Online Database For Grapefruit Juice Drug Interactions: What Have We Learned ?

I. Zadezensky[1], W.V. de Castro[1], J. Meyer[1], V. Butterweck[1] , H. Derendorf[1]

[1]Center for Food and Drug Interaction Research and Education, University of Florida, Gainesville, FL

INTRODUCTION

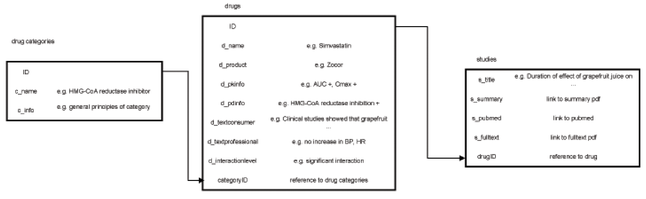
Background & Significance

- Discovery of the grapefruit juice drug interaction in 1989 [*Bailey et al.*]
- Grapefruit juice components inhibit CYP3A4 (mechanism based) [*Schmiedlin-Ren et al.*]
- Until today more than 163 scientific papers about grapefruit juice interactions have been published
- Public awareness created by mass media as CBS, MSNBC, CNN, ABC etc.
- Misconceptions about grapefruit juice drug interactions are common among the mass media
- Further confusion is generated by published case reports with high mass media impact [*Karch*]
- Misconceptions have great economic impact for the Florida region, since
- In 2005 Florida supplied 13.5% of the worlds grapefruit production, and
- The per capita consumption of grapefruit juice has declined by 50% since 1999 [*Citrus Reference Book*]

Purpose

- Create an online database available to patients and health care professionals
- Generate a source of reliable information and eliminate misconceptions
- The online database should be easily accessible and
- The online database should contain differentiated information for patients and professionals
- Patients or professionals should be able to browse by the compound name, brandname or category of their drug

MySQL Layout – database structure



METHODS

Software

- The website was programmed as a MySQL database using the software PHP4
- PHP4 allows dynamic websites. That means that the website is generated according to the user input.
- Microsoft ® Word was used to create one page summaries of published clinical trials, animal experiments or in-vitro experiments
- Webalizer 2.01 was used to record the website statistics

Literature Sources

Searches performed in:

- PubMed, Web of Sci, PDR,
- Clinical Pharmacology, WebSPIRS and Google

to create a comprehensive database of published literature.

Interaction Classification

The interaction level was determined using the classification recommended by the Pharmaceutical Research and Manufacturers of America (PhRMA) [Bjornsson et al.;J Clin Pharmacol. 2003 May;43(5):443-69]. The classification is as follows:

strong interaction : ≥ 5 fold increase in plasma AUC of Midazolam

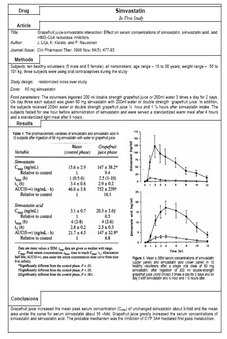
moderate interaction : >2.0 to 4.9 fold increase in plasma AUC of Midazolam

weak interaction : ≤ 2.0 fold increase in plasma AUC of Midazolam

USER FRONT END

Summary Page

1. Search function
2. Differentiated information
3. Easy browsing
4. Interaction level
5. Relevant information
6. Online summaries



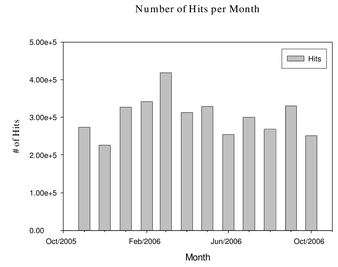
RESULTS

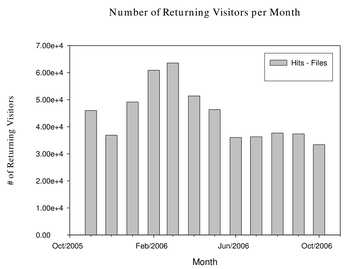
The programming of the database resulted in a set of 163 papers, currently containing 74 drugs.

- 71 drugs were prescription drugs
- 3 drugs were over the counter (OTC) drugs
- Combination drugs e.g. Vytorin (simvastatin / ezetimibe) were not studied
- All studied OTC drugs showed a weak interaction with grapefruit juice
- 48 (67.6%) exhibited a weak interaction
- 14 (19.7%) demonstrated a moderate interaction
- 6 (8.4%) showed a strong interaction
- 3 drugs (4.2%) were not tested in humans
- The online database is currently available under the URL: www.druginteractioncenter.org

Website Statistics

- 3,637,737 Hits since November 2005
- Currently estimated 14% returning visitors





CONCLUSIONS

- The great number of hits and returning visitors shows that there is a substantial need for patient and health care professionals education regarding grapefruit juice drug interactions.
- The current misconception that most drugs interact strongly with grapefruit juice seems not to hold, since most drugs seem to interact only weakly with grapefruit juice.
- Some factors however, have to be considered:
  - most clinical trials performed only single drug dosing
  - no long term grapefruit juice ingestion study was performed
  - grapefruit juice volumes and strengths varied greatly among studies
  - many studies did not measure the active compounds in grapefruit juice
  - the patients CYP 3A4 status was not assessed
  - combination drugs were not studied
  - the clinical relevance of some interactions still remains in doubt

In future, an user survey could help to explore further needs of the website users.