Pharmacogenomics: Special Considerations for Pediatric Patients

Marc S. Williams, MD, FAAP, FACMG
Director Genomic Medicine Institute
Geisinger Health System

Pharmacogenomics-Benefits

- More effective therapy
- Safer therapy
- More cost-effective therapy
- Decreased pharmaceutical utilization?
- Innovative therapies

Disclosures

- On File
- No information in presentation subject to conflict of interest

Pharmacogenomics-Limitations

- Availability of information
- Predictive accuracy
- Adoption of new technology
- Availability of new technology
- Good-bye to formularies?
- Cost implications

Pharmacogenomics-Definition

- The study of how variations in the human genome affect the response to medications.
- Pharmacogenetics vs. pharmacogenomics

Special Challenges in Pediatrics

- Children are not small adults
- Gene expression changes as healthy children grow
  - Some pharmacogenes are impacted
- Many fewer drug studies performed in children
  - Fewer opportunities to study pharmacogenomics

Prevention Adverse Events

- 2012 international prospective study in pediatric inpatients
  - 16.5% rate of ADE
  - 24% severe

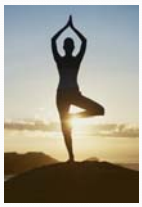

Pharmacogenomics 2010

Carbamazepine (Tegretol) Sensitivity

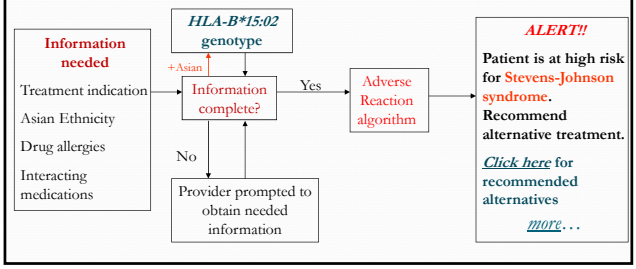
Example-Carbamazepine and HLA-B*15:02

- Small percentage of patients experience severe cutaneous ADE (Stevens-Johnson syndrome, Toxic Epidermal Necrolysis)
- Studies in Thailand and Taiwan noted higher rate of reaction
- Genetic studies identified HLA-B*15:02 as the primary risk factor
  - Higher frequency of this HLA type
  - Marked increased risk for SJS/TEN
- FDA recommends testing for "patients with ancestry in at-risk populations …"

Balancing Adverse Events and Efficacy



Clinical Decision Support for Carbamazepine



Safety and Efficacy of Codeine

- Concerns about safety and efficacy of codeine
  - Some institutions have removed from pediatric pharmacy
- Codeine and *CYP2D6*
  - Ultra-rapid metabolizer—toxicity
  - Slow metabolizer—poor pain control
  - Safety and efficacy are independent
- Challenges with *CYP2D6* genotyping

TPMT and 6-MP

- 6-mercaptopurine (6-MP)
  - Used to treat acute lymphoblastic leukemia (ALL), and inflammatory/autoimmune disease
  - Risk of bone marrow suppression
- 6-MP metabolized by Thiopurine methyltransferase (TPMT)
  - Polymorphisms in *TPMT* gene affect 6-MP metabolism
  - Associated with increased risk for complication

TPMT genotype and ALL response

- Stanulla et al (JAMA 293:1485-9, 2005)
  - Studied *TPMT* genotype
  - Measured minimal residual disease before and after 4-week treatment with 6-MP
  - Patients with at least one 'mutant' *TPMT* allele had significantly lower rate of minimal residual disease (9.1% vs. 22.8%)
- 6-MP is more efficacious in patients with at least one 'mutant' *TPMT* allele!!
  - No difference adverse events
  - MRD positive patients are 5-10 times more likely to relapse than MRD negative patients (von Dongen JJ et al. Lancet 352:1731-8, 1998)

TPMT and 6-MP

- Recommendation to test *TPMT* in patients starting 6-MP
  - If polymorphisms present avoid or adjust dose of 6-MP
  - US FDA changed label
- Problem

Questions

- Should we sacrifice increased efficacy to prevent adverse events?
- Would it be better to use same dose and monitor blood counts more closely?
- Should we raise the dose of 6-MP in wild type individuals to increase efficacy?

Balancing Adverse Events and Efficacy

- Focus is on prevention of adverse event
  - The majority of patients with *TPMT* polymorphisms do not experience bone marrow suppression
  - Wild-type individuals still experience bone marrow suppression
- What about efficacy?

ALL vs. Inflammatory Bowel Disease (IBD)

- 6-MP used to treat both
- Higher short term morbidity and mortality in ALL vs. IBD
- IBD response to 6-MP improves with lower TPMT enzyme activity (related to genotype) Cuffari et al. Clin Gastroenterol Hepatol 2:410-7, 2004

Questions

- Is the risk/benefit ratio the same for ALL and IBD?
- Should monitoring be different based on treatment indication?

Conclusions

- Pharmacogenomics will become increasingly evident in pediatric practice
- Evidence is emerging, but still inconsistent for most drug gene interaction pairs
- Electronic Health Records and Clinical Decision Support will be needed
  - AAP Genetic's Handbook has a chapter on this

Evidence Based Guidelines

- FDA: Excepting companion diagnostics only Abacavir requires PGx testing (HLA-B*57:01)
- Clinical Pharmacogenetics Implementation Consortium
  - https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC
- Several guidelines relevant to pediatric patients
- Caveat: Guidelines presume genetic information is available

Evaluation

Future Opportunities

- Oncology
  - Molecular delineation of malignancy
- Neuropsychiatry
  - Anticonvulsants (vigabatrin and Tuberous Sclerosis)
  - Methylphenidate
  - SSRIs and anti-psychotics
- Rheumatology
  - Methotrexate safety and efficacy
- Asthma
  - Variable response to beta-agonists, inhaled corticosteriods, leukotriene modifiers