TINY PATIENTS, ENORMOUS VARIABILITY:

DRUG DISPOSITION AND INFANT ALL

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INFANT ALL ≠ ALL IN CHILDREN

• Different biology
• Different prognosis
• Different drug regimens
• Different stages of physiologic development
• Different pharmacokinetics
INFANT ALL

• By definition, diagnosis prior to 1 year of age
• Drug therapy is the primary treatment modality for this disease
• Period from birth to 1 year of age a period of rapid physiologic change
• Physiologic development can greatly affect the pharmacokinetics and pharmacodynamics of drug therapy
CURRENT METHODS FOR DRUG DOSING

*Do not take into consideration developmental pharmacology or drug disposition*

i. AGE-BASED CATEGORIES

ii. NORMALIZATION OF DOSE TO BODY WEIGHT (KG)

iii. USE OF BODY SURFACE AREA (BSA)
PHARMACOKINETIC CONSIDERATIONS IN INFANTS

- Absorption
  - Administration
- Distribution
- Metabolism
- Excretion
ABSORPTION

- Gastric pH
- Gastric emptying
- Intestinal surface area
- First pass metabolism
- Dosage form or method used to administer oral agents
  - Lack of “infant” doses, lack of oral suspensions, discontinuous dosing
DISTRIBUTION

• Extracellular and total body water
  • Hydrophillic vs. Lipophilic agents

• Circulating plasma proteins
  • Nutrition/albumin

• Expression of transporters
METABOLISM

• Enzyme expression varies after birth
• Clearance of drug or hepatic handling is a function of which enzymes metabolize and a balance of their activity
• Development of phase I enzymes
• Development of phase II enzymes
  • DRUG INTERACTIONS
  • DRUG TOXICITY
EXCRETION

- Maturation of glomelular filtration at ~ 2 years
- Tubular secretion maturation ~ 1 year
- Renal reabsorption matures ~ 3 years
  - Disease involvement
  - Drug toxicity
EXAMPLE OF THE COMPLEXITY OF DRUG DISPOSITION

- Pharmcokinetics of daunorubicin within Interfant 99 protocol
- Effects of age, BSA or weight on the clearance of drug
- Plasma samples taken for analysis of daunorubicin and daunorubicinol levels
- 21 infant ALL patients who received 30 mg/m² daunorubicin
  - Dose reductions to: ³⁄₄ (22.5 mg/m²) for ages 6-12 months; ²⁄₃ (20 mg/m²) for < 6 months

Hempel et al
CLEARANCE AND VOLUME OF DAUNORUBICIN VS PATIENT AGE

Pediatric Blood & Cancer
Volume 54, Issue 3, pages 355-360, 3 SEP 2009
DOI: 10.1002/pbc.22266
http://onlinelibrary.wiley.com/doi/10.1002/pbc.22266/full#fig4
AUC (EXPOSURE) VERSUS PATIENT AGE
RESULTS AND CONCLUSIONS

• Significant variability in daunorubicin clearance
• No age dependency in pharmacokinetic parameters
• No major differences in formation of the metabolite between infants and older children
• No pharmacokinetic reason for dose reduction of daunorubicin in infants
CONVERSELY: VINCRISTINE

- Early reports of infants with leukemia being more susceptible to severe neurotoxicity
- Use of standard dose vincristine in patients < 0.5 m$^2$ led to neurotoxicity
- Limited kinetic studies indicate that utilizing a 50% dose reduction in infants approximates the levels seen using “standard” doses in older children
IDEALLY …

- Drug dose would reflect drug exposure
- Therapeutic drug monitoring (TDM) could be quickly and easily performed
- Optimal drug exposure would be established
- Toxic drug levels defined
- Clear relationship between drug exposure (kinetics) and drug effect (dynamics)
CONCLUSION

• Infant ALL occurs during a period of rapid physiologic change
• Drug disposition is affected by physiology on a variety of levels
• Enormous variability in drug exposure can exist between/within patients
• Challenge to optimize current drug therapy using evidence based dosing regimens
REFERENCES

• BARTELINK IH ET AL. GUIDELINES ON PAEDIATRIC DOSING ON THE BASIS OF DEVELOPMENTAL PHYSIOLOGY AND PHARMACOKINETIC CONSIDERATIONS. CLIN PHARMACOKINET 2006;45(11):1077-1097
• KEARNS GL ET AL. DEVELOPMENTAL PHARMACOLOGY –DRUG DISPOSITION, ACTION AND THERAPY IN INFANTS AND CHILDREN. N ENGL J MED 2003;349:1157-67
• BIONDI A ET AL. BIOLOGICAL AND THERAPEUTIC ASPECTS OF INFANT LEUKEMIA BLOOD 2000;96(1);24-33
• ADAMSON P. IT’S NOT EASY BEING SMALL (COMMENTARY) PEDIATR BLOOD CANCER 2010;54:341-343
• BROWN P. TREATMENT OF INFANT LEUKEMIAS: CHALLENGE AND PROMISE HEMATOLOGY AM SOC HEMATOL EDUC PROGRAM 2013; 2013: 596-600
• HEMPEL G ET AL. PHARMACOKINETICS OF DAUNORUBICIN AND DAUNORUBICINOL IN INFANTS WITH LEUKEMIA TREATED IN THE INTERFANT 99 PROTOCOL PEDIATR BLOOD CANCER 2010;54:355-360
• KOSTECHA RS ET AL. THE EVOLUTION OF CLINICAL TRIALS FOR INFANT ACUTE LYMPHOBLASTIC LEUKEMIA BLOOD CANCER JOURNAL 2014;4,E200; DOI:10.1038/BCJ.2014.17
• VEAL GJ ET AL. ADAPTIVE DOSING OF ANTICANCER DRUGS IN NEONATES; FACILITATING EVIDENCE-BASED DOSING REGIMENS. CANCER CHEMOTHER PHARMACOL 2016;77:685-692
The Beanstalk Program

Developmentally Focused Care for Young Children During Prolonged Hospitalization

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Workshop Objectives

• To understand the effect of long term hospitalization on child development

• To understand the impact of an oncology diagnosis and treatment on childhood development

• To gain insight into parental experiences and needs during their child’s prolonged hospitalization

• To learn about an innovative care program to address the needs of young hospitalized children
Hospital Environment

• Hospital environment does not typically foster the important experiences and interactions that promote normal child development (Goldberger, 1988, Baum et al, 2003)


• The trajectory of growth and development in children requiring lengthy hospitalization is usually altered (Lehner and Sadler, 2015)

• The hospital is a foreign environment for most parents, who may be unsure of their role in caring for their critically ill child (Lehner and Sadler, 2015)
Hospital Environment

- Behavioural qualities demonstrated by children with lengthy hospitalizations (Goldberger, 1988):
  - Social and exploratory passivity
  - Inhibited perception of ability to move/decreased movement repertoire
  - Narrow range of affective expression
  - Distractibility
  - Disinterest in fine motor tasks requiring hand-eye co-ordination
  - Minimal vocalizations
Long-term Hospitalization In Children

- Chaotic, sterile environment
- Inconsistent schedules and poor sleep routines
- Multiple caregivers and intrusive social and medical interactions
- Decreased exploratory play and movement

Negative impact on child development and parent-child attachment
Childhood Development in Oncology

- Prolonged hospitalization due to medical vulnerability, medication side effects or complications of intensive treatment.

- Treatment protocols for children with leukemia are lengthy and those considered higher risk require hospital admission for a large portion, if not all of their treatment.

- Developmental Vulnerabilities exist for a large portion of children with ALL (Janzen et al, 2015)

- Nearly ¼ of children age 2-5 being treated for ALL demonstrated motor difficulties, both during and in the years following treatment (De Luca et al, 2013)
Rationale for Program Development

• Early childhood is a critical time period in development

• Opportunity for development is too often lost or minimized in the presence of chronic disease, developmental regression occurs.

• PTs and OTs are involved with children with acquired functional impairments that might have been prevented with education, stimulation and opportunity.
The Beanstalk Program

• Established in liver/small bowel/renal transplant population in 2000 by the multidisciplinary rehabilitation team

• A developmentally focused care program for chronically ill, long-term hospitalized (>3 weeks) children (0-3 years of age), and their families
  • Multidisciplinary, family centered approach
  • Addresses limitations of hospitalization related to child development
Program Objectives

• Optimize the environment with developmentally appropriate toys and equipment

• Encourage parental attachment and normal family-child experiences

• Provide education for families, health care team and volunteers related to normal development and play strategies
Multi-Disciplinary Role

- Promote safe and appropriate use of equipment and toys and maximize environmental resources ie use of playroom
- Advocate importance of diurnal cycles and meeting rest/sleep needs
- Promote positive parent-child interactions and encourage safe handling
- Collaborate with parents in getting to know their child; celebrate special days and developmental accomplishments
- Re-inforce developmentally focused plan of care over 24 hours/7 days
Research – Parental Experiences

• Mixed-methods design described parental experiences and perceptions of the care their child received during his/her prolonged hospitalization on ward 6A at SickKids

• Examined how families relate this care to the components of the Beanstalk Program
Interplay of Components

DEVELOPMENTALLY FOCUSED CARE

PARENT
Emotional needs: reassurance and establishing parental role

CHILD
Impact of illness and hospitalization

Resources

Equipment

Care Providers

Environment
**Methods**

- **Sample**
  - Parents of all children who were part of the Beanstalk Program between 2003-2008

- **Mixed Method Design**
  - Administration of MPOC-20 (validated questionnaire examining parental perceptions of the process of delivery of care)
  - Individual in-depth interviews exploring parent experiences and perception of delivery of developmentally focused care
Subjects

- Total of 20 parents (of 21 children) completed and returned the questionnaire; total of 11 participated in interviews

- Mean length of hospitalization 127 days (55 to 387 days)

- Age range during hospitalization 0-31 months

- Hospitalized for liver/small bowel transplants, liver transplants, intestinal failure and renal transplants (21 children)
Interview Themes

1) Parents strive for positive and normal experiences for their child within the hospital environment

• “..it was very helpful to our son just to experience the (stroller), to sensitize him basically from just lying in a bed and all the tubes and make it a bit more normal.”
Interview Themes

2) Parents value the focus on child development in the midst of their child’s complex medical care

- “Beanstalk Program...meant a lot to me because it was extra support...it was kind of like a separate focus from our son’s health...like our focus was going to be on his developmental stuff and what his needs will be aside from the medical piece. Which was a big thing because we had to think of that once we kind of gotten over the medical upset and his transplant, then we had to think about...we have to get this child moving and keep him moving forward so he is with his peers.”
Interview Themes

3) Developmentally focused care helps parents shift from being overwhelmed with a medically ill child to being confident and empowered to care for their child and transition home

• “We were working on his development, we were guided, we helped and as I said we were given a package of pictures of our son to help us encourage it...so we had more than enough support...when we left the hospital we knew what we were doing...and we were more than comfortable leaving with him. Which was a big thing.”
Beanstalk in Oncology

• Brought to Oncology in 2010 with C17 Grant

• Program modification to meet the needs of unique population
  • Nipissing Developmental Screen
  • Bin system

• Committee consists of Physiotherapists, Occupational Therapist, Speech and Language Pathologist, Child Life Specialists and Nursing Representatives.

• Approximately 40 patients per year are enrolled
Conclusions

• Developmental delay exists in the paediatric oncology population and parents recognize these delays in their children

• It is important to understand and help parents strive for normalcy during their child’s hospitalization

• Parents value education, both specific to their child’s developmental needs and general information about services, conditions, development

• Developmentally focused care should be an essential component of care in the young, hospitalized children within Oncology programs
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References

Thank You

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Questions