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Herbal and Dietary Supplement (HDS) Induced Hepatotoxicity: Outline

• Definitions
• Regulatory Environment
• HDS and DILI
• The DILIN Experience
• Causality Assessment
• Summary
HDS in the US

- 42% of Americans use some form of alternative therapy
- ~19% use dietary supplements (DS)
- 20-40% of liver patients use herbal remedies
- 21% of adult prescription drug users use DS concurrently
- 69% do not disclose DS use to their conventional provider
- $17 billion in sales (2000); the average price is decreasing

Eisenberg et al. Am J Gastroenterol 2002
Strader et al. Am J Gastroenterol 2002
Seeff et al. Hepatology 2008
Gardiner Arch Intern Med 2006
Dietary Supplement: defined

http://www.fda.gov/Food/DietarySupplements/default.htm

• Dietary Supplement Health and Education Act (DSHEA) of 1994
• DS are foods, not drugs
• “a product taken by mouth that contains a ‘dietary ingredient’ intended to supplement the diet”
• Dietary ingredients
  – Vitamins
  – Minerals
  – Herbs or other botanicals
  – Amino acids
  – Enzymes, organ tissues, glandulars, and metabolites
• “New” dietary ingredient: not sold in the US in a DS prior to Oct. 15, 1994
Regulatory Environment for HDS

http://www.fda.gov/Food/DietarySupplements/default.htm

• DSHEA
  – The manufacturer is responsible for safety
  – Claims must be substantiated
  – FDA approval is not required before marketing
  – New dietary ingredients require pre-market review of safety data

  – Minimum CGMPs for manufacturing, packing, labeling, holding
  – Intended to ensure identity, purity, quality, strength, composition of DS
Regulatory Environment for HDS

http://www.fda.gov/Food/DietarySupplements/default.htm

• Manufacturer must
  – Notify FDA of intent to market a DS that contains a new ingredient
  – Disclose on label the list of ingredients, manufacturer, net contents, nutritional information
  – Ensure DS are safe before marketing
  – Record, investigate, and forward reports of SAE to the FDA
  – Provide disclaimer, that the FDA has not pre-approved/evaluated any stated health claim

• Manufacturer must not promote a DS as treatment, prevention, or cure
Regulatory Environment for HDS

http://www.fda.gov/Food/DietarySupplements/default.htm

- FDA
  - Assumes responsibility to determine if a DS is unsafe before it can take action
  - Obtains information from inspections, complaints, analyses, AEs
  - May analyze composition of DS thought to have caused injury
HDS in the US

- Groups most commonly using HDS
  - Hispanic
  - non-Hispanic Asians
  - uninsured younger
  - Female
  - highly educated
  - high perceived health status
  - use a fitness center
  - no usual primary care

- Common reasons for using HDS
  - Menopausal symptoms
  - GI complaints
  - Liver disease
  - Headache
  - Migraine
HDS and DILI

- Androstenedione
- Atractylis gummifera
- Black cohosh
- Callilepis laureola
- Chaparral
- Germander
- Greater celandine
- Green tea extract
- Kava
- Licorice
- Mistletoe
- Pennyroyal
- Pyrrolizidine alkaloids
- Senna
- Usnic acid
- Valerian

- Herbalife (not all products)
- Hydroxycut (not all products)
- Chinese herbal medicines (certain constituents)
- LipoKinetix
300 patients (Sept 04- Dec 07)
- 33 patients took HDS
  - 28, one or more HDS
  - 5, HDS in combination with prescription drugs
- Reasons for use
  - Muscle building
  - Weight loss
  - Insomnia
  - Well-being
  - Cold prevention
  - Menopausal symptoms
- Trend to higher bilirubin and longer duration of DILI due to HDS compared to prescription drugs
Hydroxycut


Hepatotoxicity Due to Hydroxycut: A Case Series


- 17 new cases
  - 8 cases at several medical centers
  - 9 of 24 FDA MedWatch cases with sufficient information
  - One died, 3 required liver transplantation

- Causality assessment, severity grading by DILIN guidelines
  - Definite = 8
  - Very likely = 5
  - Probable = 2
  - Possible = 2
HDS and the DILIN Experience
71 HDS-only cases as of 9/09

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.8 yrs</td>
</tr>
<tr>
<td>Gender</td>
<td>54.9% (male)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>70.0%</td>
</tr>
<tr>
<td>Black/African American</td>
<td>12.9%</td>
</tr>
<tr>
<td>Latino</td>
<td>16.9%</td>
</tr>
<tr>
<td>Other</td>
<td>17.1%</td>
</tr>
<tr>
<td>BMI</td>
<td>27.6 (23.8, 30.2)</td>
</tr>
</tbody>
</table>
## HDS and the DILIN Experience

71 HDS-only cases as of 9/09

<table>
<thead>
<tr>
<th>Latency</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDS to First Sign/Symptom</td>
<td>30.0 (7.0,52.0)</td>
</tr>
<tr>
<td>HDS to Onset</td>
<td>39.5 (23.5,72.5)</td>
</tr>
</tbody>
</table>
# HDS and the DILIN Experience

71 HDS-only cases as of 9/09

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>80.3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>67.6%</td>
</tr>
<tr>
<td>Itching</td>
<td>56.3%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>49.3%</td>
</tr>
<tr>
<td>Rash</td>
<td>26.8%</td>
</tr>
<tr>
<td>Fever</td>
<td>23.9%</td>
</tr>
</tbody>
</table>
**HDS and the DILIN Experience**

*71 HDS-only cases as of 9/09*

<table>
<thead>
<tr>
<th>Liver Enzymes @ Onset</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>637.0 (262.0, 1443.0)</td>
</tr>
<tr>
<td>AST</td>
<td>370.0 (146.0, 1118.0)</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>172.5 (116.0, 277.0)</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>8.0 (3.9, 12.4)</td>
</tr>
<tr>
<td>INR</td>
<td>1.1 (1.0, 1.4)</td>
</tr>
</tbody>
</table>
HDS and the DILIN Experience
71 HDS-only cases as of 9/09

<table>
<thead>
<tr>
<th>Pattern @ Onset</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestatic</td>
<td>18.5%</td>
</tr>
<tr>
<td>Mixed</td>
<td>16.9%</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>64.6%</td>
</tr>
</tbody>
</table>
HDS and the DILIN Experience
71 HDS-only cases as of 9/09

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>56.3%</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>0</td>
</tr>
<tr>
<td>Chronic</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of Illness</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week or less</td>
<td>10%</td>
</tr>
<tr>
<td>2-4 weeks</td>
<td>25.7%</td>
</tr>
<tr>
<td>&gt; 4 weeks</td>
<td>64.3%</td>
</tr>
</tbody>
</table>
### HDS and the DILIN Experience

#### 71 HDS-only cases as of 9/09

<table>
<thead>
<tr>
<th>DILIN Causality Score</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite (&gt;95%)</td>
<td>21.4%</td>
</tr>
<tr>
<td>Very Likely (75-95%)</td>
<td>35.7%</td>
</tr>
<tr>
<td>Probable (50-75%)</td>
<td>21.4%</td>
</tr>
<tr>
<td>Possible (25-50%)</td>
<td>17.9%</td>
</tr>
<tr>
<td>Unlikely</td>
<td>3.6%</td>
</tr>
</tbody>
</table>
HDS and the DILIN Experience

HERBAL PREPARATION 15
OTHER COMBINATIONS OF NUTRIENTS 10
ALL OTHER THERAPEUTIC PRODUCTS 8
ANABOLIC STEROIDS 8
HYDROXYCUT 5
HERBALS NOS W/MINERALS NOS/VITAMINS NOS 2
Challenges in Causality Assessment

• Complete case ascertainment
• Complexity and multiplicity of HDS
• Possibility of adulterants
  – Pharmaceuticals
  – Microbes
  – Chemicals
  – Heavy metals
• HDS – Drug interactions
# Product Analysis

<table>
<thead>
<tr>
<th>Ingredient/Contaminant</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content/concentration verification</td>
<td>HPLC/Mass Spec</td>
</tr>
<tr>
<td>Microbial Analysis</td>
<td>Bacterial culture DNA extraction</td>
</tr>
<tr>
<td>Heavy metals (arsenic, lead, mercury)</td>
<td>X-Ray Fluorescence Spectroscopy</td>
</tr>
</tbody>
</table>
Pilot Study of Catechins in HDS
Background/Rationale

• Green tea extract (GTE) is commonly found in many HDS
• Reported cases and animal toxicology support potential for DILI attributable to GTE, specifically catechins
• Catechins comprise 10% of GTE
Catechin
Pilot Study of Catechins in HDS

Human Pharmacology

- EGCG: 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, or 1600 mg, safe and well tolerated.
- Significant pharmacokinetic variability
- Half life, 4.6 hours
- Maximum tolerated dose of GTE, 4.2 g/m² daily, or 6.1 to 9.9 gm (mild headache, fatigue)
- Higher exposure in a fasted state
- Variable EGCG concentration per product; range of 8.65 to 17.69 mg per 100mg of GTE
Pilot Study of Catechins in HDS

Pharmacology

- Epidemiologic studies suggest association with lower risk of stomach, esophagus, and lung cancers
- Animal studies show reduction in growth of breast and prostate cancer, through induction of apoptosis;
  - Mitochondrial depolarization
  - Formation of ROS
  - GSH depletion potentiates cell death (rats, mice)
Pilot Study of Catechins in HDS

Specific Aims

1. To assay catechins in HDS that have been causally linked to DILI
2. To determine if catechins are unique to GTE-labeled HDS
3. To correlate catechin concentration with several measures, including:
   a. Severity of illness
   b. Probability of DILI
   c. Clinical pattern
4. To explore other non-catechin compounds
5. To accelerate the tempo of research with HDS
Case Presentation

• 58 year old woman
• Long history of IBS/constipation
• 8 week history of non-specific illness
  – Cough
  – Fever
  – Malaise
• Progressive complaints, with onset of jaundice and ascites
• Admitted to the hospital
Case Presentation

• Examination
  – Icterus
  – Cough

• Lab Tests
  – ALT 80 IU/L
  – AST 96 IU/L
  – Alk Phos 353 IU/L
  – TBili 4.4 mg/dL
  – INR 1.65
Sinusoidal Obstructive Syndrome

- Acute presentation
- Evolution to chronic disease
- Elevated Alk Phos predominates
- Portal hypertension
- Pyrrizolidine alkaloids, terpenes
Case Presentation

• 4 Dietary supplements
  – Green tea extract
  – Black cohosh
  – Glycyrrhiza glabra
  – Skull cap
  – Cascara sagrada

• Analysis
  – Liquid chromatograph-tandem mass spectrometry
  – Sun Il Hwang, Yongyook Lee, Herb Bonkovsky, Carolina HealthCare System, Charlotte NC
The Complexity of HDS
Quantification of Catechins using SRM
Summary

- Herbal and Dietary Supplements are used commonly and can cause DILI.
- The regulatory environment for HDS differs from pharmaceuticals.
- HDS associated DILI can take many forms, but is most commonly hepatocellular.
- Causality assessment is confounded by the complexity of HDS.
- DILIN will focus on:
  - Dissemination of experience with HDS associated DILI.
  - Refine causality assessment.
  - Product analysis.