

Pediatric Pharmacotherapy

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Outline

- ◆ **Background:**
 - ◆ Environment for Pediatric Research (Drug Development?)
 - ◆ Regulatory Climate and Influence
 - ◆ Pediatric Pharmacotherapy Defined
- ◆ **CHOP**
 - ◆ Clinical Pharmacology & Therapeutics Division
 - ◆ Laboratory for Applied PK/PD
 - ◆ Goals, objectives and infrastructure
- ◆ **Project Review**
 - ◆ Specific Case Studies - ongoing projects
 - ◆ Additional projects
- ◆ **Vision for the Future**

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Environment for Pediatric Research: The Therapeutic Orphan

- ◆ 75% prescription drugs in children "off label"
- ◆ Usage not described in package insert
- ◆ Approved indications
- ◆ Adequate controlled studies
- ◆ Consequences of off label usage
 - ◆ Benefit
 - ◆ No effect
 - ◆ Harm

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Environment for Pediatric Research: Off Label Drug Use

- ◆ Unapproved is not improper
- ◆ Decision based on safety/efficacy data
- ◆ Medical literature vs FDA
- ◆ "Best medical judgment"

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The Steps Toward Drug Approval



Environment for Pediatric Research: Pediatric Drug Development Obstacles

- ◆ Limited market (\$3.5 vs \$70 billion adult)
- ◆ Additional expense
- ◆ Small return on investment
- ◆ Pediatric formulations not cost effective
- ◆ Increased liability during clinical trials

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Pediatric Drug Development Opportunities

- ◆ Pediatric Pharmacology Research Units (1994, 1999, 2003)
- ◆ NIH RFA to promote academic-industry partnership for pharmacological research in children (13 in the US)
- ◆ CHOP PPRU awarded 1999
- ◆ FDAMA (1997)
 - ◆ Exclusivity: provides 6 month patent extension for currently approved drug if pediatric study performed
 - ◆ The Pediatric Rule: FDA can direct sponsor to study new product in the relevant pediatric population if substantial use likely or meaningful therapeutic benefit

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Pediatric Drug Development Opportunities

- ◆ Better Pharmaceuticals for Children Act (BPCA 2002)
 - ◆ Re-authorizes exclusivity
 - ◆ Establishes Office of Pediatric Therapeutics within FDA
 - ◆ Funds generic drug studies (PODS Centers)

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Legislative Summary

- ◆ PREA 2003
 - ◆ Pediatric Rule
 - ◆ Drugs in pipeline - Pediatric studies mandated
- ◆ BPCA 2003
 - ◆ Exclusivity
 - ◆ Already approved drugs - 6 mo patent protection
 - ◆ Office of Pediatric Therapeutics in FDA
 - ◆ Funds generic drug studies for children (PODS)

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BPCA Drugs Needing Study

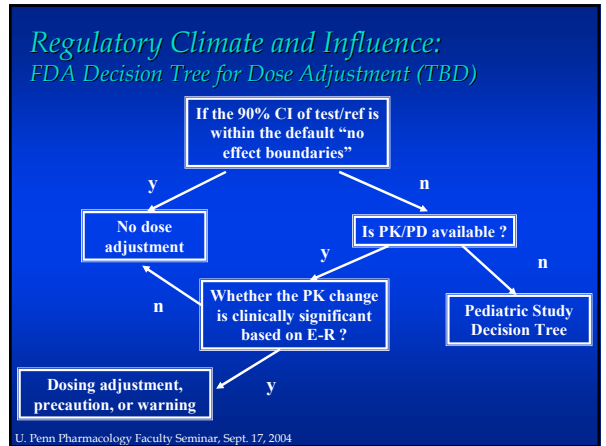
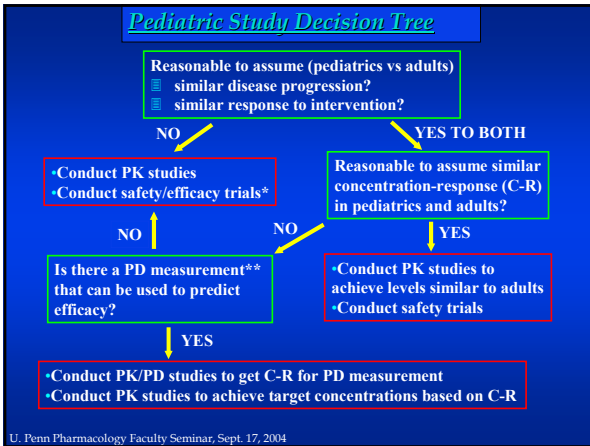
Azithromycin	Ampicillin/sulbactam
Baclofen	Diazoxide
Bumetanide	Isoflurane
Dobutamine/Dopamine	Lindane
Furosemide	Meropenem
<u>Heparin</u>	Metoclopramide
Lithium	Pip/tazobactam
Lorazepam	Promethazine
Rifampin	
<u>Sodium Nitroprusside</u>	
Spironolactone	

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Regulatory Climate and Influence: FDA Initiatives Supporting Pediatric Trials

- ◆ Provide a consistent approach to design and evaluate pediatric population PK (PPK) study.
- ◆ Develop a computer-aided pediatric "study design template"
 - ◆ user-input study design features
 - ◆ automatic assessment of study power
- ◆ Select case studies from the FDA database to test and iteratively refine the template.
- ◆ Promote a wider use of population design in pediatric PK study.

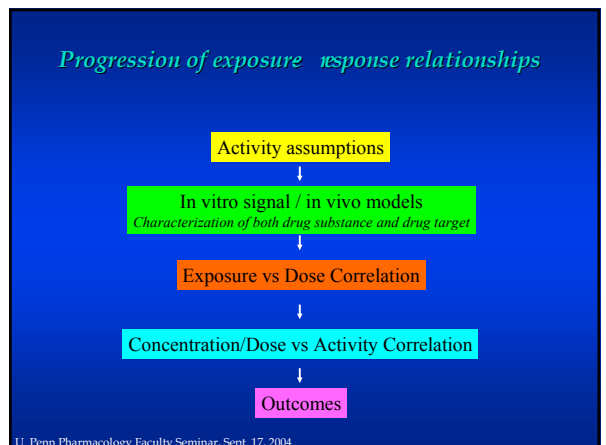
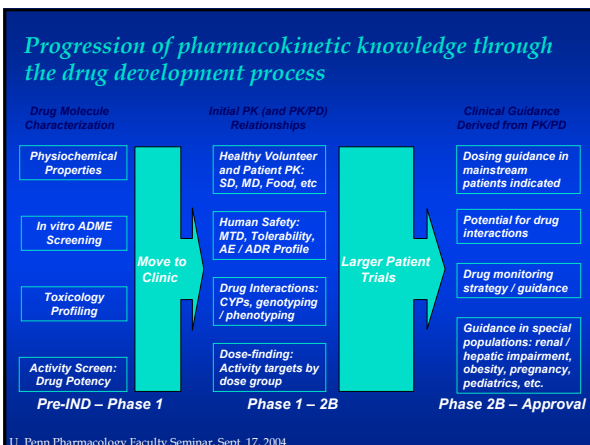
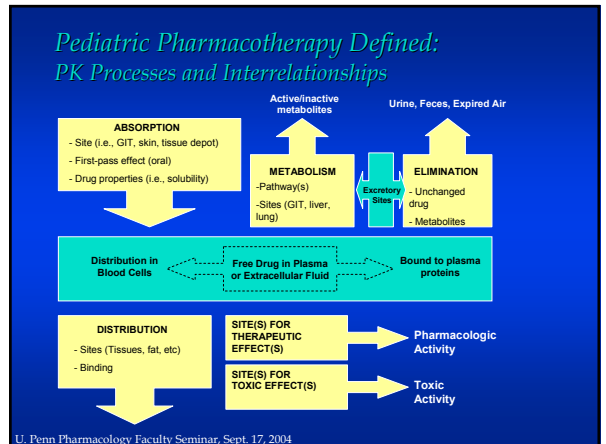
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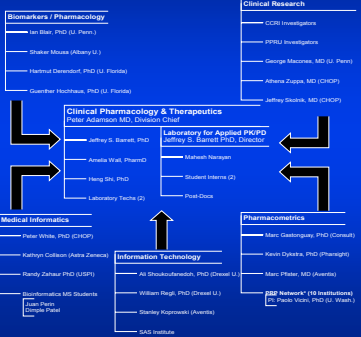
Pediatric Pharmacotherapy Defined

- Principally concerned with the **safe and effective management of drug administration.**
- Implies an understanding of drug pharmacokinetics (PK) and pharmacodynamics (PD) so that individual dosing guidance, when necessary, can be provided to optimize patient response within their individual therapeutic window.

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The Children's Hospital of Philadelphia: Clinical Pharmacology & Therapeutics



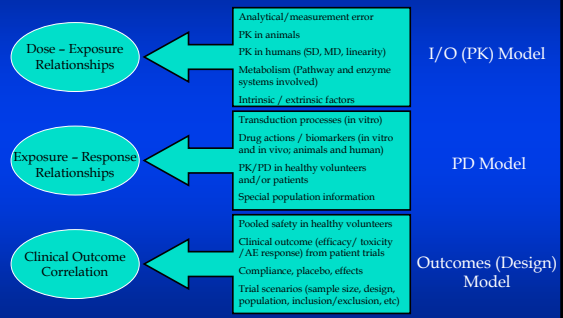
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The Children's Hospital of Philadelphia: Laboratory for Applied PK/PD- GOALS

- ◆ More informed clinical trials
- ◆ Improved patient labeling
- ◆ Improved patient outcomes
 - ◆ Fewer medication errors
 - ◆ Greater probability of therapeutic success

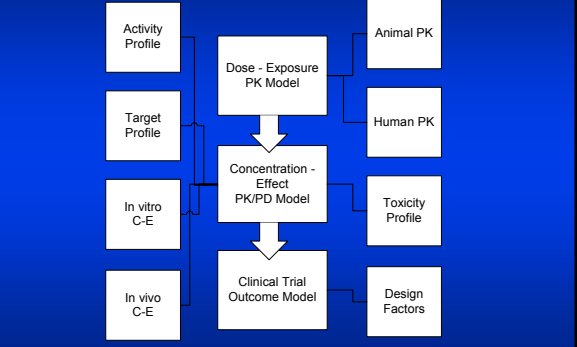
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Laboratory for Applied PK/PD – GOALS: Center for Excellence in Modeling and Simulation



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Integration of Modeling and Simulation



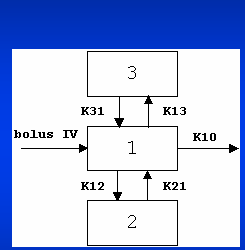
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Example: Integration of M&S into Project 2

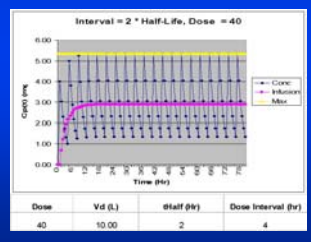
	Experimental Deliverables	Project Goals
Activity Profile	<ul style="list-style-type: none"> Cytotoxicity Experiments: IC_{50}, IC_{50}, synergy results BCL-2 inhibition: IC_{50}, IC_{50} BCL-2 modulation: ? 	<ul style="list-style-type: none"> Establish in vitro target exposure for pro-apoptotic activity - Aim 1
Target Profile	<ul style="list-style-type: none"> Sensitivity and resistance of leukemia cell lines to pro-apoptotic agents (criteria TDB) Synergy experiments: shift in IC_{50} with various pretreatment duration 	<ul style="list-style-type: none"> Establish viability of target - Aim 2 Establish optimum combination (pro-apoptotic + cytotoxic drugs) and schedule dependence - Aim 3
PK Model Dose - exposure relationship	<ul style="list-style-type: none"> Animal PK described from historical data -- PK model Allometric approach to predict exposure in the mouse model 	<ul style="list-style-type: none"> Establish viability of delivering adequate exposure based on PK principles and target activity (defined above)
PK/PD Model Concentration - Effect relationship	<ul style="list-style-type: none"> Animal and human PK/PD described from historical data (human) and in vivo pharmacology results (NOD-SCID experiments) 	<ul style="list-style-type: none"> Establish clinical utility based on feasibility of maintaining adequate exposures and managing expected toxicities - Aim 4
Clinical Trial Model Outcome relationship	<ul style="list-style-type: none"> Experimental scenarios based on relevant study designs in infant leukemia and the likely pharmacotherapeutic conditions with target agents 	<ul style="list-style-type: none"> Establish the likelihood of clinical success based on optimal clinical setting and design scenarios - Aim 5

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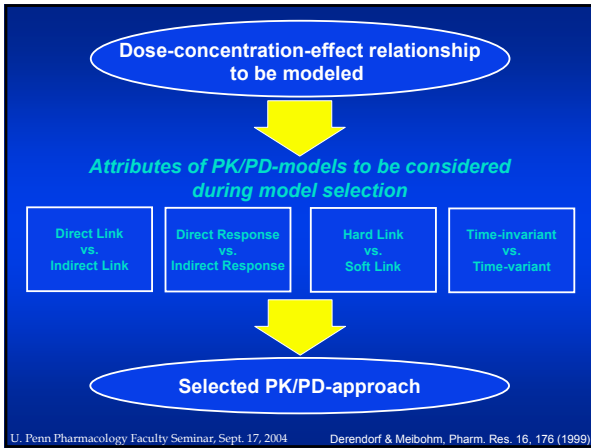
PK Model



$$C(T) = A * \exp(-\alpha * T) + B * \exp(-\beta * T) + C * \exp(-\gamma * T)$$



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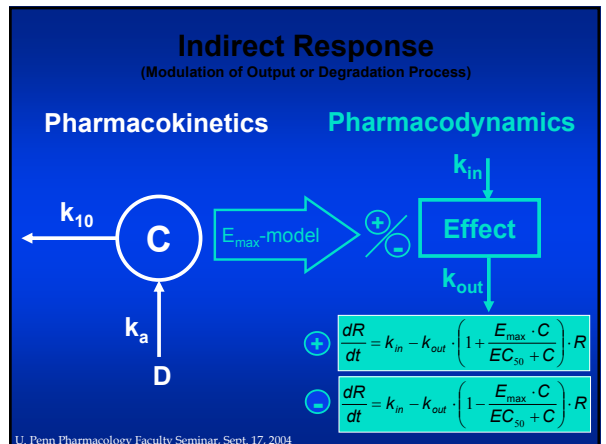
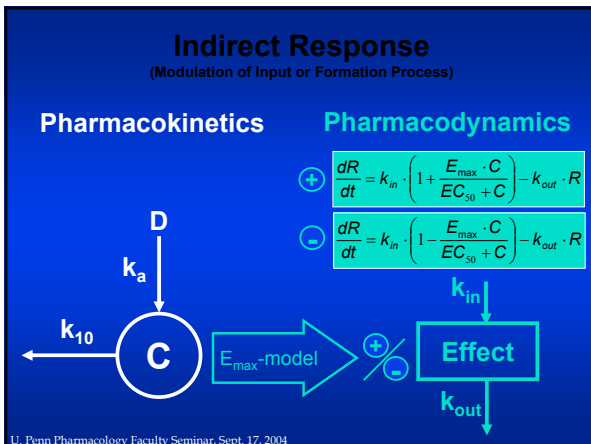
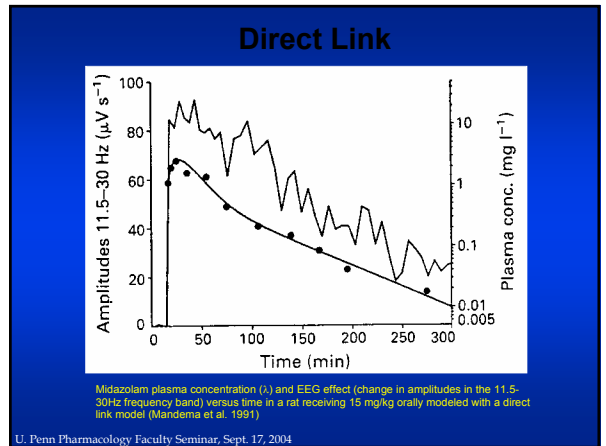
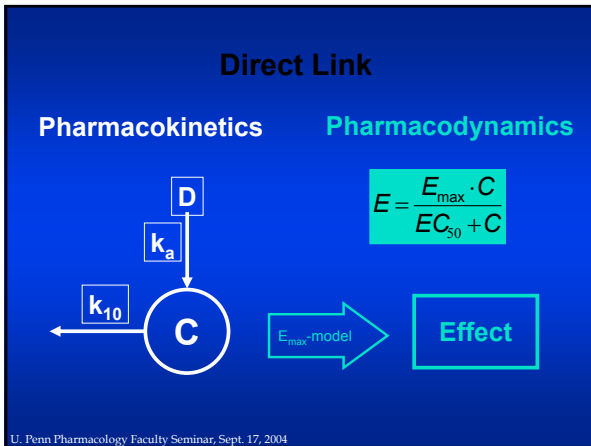


Direct link

Plasma concentration (Cp) and drug concentration at the effect site (biophase) are proportional

Concentration-effect-relationship is independent of time

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Population PK: Analysis Flow for Model Building

Define Pharmacostatistical Model

- ◆ Basic pharmacostatistical model with each parameter defined under conditions based on known PK behavior

Covariate Addition

- ◆ Individual covariates evaluated based on reduction of objective function.
- ◆ Model with highest ranking covariate added to initial model.
- ◆ Fully saturated model containing all covariates deemed significant by the ranking procedure produced.
- ◆ The redundancy of covariates examined.

Structural Model Refinement and Data Coding Revisions

- ◆ Modifications to the data set and/or model; more accurate estimate of errors with the FOCE/interaction method conducted.

Validation

- ◆ Projection of results from model building dataset (i.e., 66% subjects) into validation (33% subjects) made and compared.

Error Model Refinement and Additional Covariate Reduction

- ◆ Re-examination of error model

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Review of Current Projects:

- ◆ Midazolam Genomic PK and PPK in pediatrics
- ◆ Esmolol PPK in critically ill children
- ◆ Actinomycin / vincristine in children with cancer
 - ◆ PK/PD to predict dose intensity - toxicity relationship
 - ◆ Physiologically-based PK Modeling
 - ◆ Clinical Trial Simulation - protocol design
- ◆ Malabsorption Blood Test
 - ◆ Diagnostic test and procedure development to predict malabsorption (CF patients)

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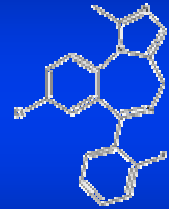
Current Projects: Pharmacogenetic Basis for Inter-Patient Variability in Midazolam Pharmacokinetics

- ◆ The oral preparation of midazolam is the most common premedication for children undergoing anesthetic or sedation procedures.
- ◆ At CHOP, approximately 15,000 children a year receive oral midazolam prior to entering the operating room.
- ◆ There is considerable variation in both effect and drug concentration observed in pediatric patients.
- ◆ The cause of this variability is unclear but may, in part, be related to age and differences in metabolism.

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Current Projects: Pharmacogenetic Basis for Inter-Patient Variability in Midazolam Pharmacokinetics

- ◆ Midazolam Chemical Name: 8-chloro-6-(o-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine
- ◆ Molecular Formula: C₁₈H₁₃ClFN₃•HCl
- ◆ Molecular weight: 362.25 Da
- ◆ Benzodiazepine derivative with an imidazole ring
- ◆ pKa = 6.15.
- ◆ Administered parenterally via intramuscular or intravenous injection or orally as a tablet or liquid suspension.



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Current Projects: Pharmacogenetic Basis for Inter-Patient Variability in Midazolam Pharmacokinetics

- ◆ Midazolam is a substrate of cytochrome P450 3A.
- ◆ Multiple polymorphisms in CYP3A4 have been identified. The most common polymorphism, A-290G, is present in approximately 50% of African-Americans and 10% of Caucasians.
- ◆ A-290G polymorphism is associated with an increased grade and stage of prostate cancer; thought to be most functionally relevant CYP3A4 polymorphism.

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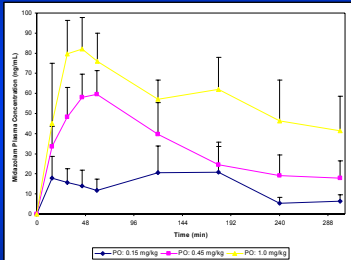
Current Projects: Pharmacogenetic Basis for Inter-Patient Variability in Midazolam Pharmacokinetics

- ◆ Functional relevance difficult to demonstrate, in part, because of lack of a pharmacologic probe to distinguish between 3A4 and 3A5 pathways.
- ◆ Midazolam use as a probe was limited by the instability of primary metabolite, 4-OH midazolam.
- ◆ CYP3A5 has had two relevant polymorphisms identified to date, CYP3A5*3 and *6; neither have functional consequences *in vitro*.
- ◆ Phenotypic expression of CYP3A5 occurs in 33% of Caucasians and 50% of African Americans.

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Current Projects: Pharmacogenetic Basis for Inter-Patient Variability in Midazolam Pharmacokinetics

Experience with Midazolam in Pediatric Populations



Payne K. et al, Eur. J. Clin. Pharmacol, 1989

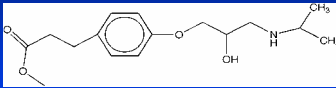
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Current Projects: Pharmacogenetic Basis for Inter-Patient Variability in Midazolam Pharmacokinetics

- ◆ Assay developed for midazolam, 1-OH and 4-OH primary metabolites and their glucuronide metabolites via LC/MS-MS
- ◆ 30 patients administered a single oral dose of midazolam with well-defined sampling for PK
- ◆ Approximately 300 additional patients dosed with midazolam (single dose) with sparse sampling for PK
- ◆ All patients genotyped to examine CYP 3A4/5 polymorphism
- ◆ Initial PK analysis on 30 subjects complete; analytical processing for 300 patient dataset ongoing
- ◆ NCA in progress; to be followed by structural model building and covariate relationship identification

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Current Projects: Esmolol PPK in critically-ill children



Basic Pharmacology

- β_2 -selective antagonist
- very short duration of action
- administered for beta blockade of short duration

Adult Clinical Pharmacology

- Rapid control of ventricular rate in atrial fibrillation/flutter
- Noncompensatory sinus tachycardia
- Initial loading dose of 500 $\mu\text{g}/\text{kg}$
- Maintenance infusion of 50 - 200 $\mu\text{g}/\text{kg}/\text{min}$

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Current Projects: Esmolol PPK in critically-ill children

Clinical Pharmacokinetics

- Ester linkage hydrolyzed rapidly by erythrocyte esterases
- No CYP dependent metabolism
- $t_{1/2\alpha} \sim 2$ min; $t_{1/2\beta} \sim 9$ min
- Apparent $V_d \sim 2$ L/kg
- Clearance 128-250 ml/kg/min
- Free acid metabolite 1/1500th the activity of esmolol; $t_{1/2\beta} \sim 3.7$ h; excreted in the urine

Assumptions for Dosing Pediatric Population

- No data to suggest that red cell esterase activity in children is different than adults
- Studies in children suggest a more rapid clearance or terminal elimination of drug relative to adults

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Current Projects: Esmolol PPK in critically-ill children

Pediatric Trials with Esmolol

ETHIC: Infants and Children Undergoing Treatment of Hypertension After Surgical Repair of Coarctation of the Aorta

ESCAPE: Pediatric Patients with Supraventricular Tachycardia

- Neither study designed for pop-PK
- Clinical settings different (OR vs Cath Lab) as well as clinical conduct
- ETHIC patients anesthetized

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Current Projects: Esmolol PPK in critically-ill children

Summary of patient demographics

	ETHIC	ESCAPE	COMBINED
Age	30 newborns: <28 days 41 infants: >28 d to <1y 72 child: $\geq 1y$ to 6y	14 child: ≥ 2 to 11y 13 adol: 12-16yr	30 newborns 41 infants 97 child/adol
Weight (kg)	newborns: 3.6 (0.4) infants: 5.8 (1.9) child: 34.3 (20)	48.9 (23.6)	23.2 (22)
Race	hispanic: 25 (17%) black: 9 (6%) white: 107 (75%) other: 2 (2%)	non-Hispanic white: 30 (88%) non-Hispanic black: 4 (12%)	
Gender	♀: 50 (35%) ♂: 93 (65%)	♀: 11 (41%) ♂: 16 (59%)	♀: 61 (36%) ♂: 109 (64%)

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Current Projects: Esmolol PPK in critically-ill children

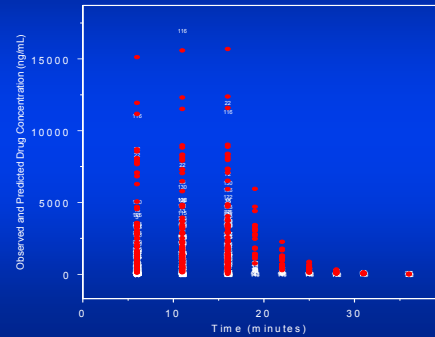
Study features and non-compartmental PK results from ETHIC and ESCAPE trials with Esmolol in critically-ill pediatric patients

	ETHIC	ESCAPE
Number	107	22
Dose (bolus)	125, 250, or 500 µg/kg	1000 µg/kg push
Dose (infusion)	125, 250, 500 µg/kg/min	15-min infusion at 300
PK sampling	0, 5, 10, and 15 min after the start of CIVI	0, 5, 10, and 15 min after load and 3, 6, 9, 12, 15 and 20 min after CIVI
Initial PK Analysis	Empirical pop. model $C(t) = Cas * (1 - e^{-kt})$	NCA 2CPM (WINSAM)
Vd (mL/kg)	ND	283 (145); [131-732]
$t_{1/2}$ (min)	4.8	6.9 [5.2-10.9]
Clearance (mL/kg/min)	Infants: 281 [267, 296] Children: 126 [83, 169]	119 (51); [25-237]

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Current Projects: Esmolol PPK in critically-ill children

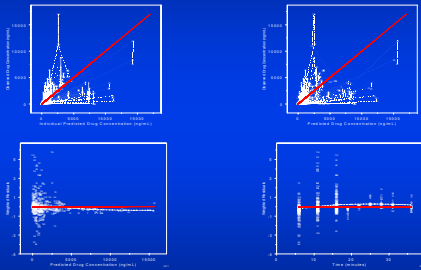
Results of Initial Modeling Efforts



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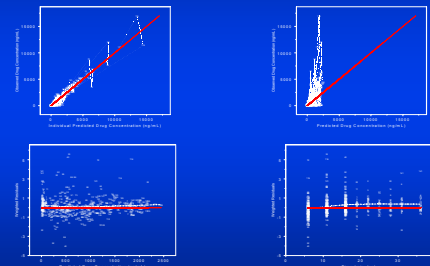
Results of Initial Modeling Efforts - Base Model



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Current Projects: Esmolol PPK in critically-ill children

Results of Initial Modeling Efforts - Allometric CL Model



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Current Projects: Esmolol PPK in critically-ill children

Results of Initial Modeling Efforts - Allometric CL Model

Parameter	Estimate	%RSE
CL (L/hr)		
θ_{CL}	10.2	14.3
θ_{CL_AGE}	0.10	60.4
V (L)		
θ_V	9.96	15.3
Q (L/hr)		
θ_Q	0.78	56.8
V2 (L)		
θ_{V2}	7.84	19.9
Inter-Individual Variance		
σ^2_{CL}	4.54	49.6
σ^2_V	0.42	136.9
σ^2_Q	1.57	219.7
σ^2_{V2}	1.81	219.9
Residual Variance		
σ^2_{all}	290.0	82.1
σ^2_{prop}	0.588	30.8

%RSE: percent relative standard error of the estimate * SE/parameter estimate * 100

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Current Projects:

Actinomycin / Vincristine in children with cancer

- Actinomycin-D (AMD) is an antineoplastic agent.
- Despite its widespread use in pediatric oncology, there is limited knowledge as to its precise mechanism of action, and there is no PK information from which safe and appropriate dosing can be derived.
- In August of 2002, the Children's Oncology Group (COG) suspended 3 active protocols for pediatric rhabdomyosarcoma after 4 chemotherapy-associated deaths from veno-occlusive disease, as characterized by elevated liver enzymes and hyperbilirubinemia, abdominal pain, and weight gain.

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Current Projects:

Actinomycin D / Vincristine in children with cancer

- There has been no subsequent evaluation as to the cause of these devastating side effects or correlation between toxicity and drug exposure.
- This has been hindered primarily by the limited pharmacokinetic knowledge of AMD.
- Because AMD is crucial to soft tissue sarcoma therapy, its use as an anti-neoplastic agent must continue and clinical evaluation is vital.

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Actinomycin D

Clinical Setting - Rhabdomyosarcoma study dosing

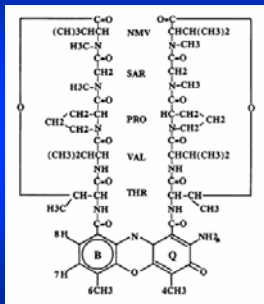
Age	VCR dose	AMD dose	CPM dose	Adjuvants
≥ 3 years	1.5 mg/m ² IV Push (max dose 2.0 mg)	0.045 mg/kg one dose (max dose 2.5mg)	2.2 g/m ² IV as 30 minute infusion with IV fluids and MESNA	Omit AMD during radiotherapy
≥ 1 year < 3 years	0.05 mg/kg IV Push (max dose 2.0 mg) If child has turned 3 years old at time of therapy use guidelines in box above (≥ 3 years)	0.045 mg/kg one dose (max dose 2.5mg)	73 mg/kg dose IV as 30 minute infusion with IV fluids and MESNA If child has turned 3 years old at time of therapy use guidelines in box above (≥ 3 years)	Omit AMD during radiotherapy
< 1 year	0.025 mg/kg IV Push* If child has turned 1 year old at time of therapy use guidelines in box above (≥ 1 year and < 3 years)	0.025 mg/kg one dose* If child has turned 1 year old at time of therapy use guidelines in box above (≥ 1 year and < 3 years)	36 mg/kg [†] IV as 30 minute infusion with IV fluids and MESNA If child has turned 1 year old at time of therapy use guidelines in box above (≥ 1 year and < 3 years)	Omit AMD during radiotherapy

* For children still less than one year of age by week 12 of protocol, call the Study Chair for recommendations of upped dose adjustment for Vincristine, Actinomycin-D, and Cyclophosphamide.

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Actinomycin D

Structure - activity data

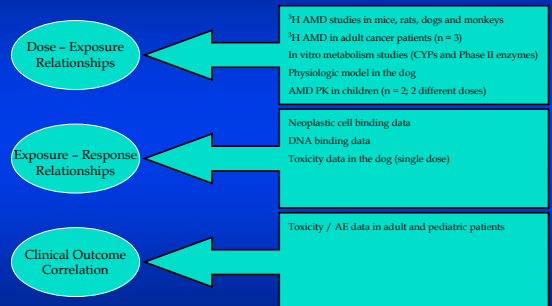


- A product of Streptomyces yeast (MW = 1255 Da).
- Cyclic polypeptide based antibiotic that inhibits RNA synthesis by binding to guanine residues and inhibiting DNA dependent RNA polymerase (Reich; Cancer Res 1963).
- The earliest report of actinomycins interacting with DNA is from 1960 (Kawamata; Nature 1960).
- Further elucidation into the stereochemistry of AMD and DNA binding was completed in 1972 via co-crystallization and hypothesized a working model for AMD activity (Jain; J. Mol Biol 1972).
- Appears to show preferential binding to neoplastic cells (Heemed; Can Res 1973), and resistance appears to be related to inefficient drug transport (reference, use Biedler, 1970).
- In clinical use since 1954 (Farber, Adv Cancer Res; 1956), and has been used against many pediatric soft tissue cancers (Frei; Cancer Chemo Rep 1974), for example Wilms' tumor and rhabdomyosarcoma.

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Actinomycin D

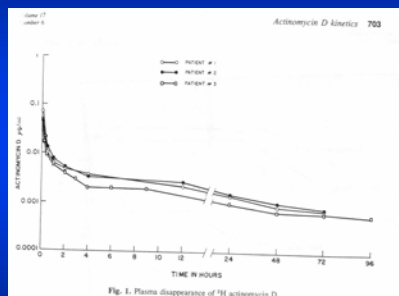
Actual prior information



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Actinomycin D

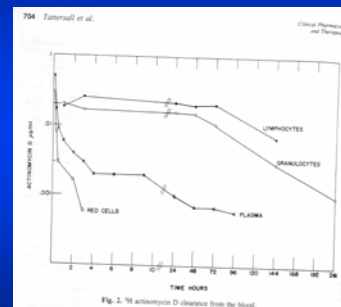
Prior Knowledge - adult PK data



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Actinomycin D

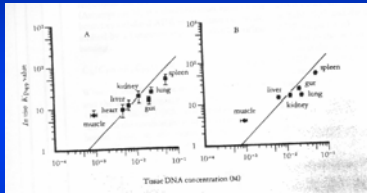
Prior Knowledge - adult cellular disposition data



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Actinomycin D

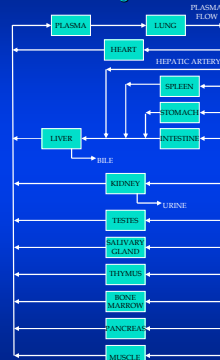
Prior Knowledge – tissue distribution and nuclear binding data



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Actinomycin D

Prior Knowledge – PBPK data in the dog



- Beagle dog, flow limited PBPK model (Lutz et. al., JPET 200(3): 469-48, 1977)
- Simulations validated against iv doses of 0.6 and 2.7 mg/m² (approximately 0.03 and 0.135 mg/kg) based on systemic and tissue exposure of ³H-AMD
- Data (exposures) used to support the model collected at 3 hours and on days 1, 2, 3, 4 and 5
- Simple mass balance relationships for each tissue based on
 - Accumulation = net perfusion - clearance

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Actinomycin D

Prior Knowledge – PK data in the children

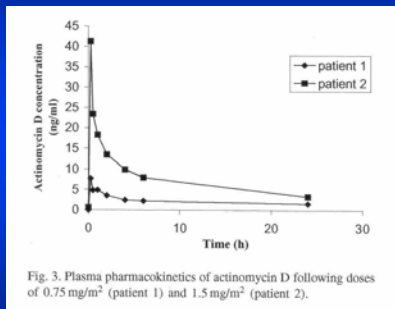


Fig. 3. Plasma pharmacokinetics of actinomycin D following doses of 0.75 mg/m² (patient 1) and 1.5 mg/m² (patient 2).

- Analytical paper (Veal et. al., 2004)
- Data in 2 patients administered different doses of AMD
- Age and BW not provided

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Actinomycin D

I/O Model: Dose-concentration prediction

- Objective is to predict AMD exposure in pediatric populations
- Propose to build relationships to scale: Dog → Human (adult) and adult → peds
- As there is no reasonable estimate of inter-subject variation, we propose to examine only the uncertainty about the prediction of mean exposure profiles
- Refine PBPK model with proper variance estimates from pilot PK studies

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Actinomycin D

PD Model: Exposure-response prediction

- The pediatric PBPK model will then be used to correlate systemic and target organ exposure with observed toxicity profiles (adult and pediatric clinical trials)
- Create transduction model which predicts intracellular time course and actions (utilize DNA binding, cellular partitioning and cytotoxicity data)
- Generate *in vitro* cell kill data with commonly prescribed co-administered agents

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Actinomycin D

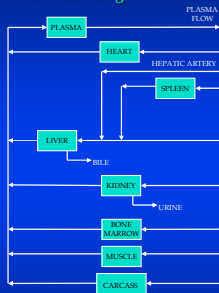
Outcomes Model: Trial Outcome prediction

- Create mean response profile (AE, toxicity) from published studies in which AMD was administered – summary data
- Assemble individual response data from Children's Oncology Group (COG) – individual data
- Examine correlation of adverse effect / tox profile with AMD dose
 - Construct outcome expressions (i.e., logistic model)

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Actinomycin D

Prior Knowledge - PBPK Reduced Model



Criteria for model reduction

- High DNA concentration
- High blood flow
- Organs potentially correlated with toxicity

Methods

- NONMEM v5, Level 1.1
- ADVAN 8 with 8 DEs defined
- 100 Subproblems

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Parameter Derivation

- ◆ Dog flows and volumes, clearances
 - ◆ Lutz et al. *Model for the kinetics of distribution of actinomycin-D in the beagle dog*. JPEI, 1977; 200(3): 469-478
- ◆ Human flows and volumes, dog variability
 - ◆ Brown et al. *Physiological parameter values for physiologically based pharmacokinetic models*. Toxicology and Industrial Health. 1997; 13(4):407-484
- ◆ Human clearance values (approx 1/3 biliary, 2/3 renal) derived from modeled data
 - ◆ Tattersall et al. *Pharmacokinetics of actinomycin-D in patients with malignant melanoma*. Clin Pharm Ther. 1975; 17(6):701-708
- ◆ Carcass R and CV calculated as mean values of all other organs
- ◆ CV for partition coefficients and organs without values were assumed to be 0.20

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Parameter Derivation

- ◆ Clearance in dog
 - ◆ Biliary - 774 mL/h
 - ◆ Renal - 936 mL/h
- ◆ Clearance in humans
 - ◆ Biliary - 1362 mL/h
 - ◆ Renal - 3729 mL/h
- ◆ Parameters in children allometrically scaled from adult parameters

$$CL = a * WT^{0.75} \quad V = c * WT^1 \quad Q = b * WT^{0.75}$$

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Model Parameters

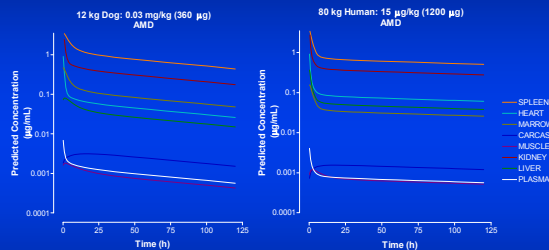
R	Dog		Adult Human	
	Q (mL/h)	V (mL)	Q (mL/h)	V (mL)
Plasma ^a	30730	500 (0.2)	340200	3400 (0.12)
Liver	30 (0.2)	3600 (0.14)	78000 (0.18)	1500 (0.16)
Kidney	45 (0.2)	5400 (0.09)	66000 (0.21)	300 (0.21)
Marrow	20 (0.2)	1200 (0.2)	27000 (0.16)	1500 (0.16)
Muscle	8 (0.2)	8280 (0.18)	54600 (0.17)	30000 (0.17)
Heart	11 (0.2)	3600 (0.07)	15600 (0.14)	350 (0.14)
Spleen	55 (0.2)	810 (0.2)	12600 (0.16)	210 (0.16)
Carcass	25 (0.2)	7840 (0.12)	86400 (0.16)	42740 (0.16)

$$^a Q_p = Q_{il} + Q_{kl} + Q_{mr} + Q_{mu} + Q_h + Q_{sp} + Q_c$$

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Interspecies Exposure Comparison

Mean Profiles



☒ Good agreement with Lutz et al.
All tissue exposures

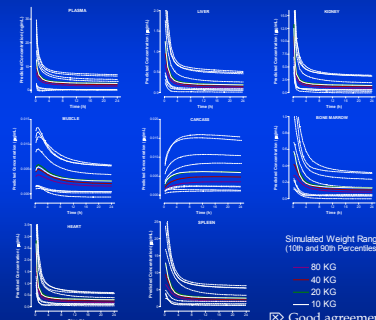
☒ Good agreement with Tattersall et al.
Human plasma exposure comparable

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Simulated Pediatric Exposure Results

Mean Response (uncertainty on mean only)

Pediatric Exposure Profiles following 1.5 mg/m² AMD



Simulated Weight Ranges
(10th and 90th Percentiles)

— 80 KG
— 40 KG
— 20 KG
— 10 KG

☒ Good agreement with Veal et al.
Pediatric plasma exposure comparable

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Clinical Outcomes

Capturing Response from Pooled Literature Data

- ◆ AE/toxicity data pooled from 17 trials with AMD
 - ◆ Patient population (cancer type); Wilms tumor, Ewing's disease rhabdomyosarcoma, malignant melanoma, breast, trophoblastic disease, endometrial carcinoma and various mixed cancers
 - ◆ Total N = 1289 patients
- ◆ Response data coded by event type, dose range, severity and frequency of occurrence (within study)
 - ◆ 3 Dose Ranges: 0 - 0.45, 0.46 - 1.35, 1.36 - 2.5 mg/m²
 - ◆ AMD-associated Events: platelet count, hemoglobin and WBC decline, myelosuppression, mucositis, nausea/vomiting, LFT elevation, and rash
 - ◆ Severity Grades: I - IV

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Clinical Outcomes

Capturing Response from Pooled Literature Data - example

Dose Range (mg/m ²)	Event	Severity	Occurrence (n)	Tot. N	Occurrence (%)
0 - 0.45	Dec_Hgb	Grade III	20	36	55.6
		Grade III/IV	78	267	29.2
	Dec_WBC	Grade III	10	36	27.8
		Grade III/IV	7	50	14.0
	Dec_Pls	Grade III	7	36	19.4
		Grade III/IV	219	281	77.9
	Myelosuppression Undefined	Grade II	84	231	36.4
		Grade III/IV	84	231	36.4
	Mucositis	All	255	772	33.0
	Nausea/Vomiting	All	106	297	35.7
	Inc_LFTs	Grade III	30	578	5.2
	Rash	Grade III/IV	78	862	9.0
		All	NA	NA	NA

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Ongoing and Future Efforts

- ◆ Metabolism Studies (ongoing)
 - ◆ Liver microsomes: CYP and phase II enzyme evaluation
 - ◆ Preliminary results suggest minimal CYP involvement
- ◆ Protein binding (ongoing)
 - ◆ Adult and pediatric evaluation
- ◆ Preliminary (pilot) PK trial in children (n = 8) - ongoing
 - ◆ Performance of new analytical method (LC/MS-MS) which detects AMD and vincristine from single injection
 - ◆ First estimate of inter-subject variation in PK parameters

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Ongoing and Future Efforts

- ◆ Design of pop-PK study to define dosing rule (n = 100 - 150)
 - ◆ Collaboration with NCI and possibly UK group
 - ◆ As sparse pediatric data are collected, population PK parameters will be estimated using a hierarchical Bayesian model given diffuse priors for those parameters that are well defined by the new data and informative, literature-based priors where necessary to support the model.
- ◆ Creation of Transduction Model for AMD intracellular dynamics - mechanistic PK/PD model
 - ◆ Incorporate DNA binding and cellular partitioning
 - ◆ Mine clinical data (COG) to explore correlation with blood chemistry and hematologic toxicities (No PK in this DB)

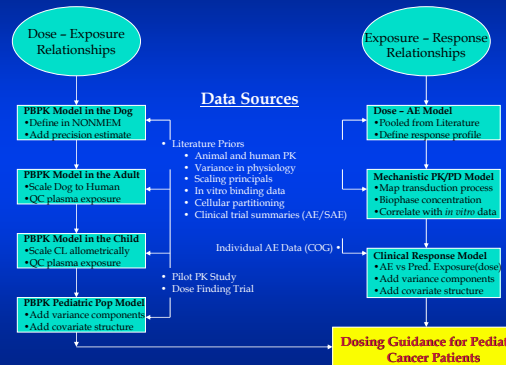
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Ongoing and Future Efforts

- ◆ Creation of Clinical Response Model for therapeutic window
 - ◆ Literature response rates, AE profile
 - ◆ Qualify literature response by COG data: stochastic model
- ◆ Create Clinical Trial Simulation Model from I/O (PK), PD and Clinical Response expressions

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Valuation of Priors



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Current Projects:

Actinomycin / Vincristine in children with cancer



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

24 June 2004

Gregory Roman, MD
Chair, Children's Oncology Group
gregor@childrensoncologygroup.org

Dear Greg,

NBI is seeking clinical data concerning vincristine and actinomycin that will enhance the safety and effectiveness of these drugs when used to treat children with cancer. These data are sought under provisions of the Best Pharmaceuticals for Children Act that exempt NBI and FDA to assure appropriate pediatric evaluations of agents that are no longer eligible for pediatric exclusivity.

The Children's Oncology Group (COG) is requested to provide a proposal describing how it will provide the requested information. The resources required for providing the requested information should be included in the COG proposal. The proposal should be made submitted as a formal supplement request to the COG Cooperative Agreement award. Please use PHS 398 forms for providing budgetary information, biographical sketches for key personnel, other support for key personnel, and for describing the research plan. Projects related to the following areas are requested, with projects relating to actinomycin described first, followed by projects related to vincristine. In order for NCI and NCI to allocate FY2004 funds, an award must be made before the end of September, 2004. Therefore, we need to receive COG's proposal by mid-August to allow time for internal review and for making the award. If the proposal can be submitted earlier in August, this would be helpful. We would like to see as much of the award

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Current Projects:

Actinomycin / Vincristine in children with cancer

The Children's Hospital of Philadelphia

Division of Clinical Pharmacology & Therapeutics
34th and Civic Center Blvd.
Philadelphia, PA 19104-6218
Tel: 215-351-2800

July 21, 2004

Dr. Gregory Roman
Chair, Children's Oncology Group
James Beatty Chair, Pediatrics
Carey Chapel, University City, 612

Re: Letter of Intent

Dear Dr. Roman and the COG Scientific Review Committee

In response to the NIH proposal for the clinical evaluation of vincristine and actinomycin in children dated June 24, 2004, we are preparing to respond to best with a proposal to address the NIH request on behalf of COG. The attached summary provides the basic overview for both projects which will coordinate our proposed drug trials for COG team members participating in the effort along with their roles on the various projects.

The proposal will contain information on specific objectives and strategies in the clinical scope of work defined by NIH. We have included these and provided some initial plans and some preliminary data. Specifically, the proposal includes: data showing efficacy in centrally administered bolus versus infusion (bolus and in combination) and clinical outcome, safety and efficacy in bolus compared with 72hr infusion of actinomycin, an end point. Necessary efforts to establish a common procedure for both bolus and three-hour drug infusion are being made. In addition, a prospective study of pharmacokinetics, including clinical trial and a prospective clinical trial to be conducted to define such a clinical trial. Additional information on the proposal, including information on the clinical trial and additional information on the proposal, is available on the COG website at www.cog.org.

We are currently engaged in the process of defining the details of this proposal and will comply with the requirements of the award letter as far as the format and content of the complete proposal. If you have any questions or concerns, please do not hesitate to contact us.

Sincerely,

John A. Bazzani, PhD, FOP
Research Associate Professor, Pediatrics

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- **Project 1:** Historical Data Mining of Efficacy / Toxicity Data – Wilms tumor (NWTS-IV and NWTS-V) and rhabdomyosarcoma (IRS-IV and IRS-V) studies.
- **Project 2:** Dosing/sampling procedure – method for utilizing a single central catheter to dose (actinomycin and vincristine) and sample (plasma for PK).
- **Project 3:** PK/PD Modeling and Clinical Trial Simulation
- **Project 4:** Prospective PK/PD/Outcome trial of vincristine and actinomycin in children (primarily less than 3 years of age)

Current Projects: Malabsorption Blood Test

- ◆ Demonstrate utility of MBT to assess the severity of fat malabsorption
 - ◆ Define utility in quantitative terms
- ◆ Propose MBT procedures for robust diagnostic application
 - ◆ Examine sensitivity of MBT to lifestyle conditions (food, enzymes, etc)
 - ◆ Explore population differences.
- ◆ Verify equivalence/superiority of MBT over "Gold Standard"

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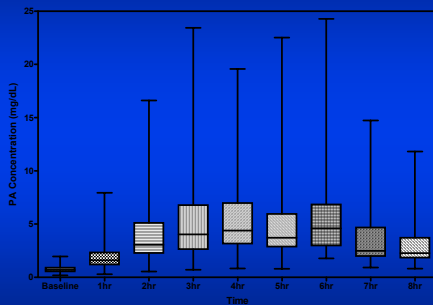
Project Assumptions

- ◆ The exposure of naturally occurring fats is an acceptable marker of fat malabsorption.
- ◆ Pentadecanoic fatty acid (PA) and Triheptadecanoic (THA), a triglyceride containing 3 heptadecanoic acids (HA) are acceptable as the target malabsorption markers.
- ◆ Direct Comparison of the MBT with the fecal recovery results will provide the ultimate clinical validation of the MBT

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PA and HA Response Characteristics

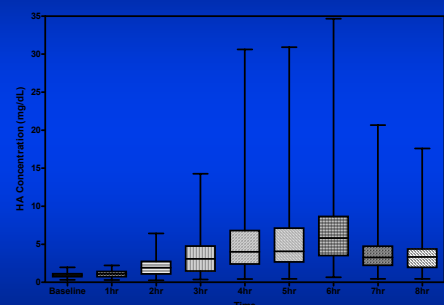
Pooled* PA Response (n = 46)



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PA and HA Response Characteristics

Pooled* HA Response (n = 46)



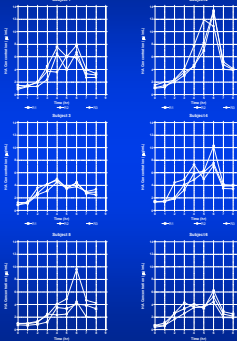
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Review of Historical Data

- ◆ 7 Studies conducted with MBT
 - ◆ Replicate Crossover Study (n = 6)
 - ◆ Orlistat Study - healthy volunteers (n = 15)
 - ◆ Enzyme Study - CF patients (n = 6)
 - ◆ Food Effect - healthy volunteers (n = 6)
 - ◆ Food Effect - CF patients (n = 6)
 - ◆ Equal Dose Study (n = 5)
 - ◆ Dose-finding (n = 8)
- ◆ Doses studied
 - ◆ PA: 2.5, 5, and 8 g
 - ◆ HA: 5, 5.5, 8 and 8.8 g
- ◆ Blood Sampling
 - ◆ Baseline sample collected every administration
 - ◆ Hourly over 8 hrs; 24-hr point recorded (n = 8)

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Clinical Response Characterization- HA

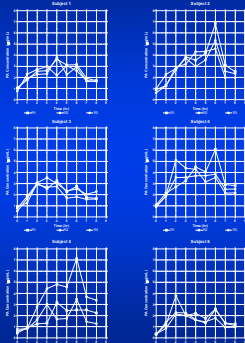


Test-Retest Study
3-way replicate crossover design (n = 6)
in healthy, adult volunteers

- ◆ Intrasubject CV (%)
 - ◆ Cmax 18.8%
 - ◆ AUC 18.8%
- ◆ Intersubject CV (%)
 - ◆ Cmax 39.4%
 - ◆ AUC 39.6%
- ◆ Profile Generalizations ?

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Clinical Response Characterization- PA



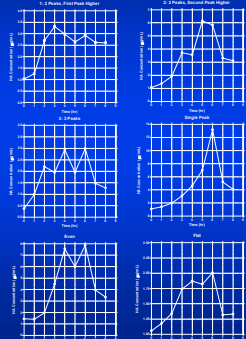
Test-Retest Study
3-way replicate crossover design (n = 6)
in healthy, adult volunteers

- ◆ Intrasubject CV (%)
 - ◆ Cmax 24.4%
 - ◆ AUC 17.4%
- ◆ Intersubject CV (%)
 - ◆ Cmax 34.7%
 - ◆ AUC 30.1%
- ◆ Profile Generalizations ?

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Review of Historical Data Variability in PA and HA Response

- ◆ SP - Single Peak
- ◆ 3P - 3 Peaks
- ◆ 1 - 1st Peak Higher
- ◆ 2 - 2nd Peak Higher
- ◆ F - Flat Peak
- ◆ Even - 1st and 2nd Peak Equal



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Review of Historical Data Variability in PA and HA Response

	PA (%*)	HA (%*)
Single	24.7	59.8
3 Peaks	2.2	0.0
1	23.7	5.2
2	39.8	17.5
FLAT	7.5	7.2
EVEN	2.2	10.3

* Percentage of category relative to the total number of profiles per fat

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Modeling Effort:

Objectives

- ◆ Describe the time course of the most relevant biomarker for fat malabsorption via PK modeling - Structural model
- ◆ Describe the population variation via nonlinear mixed effect modeling (NLMEM)
- ◆ Examine the influence of suspect covariates via NLMEM
- ◆ Propose dosing and procedural guidelines based on model based results
 - ◆ One or two point blood collection to evaluate MBT results and assess malabsorption
- ◆ Simulate pivotal trial

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Modeling Effort: Current Challenges

- ◆ Both PA and HA systemic exposure exhibit high variability with complex absorption profiles
- ◆ Existing population does not entirely reflect intended population
- ◆ Difficult to distinguish absorption characteristics from enterohepatic recirculation and meal time effects
- ◆ Small sample size (pooled data)
- ◆ Narrow dose range with single fat administration not studied

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Modeling Effort: Current Status Covariate Distribution Across MBT Trials (n=46)

	Weight ^a (kg)	Height ^b (cm)	BMI ^a (kg/m ²)	Age (years)
Mean	68.8	167.7	24.6	28.0
Median	68.4	165.4	24.5	28.0
SD	14.9	11.0	3.58	9.63
Min	40.5	146.1	17.3	12.2
Max	100	193.8	31.6	50.0

^an=44; ^bn=45

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Modeling Effort: Current Status Structural Model Results

Run	Model Description	OF	Sig Dig	ETA	COV	Comments
1	One Comp, 1st order Abs	1009	3.8	V,CLEND0,KA	Y	Abs misspecified, IPRED skewed, high SE
2	2 Comp, 1st order abs	1009	3.1	V,CLEND0,KA	N	Abs misspecified, IPRED skewed
3	1 Comp, 1st order abs, lag	965	3.3	V,CLEND0,KA	Y	Abs misspecified, IPRED skewed
4	1 Comp, 1st order abs, lag	1627	2.9	V,CLEND0,KA,ALAG1	N	Abs misspecified, IPRED skewed
5	1 Comp, Zero order abs	1129	3.3	V,CLEND0,D1	N	Abs misspecified, IPRED skewed
6	1 Comp, Zero order abs, lag	928	3.3	V,CLEND0,D1	N	Abs misspecified, IPRED skewed
7	1 Comp, Zero order abs, lag	947	3.4	V,END0,D1	N	Abs misspecified, IPRED skewed
8	1 Comp, Zero order abs, lag	1080	UR	V,END0,D1,ALAG1	N	Abs misspecified, IPRED skewed
9	1 Comp, Mixed Zero and 1st	1279	UR	V,CLEND0,KA,R1 V,END0,KA	N	Numerical difficulties with integration
10	1 Comp, Seq 1st order	1080	2.4	V,CL,KA1,KA2,ALAG3,END0 V,CL,KA1,KA2,END0,F2 V,CL,KA1,KA2,END0 V,KA1,KA2,END0	N	Abs misspecified, IPRED skewed
11	1 Comp, Nonlinear abs	1507	3.0	V,CLEND0,KS0,WMAX	N	Abs misspecified, IPRED skewed
12	2 Comp, Nonlinear abs	1355	2.9	V,CLEND0,KS0,WMAX	N	Ab misspecified, IPRED skewed
14	1 Comp, Weibull abs	1186	3.4	V,CLEND0,ALPHA	Y	Improved abs fit
15	2 Comp, Weibull abs	918	3.4	V,CLEND0,ALPHA	Y	Base Model

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Modeling Effort: Current Status Structural Model Results

- ◆ Structural model developed using data from healthy subjects with no Orlistat dosing
- ◆ Model specified using differential equations in NONMEM (ADVAN8, FOCE)
- ◆ Two compartment model with Weibull function to describe absorption process:

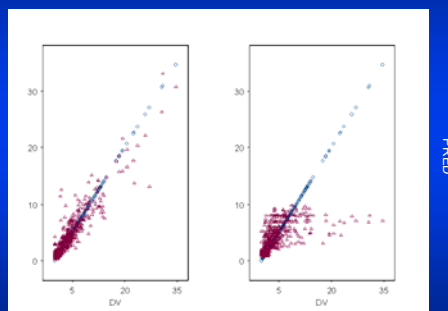
$$\frac{DX(t)}{Dt} = -\theta_1 * (1 - \exp(-(\frac{t}{\theta_2})^{\theta_3})) * X(t)$$

- ◆ Inter-subject variability modeled as:

$$P_i = P * \exp(\eta_i)$$

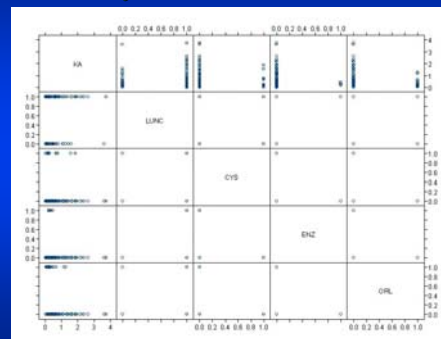
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Modeling Effort: Current Status Structural Model Results



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Modeling Effort: Current Status Preliminary Covariate Assessment



Note:
KA = θ_1 from Weibull Model

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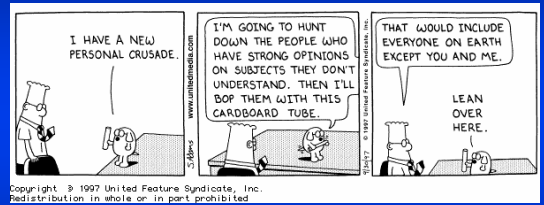
Modeling Effort: Current Status

Preliminary Covariate Assessment - Next Steps

- ◆ Examine Post-hoc estimates of other absorption parameters against suspect covariates
- ◆ Examine CL and Vd against suspect covariates
- ◆ Develop fully saturated model for n = 46 dataset
- ◆ Explore error models based on GAM analysis
- ◆ Perform backward deletion procedure to assess redundancies
- ◆ Determine final covariate model
- ◆ Refine error model
- ◆ Conduct bootstrapping for model qualification (not validation)

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And in Conclusion



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Acknowledgements / Collaborators

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John Mondick, PhD Student	Mimi Carroll, RN
Chuck Nicholson, MS Student	Donna Sylvester, RN
Dimple Patel, MS Student	
Juan Perrin, MS Student	
Richard Aplenc, MD	
Ian Blair, PhD	
A. Steven Whitehead, PhD	
George Macones, MD	
Kathryn Collison, BS	
Rita Jew, PharmD	
Marc Gastonguay, PhD	

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