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DISCUSSION PAPER ON THE IMPACT OF RENAL IMMATURITY WHEN INVESTIGATING MEDICINAL PRODUCTS INTENDED FOR PAEDIATRIC USE

Disclaimer

This document is intended to provide some basis for discussion. At this stage, it cannot be regarded as guidance to pharmaceutical industry in planning the development of a medicinal product intended to be used in the neonate.

This is the first step to a multidisciplinary guideline which will focus on the specificities of the neonate to be taken into consideration, in particular pharmacokinetic and pharmacovigilance. Safety aspects related to other organ functions are not yet considered in this paper.

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Introduction

The kidney is a major organ of drug disposition and a potential target organ for drug toxicity. The development of medicines to be used in children can rely on pharmacokinetic (PK) studies alone when pharmacodynamics (PD) are the same as in adults. However, the converse is rarely true. PK studies are used as a tool to find out whether or not some age classes behave as distinct sub-populations. However, it is expected that the neonate will behave as a specific sub-population as the influence of relative kidney immaturity and progressive maturation will affect PK and PD. Patients with renal immaturity or impairment may need alternative dose regimens and precautionary measures stated in the product labelling, for instance as warnings or even contraindications.

As part of a general policy to develop and facilitate the availability of medicinal products for children, guidance should be issued to improve the information on medicines already available for adults, or of particular interest in the paediatric age range.

A note for guidance on Clinical Investigation of Medicinal Products in the paediatric population (CPMP/EWP/462/95) was implemented and came into operation in 1997. Furthermore, an ICH guideline (CPMP/ICH/2711/99) replaced it and came into force in 2001.

This guidance is a continuation of advice already provided for methodology of paediatric PK studies and clinical safety, taking also into consideration the specificity of the neonate. In this particular population not excluded from European legislations, establishing appropriate dosing guidelines would be a very useful tool.

Background

Maturation during fetal life and after birth is a process involving all organs and functions of the growing human. As such, all the main steps of drug disposition (absorption, distribution, metabolism, catabolism, elimination/excretion) may be under the influence of still incomplete morphological stages. An incompletely absorbed compound may be less effective whereas a poorly metabolised and/or excreted compound may result in an increased risk of toxicity. Both risks will have to be evaluated. An interrelation of elimination pathways must also be considered.

Problem statement

Designing studies able to address and identify the impact of evolving renal function on drug disposition and effect during infantile kidney maturation presents specific challenges. The neonatal period is characterised by developing metabolic and somatic processes. These processes depend not only on the post-conceptual age (PCA) (gestational age (GA) + postnatal age) of the newborn - which is likely to be the best parameter of the ongoing neonatal maturation -, but also on a clinical status that can be fragile and influences this maturation. Consideration must be taken of the post-natal age as well. The kidney is a target for drug therapy, an organ for drug handling and a potential target of adverse drug reactions. Better understanding of the maturing kidney should help to anticipate possible early and late adverse effects of drugs in this population.

The influence of renal immaturity on drug safety in the neonate: what is relevant?

In most instances, the drug level (in the blood or any other compartment or organ) will determine its toxicity. Preterm (< 37 weeks GA) and term neonates (37 weeks GA or more) are at higher risk of overdosing due to immature renal function. In acutely ill children immature excretion, individual variability and acute factors (hypoxia, acidosis, etc) may result in severe overdosing. Overdosing may endanger not only the kidney itself, but also other body tissues. Potential interactions (drug combination) and/or other immature systems (liver, blood brain barrier) may further increase the risk. Transient toxic effects may only be revealed later in life justifying the long-term surveillance of (a subset of) the population exposed.

1) *Growth of the human kidney: from the foetus to the child*

Nephrogenesis is completed by the end of 34th week of gestation. The kidney of a full-term neonate (i.e. between 37 and 41 weeks of gestation) possesses a full set of nephrons, approximately 850,000 to 1,200,000 per kidney. Some events during pregnancy such as growth retardation or nephrotoxic drugs administered to the mother may negatively affect the total number of nephrons present in the neonate.

- Parameters of maturity

At birth, renal blood flow (RBF) is low because of high renal vascular resistance. Birth triggers a dramatic increase in glomerular filtration rate (GFR) due to both the disappearance of the placental shunt and the increase in blood pressure. This is the result of the decreases in vascular resistance caused by the dramatic increase in partial oxygen pressure. A large proportion of the blood flow is shifted to the superficial nephrons; the decrease in vascular resistance is greater in this part of the kidney. As a consequence the filtration area increases. RBF increases from 12 ml/minute at birth, up to 140 ml/min by two years of age. The GFR increases from 10 ml/min/1.73 m² at birth to 20 to 30 ml/min/1.73 m² after 2 weeks. Adult levels of GFR (120 ml/min/1.73 m²) are reached between 1 and 2 years of age.

- Parameters of renal immaturity

The glomerular filtration rate is a function of the PCA, so there may be two-fold to four-fold difference in GFR values between premature and full-term newborns. In extremely low birth-weight (ELBW) neonates at birth, superficial nephrons are more immature - morphologically and functionally - than juxtamedullary ones. From 26 weeks of GA at birth to 34 weeks of PCA, the increase in GFR is limited because of incomplete nephrogenesis. In the preterm infant, the maturation of renal function depends on maturation of already developed nephrons as well as completion of nephrogenesis. PCA is the best parameter to evaluate the capacity of the neonatal and infant kidney to eliminate drugs in the early postnatal period. Serum creatinine is elevated in the first days of life reflecting maternal creatinine and a low intrinsic GFR. The lower the GA at birth, the higher is the serum creatinine. A tubular creatinine reabsorption in the preterm neonate both with the existence of a slight state of dehydration may partly explain the increase of serum creatinine during the first days of life in those babies. After the first month, serum creatinine remains stable during the first two years of life, (under 44 µMol/L in the term neonate). After two years, the GFR (corrected for body surface area) is equivalent to that of adults. Kidney maturation can be assessed by measuring histological changes in size as well as disposition of glomeruli and tubules. Glomerular immaturity persists during the first months after birth while tubules increase in length and volume. A high degree of nephronic heterogeneity is also evident at that time. Renal growth during infancy and childhood correlates with both age and other parameters of somatic growth.

2) *The immature kidney as a tool for drug handling*

Neonates are more susceptible to drug-related developmental disorders as well as to adverse drug reactions (ADRs) that can only be detected later in life. In addition, certain ADRs may only be seen in preterm infants (e.g., nephrocalcinosis induced by loop diuretics). Differences in the risk of ADRs are mainly due to the difference in specific receptors' expression in the immature tubule.

- Drug glomerular filtration and drug tubular secretion

The kidney contributes to the elimination of hydrophilic drugs and metabolites in immature neonates. Drugs can either be eliminated by glomerular filtration, which is the main pathway of renal elimination in neonates, or can undergo tubular secretion, absorption, or both. The total clearance of a drug is the sum of net filtration and secretion rate, minus the net rate of absorption.

GFR matures more rapidly than tubular secretion, which explains the so-called glomerulotubular imbalance specific to neonates. The maturation of tubular transport systems of drugs parallels the increase in tubular length and mass, and also depends on the induction of transporters' expression in utero as well as after birth. Organic anion and organic cation transporters are two major drug transport systems, accounting for the kidney's capacity to eliminate drugs by tubular secretion. While there is a possibility that elimination of weakly acidic drugs in neonates in case of increased acidity of the urine is reduced, this risk is limited since H⁺ excretion is relatively reduced also.

Paradoxically the immature tubule can be mature already for a specific function: The maintenance of the positive sodium balance in neonates after few days of life is stable. However, the immature kidney has limited adaptability in case of excess administration of Na⁺, K⁺, or Pi and a higher risk of hyperosmolar toxicity.

- Tubular absorption of drugs

The renal tubular absorption process is physiologic. The absorption mechanisms along the tubule mature faster than those of tubular secretion. The proximal tubule is able to internalise most of the endogenous proteins not retained by the glomerulus. The ability of the immature proximal tubule to reabsorb proteins at this level coincides with the early expression of megalin in coated pits. Drugs like aminoglycosides undergo tubular reabsorption through this mechanism and may accumulate and concentrate with potential toxicity. These antibiotics are still widely used in neonatology, in combination with penicillins. Aminoglycoside renal clearance is proportional to the PCA. These polycationic drugs bind to the brush border membranes of the proximal tubule and this process is saturable; however binding constants are significantly lower in the immature kidney. In neonates, the volume of distribution of aminoglycosides is greater and their half-life is longer. As a consequence, and because of their pharmacodynamic effect on bacteria, relatively larger doses at much longer intervals between doses are required in neonates as compared to adults.

Additional clinical factors have to be considered which may influence renal excretion in neonates; for instance asphyxia at birth, postnatal significant hormonal changes, hypoxic episodes at a later stage, septic shock, and the use of concomitant drugs. Those factors may influence drug handling by increasing the volume of distribution, and/or modifying metabolism and excretion. Hypoxic episodes, for example, will result in hypoperfusion of the immature kidney with its high renal resistance. Some drugs highly bound to plasma proteins, such as ceftriaxone, may theoretically interfere with bilirubin binding. Other drugs such as non-steroid anti-inflammatory drugs (NSAIDs) will decrease the clearance of drugs eliminated through the kidney. This is explained by the suppression of the vasodilatory action of prostanooids on the afferent arteriola, which physiologically counteract in such a way the high vascular resistance generated by the vasoconstriction of efferent arteriola mediated by Angiotensin II.

- Biotransformation of drugs in the developing kidney

The kidney is involved in the biotransformation of drugs, facilitating excretion. Sufficient data on developmental processes of renal microsomal biotransformation systems are still lacking.

Methodological aspects in the study design of a drug given to the neonate: what is relevant?

Is stratification by age indicated for studies in the neonate?

Stratification by term and age (according to ICH E11 criteria) is needed as PK and PD parameters differ between a very preterm and a full-term neonate. In addition, as 33 weeks of GA/PCA can be considered as the cut-off of achieving nephrogenesis and thus reflect of the capacity of drug renal elimination, the preterm period should be further sub-divided in two parts: less or more than 33 weeks. As a consequence this raises concern when drugs are administered to preterms of less than 33 weeks of PCA. GA at birth and volume of distribution are inversely correlated. As the global renal maturation process is reflected both by PCA and by the postnatal age, those parameters need to be taken into account in term of drug renal excretion capability.

Do we need only PK studies or combined PK/PD studies?

PK studies help explore the immature body in terms of drug distribution and clearance, without extrapolating from data from more mature subject. However, drug response in terms of efficacy and/or toxicity may be different. In the neonate, the large volume of distribution and the lower protein binding may affect the drug activity at the target. The response of the target tissue may also be dependent on the maturational status. PK/PD studies may therefore be needed in the neonate. Any deviation from these principles should be discussed and justified. Extrapolation may be justified for PK studies for example when the drug is expected to act on a micro-organism rather than the host. However, this may only concern efficacy, but not toxicity. The PCA maturation process and its influence on PK/PD relationship must also be taken into consideration. Good examples for medicines with different PD (effects) in neonates when compared with those in children and adults are diuretics, prostanoids, angiotensin-converting enzyme inhibitors, NSAIDs, catecholamines, etc..

The use of population PK.

Population based PK/PD studies may provide a comprehensive approach to dealing with the multiple issues presented. It may allow for less invasive and patients demanding procedures and provide a more accurate picture of the impact of renal function and age on drug metabolism. In addition, population PK are encouraged as they allow for a reduction in the number of blood samples per child and invasiveness in general. This is crucial in the first days of life. In neonates, the use of a valid model of incorporated maturational profiles is recommended. Models need to be adapted to the properties of the drug (C_{max} , AUC, $t_{1/2}$,...) and individual sensitivity or response.

How do we evaluate PD in the neonate?

Most of the general clinical parameters may be assessed using non invasive techniques (e.g. cardiac monitoring, urine collection, non invasive blood pressure measurement, colour Echo-Doppler assessment of the heart and lung circulation). Transcutaneous measurement of PO₂ or PCO₂ is easily performed in preterms. The functional evaluation of the kidney is possible but kidney immaturity should be taken into account. Some tests are proposed in the table.

Late adverse effects of drug administered in the neonatal period should be assessed. For example, dexamethasone administration for a long period of time in very preterms (in chronic lung disease) is associated with an increased risk of cerebral palsy. A programme of long-term pharmacovigilance must therefore be associated with drug evaluation in the neonate. Assessing renal aspects of drug disposition and toxicity does not preclude a potential toxicity of the investigational drug on other organs (e.g CNS, liver etc)

Functional evaluation of the kidney

	IMAGING	GLOMERULAR FUNCTION	TUBULAR FUNCTION
nephrotoxic drugs	Ultrasonography	<ul style="list-style-type: none"> - Inulin or creatinine clearance - Haematuria - Microalbuminuria - Urinary albuminuria to creatinine ratio 	<ul style="list-style-type: none"> - Plasma bicarbonates - Filtration excretion rate of sodium (FE Na%), TmP/GFR - Urinary pH, urinary osmolality - Urinary calcium/creatinine, urinary magnesium/creatinine - Retinol-binding protein, (protein HC) - N-acetyl-β-D-glucosaminidase (NAG), alanine-aminopeptidase (AAP) - Antigens (glutathione S-transferase, GST, adenosine deaminase-binding protein (ADBP)?) - (Growth factors ??)
probably not nephrotoxic		<ul style="list-style-type: none"> - Plasma creatinine - Calculation of GFR - Cystatin C - Haematuria - Microalbuminuria - Urinary albuminuria to creatinine ratio 	

Analysis of data

PK parameters of importance when the kidney is immature.
Pharmacogenetics are not a priority but can be explored as add-on results.

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