Kidnet Trajectory: Where Have We Been? Where Should We Go?

Ann W. McMahon, MD, MS

Deputy Director of Science

Office of Pediatric Therapeutics

Presentation to the Pediatric Advisory Committee
September 12, 2017

History of Kidnet

- Initial discussions of PAC on octreotide in November, 2008.
- In discussion about octreotide, the PAC requested data to supplement FAERS from chart review on specific clinical/public health questions from network of pediatric hospitals.
- Data from the FDA Adverse Event Reporting System (FAERS) lacks consistent clinical detail and patient information and does not have a denominator.
- To address this issue, Kidnet started in 2011: network of 6-7 pediatric hospitals coordinated by FDA.

Kidnet #1

- First project: use and safety of octreotide and proton pump inhibitors (PPIs) in children
  - In NICUs and PICUs
- Review procedure:
  - Paper case report forms for data entry
  - Reviewers extracted retrospective data from paper or PDF charts.
  - Data entered into Access database at FDA.
  - Exported data to Excel and Stata software.
- Descriptive findings Kidnet #1 : Use and adverse events in pediatric ICUs of octreotide and proton pump inhibitors

Example of data available through Kidnet #1

- 222 children administered octreotide, N=53 died:
  - Mortality for Chylothorax and Post-surgical: 87.5%
  - Mortality for Chylothorax and Retinal Neovascularization: 44%
  - Mortality for Chylothorax: 19.5%
  - Mortality for Severe Hypoglycemia: 2%

Kidnet #2

U.S. FOOD & DRUG ADMINISTRATION

Serious Adverse Events During On-Label or Off-Label Use of Fentanyl or Azithromycin in Children in Intensive Care Units

Participating hospitals:

INOVA Children's Hospital

Children's National Health System

University of Maryland Children's Hospital

Children's Hospital of Michigan

Los Angeles Children's Hospital

Vanderbilt University School of Medicine

Why Were These Two Drugs Selected?

- Two drugs found among 135 drugs that were most frequently used in pediatric ICUs of one of collaborating hospitals.
- Most common drug groups used off-label in children are antibiotics and analgesics.*
- Fentanyl and azithromycin have on and off label use for pediatric population.

*Shah SS, Hall M, Goodman DM, Feuer P, Sharma V, Fargason C Jr, Hyman D, Jenkins K, White ML, Levy FH, Levin JE, Bertoch D, Slonim AD. Off-label drug use in hospitalized children. Arch Pediatr Adolesc Med. 2007; 161(3):282-90.

Kidnet #2

- Second project: serious adverse events: Are they more likely with off-label use in a pediatric ICU setting?
- Review procedure:
  - Data collected from electronic medical records (EMRs)- only difference from Kidnet #1
  - Some hospital systems electronically transferred to Excel spreadsheet from EMR.
  - Case report forms entered into Access database at FDA
  - Statistical software Stata and XLSTAT

Preliminary Data: Regression Analysis Separate for Fentanyl and Azithromycin

MODEL:

- Multivariate regression analysis
- Dependent variable: Serious Adverse Event (SAE) (yes/no)
- Independent variable: Off-label use
- Covariates include: gender, race, age, dose of drug by patient weight, number of comorbid conditions, number of concomitant medications, and hospital unit

FINDINGS:

Fentanyl: Off-Label use consistently associated with SAEs:
OR 3.0 (CI 1.2-7.7)
Azithromycin: Off-Label use not associated with SAEs:
OR 1.0 (CI 0.3-2.5)

STRENGTHS: Kidnet #2

- More clinical detail than Kidnet #1
- Used EMRs rather than paper charts
- Sample size slightly bigger than Kidnet #1
- Question more targeted than Kidnet #1
- Possible implication of narrow therapeutic index of fentanyl

LIMITATIONS: Kidnet #2

- Design of this study: convenience sample, retrospective chart review

Kidnet #3

- Focus on quantifying renal adverse effects of intravenous acyclovir in neonates
- Centralized **R**esearch **E**lectronic **D**ata **Cap**ture (Redcap) automated system for data entry at all sites
- Manually enter data into redcap or some variables are extracted from the electronic medical record and added to redcap database.
- Data de-identified centrally and sent to FDA

Kidnet Evolution

- Kidnet has evolved technologically
- Headed toward fully electronic data transfer: towards larger sample sizes
- Would electronically extracted data alone have disadvantages for Kidnet?
  - Might miss clinical detail obtained by medical record review (might lose data in text fields)
  - Could potentially supplement electronic data transfer with medical record review
- FDA Workshop on "Big Data" in pediatrics 9/18/2017: "Advancing the Development of Pediatric Therapeutics (ADEPT): Application of "Big Data" to Pediatric Safety Studies"
  https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm545847.htm

Strengths of Kidnet

Provides pediatric clinical detail

Has demonstrated ability to address directed questions with a sufficient sample size

Limitations of Kidnet

Limited sample size for answering many questions

To date, limitation in choosing study designs: currently cross sectional study designs

Points to Discuss

- How should we refine Kidnet going forward?
- What types of pediatric safety studies should we focus on using Kidnet?


FDA
U.S. FOOD & DRUG
ADMINISTRATION