Topic #2: Use of Exposure-Response Relationships in the Pediatric Study Decision Tree: Questions to be asked using the FDA Pediatric Database

- **Medical and clinical pharmacology perspective on the pediatric study decision tree and experience to date**
  - Rosemary Roberts, M.D.
- **Efforts to optimize pediatric clinical pharmacology studies**
  - Arzu Selen, Ph.D.

Efforts to Optimize Pediatric Clinical Pharmacology Studies

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CDER/FDA

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Focus

- **Pediatric Clinical Pharmacology knowledgebase**
- **Your input on the knowledgebase (e.g. contents, and optimizing information gained from the knowledgebase)**

Primary objectives for building a pediatric clinical pharmacology knowledgebase:

- **To better characterize factors that influence pediatric pharmacokinetic and/or pharmacodynamic parameters and optimize use of this information for dosing recommendations**

- **To utilize the available information for designing informative pediatric studies**

Pediatric Clinical Pharmacology Knowledgebase:

- **Current main source of information is the pediatric submissions to the Agency.**
- **Information from adult and pediatric literature, and if available, pertinent labeling information are also being entered.**

Pediatric Clinical Pharmacology Knowledgebase (continued):

- **Consists of study specific information such as dose, dosage form, patient demographics, study design, methods and drug and/or metabolite pharmacokinetic parameters (individual and mean data)**
  - Includes information on the pediatric decision tree

1. What other information/data should be collected for this knowledgebase?

2. Considering goals and objectives for the analysis of the FDA pediatric clinical and clinical pharmacology database:

What research questions and priorities would best serve pediatric public health and impact future pediatric studies? and what would be your recommendation on how to go about this analysis?

An example that illustrates some of our common observations in pediatric studies:

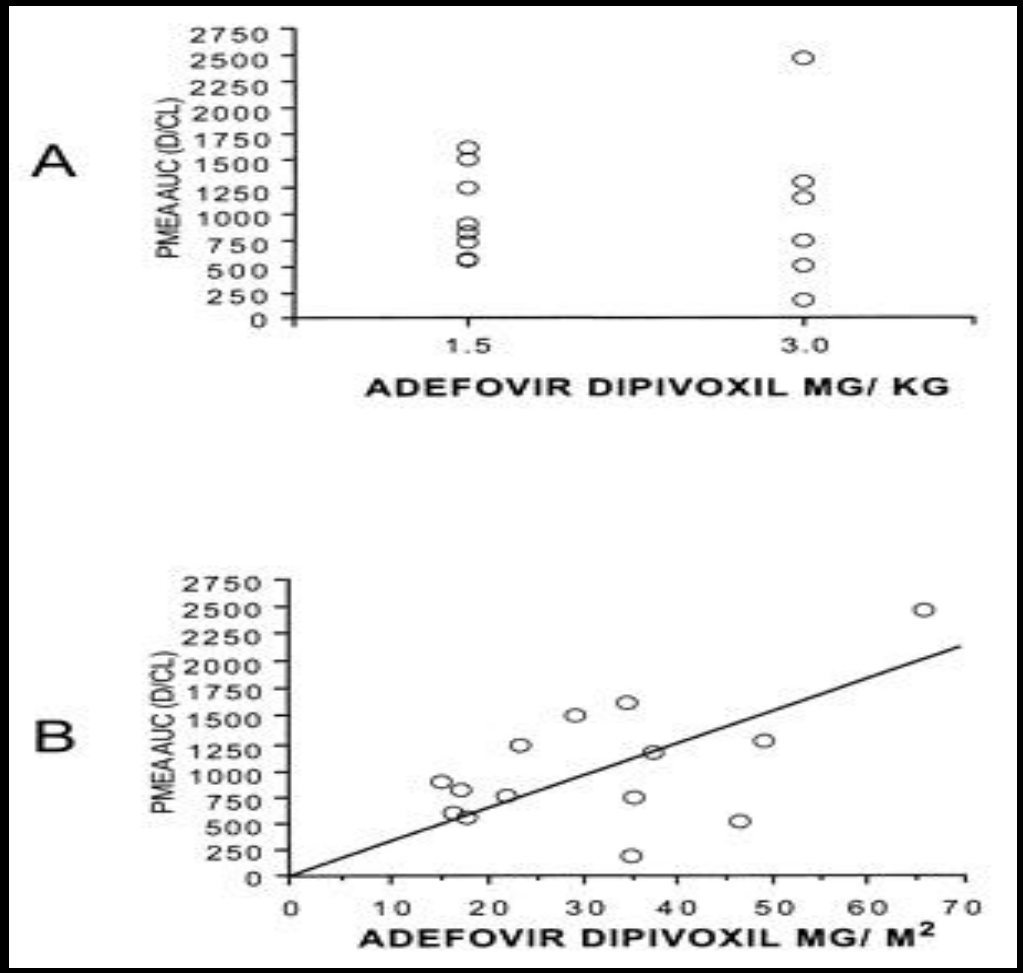
Walter T. Hughes et al.

Antimicrobial Agents and Chemotherapy,

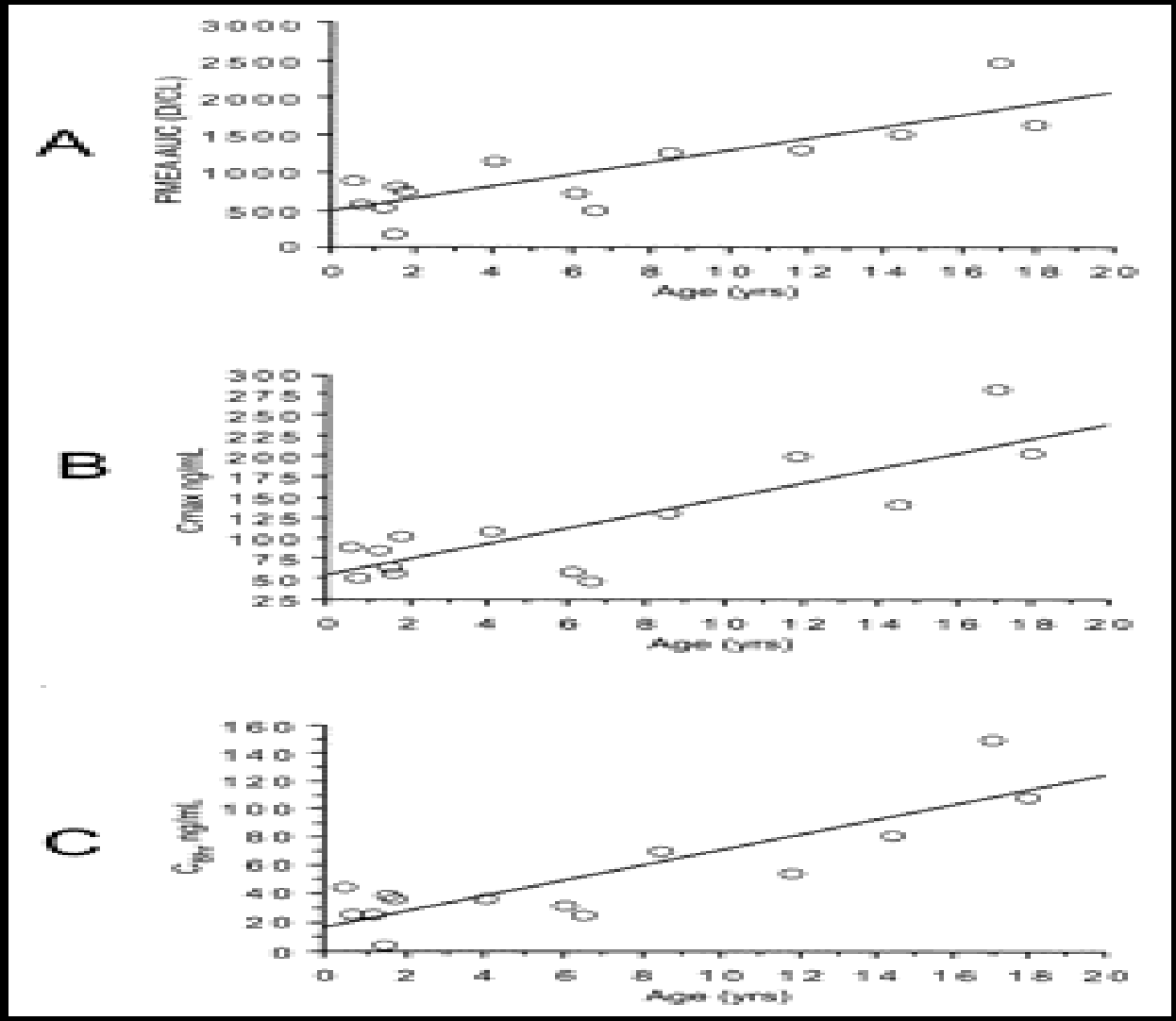
44, pages 1041-1046, 2000

- adefovir dipivoxil (1.5 or 3 mg/kg) doses were studied in 14 pediatric patients (6 months to 18 years of age)
- adefovir is primarily eliminated as unchanged drug by the kidneys

Comparison of the dose of adefovir dipivoxil and the AUC for adefovir (A) Dose based on body weight. (B) Dose based on body surface area ($r^2 = 0.81$).



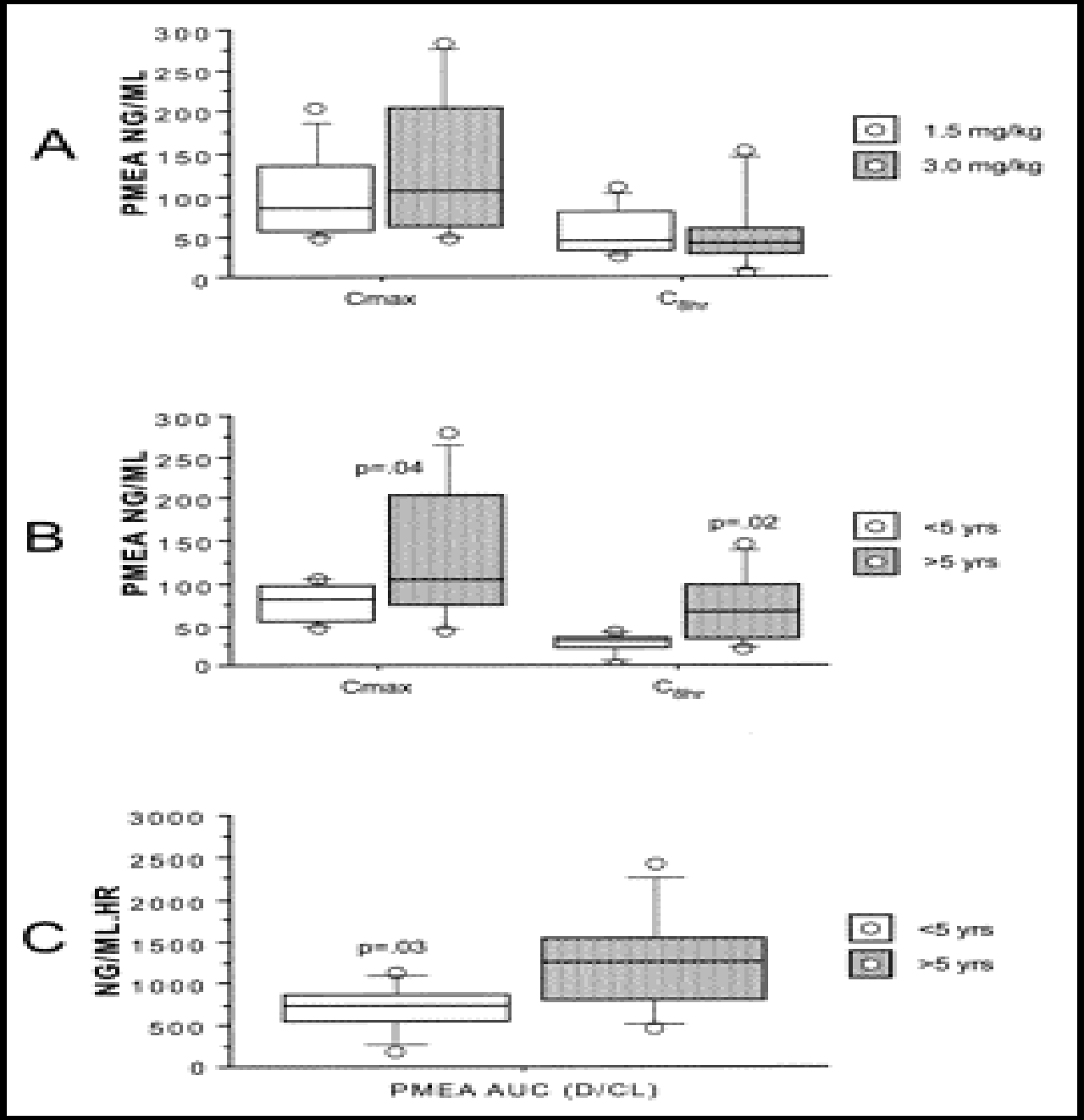
Adefovir AUC (Figure A), Cmax (Figure B) and C8 (Figure C) versus patient age



$r^2 = 0.71$

$r^2 = 0.71$

$r^2 = 0.75$


A
PMEA NG/ML
300
250
200
150
100
50
0
Cmax
1.5 mg/kg
3.0 mg/kg
B
PMEA NG/ML
p=.04
p=.02
Cmax
<5 yrs
>5 yrs
C
NG/ML.HR
3000
2500
2000
1500
1000
500
0
p=.03
PMEA AUC (D/CL)
<5 yrs
>5 yrs

Pediatrics is for Children

L. Kanner 1966

Questions to the Committee:

Goals and objectives for the analysis of the FDA pediatric clinical and clinical pharmacology database:

1.What additional information should be collected?

2.What research questions and priorities would best serve pediatric public health and impact future pediatric studies, and what would be your recommendation on how to go about this analysis?