Neonatal Excipients: a Clinical View

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Liverpool Women's

Declaration of interests

- My employers have received funds for clinical studies about APIs from: Roche, Chiesi, Johnson & Johnson, Pfizer, EC FP7, NIHR, BLISS, MRC, AMR
- I am part of the NEOCIRC consortium which has product under consideration by the EMA Formulations Working Group
- My employers receive funds for consultancy about APIs from Chiesi, BMS, Novartis, Shire, Janssen, Grunenthal
- I led ESNEE (funded by MRC)
- Chair, European Network for Paediatric Research at the European Medicines Agency
- Co-Director, International Neonatal Consortium

Topics

- The clinical context
- The therapeutic context
- The clinical frustration
- Clinical contributions to the solution

The clinical context

- Sick preterm neonates
  - Inotropes for poor brain perfusion
- "Healthy" preterm neonates
  - Vitamins
- Sick term babies
  - Anticonvulsants

Sick preterm neonates

Inotropes for poor brain perfusion

- Clinical problem
  - During the 72 hours after birth before 27 weeks gestational age
  - Poor cardiac contractility
  - Haemodynamically significant ductus arteriosus
  - Rapid changes in pulmonary vascular resistance
- Associated with
  - Mortality: 30% – 50%
  - Brain injury

Neurodisability
60% – 80% of survivors

Movement
Speech
Learning disability

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What if medicines need excipients?
How does the risk of excipient compare to the risk of the condition?

“Healthy” preterm neonates

Vitamins

- Clinical problem
  - It is very difficult to match in utero accretion of micronutrients
- Associated with
  - Poor long-term outcomes
  - Numerical estimates of numbers are difficult

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Sick term babies

Anticonvulsants

- Clinical problem
  - Seizures are common among babies with hypoxic-ischaemic encephalopathy / perinatal asphyxia
  - Also seen in other conditions: infection, metabolic, abnormal anatomy
  - Different epileptogenic mechanisms than other age groups
- Associated with
  - Treatment dilemmas
  - Poor outcomes
    - Seizures
    - Causes of seizures

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- Which drug to use
- Which dose to give
- When to give it
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…. And hope that the multiple dilutions do not lead to medication errors

Clinical Frustration

- Innovative products are not available
- Existing products are not risk assessed
- Excipient safety
  - Yes or No is not always a helpful answer
  - We need some idea about exposure / response
  - We need advice about secondary prevention
- Why do excipients need a special frame of reference?
  - When do we give excipients by themselves?

Prospective assessment of short-term propylene glycol tolerance in neonates

Karel Allegaert,[1] Sophie Vanhaesebrouck,[1] Aida Kulo,[2,3] Katrien Cosaert,[4] Rene Verbesselt,[2] Anne Debeer,[1] Jan de Hoon[2]

Arch Dis Child 2010;**95**:1054–1058.

What is already know on this topic

- Neonates are exposed to various excipients including propylene glycol (PG) to facilitate formulation of drugs.
- PG accumulation can result in hyperosmolarity, renal toxicity and lactic acidosis. These side effects have not only been reported in adults but also in neonates following extensive PG exposure (up to 3000 mg/kg/day).

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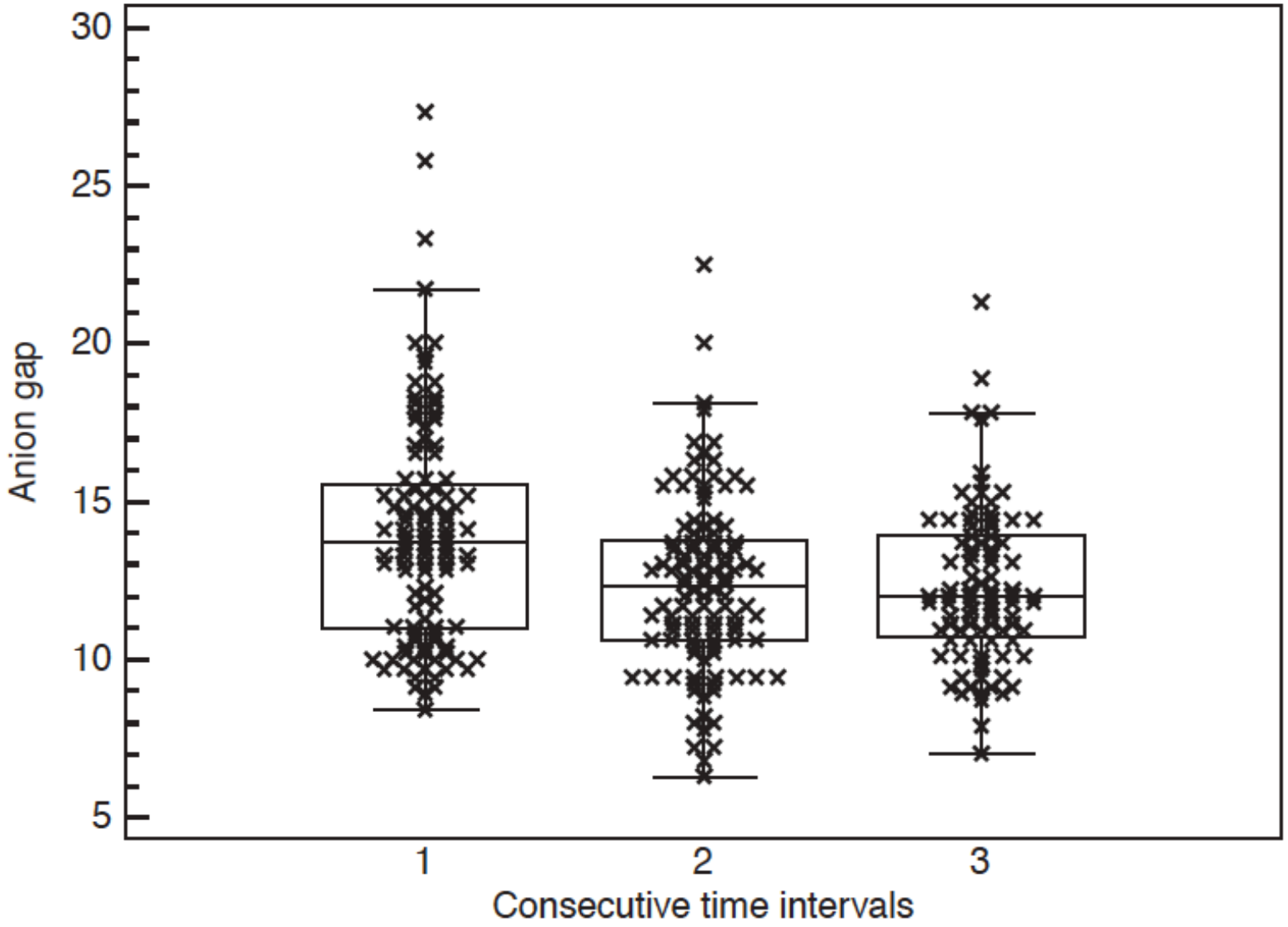


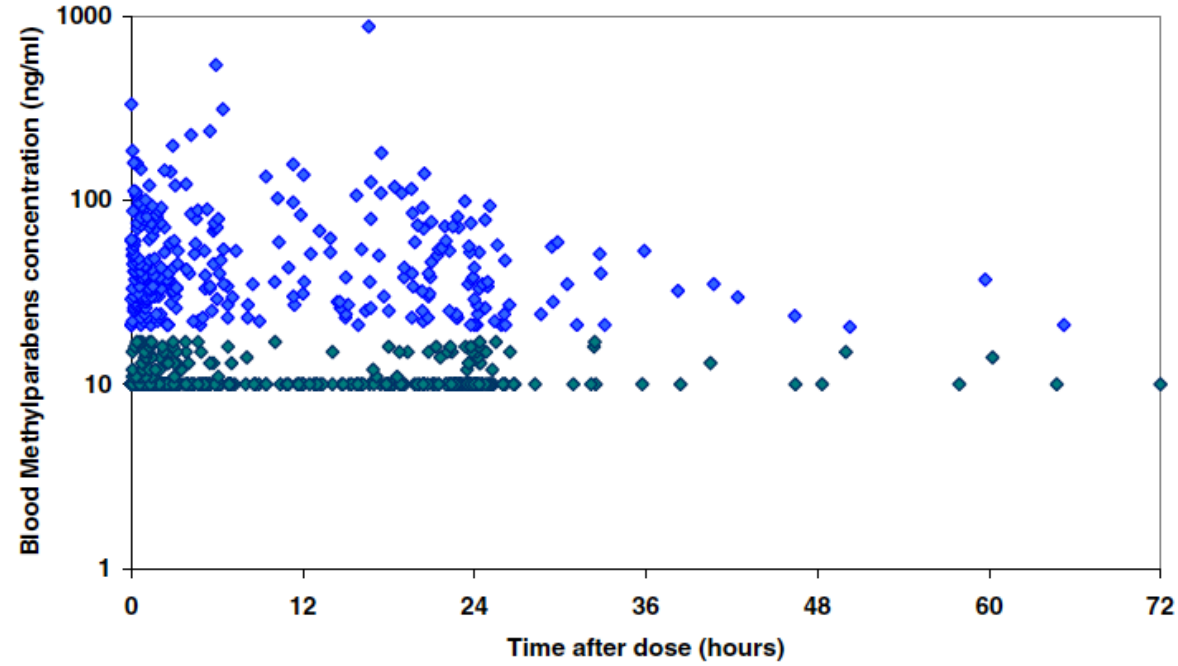
Figure 4 Anion gap recorded before (1, –48 h until exposure), during (2) and following (3, until 48 h after exposure) PG exposure in 69 neonates.

Pharm Res
DOI 10.1007/s11095-014-1520-2

RESEARCH PAPER

An Observational Study of Blood Concentrations and Kinetics of Methyl- and Propyl-Parabens in Neonates

H. Mulla • S. Yakkundi • J. McElnay • I. Lutsar • T. Metsvaht • H. Varendi • G. Nellis • A. Nunn • J. Duncan • H. Pandya • M. Turner


Blood Methylparabens concentration (ng/ml)
1000
100
10
1
0
12
24
36
48
60
72
Time after dose (hours)

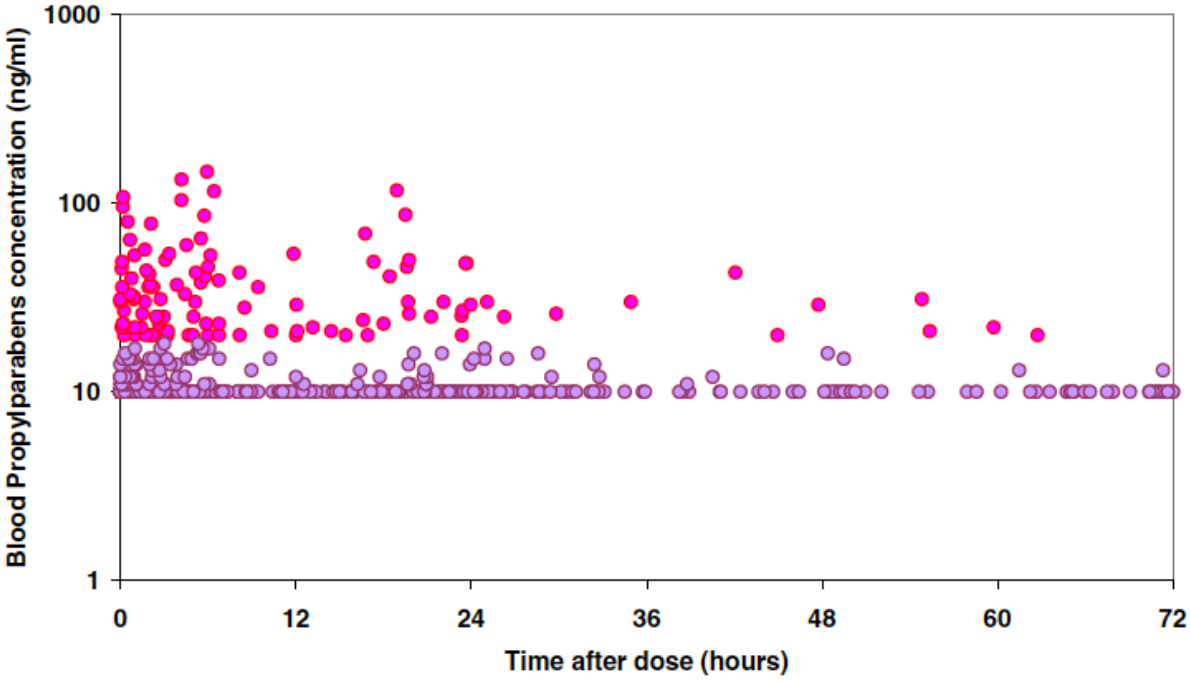

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Table IV Population Excipient Kinetic Model Estimates for Methylparabens

Parameter	Estimate	95% CI	BSV (CV%)	95% CI
$CL_{PNA<21}$ (L/h)	0.570	0.490, 0.650	43.5	39.2, 47.3
$CL_{PNA>21}$ (L/h)	0.880	0.715, 1.05	30.3	18.0, 38.9
V2 (L/1.6 kg)	1.84	1.57, 2.11	30.9	20.6, 38.5
Q (L/h)	12.2	4.63, 19.8	NE	
V3 (L)	35.4	27.1, 43.7	NE	
Ka (h^{-1})	0.10 fix		NE	
Infusion duration	0.25 fix			
F	0.0777	0.0277, 0.128	25.1	4.6, 35.2
F*	0.445	0.342, 0.548	70.2	28.5, 95.1
Additive residual error	0.44	0.38, 0.50		

Parameters are estimates with 95% confidence intervals (95% CI) from 500 bootstrap datasets. CV%: percentage coefficient of variation; *NE* not estimated

CLPNA <21, CLPNA >21 are total blood clearance in neonates of post natal age less than and greater than 21 days, respectively; Q is the intercompatmental distribution clearance between central and peripheral compartments; V2 and V3 are apparent volumes of distribution of the central and peripheral compartments, respectively; Ka, is the oral absorption rate constant; Infusion duration is the infusion period for intravenous gentamicin administration; F, is the oral bioavailability for nystatin and sodium iron feredetate; F*, is the oral bioavailability of all other oral medicines administered. Estimates of between subject variability (BSV) are shown as CV%. Additive residual error is expressed on the natural logarithmic scale

Risk

Who tolerates the risk?

- Regulators
- Clinicians
- Families
  - Parents
  - Children
- Society

Proposal for a risk-based framework for safety assessment

- Step 1: Define constraints
- Step 2: Define goal(s) of safety assessment
- Step 3: Synthesize existing knowledge
- Step 4: Identify knowledge gaps
- Step 5: Make a judicious plan to fill key knowledge gaps
- Step 6: Conduct studies
- Step 7: Synthesize new body of knowledge
- Step 8: Interpret

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Borrow from extrapolation

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- Identify role of biological / clinical constraints
  - Risks of background illness
  - Prevention / treatment
- Identify role of values

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Define Constraints

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PLOS ONE

Enhancing Communication about Paediatric Medicines: Lessons from a Qualitative Study of Parents' Experiences of Their Child's Suspected Adverse Drug Reaction

Janine Arnott[1], Hannah Hesselgreaves[1], Anthony J. Nunn[2], Matthew Peak[2], Munir Pirmohamed[3], Rosalind L. Smyth[3], Mark A. Turner[4☯], Bridget Young[1*☯]

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Talk to children, young people and families

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Define Constraints

- Identify role of biological / clinical constraints
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- Identify role of values

Beware of parentalism

k to children,
ng people and
families

Conclusions

- How often will the drug be worse than the disease?
  - We accept collateral damage from the active ingredient
  - Why not accept excipient harms?
- Clinicians can tolerate risk
- Families may, or may not, tolerate risk
  - Ask them