

# LYFJAGJAFIR BARNA

*Þórunn Óskarsdóttir*

*Klínískur lyfjafræðingur*

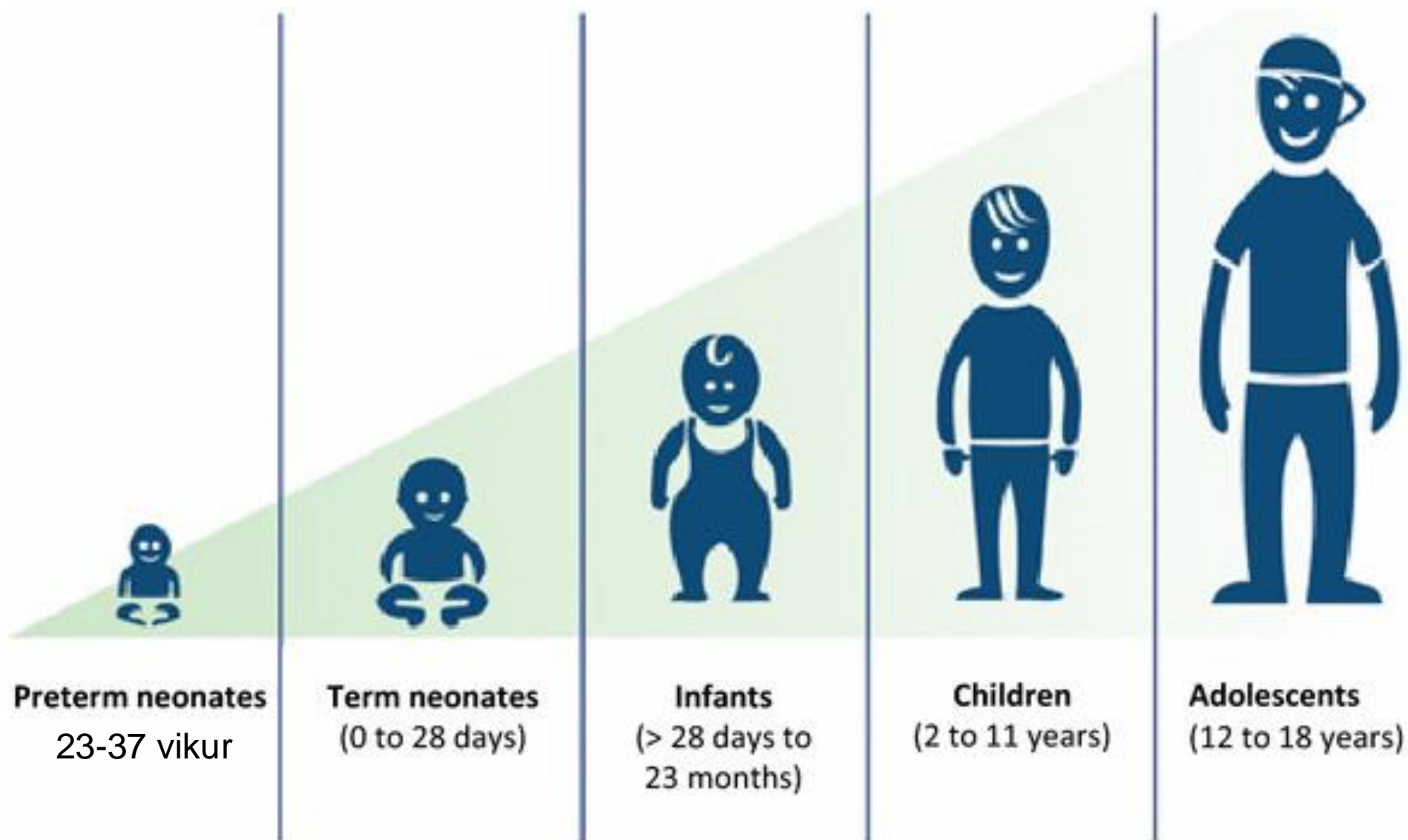
*Ágúst 2024*

## WHY CHILDREN?

- Children → **22 %**
- **Three times** more exposed to potentially dangerous medication errors compared with adults
  - dosing-strategies
  - altered kinetic parameters
- The largest group of patients to be seen by healthcare professional
- Medication administration can be challenging
  - many drugs given unlicensed or off-label



Children are not little  
adults and should not  
be treated as such



## ALDURSKILGREINING – NÝBURAR

- Gestational age (meðgöngualdur) – from date of last period
- Postnatal age – chronological age (lífaldur)

Eðlileg meðgöngulengd: 37-42 vikur

Fyrirburi <37 vikur

Nýburatímabil – til 28 daga

Lág fæðingarþyngd (LBW): <2500 g

Mjög lág fæðingarþyngd (VLBW): <1500 g

Einstaklega lág fæðingarþyngd (ELBW): <1000 g

Örburar: <500 g

## SKAMMTAR

- Einstaklingsbundnir skammtar
- mg/kg
  - Er líkamsþyngd í samræmi við aldur?
- Yfirborðsflatarmál er sennilega nákvæmara
  - Samræmi við cardiac output, vökvapörf, líkamssamsetningu og nýrnastarfsemi
  - Getur verið erfitt að meta hjá börnum
- Einstaka sinnum þörf á aðlaga skammta útfrá fullorðinsskömmtum
- Hvenær eru skammtar ekki lengur byggðir á þyngd?

### Percentage method (surface area method)

The percentage method for estimating doses is calculated as follows:

$$\frac{\text{Surface area of child (m}^2\text{)} \times 100}{1.76\text{m}^2} = \text{percent of adult dose}$$

(1.76m<sup>2</sup> being the average adult surface area.)

The relevant figures for the 'surface area of a child' can be found in the back section of the British National Formulary for Children (BNF-C).

Children are often said to tolerate or require larger doses of drugs than adults based on a mg/kg basis. The percentage method helps explain this phenomenon. Body water (total and extracellular) is

known to equate better with surface area than body weight. It therefore seems appropriate to prescribe drugs by surface area if they are distributed in the extracellular water.

#### Example

Iain is a 3 month old baby. He weighs 5.23kg. His body surface area is 0.31m<sup>2</sup>. Calculate the dose of aciclovir required for him using the percentage method. (The adult dose is 800mg).

$$\frac{0.31 \times 100}{1.76} = 17.6\%$$

**Dose is 0.176 x 800 = 140.8mg.**

Use 140mg = 3.5ml of 200mg/5ml aciclovir suspension

### Mg/kg method

The mg/kg method for estimating doses is calculated as follows:

$$\frac{\text{Adult dose (mg)}}{70\text{kg}} = \text{mg/kg dose}$$

(70kg being the average adult weight)

This method will give lower doses than the percentage method using surface areas. It is far less accurate in clinical terms but much easier to use since weights are usually more accessible than surface areas. Within limited age bands it is appropriate to state doses on a mg/kg basis. This form of extrapolation from adults is usually inappropriate for accurate therapeutic dosing, although it is unlikely to lead to toxic dosing.

#### Example

Iain is a 3 month old baby. He weighs 5.23kg. His body surface area is 0.31m<sup>2</sup>. Calculate the dose of aciclovir required for him using the mg/kg method. (The adult dose is 800mg).

$$\frac{800}{70} = 11.4\text{mg/kg}$$

**Dose is 11.4 x 5.23 = 59.6mg.**

Use 60mg = 1.5ml of 200mg/5ml aciclovir suspension

- 20 mánaða gamalt barn.
- 13,8 kg
- Omeprazole, skammtur 0,7 mg/kgx1  
→ 9,66 mg

- Ekki að fullu leysanlegt í vatni
- Breytt therapeutískt bil
- Tiltölulega öruggt
- Taflan er 10 mg

- 70 kg
- Cefotaxime 50mg/kg á 6 klst fresti (heilahimnubólga)
- Max skammtur f. fullorðna er 12 g á dag.
- Reiknaður skammtur m.v. kg er 14 g á dag.
- Hvort á að gefa **12 g** eða **14 g** í 4 skömmtum?
- Fyrir flest lyf – ekki gefa meira en max fullorðinsskammt

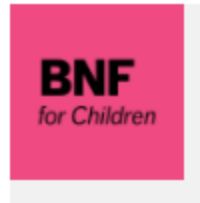


# SKAMMTAR - HEIMILDIR

 Kinderformularium



## Lyfjaupplýsingar - Sérlyfjaskrá

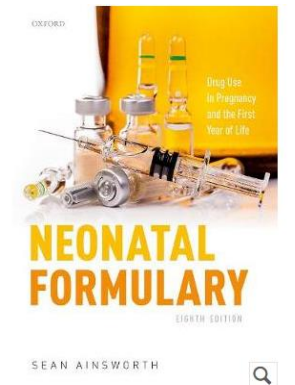
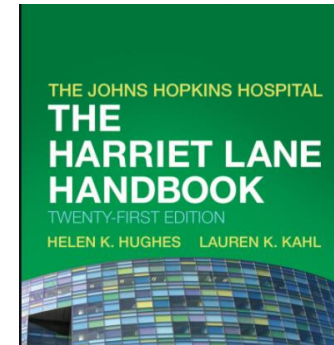


IBM Micromedex®

Home	Drug Interactions	IV Compatibility	Drug ID	Drug Comparison	NeoFax® Pediatrics
Drug Monographs		Enteral Formulas		Dosing Calculators	

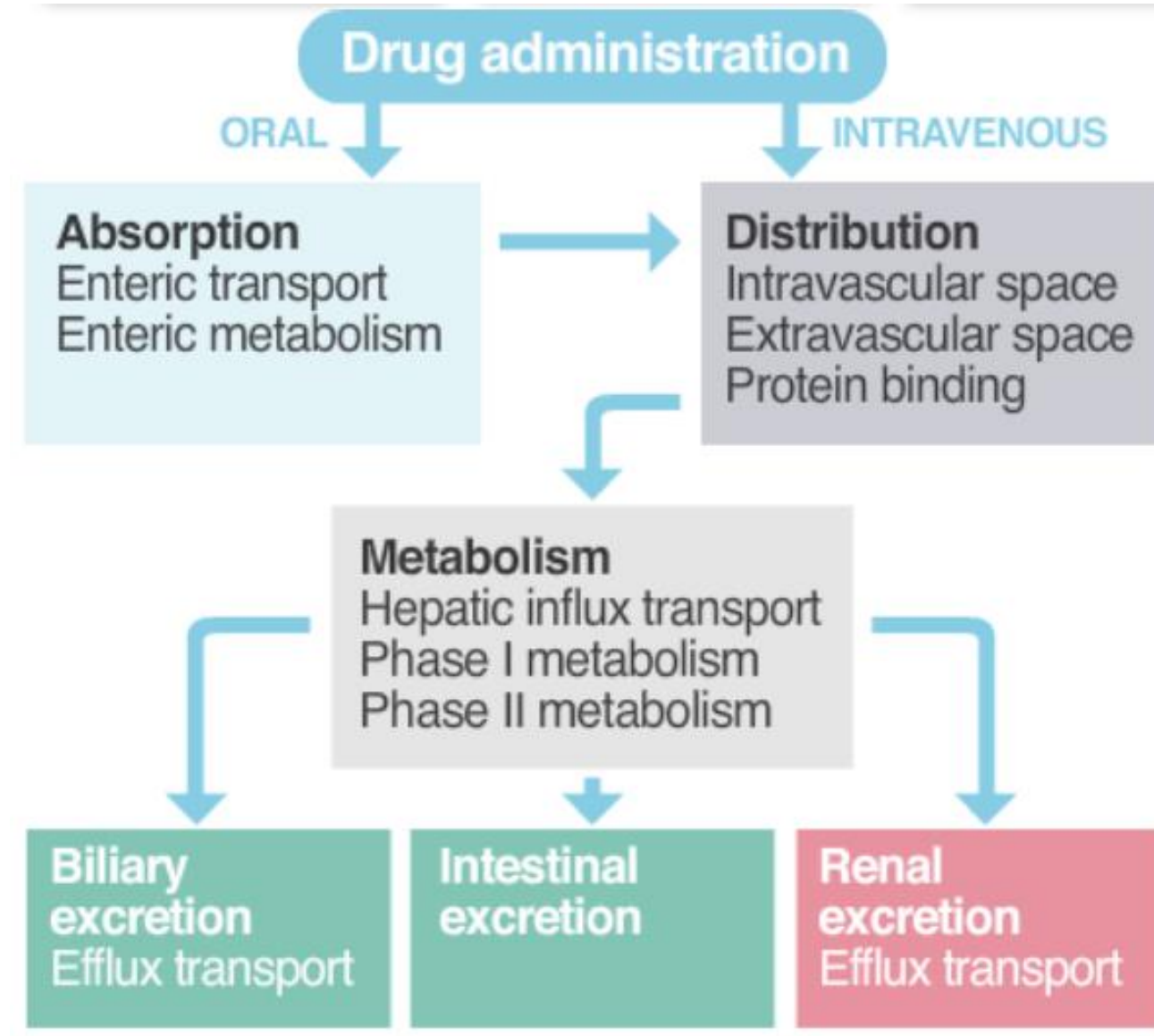
Drug Monographs

Drug Neonatal Pediatric  
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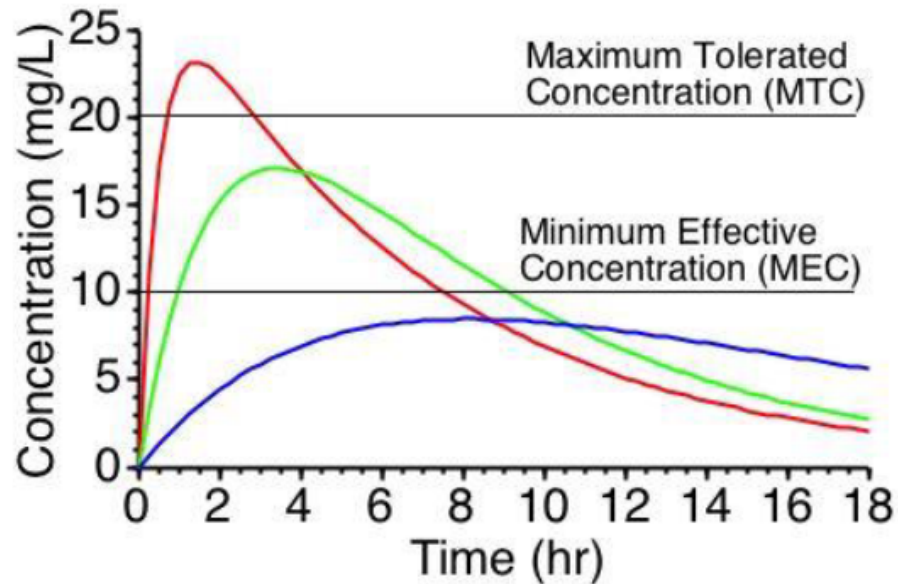
# LYFJAHVÖRF OG AÐLÖGUN LYFJA

(PHARMACOKINETICS AND DRUG HANDLING)



# Drug absorption

Important factors to be considered:

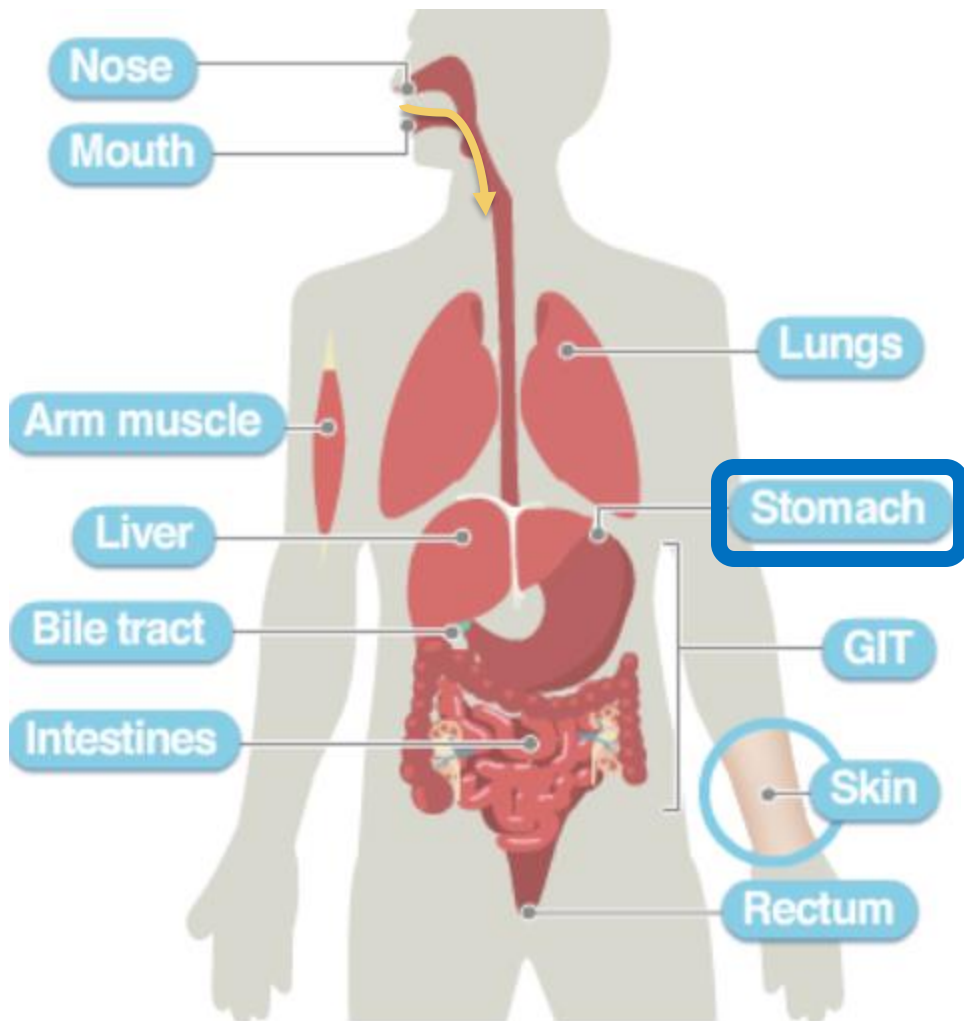


- Rate of absorption
- Extent of absorption
- Rate of excretion

The more rapidly absorbed, the higher the peak

The extent of absorption determines level of exposure

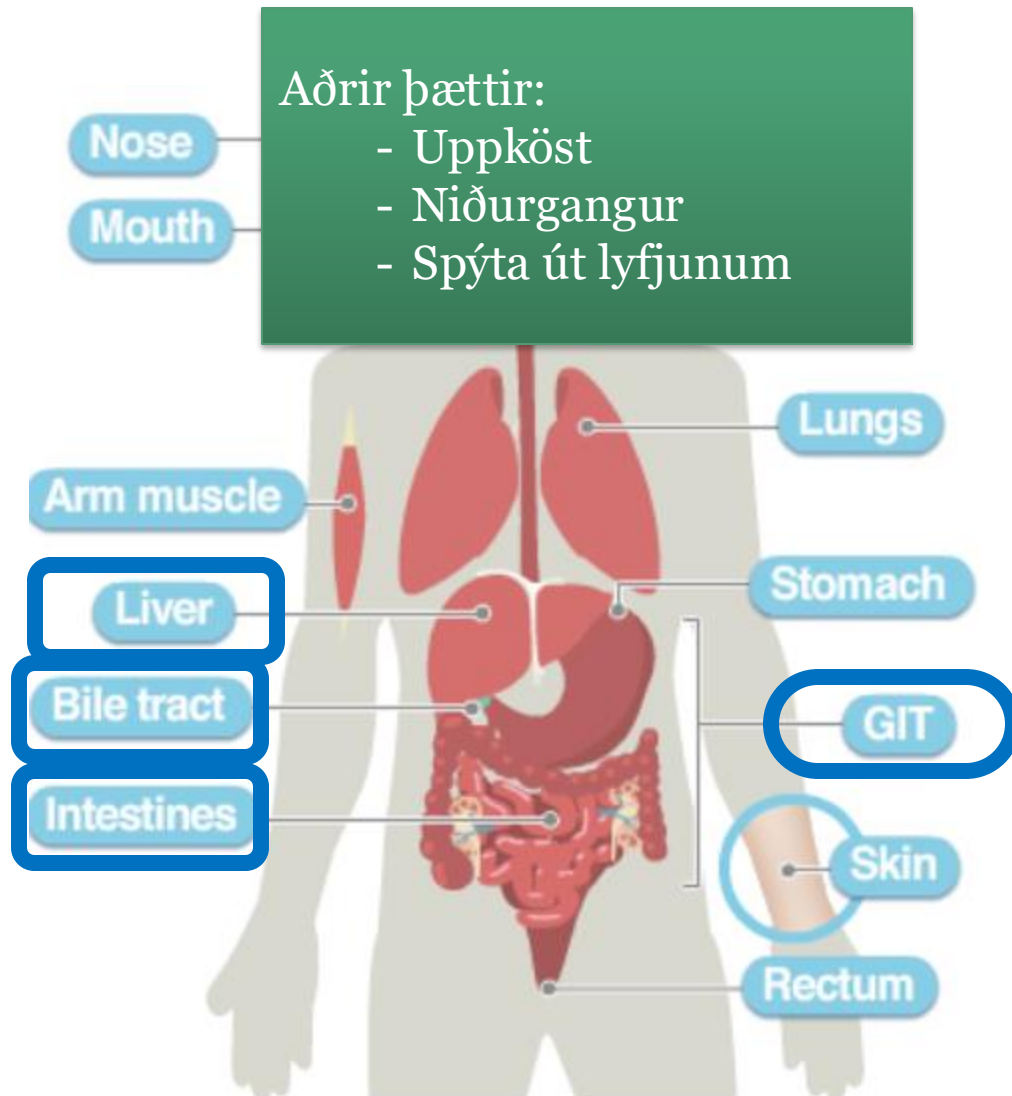
# FRÁSOG (ABSORPTION)



- Breytingar á pH og magatæmingu.
  - Við fæðingu, minna magn af magasafa
  - Minni framleiðsla á magasýrum
  - pH 6-8 (residual amniotic fluid)
  - Aukið frásog á lyfjum sem eru viðkvæm í súru umhverfi s.s. penicillin, erythromycin.
  - Minna frásog á lyfjum sem eru sýrur s.s. phenobarbital, phenytoin.
  - Sést enn frekar hjá fyrirburum þar sem óþroskaðri gastric mucosa og minni seytun magasýra.
  - pH lækkar fyrstu 1-2 vikurnar en ná fullorðinsgildum um ca. 2-3 ára. Í mjög súrum maga, lyf sem eru veikar sýrur frásogast betur.
  - Magatæming hægari hjá nýburum og fyrirburum (6-8 klst), nær fullorðinsgildum um 6-8 mánaða



# FRÁSOG (ABSORPTION)



Nýburar óþroskað gallkerfi, minni flutningur á gallsýru til þarma og minni framleiðsla brisensíma. Því minna frásog á fitu sem leiðir til að frásog fituleysanlegra lyfja s.s. diazepam er minna og t.d. Fituleysanleg vítamín.

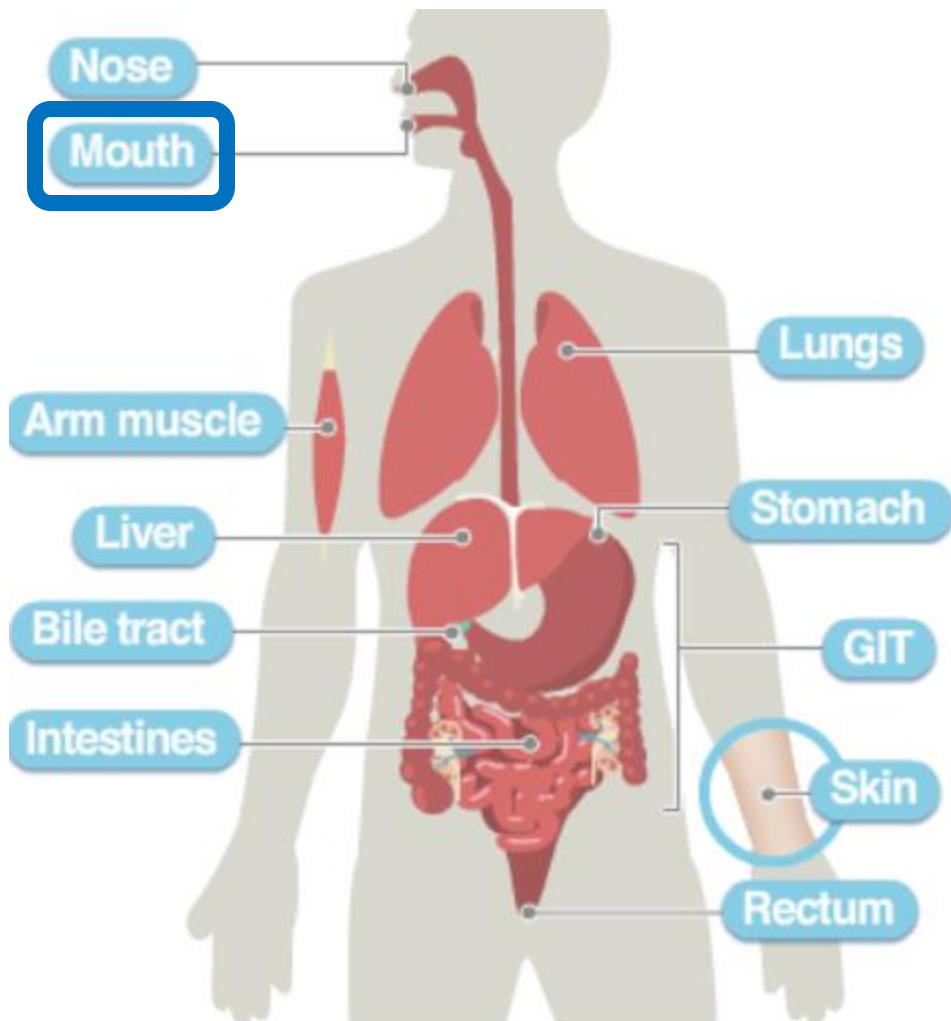
Margir þættir sem hafa áhrif á frásogið: Frásog um þarmavegginn er talið þroskað um 4 mánaða aldur.

- pH. Basísk lyf frásogast betur í alkaline umhverfi
- Þarmahreyfingar eru óþroskaðar, hefur áhrif á frásogið, eykst á fyrstu mánuðunum
- Þarmaflóran
- Lengd þarma – virkt frásogsyfirborð
- Áhrif ensíma í garnavegg á niðurbrot (first pass)

pH --- Súr lyf í súru --- Basísk lyf í basísku

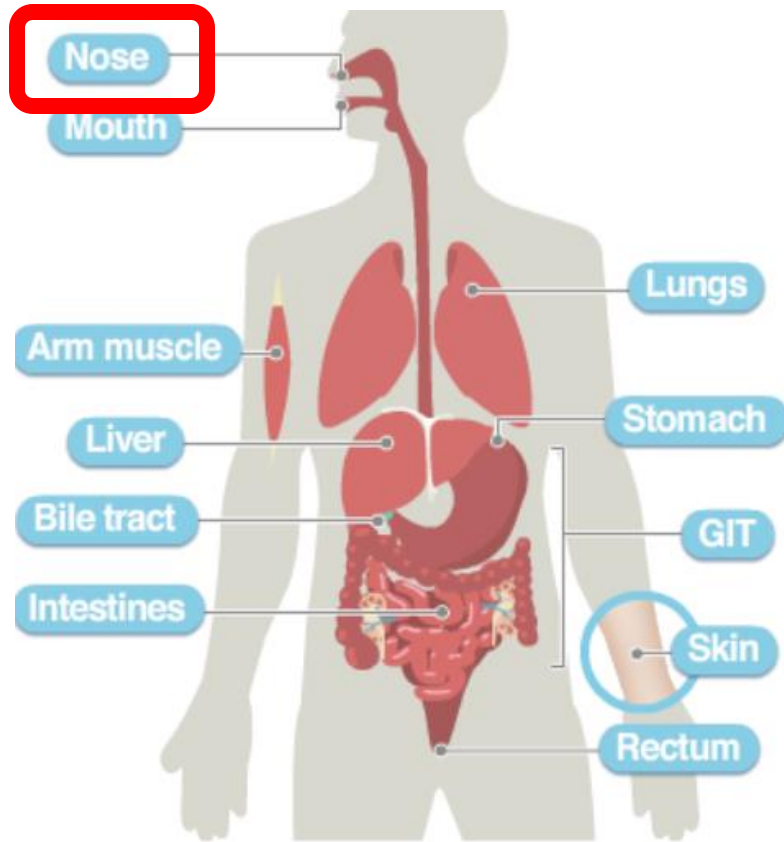
Lyf sem fara í gegnum first pass í lifur áður en þau fara í blóðrásina -> minna aðgengi

# FRÁSOG (ABSORPTION)



Gjöf í munnhol: Hratt og gott frásog.  
Dæmi: Midazolam

# FRÁSOG (ABSORPTION)



## Nef:

- Hratt frásog
- Framhjá first passa áhrifum í lifur
- T.d. Fentanyl, midazolam, dexdor



## Verkja og slævandi lyf gefin um nös\* (Börn > 6 mán)

### Gjöf lyfja með nefskammtara – nota sterkasta formið af lyfinu

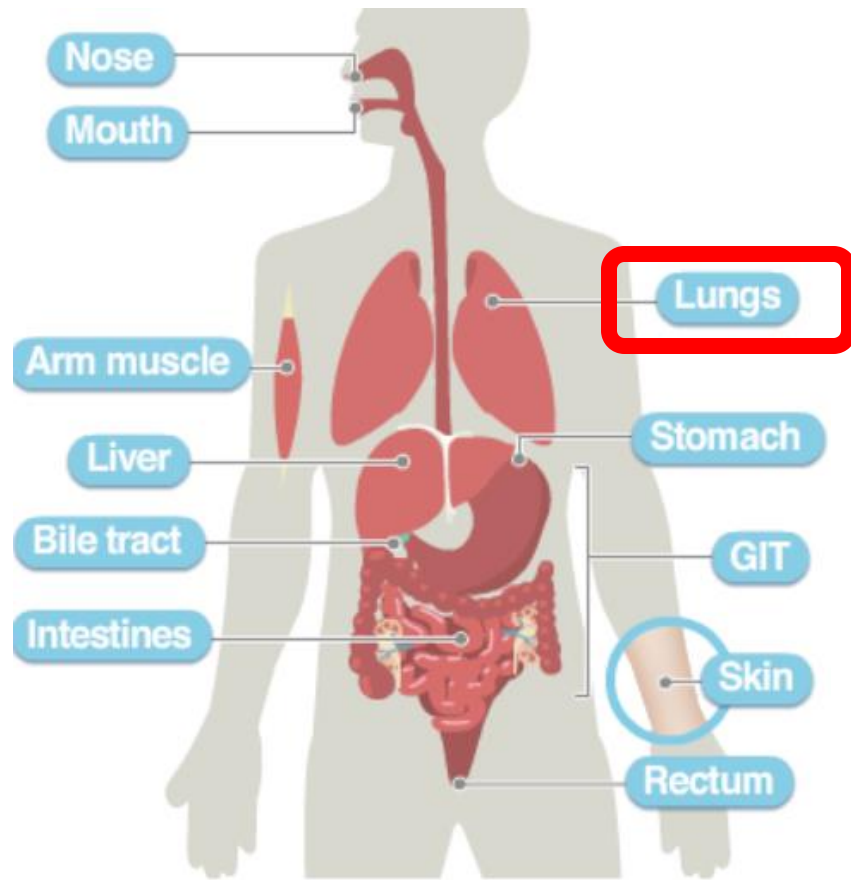
Lyfið er dregið upp í 1 ml sprautu og skipt jafnt á milli nasa (dregin er upp 0,1 ml umfram skammt vegna "dead space") Að jafnaði er gefið 0,2 – 0,5 ml í hvora nös (max 1 ml, ef gefa þarf meira magn þurfa að liða 5 – 10 mín á milli gjafa) Hentar síður fyrir börn með nefstíflur

	Skammtur	Max skammtur	Ábending og verkun
Dexmedetomidin Dexdor® **	5 – 20 kg: 1 µg/kg 20 – 50 kg: 2 µg/kg	100 µg	Slæving fyrir inngrip/rannsóknir Verkun eftir 15 – 30 mín (varir að meðaltali í 85 mín)
Midazolam Dormicum® ***	0,3 mg/kg	10 mg	Slæving fyrir inngrip/rannsóknir Verkun eftir 5 - 10 mín (varir að meðaltali í 30 mín) Er ertandi við gjöf í nös
Fentanyl ****	Börn > 1 árs (10 kg) 1,5 µg/kg	100 µg	Verkjastilling við bráðum miklum verkjum og fyrir sársaukafull inngrip Verkun eftir 5 – 10 mín (varir að meðaltali í 1 – 2 klst.)

\* Gæðaskjal - Slæving barns fyrir stutt inngrip á barnadeild 4.19.04  
 \*\*Gæðaskjal - Lyfjagjöf um nös á barni - Dexmedetomidin 4.17.05.  
 \*\*\*Gæðaskjal - Midazolam til slævingar á barnadeild 4.17.06  
 \*\*\*\*Gæðaskjal - Lyfjagjöf um nös á barni - Fentanyl 4.17.10



# FRÁSOG (ABSORPTION)



## Lungu:

- Að mestu háð gjöfni sjálfri.
- Notkun á maska í réttri stærð
- Spacer

## VORTEX GROWS WITH YOU

From toddler to adult, Vortex offers a series of facemasks for various age groups, eliminating the need to purchase a new holding chamber when changes in mask size are needed.

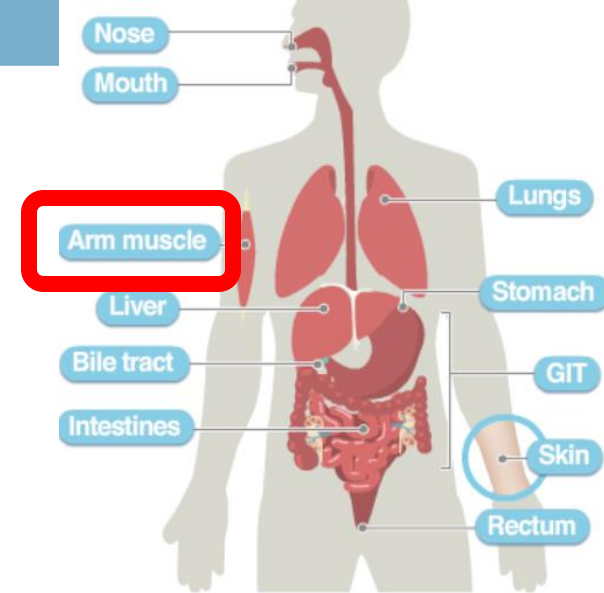




## FRÁSOG (ABSORPTION)

### IM gjöf:

- Frásog er óreglulegt, eins og getur verið hjá fullorðnum
- Sömu lyfin sem þarf að forðast IM, t.d. phenytoin, digoxin, diazepam
- Litlir vöðvar/lítið af vöðvamassa
- Minna blóðflæði í beinagrindavöðvum
- Minni vöðvasamdráttur
  - Sársaukafullt
  - Ekki nægjanlegur árangur (minna frásog)

*K vítamín gefið í vöðva til að fyrirbyggja blæðingar. Kostur í þessu tilfalli að gefa IM vegna forðaverkunar.*



Muscle Group		Birth to 18 months	18 months to 3yrs	3 - 6 years	6 - 15 years	> 15 years
	Vastus Lateralis	0.5 mL	1 mL	1.5 mL	1.5 mL	2-2.5 mL
	Deltoid	Not Recommended	0.5ml Not Recommended unless Vastus Lateralis sites are unavailable	0.5 mL	0.5 mL	1 mL

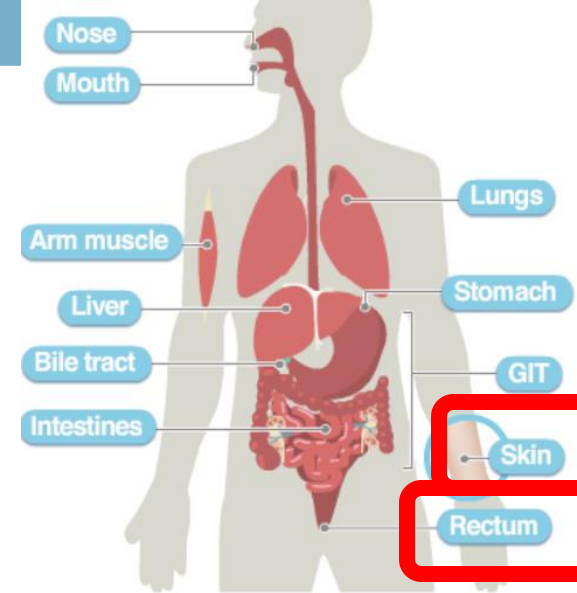
# FRÁSOG (ABSORPTION)

## Topical gjöf:

- Nýburar og ungabörn eru með  $\uparrow$  yfirborðsflatarmál:þyngd hlutfall
- Þynnri og gegndræpari húð (meiri raki)
- Hraðara og aukið frásog  $\rightarrow$  Aukin hætta á eitureinkennum
- Topical sterar – aukin hætta á systemískum aukaverkunum
- Sótthreinsandi lausn t.d. klórhexidín 2% - getur valdið bruna

## Rectal gjöf:

- Ákveðin breytileiki vegna blóðflæðis
- Getur hentað mjög vel



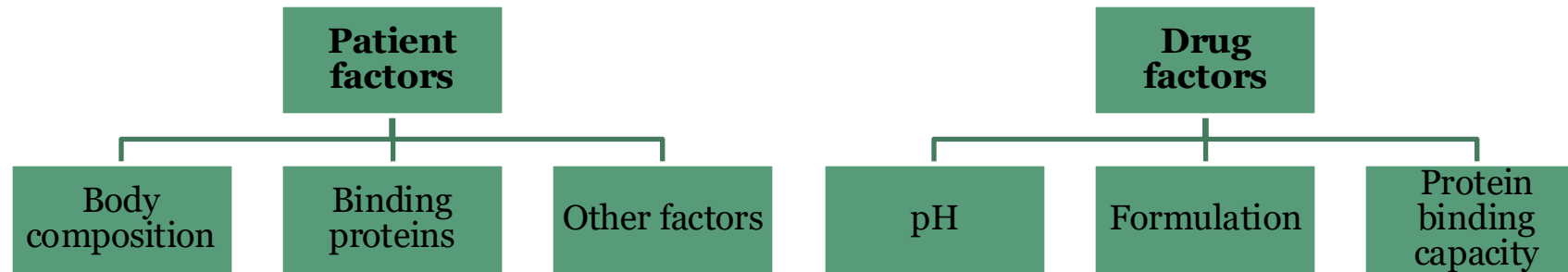
## LYFJAGJÖF Í ÆÐ (IV) HJÁ BÖRNUM

- Litlar æðar - aukin hætta á loftbólum, sýkingum, bólgum og phlebitis
- Takmarkaður æðaaðgangur - samrýmanleiki lyfja
- Minnstu börnin, aðeins 1 lumen
- Lyfjabrunnar
- Breytt lyfjahvarfafræði
- Lyf hönnuð fyrir fullorðna og oft þörf á miklum þynningum (10-100falt)



## DREIFING (DISTRIBUTION)

- Dreifing lyfja er háð eiginleikum sjúklingsins annarsvegar og eiginleikum lyfsins hins vegar.



- Mesta breytingin er á fyrsta árinu

# DREIFING (DISTRIBUTION)

Body Water Compartments (Average values)

Descriptor	Pre-Term	Full Term	4-6 months	1 year	> 1 year	Adult
Extracellular fluid volume	up to 60%	45%	30%	25%	25%	20% -25%
Total Body Water	85%	75%	-	-	-	60%
Fat Content	3%*	12%	30%	-	-	18%

- Hærri skammtar af lyfjum sem eru vatnsleysanleg

\* This value varies depending on the gestation and may be higher in babies born after 32 weeks gestation.

**Próteinbinding** – albúmin og plasmaprótein eru lægri hjá nýfæddum og því minni binding.

Dæmi: Ceftriaxone frábending 4 vikna og yngri.

-Keppir við bilirubin um prótein bindingu-> Kjarnagula (kernicterus)

-Einnig Phenytoin

# METABOLISM – NIÐURBROT/UMBROT LYFJA

- Aukin virkni lifrarensíma
  - At birth, the majority of the enzyme systems responsible for drug metabolism are either absent or present in considerably reduced amounts compared with adult values
  - Dramatic increase in metabolic rate in older children
    - 1-9 years, metabolic clearance of drugs is greater than in adults
      - Theophylline, phenytoin, carbamazepine
      - Need of higher doses
- Lifrar ensímkerfin eru einnig óþroskuð í nýburum
  - Oxidation and glucuronidation
    - Grey Baby syndrome
    - Paracetamol
- Metabolic differences
  - CYP2D6
    - Umbreytir kódein í morfín
    - Framleiðslan á þessu ensími er rokkandi, mjög lítil fyrstu vikurnar og hjá unglíngum, en mjög mikil hjá litlum börnum og krökkum
    - Ultra rapid metaboliser subtype

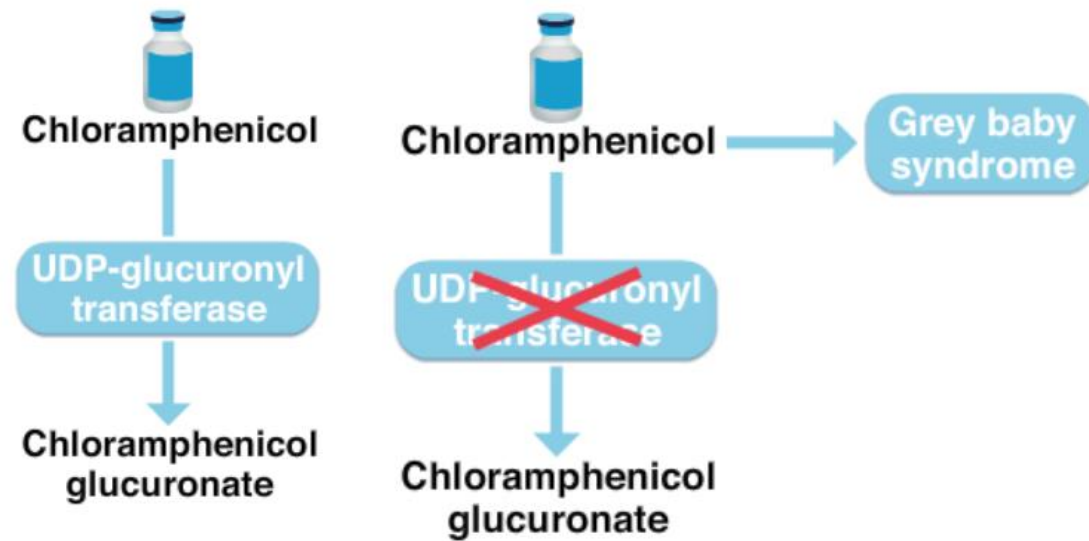
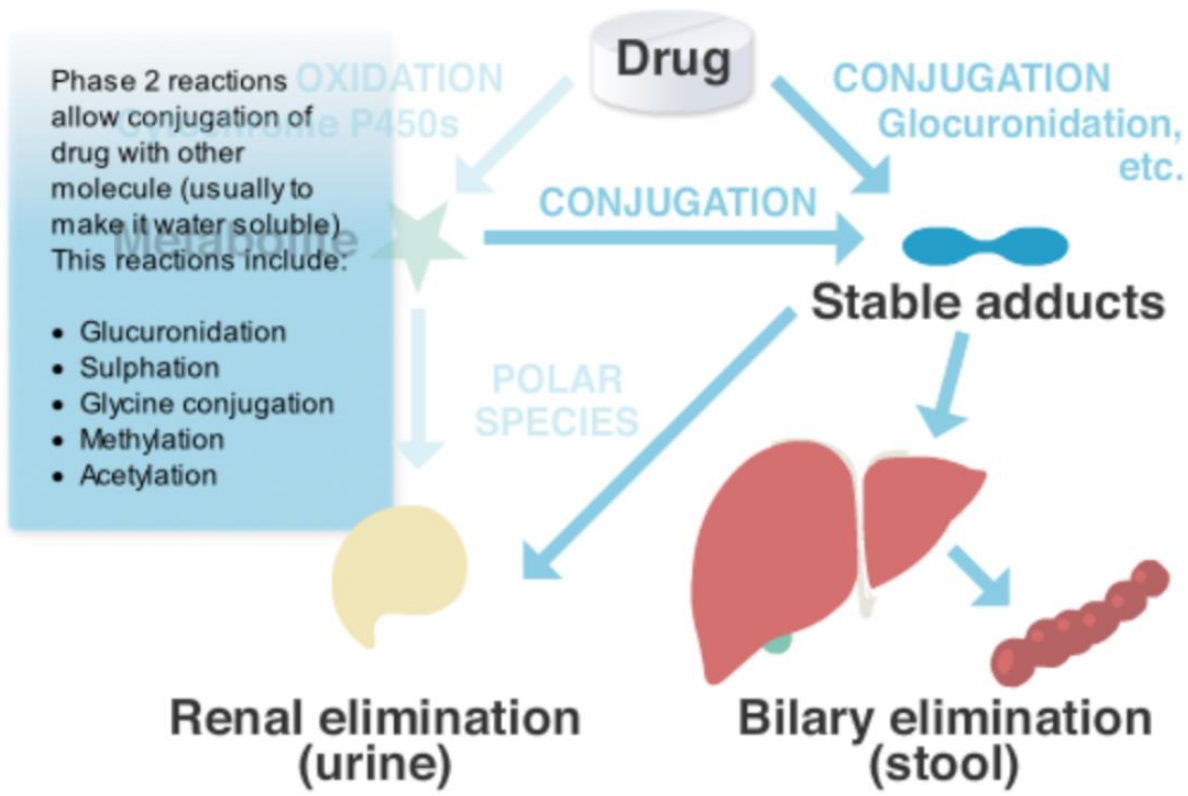


# Phase 1 metabolism – cytochrome P450

CYP Enzyme	Activity	Example
3A7	Peaks just after birth, then declines Almost undetectable in adults	Protects foetus by detoxifying dehydroepiandrosterone sulfate and retinoic acid
3A4	Appears in first week of life Activity in children > adults	Faster clearance of carbamazepine in children than adults
2C9/ 2C19	At 10 days activity ~ same as adult	Phenytoin $t_{1/2}$ : 75hrs – preterm infants 20hrs – term infants 8hrs – 2 <sup>nd</sup> week of life
1A2	Appears at 1-3 months of life Adult values achieved at 4 months and exceeded by 6 months	Caffeine / theophylline

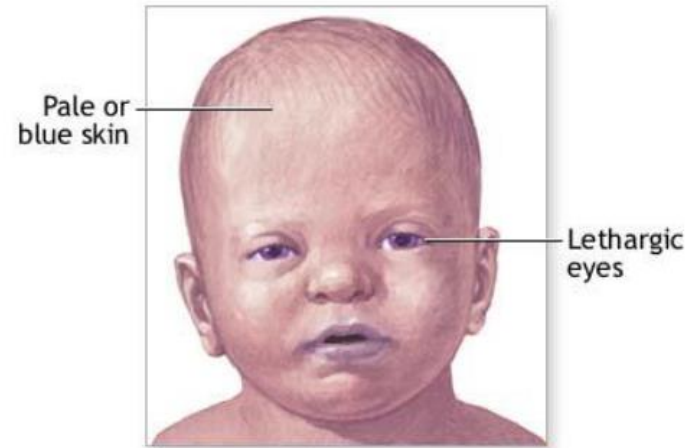
# Phase 2 metabolism

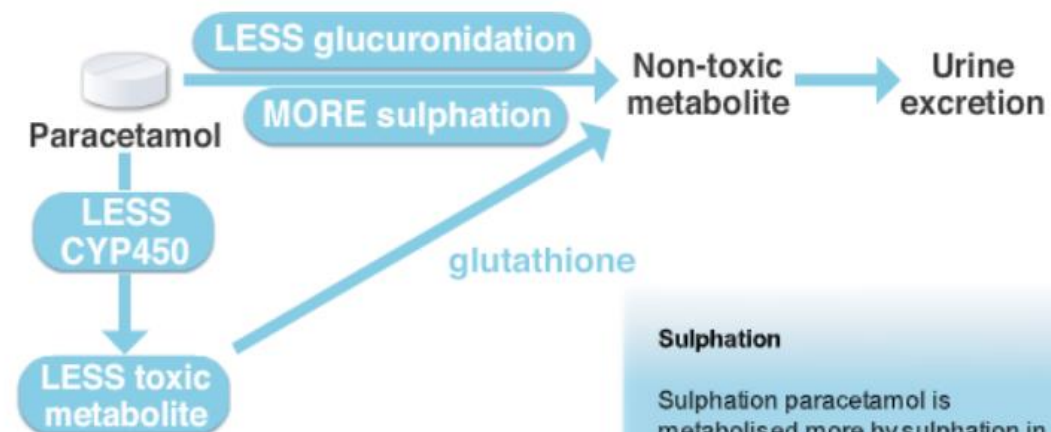
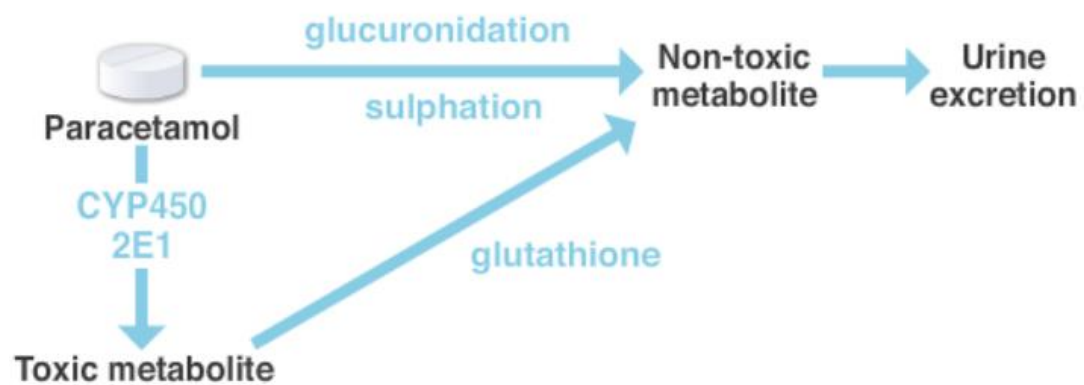
Sulphation	}	• Not greatly impaired at birth
Methylation		
Oxidation	}	• Impaired at birth
Glucuronidation		
Hydroxylation	}	• Deficient in newborns



# Grey Baby Syndrome

- Side effect of chloramphenicol in the newborn
- Lack of glucuronidation leads to build up of toxic metabolites
- Insufficient renal excretion of unconjugated drug
- Clinical features
  - Vomiting, limp body tone
  - Grey skin colour
  - Blue discolouration of lips
  - Hypotension
  - Cardiovascular collapse





**Sulphation**

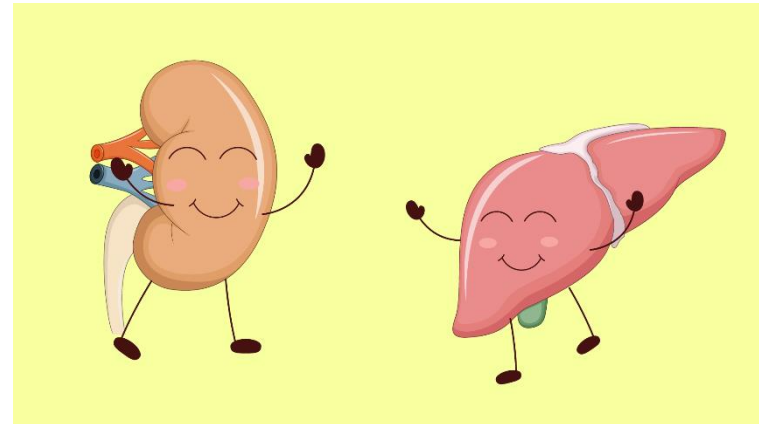
Sulphation paracetamol is metabolised more by sulphation in neonates infants.

# ÚTSKILNAÐUR

- Nýru og lifur hjá nýburum eru óþroskuð og því eiga erfiðara með að skilja út lyf. Þetta leiðir til hækkunar á serum styrk sumra lyfja.
- Því er skertur nýrnaútskilnaður hjá nýburum og ungabörnum en eykst mjög hratt fyrstu 2 vikurnar og ná fullorðins gildum á 8-12 mánuðum
  - Hægari útskilnaður
  - Lengja þarf tíma á milli gjafa

## Glomerular Filtration Rate:

- Term neonates: 20-40ml/min/1.73m<sup>2</sup>
- Pre-term neonates: >0.5ml/min/1.73m<sup>2</sup> (depending on gestational age)
- Increases rapidly in first 2 weeks of life
- Reaches adult values at 6-12 months



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Cystatin C

Bedside jafnan:  
 $36,5 * \text{hæð (cm)}$   
 / SCr ( $\mu\text{mol/L}$ )

- Cockcroft and Gault calculation for CrCl is poor predictor for GFR in children
- Use Schwarz formula in children and young people:

$$\text{Est. Creatinine clearance (ml/minute/1.73m}^2) = \frac{F \times \text{Height [cm]} \times 88.4}{\text{Serum Cr (micromol/L)}}$$

- Where F is proportional to body muscle mass, hence dependent on age and gender:

Infants: F = 0.45

Female 1-21 years: F = 0.55

Male 1-16 years: F = 0.55

Male 16-21 years: F = 0.70

Trend

[https://www.kidney.org/professionals/kdoqi/gfr\\_calculatorPed](https://www.kidney.org/professionals/kdoqi/gfr_calculatorPed)

<https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr>

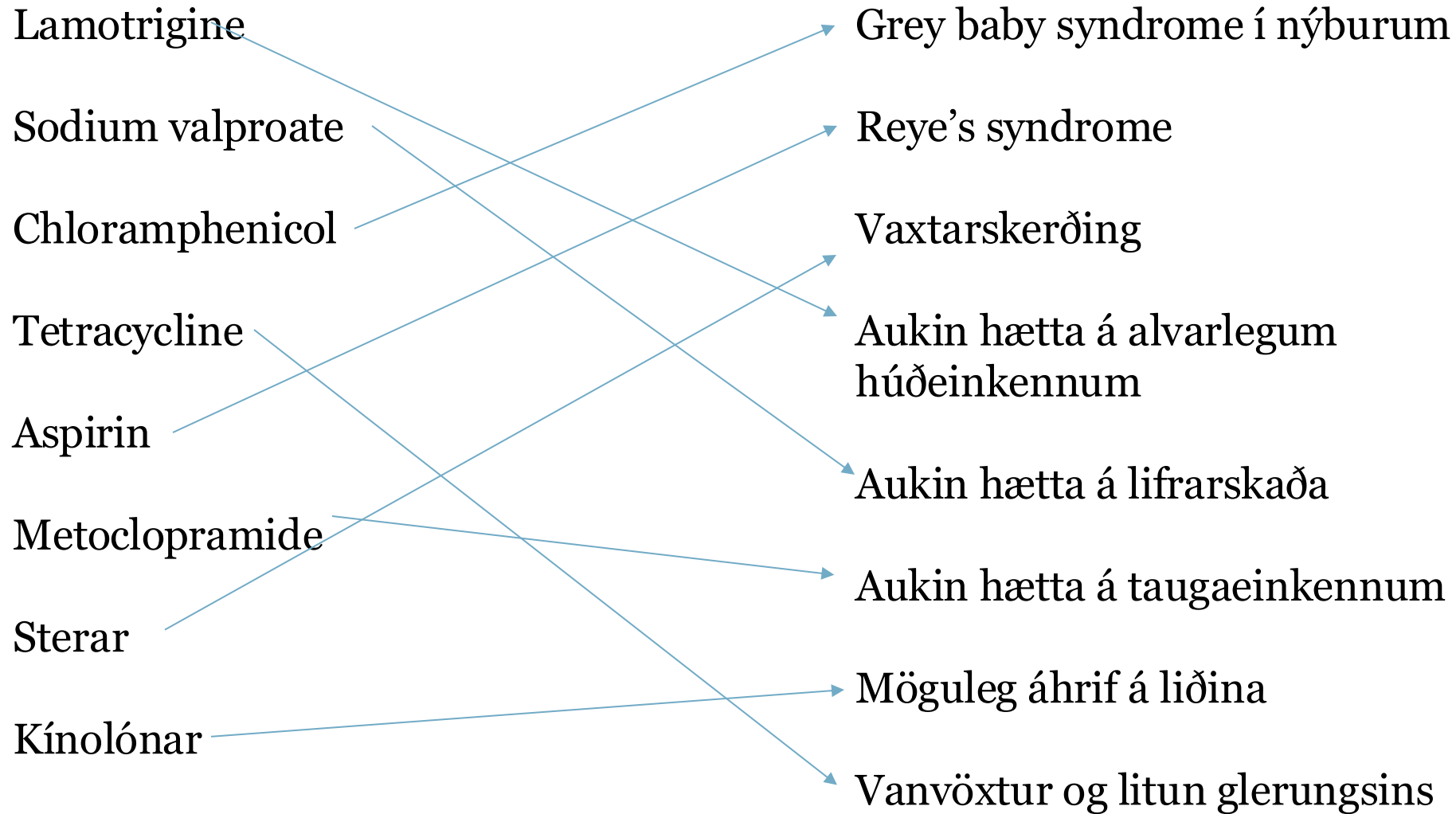


## LYFJAFORM OG LYFJAGJÖF – HJÁLPAREFNI (EXCIPIENT)

- Algengasta, sorbitól
- Sum geta verið skaðleg börnum

Excipient	Linked with
Glucose and sucrose	Obesity, and tooth decay if taken orally
Benzyl alcohol	A gasping syndrome in neonates
Ethanol	CNS effects
Aspartame	A source of phenylalanine in patients with phenylketonuria
Polyoxyl castor oils	Severe anaphylactoid reactions
Propylene glycol	CNS effects especially in neonates and children under 4 years
Colourants (e.g. tartrazine)	Hypersensitivity and behavioural disturbances





# MEDICATION ERROR

- 10 föld mistök → t.d. Flóknir útreikningar/bynningar, Þyngd undir 1 kg

## Common reasons for medication errors in children

- Incorrect use of information resources (e.g. doses described in terms of total daily dose [t.d.d] being prescribed three times a day)
- Lack of familiarity with drug (e.g. in hospitals, errors are more likely to occur in clinical areas where children are treated alongside adults such as in emergency departments or theatres)
- Use of unlicensed/off-label drugs due to lack of clinical information/experience
- Lack of licensed paediatric dose units and/or the need to use adult formulations
- Complex calculations and dilutions
- Displacement volumes
- Extemporaneous preparation of oral liquids (e.g. can be available at a range of concentrations, so care if the dose is prescribed in millilitres rather than milligrams, for example)

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Lyfjaval/lyfjaform – PO vs. IV

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mg v.s ml

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g vs. mg vs. mcg

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ml/klst vs. Mg/klst

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Mg/kg/mín .... mg/kg/klst.... ml/kg/klst.

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Amoxicillin hluti lyfs

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Tímasetningar lyfjagjafa

# SPURNINGAR