第19回 日本薬物動態学会年会
学会賞講演

演題
「CYP遺伝多型の臨床的意義
に関する研究」

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平成16年11月18日 金沢市
Frequency distribution histogram of log MR of spartein in 84 Japanese subjects (left) and pedigree of the family study (right)
REPORTED GEOGRAPHICAL FREQUENCIES OF POOR METABOLIZERS OF DEBRISOQUINE/SPARTEINE-TYPE OXIDATION

Frequencies:
- < 1 %
- > 1 - < 3 %
- > 3 - < 10 %
- > 15 %
Reported Geographical Distribution of the Frequency (%) of Poor Hydroxylators of Mephenytoin
Activity of 4-hydroxylation of S-mephentoin (% of control) vs. (μl/mg protein)
Metabolism of Omeprazole

Omeprazole (OPZ)

CYP2C19

Hydroxyomeprazole (OH-OPZ)

CYP3A4

Omeprazole sulfone (OPZ-SFN)

CYP3A4

CYP2C19
2剤OPZ/AMPC療法による除菌率はCYP2C19の多型で異なる

全体の除菌率：51.6%

Hypothetical Explanation for an Enhanced Efficacy of Dual (Omeprazole+Amoxicillin) Therapy in Poor Metabolizer (PM) Patients with Peptic Ulcer

- Omeprazole dosing to PM patients
- \( \text{H}^+ / \text{K}^+ - \text{ATPase} - \text{SH} \) (Proton pump)
- Sulphenamide
- Proton pump inhibition
-胃酸pH增加
- Amoxicillin stability
- Amoxicillin gastric availability
- Amoxicillin secretion in gastric juice
- 抗-H. pylori action

\( \uparrow \) = Enhanced
Placebo投与時の24H胃内pHモニターリング

胃液pH

Lunch Supper Breakfast

Rapid
Intermediate
Poor
Plasma OPZ concentration and intragastric pH as a function of CYP2C19 status

OPZ 20 mg

(pH)

Lunch, Supper, Breakfast

AUC for OPZ (ng·hr/ml)

homEM (n=5)
hetEM (n=4)
PM (n=6)

Gastroenterology 1998; 114: A127
Pharmacogenomics-based Tailor-made Therapy of Omeprazole in Patients with H pylori-positive Peptic Ulcer

CYP2C19 genotyping test

- homo EMs: greater dose (e.g., 80 ~ 120 mg per day)
- hetero EMs: intermediate dose (e.g., 40 ~ 60 mg per day)
- PMs: lower dose (20 mg per day)

Clinical assessment
CYP2C19のhomEMでもPPIの高用量を頻回分割投与すると完全に胃酸を抑制することができる。

対象:CYP2C19 homEM 5名
プロトコール: LPZ 30mg/dayを8:00に8日間連続内服(↓)または, LPZ 120mg/dayを8:00, 12:00, 18:00, 22:00の4回に分け, 8日間連続内服(↓↓↓↓)し, 8日目に24時間胃内pH測定を行った。

![グラフ](グラフの詳細)

A, Endoscopic finding at admission. Active bleeding from the ulcer lesion (arrow) in the duodenal bulb was observed. B, Endoscopic findings 2 months after the first triple therapy with lansoprazole, amoxicillin, and clarithromycin. The ulcer in the duodenal bulb has been cured and scarring of the ulcer was observed, as indicated by the arrow. However, results of histologic examination and rapid urease test performed during endoscopy showed that the \( H. pylori \) infection had not been cured.

C, Endoscopic findings 2 months after the third triple therapy with lansoprazole, omeprazole, cefixime, and minocycline. The ulcer in the duodenal bulb had relapsed. The arrow indicates the ulcer bed. The results of histologic examination, rapid urease test, and culture test performed during endoscopy showed that \( H. pylori \) infection has not been cured. The strain was clarithromycin-resistant but amoxicillin-sensitive.

D, Endoscopic findings 2 months after the high-dose dual therapy with omeprazole and amoxicillin. The ulcer in the duodenal bulb had been cured, as indicated by the arrow. The results of histologic examination, rapid urease test, culture test, and \(^{13}\)C-urea breath test showed that a cure of \( H. pylori \) infection had been achieved.
# Response Rates of Patients to Major Drugs for a Selected Group of Therapeutic Areas

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Response Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>30</td>
</tr>
<tr>
<td>COX-2 inhibitors (analgesics)</td>
<td>80</td>
</tr>
<tr>
<td>Asthma</td>
<td>60</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>60</td>
</tr>
<tr>
<td>Depression (SSRIs)</td>
<td>62</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57</td>
</tr>
<tr>
<td>HCV</td>
<td>47</td>
</tr>
<tr>
<td>Migraine</td>
<td>50</td>
</tr>
<tr>
<td>Oncology</td>
<td>25</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>48</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>50</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>60</td>
</tr>
</tbody>
</table>
Pharmacogenetic Tests (practical items)

- To determine drug selection
- To determine or adjust drug dosage
- To enhance therapeutic efficiency with maximizing drug effectiveness and minimizing side-effects
- To be cost-effective
- To be useful for new drug development
Pharmacogenetic Tests for Drug Selection

Examples in poor metabolizers who cannot gain therapeutic effectiveness are:

- Codeine (CYP2D6) → Morphine
- Tramadol (CYP2D6) → Hydroxytramadol
- Losartan (CYP2C9) → Active metabolite
- Amodiaquine (CYP2C8) → Desethylamodiaquine
- Proguanil (CYP2C19) → Cycloquaniol (?)
Pharmacogenetic Tests for Preventing Serious Side-effects or Adjusting Dosage in Poor Metabolizers

CYP2C9
- Warfarin
- Oral sulfonylureas (e.g., tolbutamide)
- Phenytoin

CYP2D6
- Nortriptyline
- Antipsychotics(?)
- Thiopurine methyltransferase
- Azathioprine
- 6-Mercaptouridine
- Procainamide(?)
- N-Acetyltransferase
- Isoniazid
- UDP-Glucuronosyltransferase
- Irinotecan
Pharmacogenomic Test for Evaluating Cost-effectiveness in Clinical Practice
Cost / Effectiveness of Pharmacogenomic-based (CYP2C9-genotyped) Warfarin Therapy

- Cost of treating a major bleeding episode by warfarin
  - $1245 for a hospitalized patient
  - $4149 for an outpatient
- < $100 for genotyping test

(Redman AR. Pharmacother 2001; 21: 235 – 42)
Translation of PGx to Bedside Medicine:
Predict Drug Response in Advance

1. Remove non-responders and toxic responders

2. Treat responders and patients not predisposed to toxicity

From McLeod and Evans, Ann Rev of Pharmacol and Toxicol, 2001: 41, 101-121
Pharmacogenetics (PGt): Variation in Genes Encoding for CYP Enzyme Activity

Same dose but different plasma concentrations

Patient A
- GCCCGCCTC
  - Wild type

Patient B
- GCCCACCTC
  - Mutation

Wild type

Mutation

CYP450

Concentration vs. Time

Concentration vs. Time
Which is Better?

- Genotyping  ➔  Clinical Trial

- Clinical Trial  ➔  Genotyping
Pharmacogenomics-based Clinical Trials Require a Larger Number of Patients

- Example - Angiotensin System Genes
  
  Angiotensinogen (AGT)
  
  (G → A at position 6)
  
  Increased production of AGT
  
  Angiotensin – converting enzyme (ACE)
  
  [Insertion (I) → Deletion (D)]
  
  Greater angiotensin II activity
  
  Type 1 angiotensin II receptor
  
  (A → C at position 1166)
  
  Greater sensitivity to angiotensin II

- Genotypes are subgrouped into G/G, GA, AA, I/I, I/D, DD, AA, A/C and CC

- Angiotensin system genes alone require: $3^3 = 27$ subgroup comparisons!
Applying Pharmacogenetics in Clinical Research

To precisely prescribe or design

• the right drug
  • at the right dose
  • for the right patient

(Shi MM et al. Drug Metab Dispos 2001; 29: 591-5)
# Pharmacogenetics Research Collaborators in Asia

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