THE ROLE
OF CLINICAL PHARMACOLOGY
IN HYPOTHERMIA

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XXVIII. Neonatologické dny 7. – 9.11. 2012, Aula VŠB TU Ostrava Poruba
80% OF DRUGS USED AT NICU/PICU ARE OFF-LABEL OR UNLICENSED USED DRUGS

I. EVIDENCE-BASED MEDICINE

II. INTERNATIONAL GUIDELINES

III. EMA - DRUG OF LISTS

THE ROLE OF CLINICAL PHARMACOLOGY I

PHARMACOKINETICS
PK

DRUG ABSORPTION

ELIMINATION*
CL

DISTRIBUTION
Vd

*EXCRETION METABOLISM

PHARMACODYNAMICS
PD

EFFECT vs DOSE

EFFECT vs CONCENTRATION

LOW THERAPEUTIC WINDOW

DRUG-DRUG INTERACTIONS

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THE ROLE OF CLINICAL PHARMACOLOGY II

PHARMACOKINETICS
PK

↑↓

PHARMACODYNAMICS
PD

↑↓

ANALGESICS

EFFECT vs DOSE

ANTICONVULSIVE AGENTS

EFFECT vs CONCENTRATION

AMGs

LOW THERAPEUTIC WINDOW

NEUROPROTECTIVE AGENTS

DRUG-DRUG INTERACTIONS
THE ROLE OF CLINICAL PHARMACOLOGY

PHARMACOKINETICS  PK
PHARMACODYNAMICS  PD
PHARMACOGENETICS  PG

DRUG DISPOSITION

DRUG-INDUCED TOXICODYNAMICS

DRUG-INDUCED ORGAN PROTECTION

XXVIII. Neonatologické dny 7. – 9.11. 2012, Aula VŠB TU Ostrava Poruba
AGE-DEPENDENT DEVELOPMENTAL CHANGES

PHARMACOKINETICS
PK

PHARMACODYNAMICS
PD

PHARMACOGENETICS
PG

DRUG DISPOSITION

NEONATES, YOUNG INFANTS

DISEASE-DEPENDENT PK/PD CHANGES

PHARMACOKINETICS
PK

PHARMACODYNAMICS
PD

PHARMACOGENETICS
PG

DRUG DISPOSITION

ASPHYXIA

TEMPERATURE-DEPENDENT PK/PD CHANGES

PHARMACOKINETICS
PK

PHARMACODYNAMICS
PD

PHARMACOGENETICS
PG

DRUG DISPOSITION

HYPOTHERMIA
DRUG-DEPENDENT PK/PD CHANGES

PHARMACOKINETICS
PK

PHARMACODYNAMICS
PD

PHARMACOGENETICS
PG

DRUG DISPOSITION

SPECIFIC DRUGS

XXVIII. Neonatologické dny 7. – 9.11. 2012, Aula VŠB TU Ostrava Poruba
THE INFLUENCE OF GROWTH and MATURATION ON PK/PD DRUG DISPOSITION FOR OPTIMAL DOSAGE

XXVIII. Neonatologické dny 7. – 9.11. 2012, Aula VŠB TU Ostrava Poruba
ASPYHIA - INDUCED CHANGES IN PK

John van den ANKER  Ped Research. 2005

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HYPOTHERMIA - INDUCED CHANGES IN PK

↓ DRUG ELIMINATION

↓↑ DRUG DISTRIBUTION

↑↑ RISK OF DRUG-INDUCED TOXICITY

BRAIN-PROTECTION: PHENOBARBITAL TRIALS
HYPOTHERMIA - INDUCED CHANGES IN PK

Roka A. Pediatrics 2008;121:4, 844-849

- CL-MOR ↓51%
- S-MOR HT vs NT
  18.1/12.1 ng. h⁻¹. mL⁻¹
  p=0.051

- Potential morphine toxicity
  Infusion rates >10 μg.kg per h

↑↑ DRUG/METABOLITES ACCUMULATION

SEPSIS - INDUCED CHANGES IN PK


↓↑ DRUG ELIMINATION, DISTRIBUTION

↑↑ RISK DRUG -INDUCED TOXICITY

? DRUG-INDUCED ORGAN PROTECTION

Fig.: The potential effects of asphyxia and hypothermia on drug disposition in term neonate at birth and during the first week of life

Pokorna et al.: in press
Fig: The PK differences in drug disposition (ADME) in adult, term neonate at the birth, and potential PK changes under hypothermia.

Pokorna et al: in press
# PHENOBARBITAL

Tab. Phenobarbital PK studies during hypothermia

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Investigated group</th>
<th>Vd</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalser et al/1968</td>
<td>Animals</td>
<td>not reported</td>
<td>↓</td>
</tr>
<tr>
<td>Kadar et al/1982</td>
<td>Children</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Shaible et al/1982</td>
<td>Children</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Filippi et al/2011</td>
<td>neonates</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Thoresen et al/2003</td>
<td>neonates</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
**PHENOBARBITAL**

Tab. The influence of hypothermia on a *phenobarbital* disposition

<table>
<thead>
<tr>
<th>PK changes in ↓Vd related to:</th>
<th>PK changes in ↓CL related to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓Target temperature</td>
<td>↓Target temperature</td>
</tr>
<tr>
<td>↓Body composition, blood volume</td>
<td>↓Metabolic capacity (CYP 2C19) NADPH</td>
</tr>
<tr>
<td>↓Drug’s physical and chemical properties (lipophilic drug)</td>
<td>↓Hepatic CL (low CL: <em>diazepam phenobarbital, phenytoin</em>)</td>
</tr>
<tr>
<td>↓Tissue binding capacity (large Vd drug)</td>
<td>↓Renal CL (low excretion drug <em>phenobarbital</em>, high excretion drug- <em>topiramate</em>)</td>
</tr>
<tr>
<td></td>
<td>↓Protein binding  low 20-45%</td>
</tr>
<tr>
<td></td>
<td>↓Drug interactions</td>
</tr>
</tbody>
</table>

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**Tab. Midazolam PK studies during hypothermia**

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Investigated group</th>
<th>Vd</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kern et al/1991</td>
<td>children on CPB</td>
<td>not studied</td>
<td>not studied</td>
</tr>
<tr>
<td>Fukuoka et al/2004</td>
<td>adults</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Hostler et al/2010</td>
<td>healthy volunteers-adults</td>
<td>NS</td>
<td>↓ (AUC ↑)*</td>
</tr>
<tr>
<td>Zhou et al /2011</td>
<td>animals</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Empey et al /2012</td>
<td>animals</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
## MIDAZOLAM

Tab. The influence of hypothermia on a *midazolam* disposition

<table>
<thead>
<tr>
<th>PK changes in ↓ Vd related to:</th>
<th>PK changes in ↓ CL related to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↓ Target temperature</td>
<td>• ↓ Target temperature</td>
</tr>
<tr>
<td>• ↓ Body composition (lipophilic drug)</td>
<td>• ↓ Metabolic capacity (CYP3A4,A5)</td>
</tr>
<tr>
<td>• ↓ Organ flow and blood volume</td>
<td>• ↓ Organ flow (low hepatic CL drug)</td>
</tr>
<tr>
<td>• ↓ Protein binding (97%)</td>
<td>• ↓ Renal excretion (active metabolites: 1 OH-</td>
</tr>
<tr>
<td></td>
<td>midazolam, 1-glucuronid)</td>
</tr>
<tr>
<td></td>
<td>• ↓ High protein protein binding drug (97%)</td>
</tr>
</tbody>
</table>
# Fentanyl

The summary of *fentanyl* PK studies during hypothermia (HT)

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Investigated group</th>
<th>Vd</th>
<th>CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koren et al /1987</td>
<td>animals</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Koren et al/ 1987</td>
<td>children</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Petros al/1995</td>
<td>adults on CPB</td>
<td>↑</td>
<td>NS</td>
</tr>
<tr>
<td>Statler et al/2003</td>
<td>animals</td>
<td>not reported</td>
<td>↓ *</td>
</tr>
<tr>
<td>Pettifer et al /2004</td>
<td>animals</td>
<td>not reported</td>
<td>NS</td>
</tr>
<tr>
<td>Fritz et al /2005</td>
<td>animals</td>
<td>not reported</td>
<td>↓ *</td>
</tr>
<tr>
<td>Empey et al/ 2012</td>
<td>animals</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
ANTICONVULSIVE AGENTS

**PHENOBARBITAL inj.**
20-30-40 mg.Kg$^{-1}$ i.v.

**PHENYTOIN inj.**
15-20 mg.Kg$^{-1}$ i.v.

**MIDAZOLAM inj.**
0.15-0.4 mg.Kg$^{-1}$ i.v.

S-PHENOBARBITAL  65 - 170  umol/L →  TOXICITY
S-PHENYTOIN    40 -  80  umol/L →  EFFICACY

Hall 1998, Donn 1985, Simbruner 2010

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Weight (kg)</th>
<th>PHE/EPA</th>
<th>Renal dysfunction (n)</th>
<th>CL (l/kg/h) in 10/12 neonates</th>
<th>Vd (l/kg) in 10/12 neonates</th>
<th>t1/2 (h^-1) in 10/12 neonates</th>
<th>TDM</th>
<th>Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.2±2.6</td>
<td>3.2±0.8</td>
<td>4/12</td>
<td>4/12</td>
<td>0.0046 (0.0026)</td>
<td>0.52 (0.18)</td>
<td>87.9 (32.6)</td>
<td>12/12</td>
<td>12/12</td>
</tr>
</tbody>
</table>
ANTICONVULSIVE AGENTS - PK/PD

Iida at al: Ther Drug Monit. 2001
• ke-phenytoin ↓50%  
• CL-phenytoin ↓67% adults

Filippi at al: Epilepsia 2011
• t1/2-phenobarbital: 36.8 +/- 9.4 to 86.2 +/- 10.5 h adults  
173.9/ +/- 62.5 h neonates

Filippi at al: Epilepsia 2009, 2010
• Topiramate concentrations within the therapeutic range  
(n=9/13) neonates

↓ METABOLISM

↓ ELIMINATION

ADDITIVE NEUROPROTECTION?

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PPV 3-6 h: NT 84 %
PPV 3-6 h: HT 59 %  p=0.05

TTMT: NT 1,12 (95% CI:1,016 1,234)  
p=0.023
TTNT-HT 1,38 (95% CI:1,12 1,68)  
PPV 24-48 h-NT 96,2%
PPV 24-48 h-HT 90,6% p=0.002
Fig. 1a. Fluctuation of Ge plasma concentrations (simulation)

- **Black line**: Simulation of Cpl based on an initial dosage regimen (individual demographic data) and that using individual pharmacokinetic parameters.
- **Green line**: Cpl determined after the 1st dose of Ge and C_{preh}/C_{cyst,inh} predicted and measured.
TDM: POPULATION PK/PD - NONMEM

Knibbe C. AJ., Danhof M. Int J. Pharm. 2011
### PAIN ASSESSMENT INSTRUMENTS

<table>
<thead>
<tr>
<th>Facial</th>
<th>Cry/</th>
<th>Body</th>
<th>Posture/</th>
<th>Sleep/</th>
<th>Consolabili</th>
<th>Physiol. items</th>
<th>Other</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAT</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>Respiration,</td>
<td>3 (Premature neonates = 27 wks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR, O₂ sat, BP, colour</td>
<td></td>
</tr>
<tr>
<td>PIPP</td>
<td>333</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>HR and O₂ sat</td>
<td>3 (Premature neonates = 28 wks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Premature neonates = 32 wks)</td>
</tr>
<tr>
<td>CRIES</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>HR and BP, Requires O₂</td>
<td></td>
</tr>
<tr>
<td>EDIN</td>
<td>3</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>3</td>
<td>3</td>
<td></td>
<td>3 Premature neonates = 26 - 36 wks</td>
</tr>
<tr>
<td>LIDS</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>3 Neonates</td>
</tr>
<tr>
<td>POPS</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>33</td>
<td>-</td>
<td>3</td>
<td></td>
<td>3 0 to 3 yr.</td>
</tr>
<tr>
<td>RIPS</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td></td>
<td>3 0 to 3 yr.</td>
</tr>
<tr>
<td>NAPI</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td>3 0 to 3 yr.</td>
</tr>
<tr>
<td>COMFORT</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>a) Respiratory response</td>
<td>3 0 to 3 yr.</td>
</tr>
</tbody>
</table>
POSTOPERATIVE PAIN

Algorithm for postoperative management

 Improvement

Vas ≥ 4
Comf ≤ 17
Φ investigate causes

Bolus morphine every 10 min,
max. 3 times per hour
< 3 months old  10 µg/kg
≥ 3 months old  15 µg/kg

Vas ≥ 4
Comf ≤ 17

No improvement
in scores
consultation with ICU-physician

Vas < 4
Comf ≤ 17
Φ investigate causes

Midazolam 0.05-0.1 mg/kg bolus c.q. infusion (after consultation IC physician)

Vas < 4
Comf ≤ 17
No direct action

Φ investigate causes and when possible improve positioning,
give pacifier, diminish noise, decrease light etc.

Pain assessment
During routine care or when patient seems uncomfortable

Improvement

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CONCLUSIONS

PHARMACOKINETICS
PK

PHARMACODYNAMICS
PD

PHARMACOGENETICS
PG

DRUG DISPOSITION

THE ROLE OF
PK/PD
TO INDIVIDUALIZE

THE ROLE OF
PK/PD
TO OPTIMIZE

Dick Tibboel,
Erasmus MC- Sophia Children’s Hospital, Rotterdam

Karel Allegaert,
Universitaire Ziekenhuizen Leuven

John N. Van Den Anker, Children's National Medical Center, George Washington University, School of Medicine and Health Sciences