

Drug Interactions

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Overview

- Drug Interactions (DI) and Toxicity
- Common DI Categories
- Identification of DIs
- Knowledge and Dissemination
- Concluding comments

Types of DI and Toxicity

- Target drug reaches sub-therapeutic levels
 - Proton pump inhibitors and atazanavir
- Target drug reaches therapeutic levels
 - Without added toxicity
 - Benign
 - Beneficial - ritonavir boosting
 - With known toxicity
 - Zidovudine and anemia
 - Manageable, Tolerable, or limiting
 - With previously unreported toxicity
 - Perhaps seen in Phase I studies?

Common Categories of DI

- Drug-Drug
 - Prescription, OTC, herbal
- Drug-Disease
 - Anemia and pegylated interferon/ribavirin
- Drug-food
 - Warfarin and vitamin K
 - Nutritional supplements
- Drug-alcohol
 - Efavirenz

Identifying DI and Toxicities

- Drug Development and Clinical trials
 - Preclinical
 - Metabolism, toxicity
 - Phase I PK studies
 - Maximize potential effect while minimizing toxicity
 - Focus on specific toxicities (CV) and preclinical events
 - Phase II/III - efficacy and toxicity
 - Young, very healthy population
 - Relatively short period of time on medications
 - Few co-administered medications permitted
 - Toxicities reported out only at the highest grades

Characteristics of NDA Clinical Trial Populations

	atazanavir	maraviroc
Treated sample	ARV naive 405	Treated 426
Age - mean	34 (18 - 73)	46 (21 - 73)
Sex - % male	65%	90%
Race	33% white 36% hispanic	85% white
Adverse event reporting	Treatment emergent	
Trial length	24 weeks	24 week

Ongoing Learning of DI and Toxicities Post-Approval

Early

- Assumptions based on known clearance

Midterm

- Case reports (MedWatch)
- Scientific meetings

Late

- Post-marketing trials

Prescriber Knowledge of DI

- Multiple sources
 - Package insert
 - Manufacturer (DI center)
 - Web sites (numerous)
 - Educational forums
 - Medline

Issues with Implementing Knowledge

- Right data at the right time
 - In Clinic with the patient
 - At the time of prescribing
 - Prescription ordering systems
- Formulary oversight may limit easy access to “safe” options

Why the VA Cares

- Over 21,000 HIV positive veterans seen in outpatient care in Jan - Jun 2007
- Mean/Median age - 52 years
 - 20% 60 YO and older (≈ 4,300)
 - 57% 50 YO and older

Source: National Clinical Case Registry, July 2007

What would help us

- Increase likelihood of identifying a DI by increasing knowledge of toxicities
 - RCT populations (report out all toxicities)
 - Observational studies
 - Provider reporting - MedWatch
- Improve timeliness/dissemination of knowledge
 - At the time of prescribing
 - All-in-one web tools
- Improve models for predicting interactions/toxicities
 - Decision tree analyses (AI)
 - Pharmacogenomics (HLAB*5701)

Questions