



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Organ Maturation Tables

Possibly identifying maturation related adverse drug reactions

Presented by: Janina Karres
Paediatric Medicines

An agency of the European Union





The Rationale

- Better use of Eudravigilance data for paediatric medicines.
- ADRs in adults and children are different (types, drugs).
- Differences may also be due to increased susceptibility to some ADRs because organs are still immature.
- Can we identify possible ADRs that are maturation related?



Methodology

- Identify key literature on OM (articles, book chapters, guidelines)
- Prepare OM table (specify maturation of key sub-functions, enzymes, main structures within organ)
- Send OM tables for Expert Review (experts in the field, PDCO,..)
- Finalize



Renal system maturation

Renal system Function / Age subsets	0 – 1 year	1 – 2 years	2 – 3 years	Up to 18 years
Glomerular filtration rate (GFR)	Due to haemodynamic changes during and just after birth, GFR increases rapidly in the first two weeks of life. Afterwards, GFR corrected for body surface area increases more slowly to reach adult levels between 1 to 2 years of age.			
Tubular secretion	The renal tubular secretion capacity increases over the first months of life and then declines to reach the adult level (per unit of body area) at ~ 7 months to 1 year of age. The organic anion pathway matures faster than the organic pathway.			
Tubular reabsorption	The development and maturation of the glomerular permeability functions and the renal tubular reabsorption are gradual and continuous processes from birth to adolescence. The key stage of their maturation is at ~ 1 and 3 years of age.			

References:

1. Guideline on the investigation of medicinal products in the term and preterm neonate. CHMP and PDCO, EMEA, London 25 June 2009.
2. Paediatric Drug Development. Mulberg AE, Silber SA, Van den Anker JN. John Wiley & Sons, 2009.



Liver maturation

Age (after birth) and maturation period		1 month	2 months	3 months	4 months	5 months	6 months	12 months	15 months	2 years	5 years	
Phase I Enzymes	Hepato-biliary system and metabolic pathways											
	CYP3A4 (midazolam, itraconazole)											
	CYP1A2 (caffeine, theophylline)											
	CYP2D6 (dextromethorphan)											
	CYP2C9/CYP2C19 (benzodiazepines, proton pump inhibitors)											
Phase II Enzymes	CYP2E1 (acetaminophen, halothane, ethanol)											
	FMO (chlorpromazine, promethazine)											
	Glucuronidation UGT1A (acetaminophen)											
	Glucuronidation UGT2B (chloramphenicol, morphine)											
	Sulfation SULT1A1/SULT1A3 (acetaminophen; iodothyronines and catecholamines in foetus)											
	NAT2 (caffeine, isoniazid)											
	Bile flow (reaching up to the adult levels)											

Reference:

Mulberg AE, Silber SA, van den Anker JN; Paediatric Drug Development: Concepts and Applications; Developmental hepatic pharmacology in paediatrics; 2009; p. 243.



Brain maturation

Brain/brain elements	Period of maturation (postnatal months and years of age)	1 m	6 m	12 m	18 m	24 m	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10 y	11 y	12 y	13 y	14 y	15 y	16 y	17 y	18 y	
Neural tube differentiation	Up to 1st month of age																						
Blood brain barrier	Until 6 th month of age																						
Proliferation and organization of synapses	50% at 2 yrs; 100% at 4 yrs																						
Myelination	50 % of corpus callosum at 18 months; up to 20-30 yrs																						
Brain size	80% at 2 yrs; 90% at 5 yrs; remodelling of white and gray matter up to 20-30 yrs																						
Cortical gray matter maturation (motor & sensory systems, memory, audio-visual input, object recognition)	1. Frontal lobe: 11 yrs girls & 12.1 yrs boys 2. Temporal lobe: 16.7 yrs girls & 16.2 yrs boys 3. Parietal lobe: 10.2 years girls and 11.8 yrs boys																						
Subcortical gray matter maturation (control of movement and muscle tone, higher cognitive functions, attention, affective states)	Nucleus caudatus size peak: 7.5 yrs girls & 10.0 yrs boys																						
Amygdala and hippocampus maturation (emotion, language, memory)	Between 4 yrs and 18 years																						
White matter maturation	1. Lobar white matter volumes increase up to 30 years 2. Corpus callosum: between 4 yrs and 18 years (integrating left & right hemispheres; unification of sensory fields, memory storage and retrieval, attention & arousal, enhancing language and auditory functions)																						
Prefrontal cortex maturation	Up to the late adolescence – 17-18 yrs																						
Neurotransmitter system maturation (NMDA receptors)	Up to 3 years of age																						
Cholinergic and serotonergic systems	Through childhood and adolescence, in individuals possibly into adulthood																						

1. Volpe JJ, Neurology of the newborn, 5th ed., Elsevier Health Sciences, Philadelphia 2008, p5

2. Benes F, The development of the pre-frontal cortex, the maturation of neurotransmitter systems and their interactions, in: Handbook of developmental cognitive neuroscience (Nelson CA, Luciana M, eds) , MIT press, 2001



Lung maturation (under construction)

Development of the Pulmonary System

		Fertilization										Birth							
Age subset		Embryogenesis		Foetal development						Neonate/ Infant		Child							
		0 w	5 w	10 w	15 w	20 w	25 w	30 w	35 w	40 w	1y	2y	3y	4y	5y	6y	7y	8y	
Stage	Embryonic																		
	Pseudo-glandular																		
	Canalicular																		
	Saccular																		
	Alveolar (proliferation)																		
	Microvascular maturation																		
	Alveolar (expansion) (Normal lung growth period)																		

References:

- [Zoetis T, Hurtt ME](#). Species comparison of lung development. *Birth Defects Res B Dev Reprod Toxicol*. 2003;68(2):121-4. Review.
- [Zeltner TB, Burri PH](#). 1987. The postnatal development and growth of the human lung. II. Morphology *Respirat Physiol* 67:269–282.
- [Burri PH](#). 1996. Structural aspects of prenatal and postnatal development and growth of the lung. In: McDonald JA, editor. *Lung Growth and Development*. New York: Marcel Dekker. p1–35.
- [Thurlbeck WM](#). 1975. Postnatal growth and development of the lung. *Am Rev Respir Dis* 111:803–844.
- [Dietert RR, Etzel RA, Chen D, Halonen M, Holladay SD, Jarabek AM, Landreth K, Peden DB, Pinkerton K, Smialowicz RJ, Zoetis T](#). 2000. Workshop to Identify Critical Windows of Exposure for Children's Health: Immune and Respiratory Systems Work Group Summary. *Environ Health Perspect* 108(Suppl 3):483–490.



GI-system maturation (under construction)

	0-1 d	1 wk	2 wks	4 wks	6 wks	3-5 mo	9 mo	1y	2y	3Y	6Y	12y	18y
GI FUNCTION (general)	Most of the GI function development is complete by end of infancy												
STOMACH													
GASTRIC SECRETION													
Mucosa	Thin at birth												
Gastric pH	pH 4-6				pH 1.5 - 3								pH 1.5-2.5
Hydrochloric acid	Reduced secretion												
Gastrin	Reduced production												
Pepsinogen/Pepsin						50%			100%				
Gastric lipase	Reduced production												
GASTRIC EMPTYING	Reduced												
GASTRIC ABSORPTION	Linked with high pH in neonates/infants-					dependent on type of food							
SMALL INTESTINE													
PERISTALTIC	Less frequent, relies on feeding patterns												
ABSORPTION	Slower but same total												
MUCOSA + IgG TRANSPORT	Higher mucosal permeability for macromolecules: specific (IgG and EGF) and non-specific endocytosis												
Maternal IgGs are also transferred to offspring in utero.													
CRYPT VILLUS PROLIFERATION	50%												
ENZYME ACTIVITY													
Lactase						Increased							
Alkaline phosphatase						Decreased							
LARGE INTESTINE													
ELECTROLYTE BALANCE	Na ⁺ -K ⁺ ATPase: sodium absorption and anion exchange reduced												
RECTAL CONTRACTIONS	Greater number of high-amplitude pulsatile contractions												



GI-system maturation (under construction)

	0-1 d	1 wk	2 wks	4 wks	6 wks	3-5 mo	9 mo	1y	2y	3Y	6Y	12y	18y
GI-TRACT													
MICROBIAL COLONIZATION													
Types of microbes present:	Coliforms and streptococci most common (E. coli, streptococci, bacteroides, and bifidobacteria)												
	Anaerobic bacteria such as bacteroides, bifidobacteria, and clostridia found as well												
Breast-fed infants	Mostly bifidobacteria (limit growth of pathogens by lowering instinal pH)												
Formula-fed infants	Mostly lactobacillus (limit growth of pathogens by lowering instinal pH)												
Solid foods	Solid foods: "obligate anaerobes" increase												
INTESTINAL ENZYMES													
CYP1A1	Increases over time to adult levels												
Glutathione-S-transferase	Decreases over time to adult levels												
Epoxide hydrolase and glutathione peroxidase	Little age dependence												
P-gp/MDR1	No data in children												
PANCREAS													
PANCREATIC ENZYMES													
No response to cholecystokinin or secretin	No response to cholecystokinin or secretin												
Lipase	Lipase												
Trypsinogen	Trypsinogen												
Amylase	Amylase												
Enterokinase	Enterokinase												
Chymotrypsin	Chymotrypsin												
Carboxypeptidase	Carboxypeptidase												

References:

- Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Delopmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med. 2003 Sep 18;349(12):1157-67. Review.
- Walthall K, Cappon GD, Hurtt ME, Zoetis T. Postnatal development of the gastrointestinal system: a species comparison. Birth Defects Res B Dev Reprod Toxicol. 2005 Apr;74(2):132-56.



The Application

Standard EudraVigilance Paediatric (SEVP) Query for *Drug X*

- PDCO concerns over potential renal toxicity in children (*Drug X*)
- Standard EV paediatric analysis was performed
- Paediatric age group analysis was performed also by kidney maturation stage (below and above 3 years).



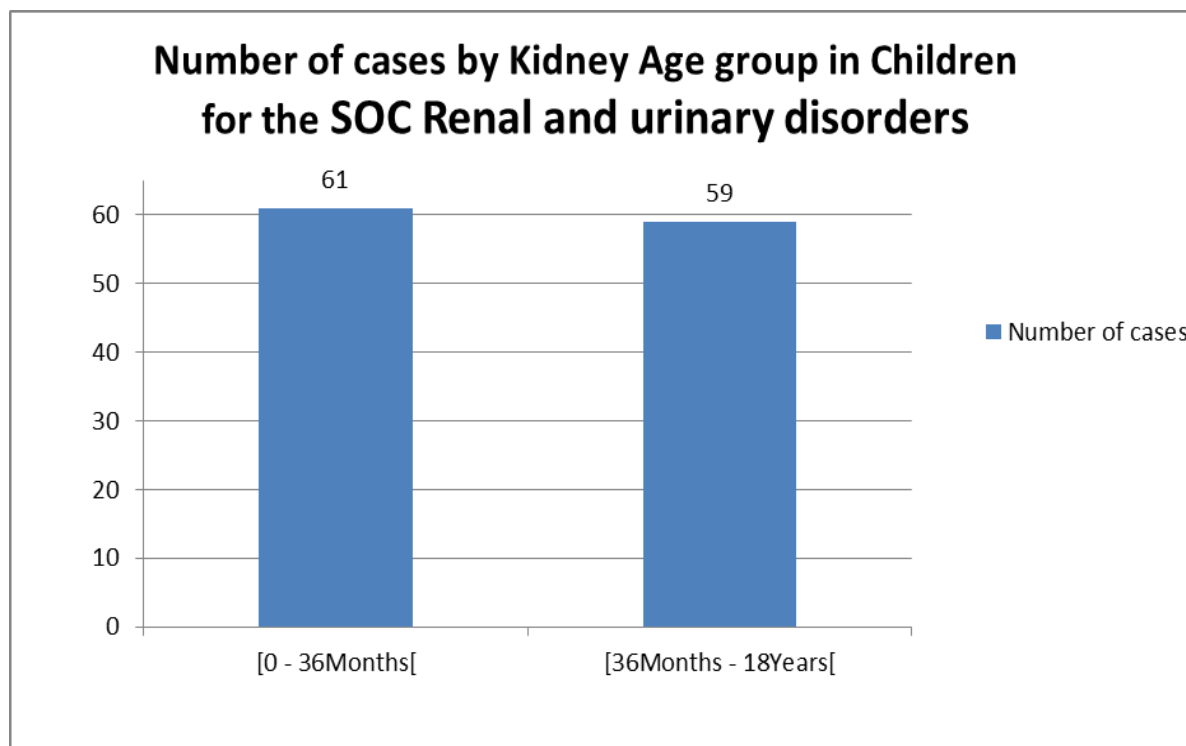
Statistics children vs adult

<i>Drug X</i>	Paediatric cases	<u>Ratio 1</u> Children vs. adult (95% CI)	<u>Ratio 2</u> <i>Drug X</i> vs. other drugs in children (95% CI)	<u>Ratio 3:</u> <i>Drug X</i> vs. other drugs in adults (95% CI)
SOC 'Renal and urinary disorders'	120	3.13 (2.72-3.62)	14.91 (13.05-17.04)	2.66 (2.52-2.82)



Analysis of the specific paediatric issue

-> per the predefined age group categories taking into account the specific maturation of the kidney:





Conclusion

Information on organ maturation allows for:

- Better use of Eudravigilance data for paediatric medicines.
- Help identifying maturation related adverse drug reactions.