Panel Discussion

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Application of pharmacogenetics/pharmacogenomics technology to drug development

Survey of CMR International Institute for Regulatory Science, 2003

NAS: new active substances
Pharmacogenomics in Drug Regulation in Korea

- No NDA file including PGt/PGx data was submitted to KFDA, yet.
  - No experience of reviewing

- KFDA (discussion with regulatory agencies):
  - highly concerned
  - positive to review the data
  - intramural fund for research on the application of PGt/PGx to regulatory review (10 years)
  - plan to prepare a guidance for PGx application to drug regulation
  - Pharmacogenetics study group in KFDA
Pharmacogenomics Researches in Korea: Research Projects

- **Korean Pharmacogenomics Research Network (KPRN)**
  - Project Leader: Prof. Sang-Goo Shin
  - Schedule: FY 2003 – FY2011 (9 year term)
  - Budget: 21 million USD for 9 years, funded by MOHW
  - Discovery of polymorphisms related to drug safety and efficacy in a Korean population
  - 5 Centers for ADR, drug metabolism, transporters, respiratory drugs, CNS drugs and others

- **National Research Lab. for Pharmacogenomics**
  - Project Leader: Prof. Jae-Gook Shin and Dr. Hyung Doo Shin
  - Schedule: FY 2003- FY 2007
  - Budget: 3.3 million USD for 5 years, funded by MOST
  - Development of Pharmacogenomics technology in Korea
Other Projects related to PGx in Korea

- **Hap Map Projects**
  - Haplotyping and LD mapping, chromosome 22
  - 9 million USD for 5 years

- **The Center of Functional Analysis of Human Genome**
  - Functional genomics of gastric and liver cancers
  - 90 million USD for 10 years

- **Disease and Pathogenic Microbe Genomics**
  - Disease and pathogen related functional genomics
  - 62 million USD for 10 years
  - 11 center for specific disease and 3 centers for pathogenic microbe
Academic Activities of Pharmacogenomics in Korea

- Pharmacogenomics Research Study Group
  - Established at June, 2001
  - 100 members working at university and drug industry
  - Regular seminar and symposium

- Pharmacogenomics Research Center (PGRC), Inje University, Busan
  - Established at Jan. 2003
  - Research and training on pharmacogenomics

- International Symposia
  - Yonsei Biomedical Symposium on Pharmacogenomics: Feb. 2003, Seoul
  - Pharmacogenomics: Impact on Clinical Trial – Oct. 2003, by NITR, KFDA, Seoul
  - Pharmacogenomics: A step toward personalized pharmacotherapy – Feb. 2004 by KPRN and PGRC, Busan
Korean Society of Pharmaceutical Medicine (KSPM) survey

- Currently, around 50 members
- Male : female (7:3)
- Working at Multinational company (83%), domestic and CRO etc.
- Age group: 40~44 (43%) > 35~39 (27%) > 45~49 (13%) > over 50 (10%) > under 35 (7%)
- Careers in Pharmaceutical industry: 3 ~ 5 yrs(43%) > 6 ~ 10 yrs (20%) = under 1 year (20%) > 1 ~ 2 yrs (13%) > over 10 years (3%)
- Clinical specialist (97%): IM (38%) > FM (22%) > Psy (13%) > Ped (6%), and others (22%)
- High academic degree: MD. PhD (60%), MD. MS (33%)
- Previous job: faculty in university hospital (55%) and general hospital staff (25%)

2004 survey result provided by KSPM
Trainings of Clinical Trialists in Korea

- Pharmaceutical Medicine or Reviewer

- No previous specific program for training of Pharmaceutical medicine.
  - After recruiting, trained by themselves

- Development of training program of clinical trialists
  - by Korean Health Industry Development Institute, MOHW
  - On going the development of protocol for training program
  - Start from FY 2005 – for 10 years (not confirmed)
  - Training of reviewer, clinical investigator, clinical pharmacologist, biostatistician, clinical trial pharmacist, clinical research nurse, CRC/CRA, etc.
  - KFDA – considering the training program of reviewers
Bridging Issues in Korea

- Acceptability of Asian Data
  - Asian; Same ethnicity?
  - Mutual recognition of Asian data?

- Statistics
  - Statistically meaningful sample size?
  - Multinational study; subgroup analysis?

- Many study design issues
  - Similarity?
  - Titration drug
  - Placebo
Propose the different diet between two ethnic subjects: hot pepper and garlic

Capsaicin: increase CYP450 activity in rat and mouse
(Iwana et al., 1989; Kim et al., 1998)

Kwon and Yokoi et al., Pharmacogenetics 2001
### Effects of Hot Pepper on the CYP2A6 activity in healthy Korean subjects

(Preliminary data)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Pepper restricted</th>
<th>Pepper containing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>4.22 ± 1.15</td>
<td>4.69 ± 0.95</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.71 ± 0.17</td>
<td>0.55 ± 0.21</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>8.72 ± 6.27</td>
<td>3.68 ± 1.82*</td>
</tr>
<tr>
<td>Vd/F (L/kg)</td>
<td>9.79 ± 2.07</td>
<td>7.42 ± 2.42</td>
</tr>
<tr>
<td>Cl/F (L/h/kg)</td>
<td>1.03 ± 0.53</td>
<td>1.60 ± 0.60*</td>
</tr>
<tr>
<td>AUC (ng/ml•h)</td>
<td>39.4 ± 17.2</td>
<td>21.4 ± 11.0*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2hr cotinine/nicotine ratio</th>
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</thead>
<tbody>
<tr>
<td>hot pepper restricted</td>
</tr>
<tr>
<td>hot pepper included</td>
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</table>

**Hot pepper restricted diet**
- restriction of hot pepper and garlic in regular diet for 7 days

**Hot pepper containing diet**
- 15g daily dose
Abacavir hypersensitivity

- A potent HIV-1 nucleoside reverse transcriptase inhibitor
- High incidence of severe hypersensitivity (average 5%) – 2-4 death per 10,000 treated patients
- Two studies: HLA-B polymorphism (HLA B5701)
  - Prospective study of 200 patients
    - 18 cases: 14 (+) marker, 4 carriers in 167 tolerant patients
    - 78% sensitivity, 98% specificity (100% by haplotype with 2 more markers)
  - Retrospective case/control study
    - 85 cases/115 control
    - 46% sensitivity, 96% specificity (55% and 99% for Caucasians only)
- Ethnic difference: 9 African descent cases – no carriers
- Reduce incidence from 9% to 2.5% by genotype based therapy in Australian group
## HLA B-57 association to abacavir ADR in different ethnicity

<table>
<thead>
<tr>
<th>Ethnicity / Gender</th>
<th>Case / Control</th>
<th>Allele Frequency Case / Control</th>
<th>Allelic Association p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ethnicities</td>
<td>165 / 139</td>
<td>17% / 2%</td>
<td>2.51 x 10-11</td>
</tr>
<tr>
<td>Whites</td>
<td>82 / 74</td>
<td>23% / 1%</td>
<td>7.27 x 10-10</td>
</tr>
<tr>
<td>White Male</td>
<td>56 / 52</td>
<td>23% / 1%</td>
<td>1.34 x 10-7</td>
</tr>
<tr>
<td>White Female</td>
<td>26 / 22</td>
<td>23% / 2%</td>
<td>2.69 x 10-3</td>
</tr>
<tr>
<td>Blacks</td>
<td>36 / 29</td>
<td>8% / 5%</td>
<td>0.07</td>
</tr>
<tr>
<td>Black Male</td>
<td>21 / 19</td>
<td>10% / 8%</td>
<td>1.00</td>
</tr>
<tr>
<td>Black Female</td>
<td>15 / 10</td>
<td>7% / 0%</td>
<td>0.51</td>
</tr>
<tr>
<td>Hispanics</td>
<td>43 / 27</td>
<td>11% / 0%</td>
<td>1.27 x 10-2</td>
</tr>
<tr>
<td>Hispanic Male</td>
<td>32 / 21</td>
<td>9% / 0%</td>
<td>0.08</td>
</tr>
<tr>
<td>Hispanic Female</td>
<td>11 / 6</td>
<td>14% / 0%</td>
<td>0.54</td>
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Acknowledgement

- **KFDA**
  - Tae Moo Yu, PhD
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  - Hae Joo Chung, PhD
  - Kyung Won Suh

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