tumor Necrosis Factor (TNF) and Mitogen-Activated Protein Kinase 8 (MAPK8)

The relevance of tumor necrosis factor (TNF) or mitogen-activated protein kinase 8 (MAPK8) polymorphisms on the immune response to HBV vaccination (at birth, 1 and 6 months) in 753 infants of HBsAg positive, HBeAg negative mothers has been explored. Formula feeding and MAPK8 polymorphisms (rs17780725, AA versus GA or GG genotype), but not TNF polymorphisms, were associated a "low responder" profile (antibody titers, 5.8% of the cases) after hepatitis B vaccination (OR = 2.9) at 7 months.[64]

Vitamin D Binding Protein SNPs

Vitamin D protein (6 different diplotypes) genotype affects 25 OH-vitamin D concentration and efficiency of D3 supplementation (either 10 or 30 µg/day) in infants. Major allele homozygote haplotypes and diplotype 1 (1S/1S, 1F/1S and 1F/1F) result in higher 25 OH-vitamin D concentrations compared to diplotype 2 (1S/2, 1 F/S, and 2/2) with a mean effects size from −4.4 nmol/l to −10.9 nmol/l at 24 months (median 25OH vitamin D 114 and 118 nmol, so 4% and 9% lower), for $Haplo_{3SNP}$ and $Haplo_{4SNP}$ the effect size was −12.6 to −33.7 nmol/L (so 11 and 29% lower).[65]

Corticotrophin-Releasing Hormone Receptor-1 (CRHR1) Polymorphisms

77/126 cases included in the TOLSURF trial (RCT on late surfactant to prevent bronchopulmonary dysplasia in ventilated preterms, receiving inhaled nitric oxide), and exposed to dexamethasone or hydrocortisone, a panel of candidate SNP associations were tested, with the change in respiratory severity score as dependent variable. Using this explorative approach, genetic variation in CRHR1 polymorphism was associated with differences in absolute decrease in respiratory severity score (RSS) at day 7 (Rs7225082, each T allele is associated with a smaller decrease in RSS at day 7 (RSS change: −44, −50 or −31% for GG, GT and TT respectively, 1.6-fold variability).[66]

Nuclear Receptor Subfamily 1

The previously mentioned nevirapine PK study also explored the relationship between nuclear receptor subfamily 1, group I, member 2 and member 3 (NR1I2, NR113) polymorphisms in the same cohort. In the multivariate model to explore the between individual PK findings, age, sex, co-medication, tuberculosis co-infection and PGx markers were retained. In addition to *CYP2B6 rs3745274, NR1I2 rs6785049* was also retained in the model (GA versus GG). Combining the individual observations in CYP2B6 and NR1I2 polymorphism, a 3-fold variability in nevirapine $AUC_{0\text{-}12h}$ was described.[42]

Vitamin K Epoxide Reductase Complex 1 (VKORC1) Polymorphism

We retrieved 4 datasets reporting on VKORC1 polymorphisms (3/4 also reported on CYP2C9 polymorphism), but we would like to restress that the pooled number of infants is limited. Using an adult PK/PD model bridging effort to children for warfarin, the INR response was predicted reasonably well in 64 children (age and weight range, 0.05–18.9 years and 3.4–94 kg), be it with a tendency to overpredict INR (or underpredict dose) in children <2 years. It was hereby extrapolated from adult findings that VKORC1 (A/A versus G/G) polymorphisms explained up to a 2.1-fold difference in warfarin maintenance dose.[24] In 48 pediatric cases (age range 0.42–19.25 years), age and VKORC1 genotype were major factors for the weight normalized warfarin dose and INR. The anticoagulant effect of warfarin in patients with the VKORC1 1173CT or 1173CC genotype was 52.3% of that in patients with the 1173TT genotype. However, only 3/48 cases were <1 year.[67] In a cohort of 123 children (only 2 infants included), VKORC1 polymorphisms (GG, to AA, 2.52 versus 1 mg/day, 1.3-fold difference) affected dosing.[25] In a multivariate model, BSA and indication explained 45% of the variability in acenocoumarol dose requirement (INR targeting), adding VKORC1 (GG, AG, AA=5, 3.99, 2.7 mg/day, 1.3-fold difference), CYP2C9 (*2 or *3, CC/AA, CC/CA, CT/AA, TT/AA = 2.6-fold) and CYP2C18 (GG, AG or AA = 1.33-fold) resulted in 61.8% explained.[25] Finally, in a dataset with 118 cases (age range 3 months to 18 years, 19 cases <3 years) on acenocoumarol, VKORC1 polymorphisms contributed to the variability in dosing.[26] VKORC1 (GG, GA to AA: 31, 22, 9.7 mg/week) displayed a 3.2-fold difference in weekly dosing. In a multiple regression model, height (48.1%), target INR (4.4%), CYP2C9 (2%), and VKORC1 (18.2%) resulted in an explained variability of 69.7%.[26]

Angiotensin Converting Enzyme (ACE) Variants

Chen et al studied personalized tacrolimus dosing requirements by recipient and donor polymorphisms in 90 liver transplant children (age range 4–120 months), including CYP3A5 (positive), ABCB1. (negative), but also ACE variants were explored. However, no effects of ACE variants on dosing requirements were observed.[36]

Discussion

Retained records relate to phase I [CYP1A2, CYP2A6, CYP2B6, CYP2C8/C9/C18, CYP2C19, CYP2D6, CYP3A5, CYP2E1], phase II [GST, NAT, UGT], transporters [ABC transporters, OTC], or receptor/post-receptor mechanisms

[OPRM-1 and post-receptor mechanisms, TNF, MAPK-8, vitamin binding protein diplotypes, CRHR-1, NR subfamily 1, VKORC1, or ACE enzymes variants].

Based on the available overview, we conclude that the majority of reported pharmacogenetic studies explored and extrapolated observations previously described in older populations. The researchers hereby commonly quantified the impact of these polymorphisms in neonates or infants, integrated in the ontogenic process. The between study comparisons are further complicated by a diversity in methods and polymorphisms sets explored, and rather small datasets in neonates or infants.

In this way, "appearance" of PGx signals similar as reported in adults suggests that the phenotypic activity or expression in neonates or infants already sufficiently reflects "adult level of activity" and "phenoconversion": integrated developmental pharmacogenetics are the key. To further illustrate this, we can compare the observations on CYP1A polymorphisms (caffeine) with CYP2D6 ontogeny (dextromethorphan, tramadol).[18,30–32] For caffeine, CYP1A2 polymorphisms are not yet relevant in the metabolic elimination of methylxanthines in neonates, in contrast to observations on the relevance of CYP1A2 polymorphisms in adults.[68] This can simply be explained by the fact that CYP1A2 activity is almost absent in the first months of life, and caffeine elimination is almost exclusively renal.[69,70] The same holds true for acetaminophen metabolism. Postnatal age was the main determinant of urinary metabolites and the serum acetaminophen concentrations, while none of the CYP enzyme polymorphisms contributed to acetaminophen disposition.[41] This is to a large extent anticipated, as only CYP2E1 is involved in acetaminophen metabolism, and this iso-enzyme displays a slow ontogeny pattern, only reaching the adult level of activity after infancy.[69] In contrast, CYP2D6 ontogeny occurs already in early infancy, so that it is anticipated that the CYP2D6 activity score will already contribute to the variability, to remain relevant throughout human life.[71] The same is true for eg transporters, as OCT1 allele frequency already contributes to plasma concentrations of M1. This informs us that OCT1 is indeed already sufficiently well expressed in neonates.[61] Additional information on the ontogeny pattern has been explored, based on a physiologically-based pharmacokinetic morphine modelling effort in 85 neonates and young infants (PMA 24.9–57.3 weeks). Comparing the wild, to the hetero- or homo-haplotype, there were not yet differences in morphine clearance in the 24–34 weeks group, while these differences appeared (about 2-fold differences) at 34–40 (19.3, 15.5 and 10.9) and 40–58 weeks (38.7, 30 and 20 L/h, standardized to 70 kg).[62] In a next step, PGx studies in neonatal life should go beyond confirmation of these associations and explore the impact of PGx as a covariate limited to maturation of perinatal life (ie fetal malformations, breastfeeding or clinical syndromes following placental transfer, or iso-enzymes that are more active in perinatal life, like CYP3A7).[72] Applying population PK analyses hereby strengthens the analysis when based on a relatively small number of observations, and can be integrated with similar datasets in older populations, as illustrated by the tramadol example.[70]

Conclusion

We conducted a systematic review to identify, describe and quantify the impact of PGx on PK and PD in neonates and infants. We conclude that the majority of reported PGx studies were reported in the past 20 years. These studies commonly extrapolate observations already described in older populations, to subsequently quantify the impact of these polymorphisms in neonates or infants. There is still uncertainty on the power and extent of observations needed in neonates to truly confirm or reject these already described observations in older populations.

In a next step, PGx studies in perinatal life should go beyond confirmation of these associations and explore the impact of PGx as a covariate limited to perinatal life or early infancy. The challenge is to identify the specific factors, genetic and non-genetic, that contribute to the best benefit/risk balance with the need for big datasets/populations.

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Disclosure

The authors report no conflicts of interest in this work.

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