Caffeine Citrate Dosing Adjustment to Maintain Target Caffeine Concentration in Preterm Neonates

Dr. Gilbert Koch, PhD

Pediatric Pharmacology and Pharmacometrics,
Children's University Hospital Basel, Switzerland

in collaboration with

Department of Neonatology
Children's University Hospital Basel, Switzerland

Background - Caffeine

Since the 1970s caffeine is used to treat **apnea of prematurity** (stop of breathing for at least 20 seconds) in **preterm neonates**

Nowadays virtually all preterm neonates are treated with caffeine; start of caffeine treatment immediately after birth; median caffeine treatment length is 6-7 weeks

Caffeine *is likely the most used drug worldwide in preterm neonates*

Background – Caffeine Clearance

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Caffeine clearance **dramatically increases** in preterm neonates due to **maturation** of liver metabolism

Change of caffeine half-life:

- **First days of life:** approx. **120 - 150 hours**
- Postnatal age of **3 - 4 weeks:** approx. **60 - 80 hours**
- Postnatal age of **6+ months:** approx. **3 - 7 hours** (similar to half-life observed in adults)

Background – Current Dosing Strategies

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Current dosing recommendation of caffeine citrate (not changed over the last 40 years)**:**

Loading dose of 20 mg/kg

Maintenance dose of 5 mg/kg/day

[Aranda 1979], [Schmidt 2006]

This dosing regimen does not take the dramatic increase in clearance during the first weeks of life into account!

Therapeutic target concentrations (changed over the last 40 years):

5 to 15 mg/L => **15 to 20 mg/L**

(1980s) (2010s)

[LeGuennec 1985], [Kahn 2016]

Safety profile: Peak concentrations above 30-35 mg/L can be associated with adverse events (e.g. CNS related safety signals)

Key Questions in Clinical Practice

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1) What is the **impact of increasing caffeine clearance** on caffeine concentrations with a **fixed maintenance dose** of 5 mg/kg/d?

2) What **adjustments** in maintenance doses are **necessary** to assure a **stable caffeine** trough concentration **above 15 mg/L** during the first 8 weeks of life?

3) What peak concentrations are obtained with **higher loading doses**?

=> We provide **quantitative** answers with **simulations** from **pharmacokinetic models**

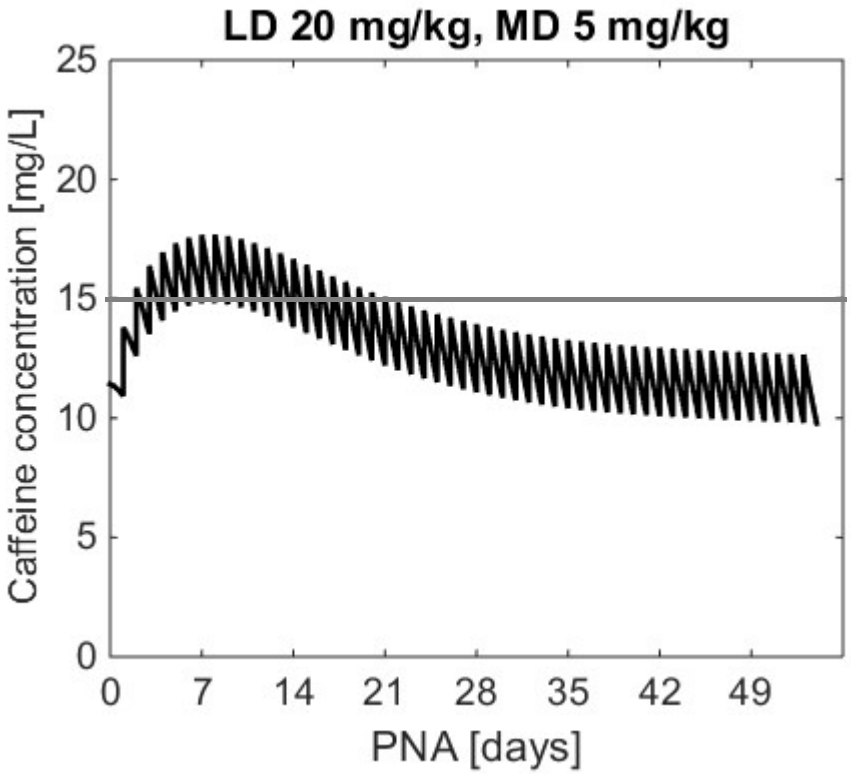
Methodology for Simulations

- Investigate the **typical** / average male preterm neonate with a **gestational age of 28 weeks** and a **birth weight of 1150 gr**

- Develop a pharmacokinetic model (based on available models from population preterm studies published in literature) that take **effects of gestational age, weight and post-natal age on clearance and volume of distribution** into account

- **Perform simulations** for different dosing strategies to answer the previous questions

What is the impact of increasing caffeine clearance on caffeine concentrations with fixed maintenance doses of 5 mg/kg/d?

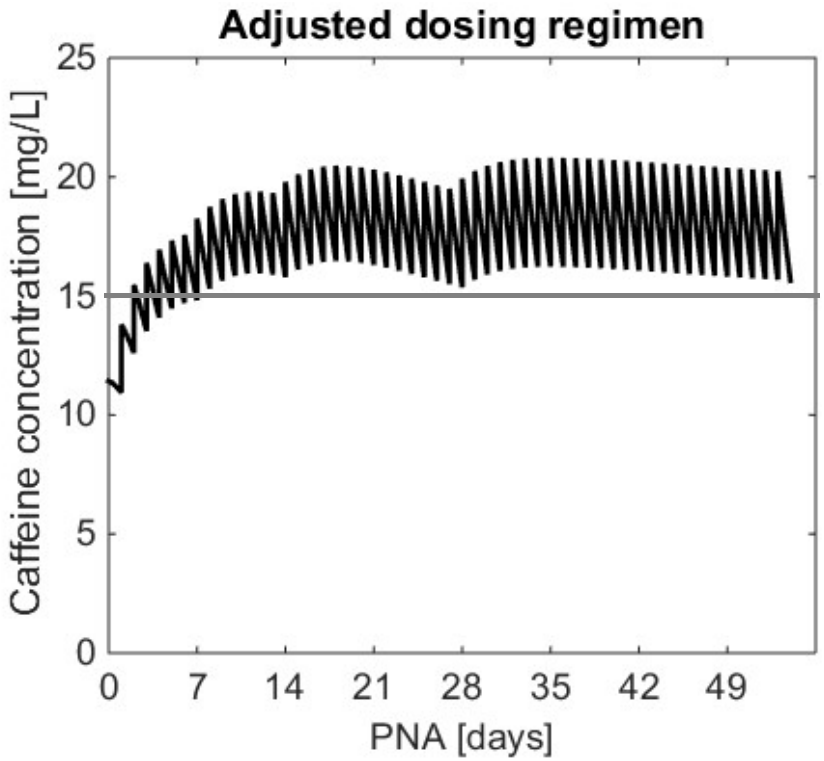


Maximal trough of 15 mg/L after one week

Trough of 10 mg/L after six weeks

Decrease of up to 35% of caffeine concentration after 8 weeks

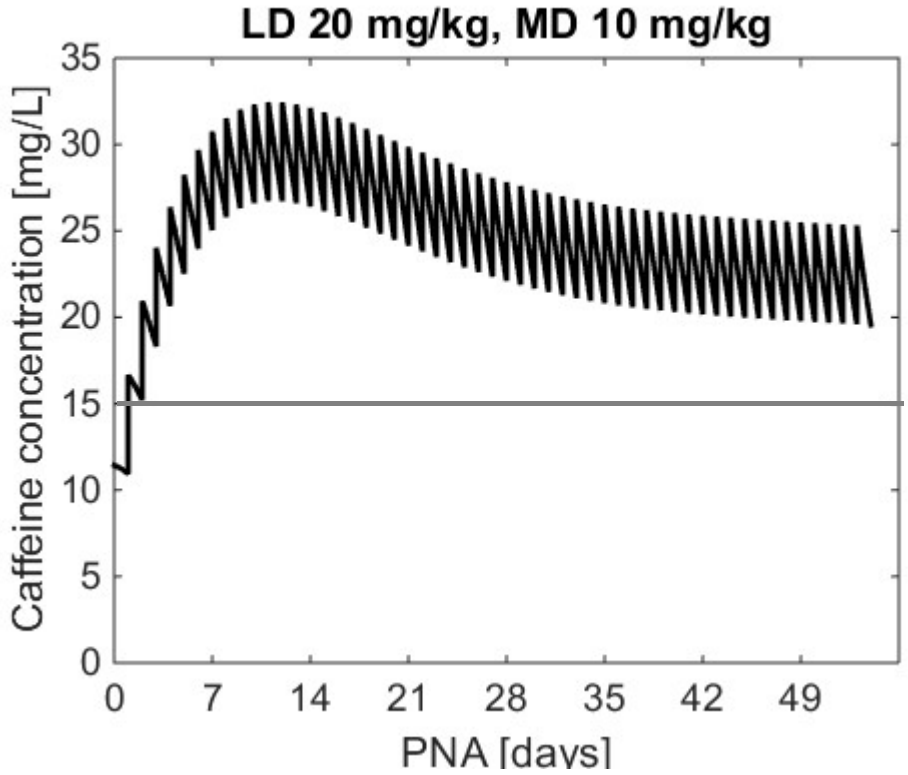
What adjustments in maintenance doses are necessary to assure a stable caffeine trough concentration during the first 8 weeks of life?



Exact dosing scheme: 6 mg/kg/d in the 2nd week,
7 mg/kg/d in the 3rd to 4th week
8 mg/kg/d in the 5th to 8th week

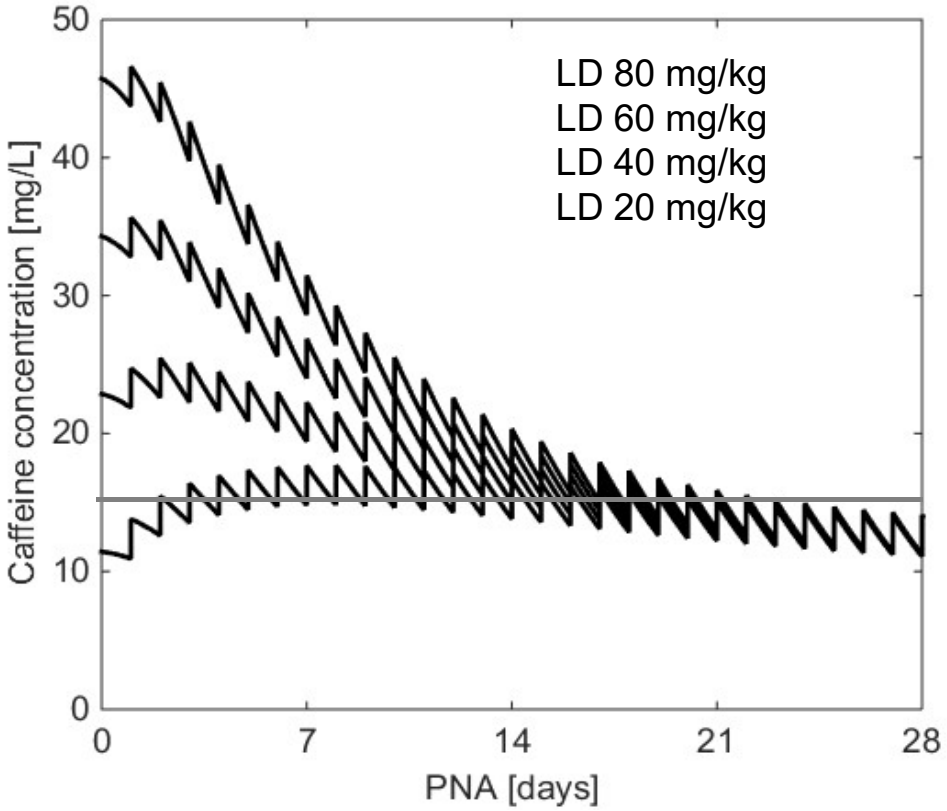
Roughly: Increase MD by 1 mg/kg/d every 1-2 weeks

What adjustments in maintenance doses are necessary to assure a stable caffeine trough concentration during the first 8 weeks of life?



Maintenance dose: **10 mg/kg/d**

What peak levels are obtained with higher loading doses?



- **Unsafe concentrations** for LD > 40 mg/kg in the first week
- Because of MD 5 mg/kg/d, concentration **drops below lower therapeutic target** (<15 mg/L) after 3 weeks

Conclusions

- Current standard dosing is not sufficient to account for rapid clearance maturation
- **Simple maintenance dose adjustments** produce constant caffeine exposure in the **therapeutic range**:
  - Simple stepwise **increase of MD of 1 mg/kg every 1-2 weeks**
    => Stable caffeine concentration above 15 mg/L
  - Direct application of MD of 10 mg/kg/d
    => Caffeine concentration in the expected safe range
- Higher loading dose (> 40 mg/kg) is associated with
  - unsafe caffeine levels (> 30-35 mg/L) in the first week
  - caffeine concentrations below therapeutic target (< 15 mg/L) afterwards

Acknowledgments and Questions

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