Precision Therapeutics in the NICU:
How to rethink the “dose – exposure – response” paradigm

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Clinician’s Dilemma

- Clinical Response
  - Close the Patent Ductus Arteriosus
  - Wean the ventilator
  - Control Pain

- Drug Exposure
  - Concentrations for Efficacy
  - Concentrations for Toxicity Risk
  - “Therapeutic Window”

- Drug Dose
  - Size related?
  - Age related?
  - Clinical scenario related? (i.e. HIE)

Neonatal pharmacology studies are population based, but prescribing “on average” leads to extreme variability in drug exposures, even with standard weight-based dosing.

Precision Therapeutics?
Outline

Cases examples of the need for Precision Therapeutics in Neonatology
- NSAIDs
- Steroids for BPD

Neonatal Pharmacogenetics
- Opiates / Tramadol

Model-driven Individualized Dosing
- Vancomycin
- Ganciclovir

Novel Drug Formulations to make Neonatal Precision Therapeutics feasible

Case: NSAIDs for PDA closure

PDA treatment outcomes are unpredictable

Effective
Minimal Side Effects

Effective
Acute Kidney Injury

Not Effective
Minimal Side Effects

Not Effective
Intestinal Perforation

No further Treatment
Renal function recovers
Heart Surgery
Bowel surgery (and heart surgery later)
Case: NSAIDs for PDA closure

Mitra et al, JAMA, 2018
Smyth et al, British J Clin Pharm, 2004

14-fold variation

Individualized Patient Approach

• CYP450 polymorphisms
• Genetic factors
• Environmental factors

DOSE → PK → EXPOSURE → PD → RESPONSE

CLINICAL RESPONSE

Lewis, J Perinatology, 2018
Genotype to Phenotype

Clinical Trait = phenotype

Wild type protein

Variant protein

Genetic Variation in Drug Metabolism

Major Drug Metabolizing P450s

CYP2D6

Zanger & Schwab, Pharmacology and Therapeutics, 2013
Indomethacin Metabolism – Preterm Neonates

Pilot data:
- 16 preterm infants
- 23-29 weeks GA
- urine collected for 10 days

Figure 1: Three distinct patterns of indomethacin urine recovery among preterm infants (P<0.001).

- **Group 1**: primarily IND-glucuronide
- **Group 2**: mix of metabolites
- **Group 3**: primarily O-desmethylindomethacin

Indomethacin → O-Desmethylindomethacin (ODM)

Indomethacin-glucuronide (INDGluc)

CYP2C9

UGT2B7 / 1A9
Individual Patients - Indomethacin

Indomethacin

- Indomethacin-glucuronide (INDGluc, IND-G)
- O-Desmethylindomethacin (ODM)

CYP2C9

UGT2B7 / 1A9

Case: Steroids for BPD

Neonatal Placebo-controlled RCTs

Inhaled Therapies for BPD

Desselas, PLOS One, 2017
Clouse, PLOS One, 2016
Systemic Steroids for BPD

Change in Respiratory Severity Score (RSS)
RSS = Mean Airway Pressure x FiO2
Treatment Day 0 – Treatment Day 7
(negative number = respiratory improvement)

Black = dexamethasone
Grey = hydrocortisone

Are there markers which can distinguish a responder from a non-responder before treatment or early in the treatment course?

Systemic Steroids

Clinical efficacy of systemic steroids to improve lung disease in emerging BPD is highly variable and unpredictable.

Hypothesis: Single Nucleotide Polymorphisms (SNPs) in known steroid metabolism and response genes are associated with short-term phenotypic response to systemic steroids in preterm infants with evolving BPD

Genes and SNPs from steroid pharmacogenetic literature (12 candidate genes)
Cohort of infants from TOLSURF study with genetic and phenotypic data (N=77)
Regression tests for associations between genetic variations and steroid response
PharmacoGenomics – CRHR1 SNP rs7225082

Change in Respiratory Severity Score. Each line represents the change in RSS between the day before treatment and 7 days of treatment. (a) African American (b) Non-Hispanic White (c) Frequency of alleles in continental populations from the 1000 Genomes Project.

Rs7225082 was also significantly associated with % change at Day 7 (meta p-value=1.8x10^{-4})

T allele at rs7225082 was associated with a smaller absolute change in RSS at day 7, i.e. lower response to systemic corticosteroids (AA: average decrease in absolute change in RSS=1.2, p=0.017; NHW: average decrease in absolute change in RSS=1.74, p=0.016; meta p-value=2.8x10^{-4})

Lewis et al, Pediatric Research, 2019

PharmacoGenomics

CRHR1 is implicated in endogenous steroid homeostasis and modulation of inflammation.

There is biologic plausibility that genetic variation at this locus could contribute to variability in exogenous steroid response.
Progress in Neonatal Precision Therapeutics

Pharmacogenomics

Model-driven dose individualization

Novel drug formulations

Pharmacogenomics
Why pharmacogenetics?  
Risk of Opiates

Cumulative Morphine Exposure and Cerebellar Growth\(^1\)

- 136 preterm (24-32 weeks) infants, serial MRI and 18 month developmental testing
- Cumulative morphine dose was significantly associated with cerebellar volume after adjusting for multiple clinical confounders
- Greater morphine exposure also predicted poorer motor (P < .001) and cognitive outcomes (P = .006) at 18 months CA, an association mediated, in part, by slower brain growth overall.

1 Zwicker et al, J Peds, 2016

OCT1 and Morphine
OCT 1 and Morphine Clearance

Morphine clearance INCREASES with age

Morphine clearance INCREASES with functional OCT1

Hahn et al., Clinical Pharmacology and Therapeutics, 2018

Neonatal Tramadol Pharmacogenetics

Allegaert et al., Pediatric Research, 2008
Allegaert et al., J Pharmacogenomics and Pharmacoproteomics, 2012
Dose Individualization

Model-driven Dose Individualization: NeoVanco

Preliminary Results: NeoVanco Model-Based Precision Dosing

- Improved Achievement of Target Exposures

Proportion of Neonates with Trough < 5 mg/L

Frymoyer, J. Pediatric Infect Dis Soc, 2017
Goswami S, Frymoyer A. ASCPT Abstract, 2018
Model-driven Dose Individualization: Ganciclovir for Congenital CMV

Need for Novel Drug Formulations
Manipulation of Dosage Forms

Number of respondents

Clinical specialties of questionnaire respondents

Initiatives to Improve Dosing

Standardize Safety

Standardize 4 Safety Initiative

Standardize 4 Safety is the first national, interprofessional effort to standardize medication concentrations in order to reduce errors and improve transitions of care.
Mini-tablets

- Prospective cross-over study
- 151 neonates (inpatients; aged 2-28 days; median 4 days)
- Acceptability and swallowability of 2 mm uncoated mini-tablets compared with 0.5 mL syrup
- For some active pharmaceutical ingredients 1 mini-tablet with 2-3 mg of active ingredient may suffice (ie, enalapril)

3-D Drug Printing

Figure 3. Examples of the Needs for Personalized Dosing. There is a need, for example, for age-appropriate formulations for pediatric and older patients. In addition, differences in gender, lifestyle, metabolic capacity, and ethnicity have a role in how individual metabolizes drugs, and many diseases can compromise the metabolic activity of patients.

Figure 4. Personalizing Dosage Forms by Means of Printing Technologies in Hospital Pharmacies or at the Point of Medication (PoM).

Klingmann et al; J Peds; 2015

Sandler et al; Trends in Pharmacological Sciences; 2016
3-D Drug printing

- March 2016, first 3-D printed formulation of levetiracetam
- Potential for custom doses
- Disintegrates immediately with sip of fluid

Conclusion

- Population-based drug dosing in neonates leads to a highly variable drug exposures and clinical response
- Precision therapeutics requires careful research into the variables that make each child unique (ontogeny, genetics,…)
- Novel tools (pharmacogenetics, model-based dosing, precise drug formulations) will allow neonates to benefit from therapeutic advances