

# Pharmacogenomics in the newborn

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*Learned lessons, changing practice and cutting-edge research*

## Abstract

Genetic variation is an important determinant affecting the individual response to drugs. Considering the high variability in each individual genotype, the development of individualized therapies, according to the intrinsic features of the single patient, represents one of the most challenging problems in pharmacology. Pharmacogenetics analyzes the relationship between drug response and individual genetic differences, while pharmacogenomics analyzes the effect of genetic variations in patients' response to different drugs. The aim of these two research fields is to predict either drug response or the potential for the development of drug-related side effects. In particular, an important endpoint of pharmacogenomics should be to identify which group of patients responds positively, which patients are nonresponders and who will develop adverse reactions for the same drug and dose. Nevertheless, the utility of the pharmacogenetic and pharmacogenomic information as predictor of the activity of a specific drug-metabolizing enzyme or transporter should be cautiously limited to those developmental periods in which genotype-phenotype concordance is known. This means that in the perinatal period a special attention on the peculiar pharmacokinetic properties typical of this life period should be guaranteed. This means that effective and safe drug administration during fetal and neonatal life should consider the interindividual genotypic variability leading to different expression and activity of various enzymes. Both pharmacogenetics and pharmacogenomics may have a crucial role in the achievement of an individualized medicine. Prospective clinical trials analyzing the utility, safety, and cost-effectiveness of an individualized medicine based on the individual genotype are required.

## Keywords

Neonate, adverse drug reaction, pharmacogenomics, pharmacometabolomics, drug metabolism, pharmacogenetics.

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## Introduction

The proper approach to a correct therapy during the first life periods requires a wide knowledge about the physiological pharmacokinetic and pharmacodynamic characteristics of each specific age. The different life periods are characterized by typical developmental changes concerning drug Absorption, Distribution, Metabolism, and Excretion (ADME). The response to drugs in terms of both efficacy and toxicity even in the same life period is characterized by wide interindividual variability and affected by a large number of factors such as sex, body weight, health status. More recently genetic variation was recognized as an important determinant of individual variability of drug response. Significant differences exist among different countries and ethnies concerning the recurrence of polymorphisms influencing drug response by affecting drug metabolism and action [1,2]. Considering this high variability in each individual genotype, the development of individualized therapies, according to the intrinsic features of the single patient, represents one of the most challenging problems in pharmacology [3]. The existence of a large number of factors which contribute to the difficulties in accurate drug prescribing and dosing increases the risk of adverse drug reactions in the neonatal population [4]. Numerous deaths every year are caused by fatal drug reactions; the potential causes include not only the severity of the disease being treated, drug interactions, nutritional status, and renal/liver functions, but also the inherited differences in drug metabolism and genetic polymorphisms [5].

An extremely high rate of drugs routinely used in neonatal clinical practice is still administered off-label [6]. The highest rate (up to 90%) of patients receiving off-label treatments is commonly recorded in the neonatal intensive care units (NICU), where very low birth weight (VLBW)

infants are usually hospitalized. This means that the drug, although properly registered, is used in a way which does not reflect exactly what indicated by the producing industry concerning dosage, way and frequency of administration, clinical indications, and/or drug preparation. Obviously, despite the off-label use of these drugs, therapies should always be in agreement with the rules of the institution and be approved by the local ethical committee. However, although extreme caution is used before the administration of off-label therapies, a higher risk of therapeutic errors and drug-related adverse reactions is recorded. In particular, because of the lack of evidence-based data about neonatal pharmacology, the neonate has been suggestively defined as “therapeutic orphan” [7].

Recent advances in technologies opened new fascinating fields of research which could help in the achievement of an extremely individualized therapy. In particular, the “-omics” era allowed innovative analytical approaches leading to a deeper knowledge of various biological systems. The ‘omics’ technologies represent diagnostic approaches analyzing the different molecules (gene, proteins, metabolites) making up a cell, a tissue or an organism. These recent analytical evaluations are able to analyze simultaneously numerous measurements on a single biological sample and to generate a fingerprint of the specific state of an organism. Genomics, transcriptomics, proteomics and metabolomics are today the main ‘omics’ technologies [8, 9].

## Pharmacogenomics

Two important fields of interest are developing in genetic research in order to improve drug efficacy and to understand the mechanisms and clinical consequences of drug exposure, i.e. pharmacogenetics and pharmacogenomics. Pharmacogenetics analyzes the relationship between drug response and individual genetic differences, while pharmacogenomics studies all genes involved in drug response [10]. More specifically, pharmacogenomics analyzes the effect of genetic variations in patients’ response to different drugs, and has the aim to predict either drug response or the potential for the development of drug-related side effects. Research about pharmacogenomic medicine has drastically increased during the last decade, and the application of the current knowledge in daily clinical practice might markedly modify the therapeutic approach

to patients. Pharmacogenomics tries to correlate specific genetic variations, most frequently in the form of single nucleotide polymorphisms, copy number variations, deletions, and duplications, with an associated drug response. These variations can result in altered protein structure and function, therefore leading to unique pharmacokinetic and pharmacodynamic profiles in individuals. The individual variability in response to any drug is mostly dependent on DNA sequence variations across the human genome, i.e. the haplotype map (HAP MAP). Altered products, including enzymes, receptors, neurotransmitters, growth factors, transporters and other proteins may be the consequence of single nucleotide polymorphisms. An important endpoint of pharmacogenomics should be to identify which group of patients responds positively, which patients are nonresponders and who will develop adverse reactions for the same drug and dose. Pharmacogenomics may represent a powerful, valuable tool in therapeutics in those cases in which the genotype can be properly and reliably translated into a qualitative analysis of phenotype [11]. Nevertheless, the utility of the pharmacogenetic and pharmacogenomic information as predictor of the activity of a specific drug-metabolizing enzyme or transporter should be cautiously limited to those developmental periods in which genotype-phenotype concordance is known. This means that in neonatal period a special attention on the peculiar pharmacokinetic properties of the neonates should be guaranteed.

Pharmacogenomics can be applied to maternal, fetal, and neonatal medicine. In particular, among the mother-fetus pairs, also placental pharmacogenomics should be considered. Besides its role as a mechanical barrier and its origin in fetal trophoblast, the placenta expresses various enzymes which are involved in drug metabolism. These enzymes include cytochrome P450 (CYP) enzymes, superoxide dismutase, glutathione reductase, glutathione peroxidase, and glutathione S-transferases. Therefore, the presence of allelic variations affecting the expression of these enzymes may influence both fetal and neonatal individual susceptibility to various drugs. Examples of alleles with changeable placental expression of the CYP gene include CYP2J2, CYP4B1, CYP2C19, CYP2C9, CYP2D6 and CYP3A7. Recent studies analyzed various fetal and neonatal genetic CYP enzyme variants and their role in drug toxicities. Although the risk

of exposure to 'high risk' teratogens, such as thalidomide or isotretinoin, is low, it is not clear yet what predisposes certain fetuses to the harmful effects of the more commonly used 'moderate risk' medications, such as anticonvulsants and anticoagulants. Many compounds involved in altered pregnancy outcomes, such as androgens, estrogens, retinoic acid, and thyroxine, may also have an important role in the synthesis and catabolism of endogenous molecules involved in fetal growth and development [12]. These molecules, administered with therapeutic dosage, may lead to abnormal cellular function due to their competition with endogenous substrates and ligands.

The variations of gene expression in different fetal tissues such as liver, kidney, heart, and lungs can affect the fetal pharmacogenomics in causing birth defects. An example of such interaction regards the role of acetaminophen metabolism for the risk of gastroschisis. In fact, the enzymes involved in this metabolic pathway (glucuronidase and sulfotransferase, *SULT*) are absent during fetal life. The attempt to characterize the expression of sulfation enzymes (such as *SULT1A1*, *SULT1A2*) during fetal and postnatal life highlighted numerous differences between pre- and postnatal enzyme profiles. Consecutively, in this specific case pharmacogenetic analyses of acetaminophen-associated gastroschisis could be of relevant importance [13]. Furthermore the individual response of the neonate to compounds used by the mother during pregnancy is a new field of research. Multiple studies correlated selective serotonin reuptake inhibitors assumed during pregnancy with neonatal respiratory distress, persistent pulmonary hypertension, jaundice, feeding difficulties, neurological signs, congenital heart defects. Prenatal alcohol and nicotine exposure can also be determinant for the development of growth restriction, mental delay, cardiac abnormalities, and other malformations affecting postnatal outcome, and the response to such exposure might be influenced by different genotypes.

During postnatal life, neonatal pharmacogenomics could be important to optimize the dosage of neonatal drugs according to the week of development, with the aim of minimizing their toxicity and increasing their efficacy. One of the areas of interest is the metabolism of opioids. Gasche et al. in 2004 [14] and Koren et al. in 2006 [15] reported adverse effects in neonates breast-

fed by mother who assumed codein. Codein is converted to morphine by the CYP2D6 through glucuronidation. Glucuronides are eliminated by the kidney and can be accumulated for renal failure. A duplication of the CYP2D6 gene indicates an ultra-metabolizer of codein and determines elevated morphine concentrations.

### Pharmacometabolomics

Besides pharmacogenomics, also pharmacometabolomics is a rapidly developing field which refers to the direct measurement of metabolites in individual's body fluids to predict or evaluate the metabolism of pharmaceuticals [4]. In clinical practice, only a limited number of metabolites are routinely measured in the biofluids of newborns by conventional analytical methods to study the metabolic status of the organism [16, 17]. Several biological samples, including blood (serum or plasma), urine, saliva, gastric/pancreatic juice, lung aspirates, cerebrospinal fluid, synovial fluid, seminal fluid, blister and cyst fluids, and dialysis fluids can be exploited for metabolomic studies. To date, metabolomics seems to have promising applications in the clinical management of neonates and resulted a useful tool for pharmaceutical research. A challenging issue of pharmacometabolomics is the attempt to predict the metabolism and toxicity of a specific drug based on the analysis of a pre-dose individual metabolic profile. In neonatology, metabolomics may theoretically predict the outcome of specific treatments by monitoring the drug-related changes in metabolites induced by the medication itself. Consecutively, using metabolomics in clinical practice could lead to individualized drug therapy, thereby decreasing the side effects of drugs and increasing their efficacy. Preliminary studies investigated a range of topics such as gestational age-related metabolic maturation, intrauterine growth retardation, perinatal asphyxia, inborn errors of metabolism, respiratory distress syndrome, and patent ductus arteriosus [4]. Being the inherited differences in drug metabolism identifiable, it could be put forward that a decreased rate of deaths due to fatal drug reactions might be achievable [6].

### Conclusions

Effective and safe drug administration during fetal and neonatal life should consider not only the well

known developmental physiologic characteristics of ADME, but also the interindividual genotypic variability leading to different expression and activity of various enzymes. Both pharmacogenetics and pharmacogenomics may have a crucial role in the achievement of an individualized medicine. Prospective clinical trials analyzing the utility, safety, and cost-effectiveness of an individualized medicine based on the individual genotype are required.

### Declaration of interest

The Authors declare that there is no conflict of interest.

### References

1. Poolsup N, Li Wan Po A, Knight TL. Pharmacogenetics and psychopharmacotherapy. *J Clin Pharm Ther.* 2000;25(3):197-220.
2. Silva H. Ethnopsychopharmacology and pharmacogenomics. *Adv Psychosom Med.* 2013;33:88-96.
3. Ma Q, Lu AY. Pharmacogenetics, pharmacogenomics, and individualized medicine. *Pharmacol Rev.* 2011;63(2):437-59.
4. Antonucci R, Pilloni MD, Atzori L, Fanos V. Pharmaceutical research and metabolomics in the newborn. *J Matern Fetal Neonatal Med.* 2012;25(Suppl 5):22-6.
5. Dotta A, Chukhlantseva N. Ontogeny and drug metabolism in newborns. *J Matern Fetal Neonatal Med.* 2012;25(Suppl 4):83-4.
6. Dotta A, Braguglia A, Salvatori G. Pharmacological research in neonatology. *J Matern Fetal Neonatal Med.* 2011;24(Suppl 1):44-6.
7. Orzalesi M, Corchia C. The newborn infant: iatrogenic target or therapeutic orphan? A critical look at neonatal care. In: Guignard JP, Gouyon JP, Simeoni U (Eds.). *Developpement renal et programmation des maladies cardiovasculaires.* Elsevier, Paris. 2005, pp. 31-39.
8. Patti GJ, Yanes O, Siuzdak G. Metabolomics: the apogee of the omic trilogy. *Nat Rev Mol Cell Biol.* 2012;13(4):263-9.
9. Fanos V, Van den Anker J, Noto A, Mussap M, Atzori L. Metabolomics in neonatology: fact or fiction? *Semin Fetal Neonatal Med.* 2013;18(1):3-12.
10. Shastry BS. Pharmacogenetics and the concept of individualized medicine. *Pharmacogenomics J.* 2006;6(1):16-21.
11. Leeder JS, Kearns GL. Interpreting pharmacogenetic data in the developing neonate: the challenge of hitting a moving target. *Clin Pharmacol Ther.* 2012;92(4):434-6.
12. Blumenfeld YJ, Reynolds-May MF, Altman RB, El-Sayed YY. Maternal-fetal and neonatal pharmacogenomics: a review of current literature. *J Perinatol.* 2010;30(9):571-9.
13. Adjei AA, Gaedigk A, Simon SD, Weinshilboum RM, Leeder JS. Interindividual variability in acetaminophen sulfation by human fetal liver: implications for pharmacogenetic investigations of drug-induced birth defects. *Birth Defects Res A Clin Mol Teratol.* 2008;82(3):155-65.

14. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, Desmeules J. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med.* 2004;351(27):2827-31. Erratum in: *N Engl J Med.* 2005;352(6):638.
15. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet.* 2006;368(9536):704.
16. Fanos V, Barberini L, Antonucci R, Atzori L. Pharmacometabolomics in neonatology: is it a dream or a fact? *Curr Pharm Des.* 2012;18(21):2996-3006.
17. Fanos V, Iacovidou N, Puddu M, Ottonello G, Noto A, Atzori L. Metabolomics in neonatal life. *Early Hum Dev.* 2013;89(Suppl 1):S7-S10.