- Workshop on Regulatory and Scientific Issues Related to the Investigation of Medicinal Products Intended for Neonatal Use
London, UK, 2006-10-11

Lessons learnt from medicinal products used in neonates –

What are the needs with regard to formulation?

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History of major ADR in neonates and fetuses

Table 1. Major adverse drug reactions in neonates and the fetus

Year	Drug/compound	Age group	ADR	Mechanism
1886	Aniline dye	Neonates	Methaemoglobinaemia	Percutaneous absorption
1956	Sulphisoxazole	Neonates	Kernicterus	Protein displacing effect on bilirubin
1959	Chloramphenicol	Neonates	Grey baby syndrome	Impaired metabolism
1961	Thalidomide	Fetus	Phocomelia	Production of toxic metabolites by fetus

Table 2. Major formulation errors in neonates

Year	Drug	Error	Deaths	Age group	Country
1972	Talc baby powder	Contained 6.3% hexachlorophene	36	Infants and young children	France
1982	Sodium chloride water	Benzyl alcohol concentrations high	10	Neonates	USA
1984	Vitamin E	Emulsifiers toxic?	38	Neonates	USA
1996	Magnesium sulphate	Concentration doubled	?	Neonates	UK

J. McIntyre, I. Choonara, Biol. Neonate 86:218-221 (2004)

1995	Acetaminophen syrup	Glycerol contained DEG	85	Neonates, infants	Haiti
1999	KCl solution	Labelling: glucose solution	2	Neonates	Belgium
•	•	•	•	•	•
•	•	•	•	•	•
•	•	•	•	•	•

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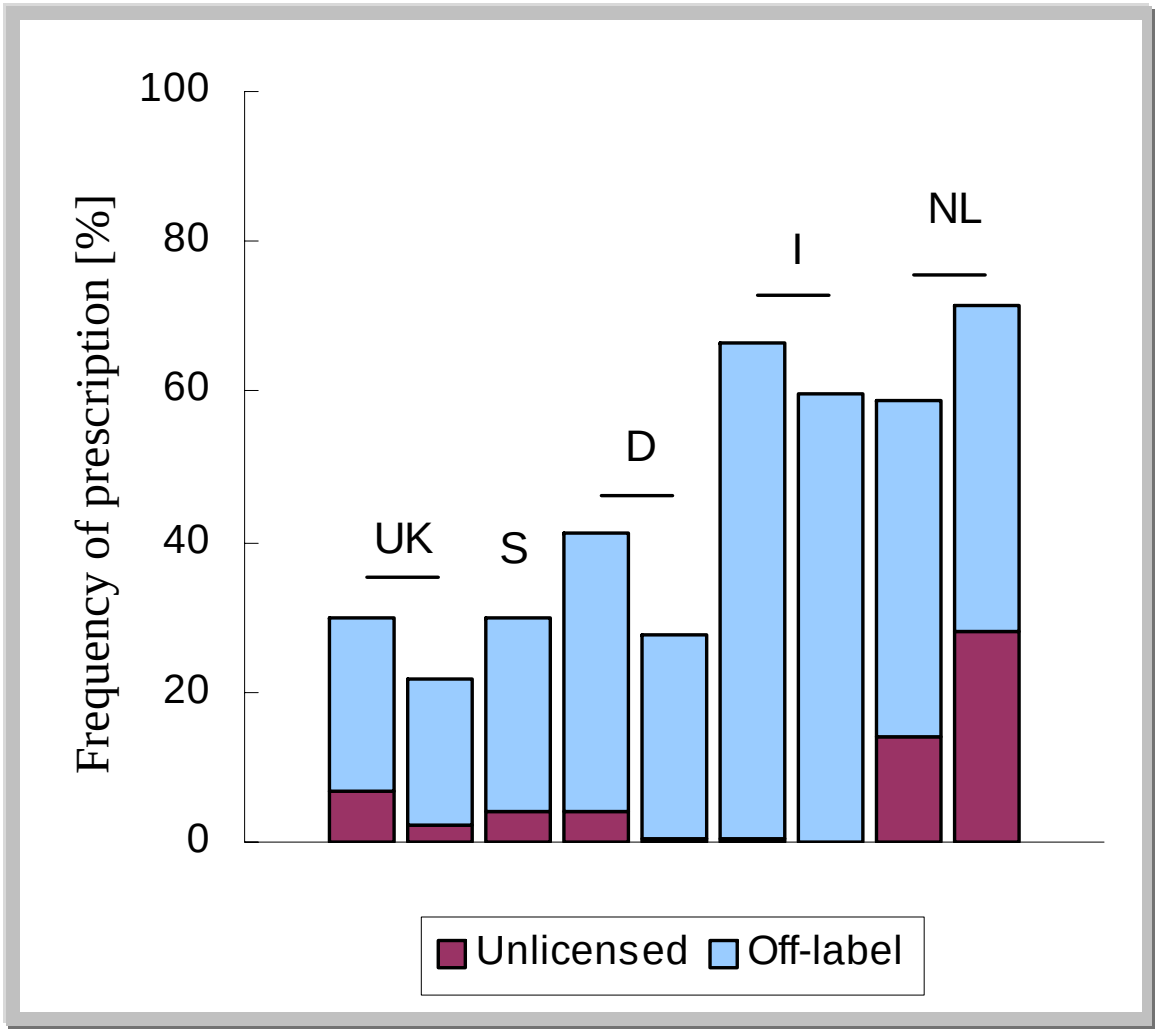
Off-label/Unlicensed use in paediatrics: Hospitals

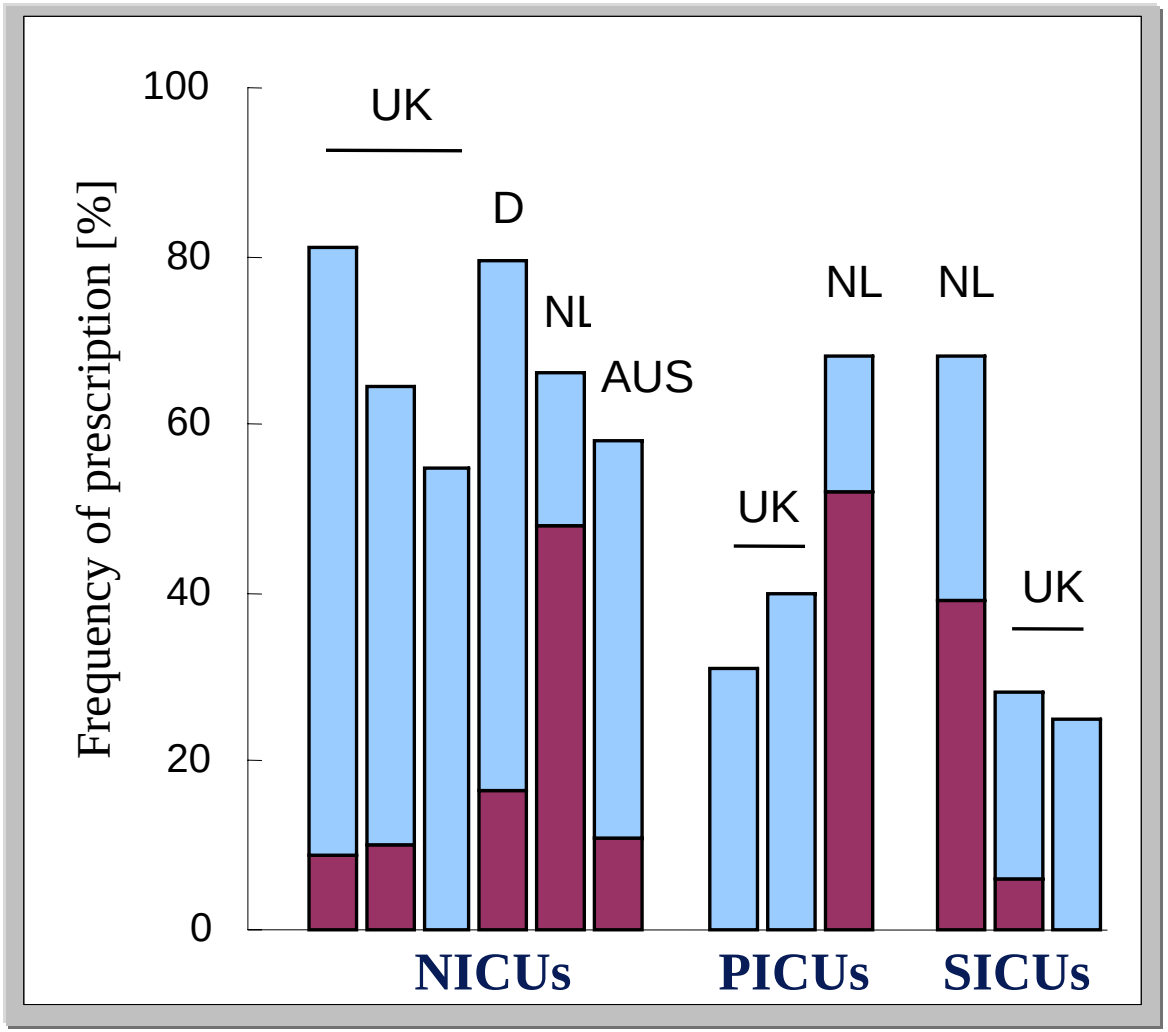


J. Breitkreutz, habilitation thesis,
Westf. Wilhelms-University. Münster, Germany (2004)

<u>Off label</u>
dose
age
indication
contraindication
route

<u>Unlicensed</u>
Preparations of
chemicals,
drug substances,
drugs;
investigational
drugs

Off-label/Unlicensed use in paediatrics: Intensive care units



J. Breitkreutz, habilitation thesis,
Westf. Wilhelms-University. Münster, Germany (2004)

Off-label/Unlicensed use of marketed drugs in paediatrics

Age	Inadequate dosing information	Dose information, but no paediatric dosage form
< 1 month	80.5%	26.5%
1-3 months	79.1%	25.1%
3 months -2 yr	77.5%	23.3%
2-6 years	73.2%	21.9%
6-12 years	71.6%	24.0%

E. Tan, N. E. Cranswick et al., Med. J. Aust. 179:195-198 (2003)

Criterias for drug dosage forms appropriate for children

1. sufficient bioavailability (despite childrens‘ particularities)
2. nontoxic excipients regarding age group and administration
3. palatable or acceptable organoleptic properties
4. acceptable dose uniformity
5. easy and safe administration
6. socio-cultural acceptability (no stigmatisation)
7. precise and clear product information
8. must be appropriate for parents

J. Breitkreutz, J. Boos, Exp. Opin. Drug Deliv., submitted (2006)

Formulations of choice for newborns

Route / Dosage Form	*Preterm newborn infants*	*Term newborn infants (0d-28d)*	*Infants and Toddlers (1m-2y)*	*Children (pre school) (2-5y)*	*Children (school) (6-11y)*	*Adolescents (12-16/18y)*
Peroral						
Solution/ Drops			5	5	4	4
Emulsion/ Suspension			4	5	4	4
Effervescent DF*			5	5	4	4
Powders/ Multiparticulates			2	4	4	5
Tablets			1	3	4	5
Capsules			1	2	4	5
Orodispersable DF			3	4	5	5
Chewable tablets			1	3	5	5
Nasal						
Solution			4	4	4	4
Semisolid DF			3	4	4	4
Rectal						
Suppositories			5	4	3	2
Rectal Enema			4	3	3	2
Rectal capsules			4	4	4	3
Topical/ transdermal						

Emea Reflection Paper, Formulations of choice for the paediatric population (2005)

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Formulations of choice for newborns (cont'd)

Route / Dosage Form	*Preterm newborn infants*	*Term newborn infants (0d-28d)*	*Infants and Toddlers (1m-2y)*	*Children (pre school) (2-5y)*	*Children (school) (6-11y)*	*Adolescents (12-16/18y)*
Ointment, Cream, Gel			4	5	5	5
Liquid DF			4	5	4	4
Transdermal Patch			2	4	4	5
Parenteral						
i.v. Solution			4	4	4	3
i.m.			3	4	4	3
s.c.			4	4	4	3
Pump system			4	4	4	3
Pulmonary						
Nebuliser			4	5	4	3
MDI / Spacer			4	5	4	4
DPI			3	4	5	5
Ocular						
Eye drops			4	4	5	5
Semisolid DF			4	4	4	4

*DF: Dosage Forms

Emea Reflection Paper, Formulations of choice for the paediatric population (2005)

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Ranking of Drug Formulations for Preterm and Term Newborn Infants

1. **Parenterals (predominantly i.v.)**
2. **Oral liquids**
3. **Rectal formulations**
4. **Topical formulations**
5. **Nasal formulations**
6. **Solid orodispersable formulations?**
7. **Oral multiparticulates?**

Parenteral formulations in German paediatric wards: Errors in preparation and administration

	Taxis/Barber, 2004	Wirtz et al., 2003	Hoppe-Tichy et al., 2002
Incidence	48 %	34 %	not mentioned
Impact	3 % severe 31 % moderate 13 % minor	26 % severe or moderate	not judged
Types of errors	solvent dose --- omission incompatibility	--- dose infusion rate omission incompatibility	solvent dose rate --- --- dosage form solvation/dilution labelling

K. Taxis, N. Barber, Eur. J. Clin. Pharmacol. 59: 815-817 (2004)
V. Wirtz, K. Taxis, N. Barber, Pharm. World Sci. 25:104-111 (2003)
T. Hoppe-Tichy et al., Krankenhauspharmazie 23: 11-17 (2002)

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Errors producing conditions

Table 1 Error producing conditions (n=136) relating to 85 human errors (mistakes, slips and lapses)

Error producing condition	No (%) of human errors	Factors
Handling technology	67 (79%)	Lack of knowledge, routine and experience in: • [redacted] • [redacted] Inadequate use of technology, e.g. drug charts (n=10)
Design of technology	27 (32%)	Ambiguous manufacturer leaflets (n=3) Unsuitable working environment (n=5) [redacted] Unsuitable preparation procedures (n=5)
Communication	14 (16%)	Communication problems between: • nurses (n=10) • nurses and pharmacists (n=1) • doctors and other health professionals, e.g. ambiguous prescriptions (n=3)
Workload	13 (15%)	Several tasks at the same time (n=7) End of shift (n=3) Lack of qualified staff (n=3)
Patient related factors	8 (9%)	Limited venous access (n=6) Non-cooperative patient (n=2)
Supervision	5 (6%)	Lack of supervision of student nurse/agency nurse (n=5)
Other factors	2 (2%)	Trying to save disposable equipment (n=2)

K. Taxis, N. Barber, Qual. Saf. Health Care 12: 343-348 (2003)

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Potential errors or mishandling of parenteral formulations

Handling of technology: Drug preparation

correct solvent
osmolarity
complete solvation/dilution
correct dose
total fluid volume
correct dosage form
complete labelling
sterility

Handling of technology: Drug administration

aseptic conditions / handling
intravenous flow rate
site of injection
administration omission
drug incompatibility in line

Potential errors or mishandling of parenteral formulations

Some Examples: Drug preparation

Solvents / Osmolarity

- Using WFI for dissolving/diluting instead isotonic NaCl or Ringer solution => hypotonic solution

- for some drugs (Dobutamine, Piperacillin) use WFI first, then add isotonic solution, otherwise recrystallization or instability

- Sodium benzoate dissolved in isotonic NaCl or Ringer => isotonic, but hypernatriemia. KCl supplement is favorable.

- Lag volume of syringes. Use solvent first, then drug solution.

- Unsufficient mixing

Paediatric vs. Adult Vials

Table 1 Clinical characteristics and amikacin plasma concentrations in relation to target concentrations

Clinical	Adult vial	Paediatric vial
Number of neonates	75	56
Neonatal survival (day 28)	70 (93%)	55 (98%)
GA (w) median (range)	28 (24–30)	28 (24–30)
Birth weight (g)*	1130 ± 332	1080 ± 314
Prenatal indomethacin	2 (3%)	2 (4%)
Prenatal betametasone	56 (75%)	46 (82%)
Ibuprofen co-administration	40 (53%)	13 (23%)
Plasma concentrations		
Peak amikacin (mg/l)*	38.3 ± (13.1)	40.9 ± 9.1
Trough amikacin (mg/l)*	4.8 ± (2.6)	4.3 ± 1.8
Peak result in target zone	70 (93%)	55 (98%)
Trough result in target zone	47 (63%)	41 (73%)
Both results in target zone	44 (58%)	40 (72%)

* Mean ± SD

K. Allegaert, B. J. Anderson et al., Paed. Perin. Drug Ther. 7: 59-64 (2006)

Potential errors or mishandling of parenteral formulations

Some Examples: Drug administration

Dosage form

Not to be injected

Infusion rate/time

<u>rapid infusion</u> of
- lorazepam
- haloperidol
not licensed

high risk for
- vancomycin

<u>Lag volume</u> of infusion lines

Dosing

single / multiple doses
incorrect doses

incompatible drugs

incompatible excipients in drug combination

V. Wirtz, K. Taxis, N. Barber, Pharm. World Sci. 25:104-111 (2003)
T. Hoppe-Tichy et al., Krankenhauspharmazie 23: 11-17 (2002)

Toxicity of excipients

Benzyl alcohol, Sodium benzoate, Benzoic acid

Gasping-Syndrom

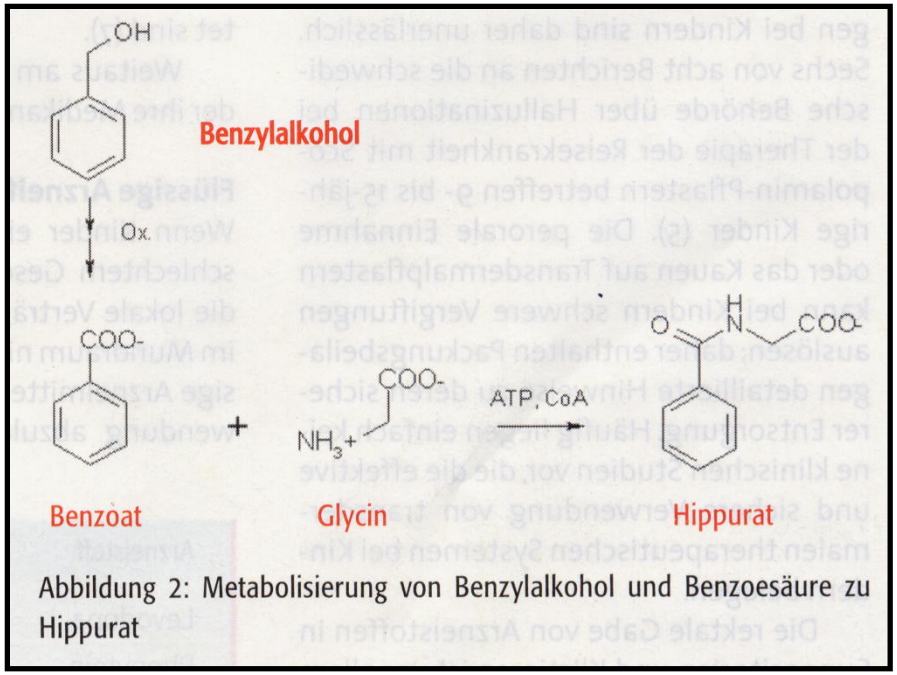

Abbildung 2: Metabolisierung von Benzylalkohol und Benzoesäure zu Hippurat

J. Breitkreutz et al., [in German] Pharm. Ztg. 147: 3210 (2002)

Benzyl Alcohol: Toxic Agent in Neonatal Units

Little et al., Pediatrics 72: 356 (1983)

Benzyl Alcohol Toxicity: Impact on Mortality and Intraventricular Hemorraghe Among Very Low Birth Weight Infants

Hiller et al., Pediatrics 77: 500 (1986)

Benzyl Alcohol Toxicity: Impact on Neurologic Handicaps Among Surviving Very Low Birth Weight Infants

Benda et al., Pediatrics 77: 507 (1986)

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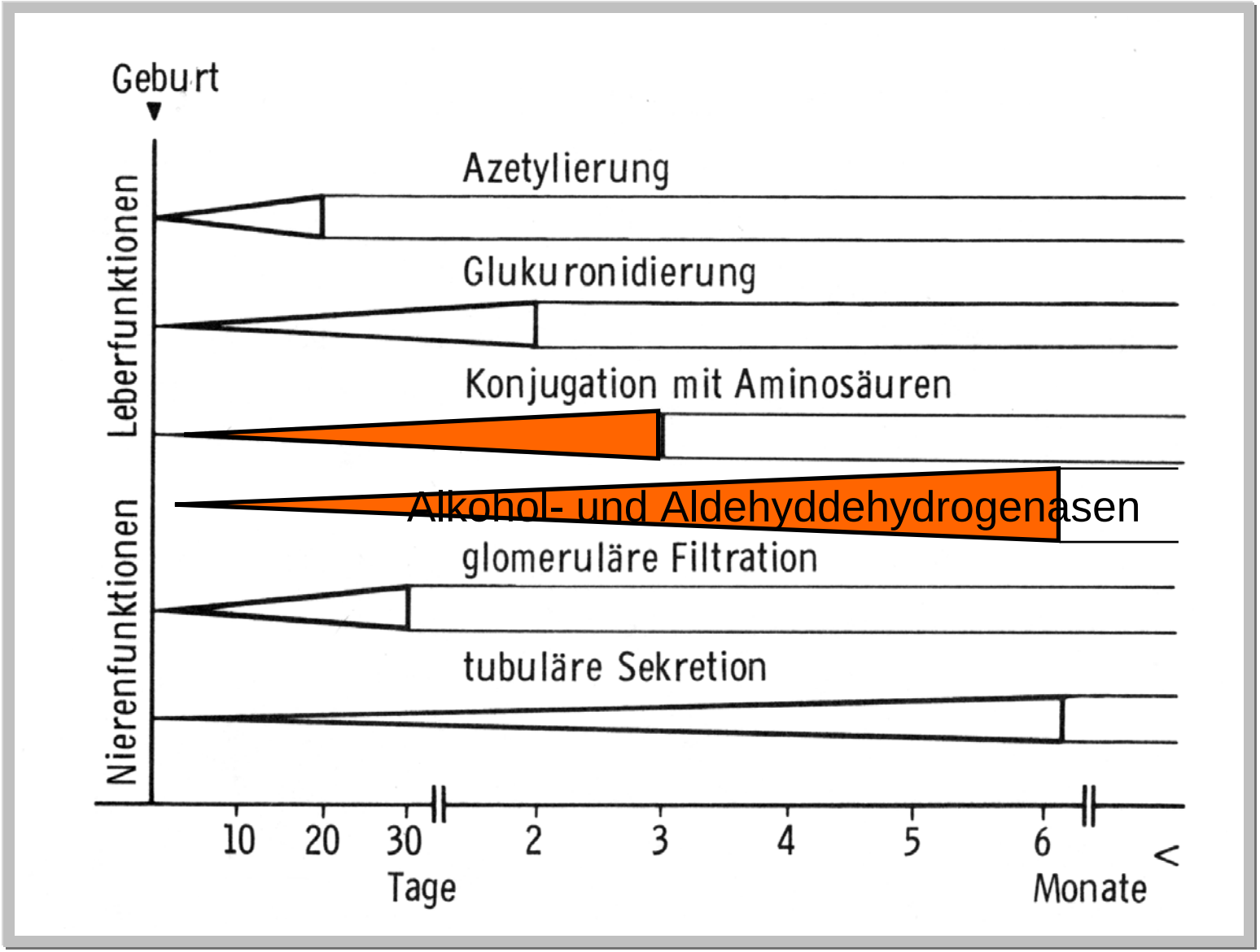
Incomplete metabolisation of benzyl alcohol



Modified from Gladtke/Heimann 1992

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Toxicity of excipients

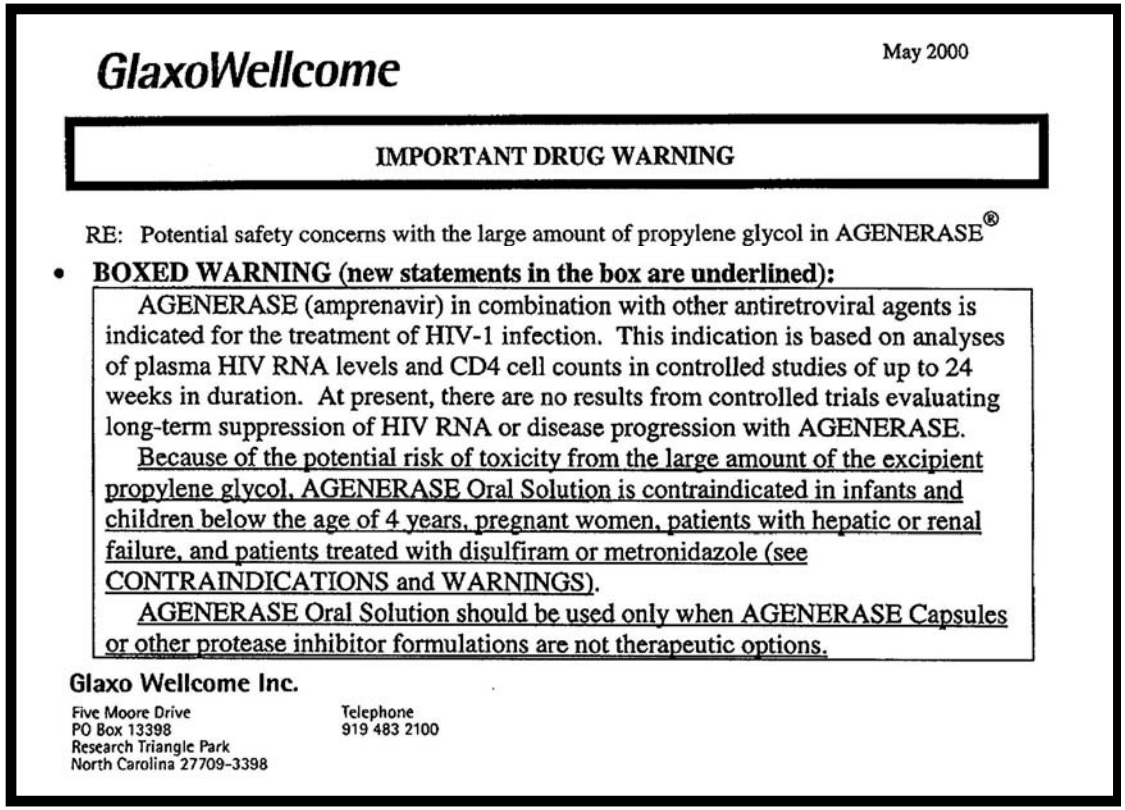
Propylene glycol

Hyperosmolality in Small Infants Due to Propylene Glycol

Glasgow et al.,
Pediatrics 72: 353 (1983)

Propylene Glycol: Increased Incidence of Seizures in Low Birth Weight Infants

Getson et al.,
Pediatrics 79: 622 (1987)



GlaxoWellcome

May 2000

IMPORTANT DRUG WARNING

RE: Potential safety concerns with the large amount of propylene glycol in AGENERASE®

- **BOXED WARNING (new statements in the box are underlined):**

AGENERASE (amprenavir) in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of up to 24 weeks in duration. At present, there are no results from controlled trials evaluating long-term suppression of HIV RNA or disease progression with AGENERASE.

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, AGENERASE Oral Solution is contraindicated in infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole (see CONTRAINDICATIONS and WARNINGS).

AGENERASE Oral Solution should be used only when AGENERASE Capsules or other protease inhibitor formulations are not therapeutic options.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398
Telephone
919 483 2100

Propylene Glycol: The Safe Diluent that Continues to Cause Harm

Glover et al., Pharmacotherapy 16: 690 (1996)

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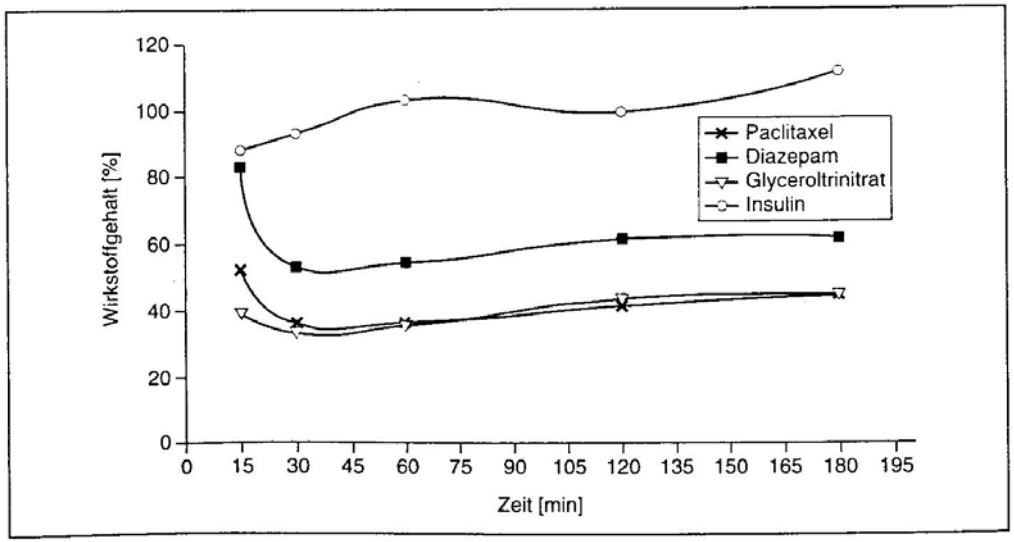
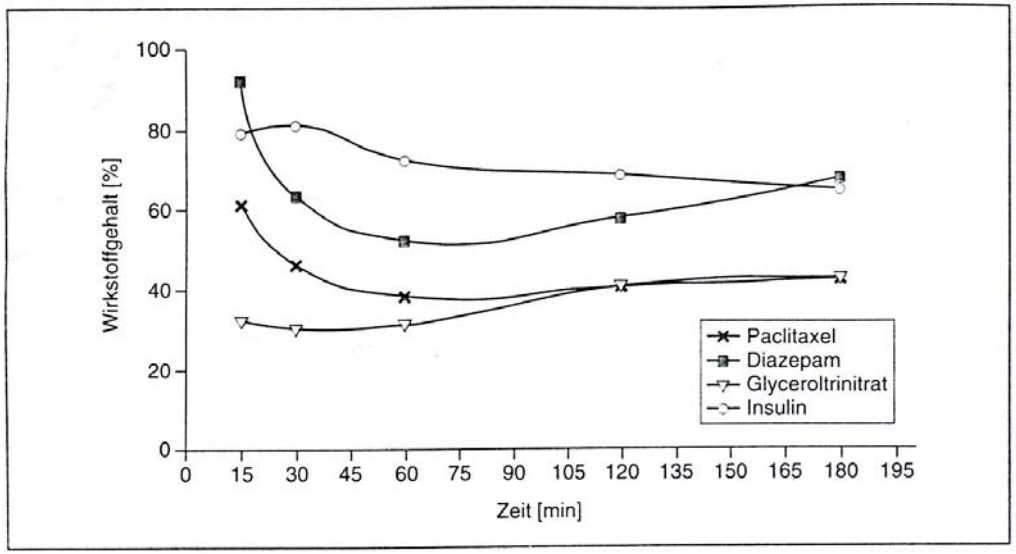
Adsorption and Penetration into Tube Material



PVC

W. Lemm,
Krankenhauspharmazie
19: 560-562 (1998)



Polyurethan

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Desorption from Tube and Packaging Material

Diethylhexyl phthalate, DEHP

Plasticizer in PVC plastics
- tubes (e.g. Baxter Clintec Benja-Mix) : 400 mg/L in fat emulsion!
- valves (e.g. Medex Medical MX453-SL)
- perfusor-tube (e.g. B. Braun Melsungen N872296/0)
- intravenous transducer / blood pressure device
  (e.g. Combitrans B. Braun Melsungen)

Butylhydroxytoluol, BHT

Antioxidative agent in Polyurethan plastics

Diphenylmethandiisocyanate

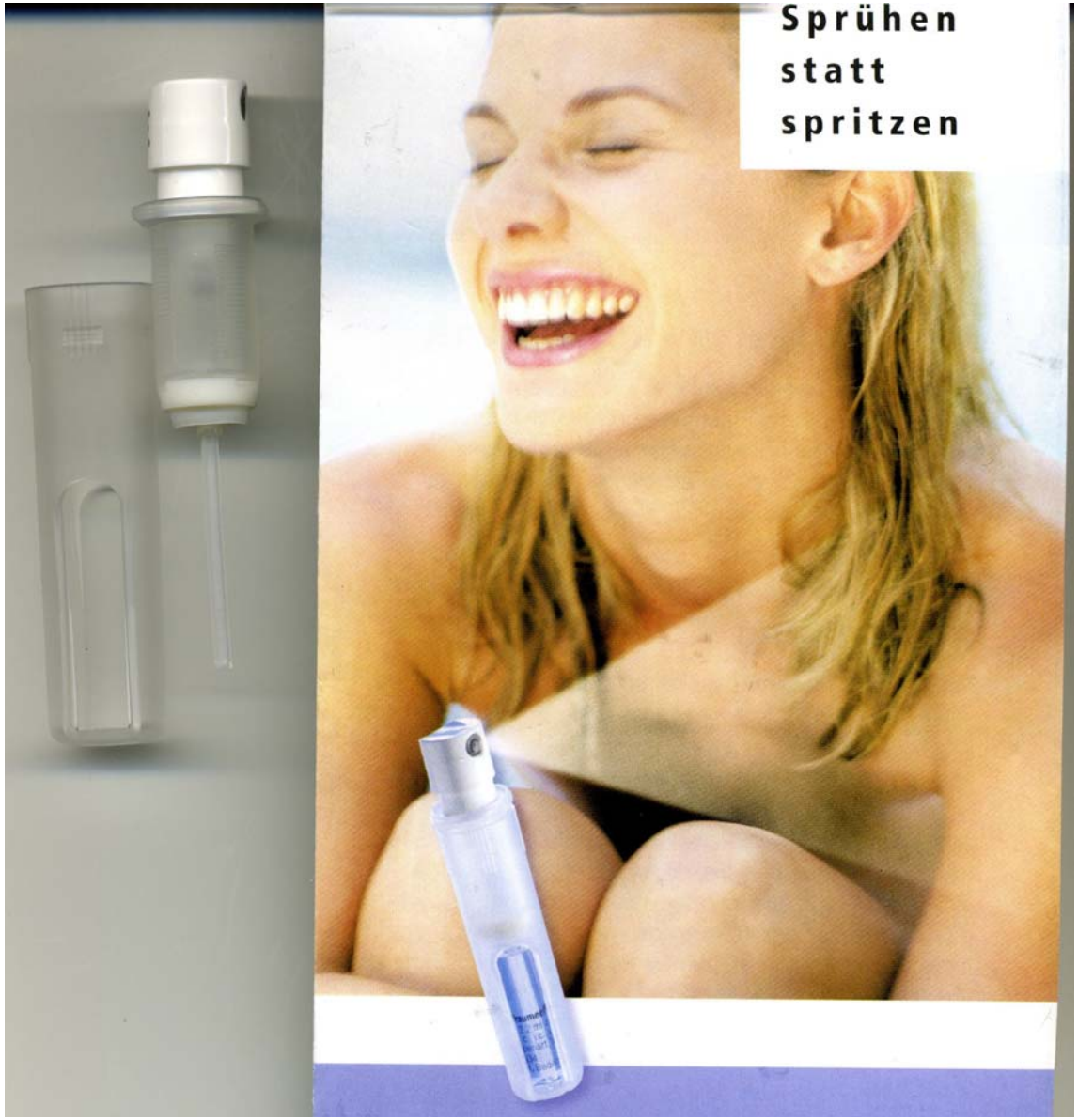
Monomer of Polyurethan

Aluminium

Ions in ampoules and glass containers
e.g. Frusemide ampoules 556 µg/L, Heparine ampules 809 µg/L

I. Wurdack, W. Kittlaus, A. Pecar, R. Bernard,
Krankenhauspharmazie 27: 334-339 (2006)

Alternative drug administration sites



„spraying instead injecting“

Stability?

Bioavailability?

Toxicity?

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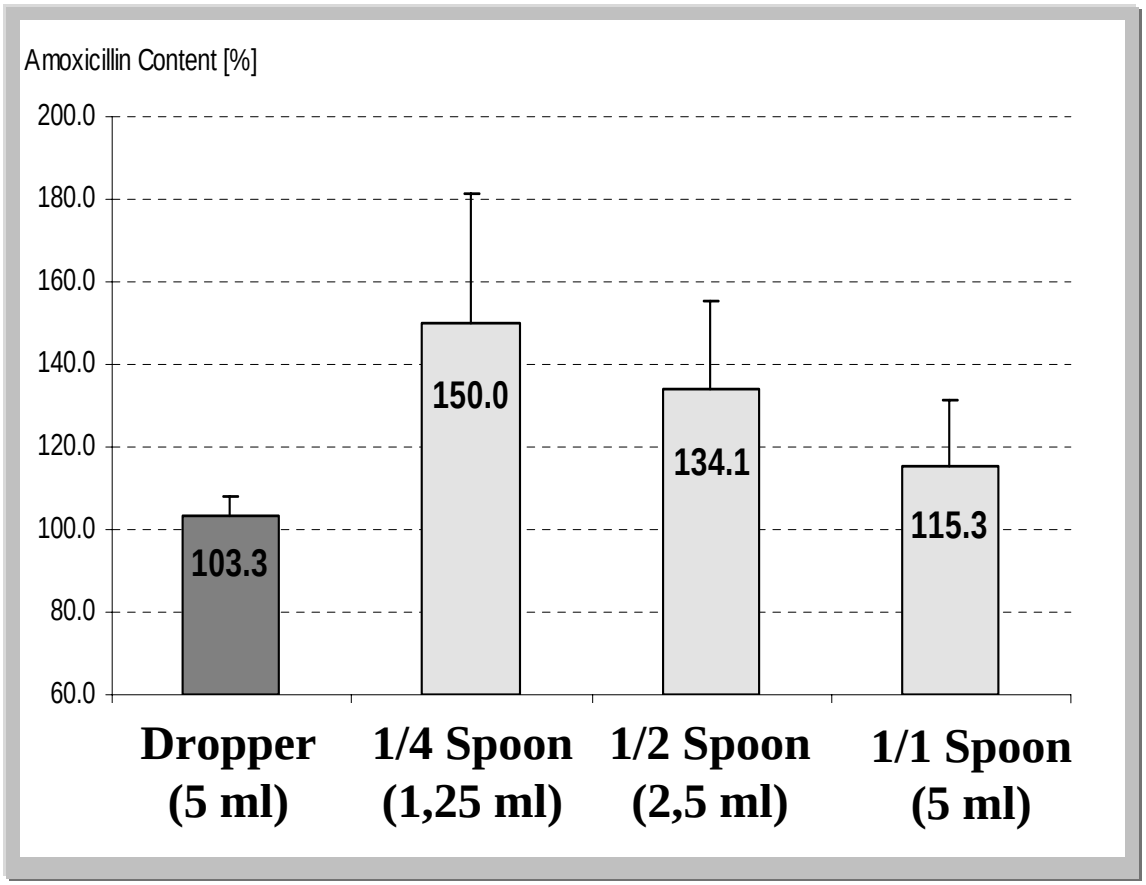
Braun/Heel, Germany

Oral liquids: Content uniformity using dosing spoons



K. Griessmann, J. Breitkreutz, P. Schoettler, M. Tawab, M. Schubert-Zsilavecz, [in German] Monatssschr. Kinderheilkd. 153: 735-740 (2005)

Oral liquids: Novel dosing instruments

Oral Syringe

Ibuprofen suspension,
De Bakker / Boots Healthcare

Pacifier

Nystatin suspension,
Bioglan

Dropper tube

Codeine drops,
Stella / Abbott

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Components of flavours

Strawberry 4-Hydroxy-2,5-dimethyl-3-furanone = Furaneol®

Raspberry 4-Hydroxyphenyl-2-butanone

Orange flavour in Zyvoxid suspension:

Acetone, maltodextrin, α-tocopherol-acetaldehyde, modified starch, anisaldehyde, monomethyl succinate, β-Caryophyllen, orange aldehydes, n-butyric acid, orange oil FLA CP, butylbutyryl lactate, orange oil Valencia 2X, decalactone-δ, orange oil 5X Valencia, dimethyl benzylcarbacetate, orange essence oil, ethylalcohol, orange fruit ketones, ethylbutyrate, orange terpens, ethylmaltol, peppermint oil, ethyl vanillin, propylenglycol, furaneol, tangerine oil, grapefruit terpens, vanille extract, heliotropin, water

W. Kircher (2003)

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Solid formulations (vs. liquid forms)

Advantages

- Nontoxic excipients
- Price
- Various opportunities for taste masking
- Modified release options
- Stability (storage & in-use & different climates)
- High content uniformity
- Easy administration

Disadvantages

- Dimensions: swallowing
- Requires liquid for swallowing
- Aspiration (safety)
- Difficult dose adaption
- Varying bioavailability

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Buccal / orodispersable drug formulations

1. Fast-dissolving drug formulations (FDDF)
2. Self-emulsifying drug delivery systems (SEDDS), Melting tablets
3. Mucoadhesive strips

1.

2.

3.

Rectal administration

Drug	peroral	suppository base	rel. BA [%]
Levodopa	Kapseln	Kakaobutter	0
Phenytoin	Suspension	Hartfett	0
Allopurinol	Tablette	Kakaobutter	6
Tamoxifen	Tablette	Hartfett	28
Phenoxymethylpenicillin	Tablette	Hartfett	33
Acetylsalicylsäure	Tablette	Kakaobutter	63
Paracetamol	Tablette	Kakaobutter	68
Piroxicam	Lösung	Hartfett	78
Theophyllin	Tablette	Hartfett	79
Naproxen	Tablette	Hartfett	97
Coffein	Tablette	Hartfett	107

Tabelle 3: Rektale Bioverfügbarkeit ($AUC_{rect}/AUC_{p.o.}$) von ausgewählten Arzneistoffen (modifiziert nach 6)

(6) W.S.A. Sakran, *Dissertation* (1994), Kairo/Münster

J. Breitkreutz, P. Kleinebudde, J. Boos, Pharm. Ztg. 147: 3210-3218 (2002)

Conclusions

Formulations appropiate for neonates:

Mainly parenteral administration, but:

- Correct drug preparation and administration are big issues
- Drug/drug and drug/excipient interactions may occur
- Adsorption/desorption from infusion devices
- Special formulations for neonates would be favourable, but cause additional costs

Oral formulations should be liquid

Alternative concepts and drug formulations are to be developed