Transporters in Liver

- OCT1
- NTCP
- OATP1B1 (OATP2)
- OATP1B3 (OATP8)
- OATP2B1 (OATP-B)
- OAT2
- MRP3
- MRP4
- MRP2
- BSEP
- MDR1
- BCRP
- MRP6

Uptake of Drugs

Blood Vessel

Uptake of Drugs

Hepatocyte

Metabolism

Metabolic Enzyme

Secretion into Bile

Bile Duct
Drug Metabolism in Liver
e.g. Pravastatin (Anti-hyperlipidemia)

OATP1B1 (OATP2)
OATP1B3 (OATP8)

Uptake of Drugs

Hepatocyte

Bile Duct

Blood Vessel
Main Transporters Expressed in Liver, Kidneys, Small Intestine and Brain

Red colored transporters are those focused on in my laboratory.
Role of Transporters in Xenobiotic Detoxification

ABC (ATP binding cassette) transporter

SLC (solute carrier) transporter

Brain intercellular fluid

Blood brain barrier (Brain capillary endothelial cells)

Concentration gradient of xenobiotic

Blood

Liver, Kidney

Concentration gradient of xenobiotic

Bile, Urine

Concentration gradient of xenobiotic

Blood

Liver, Kidney

Bile, Urine

Increased Sensitivity to the Neurotoxic Pesticide Ivermectin in Mdr1a (-/-) Mice

Tissue Concentration Ratio of Ivermectin between Mdr1a (+/+), and (-/-) Mice

Brain, Muscle, Heart, Kidney, Liver, Gall bladder, Lung, Stomach, Small intestine, Colon, Fat (neck), Fat (organ), Testis, Epididymis, Spleen, Thymus, Plasma

Figure removed due to copyright restrictions
In duodenum, P-gp expression levels altered depending on SNPs. Similar correlation between P-gp expression and SNPs in brain could be expected to lead to altering intracerebral drug concentration.

A clinical study in healthy volunteers

$[^{11}\text{C}]$verapamil - Non-invasive measurement of intracerebral drug concentration with PET scans.

(in collaboration with Dr. T. Suhara, National Institute of Radiological Science)


Individual Difference in P-gp Gene Polymorphism, Xenobiotic Excretion in Brain Capillary, and Drug Penetration into Brain
Oseltamivir (TAMIFLU): Anti-influenza drug

- Oseltamivir is the prodrug form of Ro64-0802, a selective inhibitor of influenza virus neuraminidase.
- In Japan, prescriptions for oseltamivir in 2006 exceeded 10 million.
- Abnormal behavior in young patients with influenza being treated by oseltamivir have been reported.

**Parent form**

**Ro 64-0802 (pharmacologically-active form)**

- M.W. : 312.40
- Log D (at pH7) : -0.30
- pKa : 14.68 (Acidic) 8.81 (Basic)

- M.W. : 284.35
- Log D (at pH7) : -2.05
- pKa : 4.13 (Acidic) 9.26 (Basic)
Since being launched in 2001, abnormal behaviors including jumping and falling from balconies have occurred in 211 cases of oseltamivir treatment in Japan (as of June 2007).

Incidence of the abnormal behavior by age was 33.6% in less than 10 years, 44.5% in 10-19, reaching 78.1% in total. The adverse effects of abnormal behavior was reported mostly by the patients aged 19 and younger (from YAKUJI NIPPO).

Although causal relationship between oseltamivir exposure and abnormal behavior remains unclear, in March 2007 Japan’s Ministry of Health and Welfare directed that the drug be not prescribed to teenagers.

Precise scientific epidemiologic analysis of clinical data should be required before drawing conclusion on the causal relationship.

Given that a cause of abnormal behavior is the oseltamivir exposure, ‘what mechanism could be plausible’ is discussed in this study by examining the following pharmacokinetic mechanism prior to the results of epidemiological analysis.

1. Pharmacokinetic regulatory mechanism of oseltamivir and its acid form in peripheral tissues
2. Brain penetration of both compounds and relevant molecular mechanism
Brain Distribution Mechanism in Anti-influenza Oseltamivir (Tamiflu)

Oseltamivir (Tamiflu)

P-gp KO largely increases the brain concentration of tamiflu.

Brain endothelial cells (BBB)

Central nervous system (CNS)

Esterase

Blood

Liver

Decreased brain P-gp concentration in young rats results in increase of brain Tamiflu concentration.

Days after birth

Brain Distribution Mechanism in Anti-influenza Oseltamivir (Tamiflu)
Probability of Adverse Effects
(1 in 10,000)

- $F(\text{Tox}) = F_{\text{mdr}1} \times F_{\text{other trans}} \times F_{\text{ces}}$

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<th>0.1</th>
<th>0.1</th>
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</table>
Virtual Clinical Trials

Collection of individual variability data on physiological and biochemical parameters

A variety of virtual persons on computer

Real person

Virtual person
Time Course of Plasma Concentration of Midazolam after 2 mg Oral Administration

Approx. 10-fold individual differences are shown in the CYP3A4 substrate without definite gene polymorphisms.

‡ Provided by Dr M. Kato (Chugai Pharmaceutical)
Factors responsible for individual variation
(Dominant factors of pharmacokinetics)

Body weight
Liver weight
Enzyme level
Transporter level
Serum protein concentration
Hepatic blood flow rate
Glomerular filtration rate
Virtual Person with various conditions

- Body weight
- Liver weight
- Enzyme level
- Transporter level
- Serum protein concentration
- Hepatic blood flow rate
- Glomerular filtration rate

Parameters generated from random numbers
Pharmacokinetics of Midazolam

**Japanese**

63.6 ± 7.4 kg

**Europeans & North Americans**

83.2 ± 10.6 kg

Common parameters

- CLint,h: 16.3 mL/min/mL liver (individual difference: 33%)
- Liver volume: 19.5 ± 2.2 mL/kg
- Liver perfusion: 1.22 ± 0.16 mL/min/mL liver

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>CV (%)</th>
<th>Mean (SD)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European American</strong> (n=20) (Tateishi, T et al., CPT 69: 333-339, 2001)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Body weight kg</td>
<td>83.2 (10.6)</td>
<td>12.4%</td>
<td>82.5 (11)</td>
<td>13.1%</td>
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<tr>
<td>CLiv mL/min</td>
<td>412 (124)</td>
<td>30%</td>
<td>411 (131)</td>
<td>32%</td>
</tr>
<tr>
<td>mL/min/kg</td>
<td>4.99 (1.53)</td>
<td>31%</td>
<td>4.97 (1.37)</td>
<td>28%</td>
</tr>
<tr>
<td>CLpo mL/min</td>
<td>1728 (1005)</td>
<td>58%</td>
<td>1639 (1063)</td>
<td>65%</td>
</tr>
<tr>
<td>mL/min/kg</td>
<td>20.9 (12.1)</td>
<td>58%</td>
<td>19.8 (12.3)</td>
<td>62%</td>
</tr>
</tbody>
</table>

| **Japanese** (n=19(iv), n=22(po)) |           |        |           |        |
| Body weight kg     | 63.6 (7.4) | 12.3%  | 63.1 (7.7)| 12.3%  |
| CLiv mL/min        | 311 (70)   | 23%    | 315 (98.2)| 31%    |
| mL/min/kg          | 4.95 (0.96)| 19%    | 4.97 (1.37)| 28%    |
| CLpo mL/min        | 1413 (730) | 52%    | 1253 (808)| 64%    |
| mL/min/kg          | 22.4 (11)  | 49%    | 19.8 (12.3)| 62%    |
Studies on Magnitude of Inter-Individual Variations in Blood Levels of Oseltamivira and Its Active Metabolite

- Analysis by Monte Carlo simulation
- Individual variation of drug exposure (Virtualizable of large-scale clinical study)

Mathematical model indicative of blood concentrations

Gene mutation frequency & functional change of metabolic enzyme & transporter

Pseudo-random numbers

Inter-individual deviation of blood flow rate, protein binding and GFR

PK parameters used for the simulation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>CV</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qh</td>
<td>1700 (mL/min)</td>
<td>19.5%</td>
<td>1</td>
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<tr>
<td>Qf</td>
<td>1127 (mL/min)</td>
<td>8.3%</td>
<td>2</td>
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<tr>
<td>Eh</td>
<td>0.735</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Fh</td>
<td>0.265</td>
<td>-</td>
<td>3</td>
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<tr>
<td>f_b_osel</td>
<td>0.460</td>
<td>5.8%</td>
<td>4</td>
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<tr>
<td>R_b_osel</td>
<td>1.270</td>
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<td>5</td>
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<tr>
<td>f_b_活性体</td>
<td>1.53</td>
<td>5.8%</td>
<td>4</td>
</tr>
<tr>
<td>R_b_活性体</td>
<td>0.64</td>
<td></td>
<td>5</td>
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<tr>
<td>GFR</td>
<td>125 (mL/min)</td>
<td>30%</td>
<td>6</td>
</tr>
<tr>
<td>CL_R_plasma_活性体</td>
<td>20.0 (L/hr)</td>
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<td>7</td>
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<tr>
<td>CL_secrenalin_活性体</td>
<td>330 (mL/min)</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>CL_int_renal_活性体</td>
<td>305 (mL/min)</td>
<td>30%</td>
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<tr>
<td>CL_int_iver_osel</td>
<td>12000 (mL/min)</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

- Capable of treating the drug exposure deviation generated by the combination of multiple variational parameters as a distribution map in tens of thousands scale of people.
- Drug exposures in patients, which were missed in clinical studies due to the low frequencies despite of the large functional changes, are valuable.

3. From the simulation results (assumed to be FaFg=1)
5. Application Materials. Use hematocrit level of 0.45.
8. Calculated by neglecting reuptake.
Studies on Magnitude of Inter-Individual Variation of AUC in Active Metabolite Concentration in Brain

Assumption 2. \( ① \ll ② \)
(Assuming that AUC of the active form concentration in brain is defined mainly by its uptake from blood side.)

Functional change of OAT3, MRP4, MDR1, and CES1A in the subject with the highest brain exposure of active form in each assumption.

<table>
<thead>
<tr>
<th></th>
<th>OAT3</th>
<th>MRP4</th>
<th>MDR1</th>
<th>CES1A</th>
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<tr>
<td>#38227</td>
<td>1 &gt;&gt; 2</td>
<td>排泄 &gt;&gt; 代谢</td>
<td>0.14</td>
<td>0.56</td>
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<tr>
<td>#47772</td>
<td>1 &gt;&gt; 2</td>
<td>排泄 = 代谢</td>
<td>0.12</td>
<td>0.79</td>
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<tr>
<td>#13386</td>
<td>1 &gt;&gt; 2</td>
<td>排泄 &lt;&lt; 代谢</td>
<td>0.07</td>
<td>0.63</td>
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<tr>
<td>#39954</td>
<td>1 &lt;&lt; 2</td>
<td>-</td>
<td>0.05</td>
<td>0.77</td>
</tr>
</tbody>
</table>

(Activity level in wild type = 1)

- AUC of oseltamivir concentration in brain increased maximum almost 10 times mean value.
- The number of subjects whose AUC increased more than 7 times were 30 out of 50000.
Hepatobiliary drug transporters

- MRP3
  - pravastatin, robastatin, pitavastatin, cerivastatin, valsartan, telmisartan, temocapril, nateglinide, repaglinide bozentan
  - Glucuronic acid conjugate
  - ATP
  - ADP

- OATP 1B1
  - pravastatin, robastatin, pitavastatin, olmesartan valsartan, telmisartan, methotrexate, SN-38, cefodizime, glucuronic acid conjugate, glutathion conjugate

- OATP 1B3
  - pravastatin, robastatin, pitavastatin, valsartan, telmisartan

- NTCP
  - telmisartan fexofenadine
  - Bile acid
  - Na+

- OCT1
  - metformin cimetidine
  - salicylic acid indomethacin, etc

- OAT2
  - many drugs including digoxin vinblastine

- BSEP
  - fluoroquinolone, pitavastatin, robastatin, sulfasalazine, methotrexate, sulfoconjugate

- MRP2
  - glucuronic acid conjugate

- BCRP
  - GTP

- MDR1/P-gp
  - many drugs

* Many important drugs for medication
* Vectorial transport (similar in substrate recognition of transporters for uptake and excretion)

Hepatobiliary drug transporters
**Enterohpatic Circulation**

- **Pravastatin**
- **Small intestine**
- **Liver**
- **OATP1B1**
- **MRP2**

**Uptake to Liver**
- Binding to intracellular HMG-CoA reductase
- **OATP2B1 (OATP-B)?**

**Excretion to Bile**
- ADP to ATP

**Transporter Group Involved in Enterohpatic Circulation of Pravastatin**
- Efficient Transport to Liver

References:
- Yamazaki et al. AJP 264:G36, 1993
- Nakai et al. JPET 297:861, 2001
- Sasaki et al. JBC 277:6497, 2002
- Yamazaki et al. DMD 25:1123, 1997
- Kobayashi et al. JPET 306:703, 2003
Establishment of Double-Expression Cells

**Apical (Bile duct side)**
- MRP2
- OATP1B1

**Basal (Blood side)**
- MRP2
- OATP1B1

**Immunostain image**
- MRP2: red
- OATP1B1: green
- Nuclei: blue

[Sasaki M et al., J Biol Chem, 277, 6497-503 (2002)]

**Trans-cell Transport in Pravastatin Double-Transfectant**

**OATP1B1/MDR1**

**OATP1B1/MRP2**

**PS**

\[
PS_{\text{net}} = \frac{PS_1 \times PS_3}{PS_2 + PS_3}
\]

**Utilization of Co-expression System of Uptake-Excretion-Transporters**

‡ Matsushima S et al., J Pharmacol Exp Ther, 314, 1059-67 (2005)
Adverse Effects of Cerivastatin - Drug-Drug Interaction with Gemfibrozil -

There have been 52 deaths (31 in the US) from the adverse effect rhabdomyolysis in patients taking cerivastatin. Twelve of the 31 patients in the US were confirmed to take concomitant fibrate group anti-hyperlipidemic agents. [from British Medical Journal 323, 359 (2001) & British Medical Journal 323, 415 (2001)]

Yakuji Nippo, Aug. 27, 2001
Yakuji Nippo, Aug. 15, 2001

Cyclosporine A

Uptake to liver

Low risk of interaction has been considered in cerivastatin due to its multiple metabolic pathways.


Elucidation of Primary Action Point in the Interacting Drug and Detoxification of Cerivastatin in Liver
Mobilization of Pravastatin (Anti-hyperlipidemia)

Oral administration → Gl tract

Gl tract → Absorption → Liver → Bile

Liver → Metabolism → Plasma

Plasma → Distribution → Muscle

Muscle → Excretion → Feces

Liver → Excretion → Kidney

Kidney → Excretion → Urine

**Drug actions**

**Adverse effects**

*Modified figure from J. Azuma: 「クスリに弱いヒト」と「困ったクスリ」たち (Individual Difference of Reactivity to Drug), Jiho, Inc., Tokyo, 2001*
Relation between simvastatin-induced myopathy and genetic polymorphism of OATP1B1

Case=85 vs control 90: ca 300,000 marker SNPs

-Log10 P value

Significant link \( r^2 > 0.95 \) between Marker SNPs and SLCO1B1 T521C (V174A)!

OATP1B1 polymorphism seriously affects the adverse reactions.

Significant correlation with the event

Years since Starting 80mg of Simvastatin

Cumulative Percentage of patients who have had a myopathy

Odds ratio of this SNPs for simvastatin-induced myopathy

521CT vs TT → 4.5 fold

521CC vs TT → 16.9 fold

Physiological Model and Prediction of Time Course in Plasma Level

- **i.v.** 0.134mg/kg (Actual value*)
- **p.o.** 0.26mg/kg (Actual value*)

**Blood**

\[ V_b \cdot \frac{dC_b}{dt} = Q_b(C_i - C_b) - CL_r \cdot C_b \]

**Intracapillary**

\[ V_{i,j} \cdot \frac{dC_{i,j}}{dt} = Q_h(C_{b,j} - C_{i,j}) - f_b \cdot PS_{inf} \cdot C_{i,j} + f_h \cdot PS_{eff} \cdot C_{H,j} \]

**Hepatic parenchymal cells**

\[ V_{H,j} \cdot \frac{dC_{H,j}}{dt} = f_b \cdot PS_{inf} \cdot C_{i,j} - f_h \cdot (PS_{eff} + CL_{met} + PS_{bile}) \cdot C_{H,j} \]

Extrapolated parameters in vivo from in vitro data
Mathematical Model for Prediction of Drug Concentration

**Blood**

\[ V_B \frac{dC_B}{dt} = Q_{LU} \left( \frac{C_{LU}}{K_{p,LU}} - C_B \right) - CL_RC_B \]

**Lung**

\[ V_{LU} \frac{dC_{LU}}{dt} = Q_{BR} \frac{C_{BR}}{K_{p,BR}} + Q_{MU} \frac{C_{MU}}{K_{p,MU}} + Q_R \frac{C_R}{K_{p,R}} + Q_H C_{HES} - Q_{LU} \frac{C_{LU}}{K_{PLU}} \]

**Brain, Muscle, Kidney**

\[ V_i \frac{dC_i}{dt} = Q_i \left( C_B - \frac{C_i}{K_{p,i}} \right) \]

**Liver→Efficacy Target**

\[ V_{Hi} \frac{dC_{Hei}}{dt} = \left( \frac{PS_{inf}}{5} \right) f_B C_{Hei} + \left( \frac{PS_{dif}}{5} \right) f_B C_{Hei} - \left( \frac{PS_{diff}}{5} \right) f_T C_{Hi} - \left( \frac{PS_{bile}}{5} \right) f_T C_{Hi} \]

**Extra cellular space of liver ①**

\[ V_{HE1} \frac{dC_{HE1}}{dt} = Q_H \left( C_B - C_{HE1} \right) - \left( \frac{PS_{inf}}{5} \right) f_B C_{HE1} - \left( \frac{PS_{dif}}{5} \right) f_B C_{HE1} + \left( \frac{PS_{diff}}{5} \right) f_T C_{Hi} + k_a F_a X_{Gl} \]

**Extracellular space of liver ②**

\[ V_{HEi} \frac{dC_{HEi}}{dt} = Q_H \left( C_{HE(i-1)} - C_{HEi} \right) - \left( \frac{PS_{inf}}{5} \right) f_B C_{HEi} - \left( \frac{PS_{dif}}{5} \right) f_B C_{HEi} + \left( \frac{PS_{diff}}{5} \right) f_T C_{Hi} \]

**Intra-gastrointestinal duct**

\[ \frac{dX_{Gl}}{dt} = \sum \left( \frac{PS_{bile}}{5} \right) f_T C_{Hi} - k_a F_a X_{Gl} \]
Mathematical Model for Prediction of Drug Concentration

**Blood**

\[ V_B \frac{dC_B}{dt} = Q_{LU} \left( \frac{C_{LU}}{K_{p,LU}} - C_B \right) - CL_R C_B \]

**Muscle \rightarrow \text{Adverse Effect Target}**

\[ V_i \frac{dC_i}{dt} = Q_i \left( C_B - \frac{C_i}{K_{p,i}} \right) \]

**Liver \rightarrow \text{Efficacy Target}**

\[ \frac{V_{Hi}}{5} \frac{dC_{Hi}}{dt} = \left( \frac{PS_{inf}}{5} \right) f_B C_{HEi} + \left( \frac{PS_{dif}}{5} \right) f_B C_{HEi} - \left( \frac{PS_{dif}}{5} \right) f_T C_{Hi} - \left( \frac{PS_{bile}}{5} \right) f_T C_{Hi} - \left( \frac{PS_{met}}{5} \right) f_T C_{Hi} \]
Pharmacokinetics of Capecitabine

Capecitabine is metabolized by various enzymes:
- Carboxylesterase in the Small Intestine
- Cytidine deaminase and dThd-Pase in the Liver
- Enzymes in the Tumor

The metabolites include 5'-DFCR, 5'-DFUR, and 5-FU.

† H. Ishitsuka, 2000, Investigational New Drugs 18, 343-354
5-FU Levels after Drug Administration (HCT116 human colon cancer xenograft model)

Species Difference in Tissue Distribution of Metabolic Enzyme

Cyd deaminase activity (nmol 5'-dFUrld/mg protein/min)

- **Human**
  - Heart: 3
  - Lung: 3
  - Liver: 14
  - Spleen: 9
  - Kidney: 24
  - Stomach: 32
  - S. Intestine: 4
  - L. Intestine: 6
  - Breast: 16
  - Thyroid: 19
  - Ovary: 3
  - Cervix: 7
  - Bladder: 15
  - Blood: 4

- **Rat**
  - Brain: 3
  - Heart: 3
  - Lung: 3
  - Liver: 3
  - Spleen: 3
  - Kidney: 3
  - Stomach: 1
  - Deodenum: 3
  - Jejunum: 3
  - Ileum: 1
  - Colon: 2
  - Rectum: 3
  - Bone Marrow: 1
  - Thymus: 3
  - Plasma: 3

- **Monkey**
  - Brain: 3
  - Heart: 3
  - Lung: 3
  - Liver: 3
  - Spleen: 3
  - Kidney: 3
  - Stomach: 2
  - Deodenum: 3
  - Jejunum: 3
  - Ileum: 1
  - Colon: 2
  - Rectum: 3
  - Bone Marrow: 1
  - Thymus: 3
  - Plasma: 3

- **Mouse**
  - Brain: 3
  - Heart: 3
  - Lung: 3
  - Liver: 3
  - Spleen: 3
  - Kidney: 3
  - Stomach: 1
  - Deodenum: 3
  - Jejunum: 3
  - Ileum: 1
  - Colon: 2
  - Rectum: 3
  - Bone Marrow: 1
  - Thymus: 3
  - Plasma: 3

Onodera H. et al., 2000
PBPK model integrating metabolic enzyme activity for capecitabine

Vmax3S1
Km3S1+C

Vmax3S2
Km3S2+C

Vmax3S3
Km3S3+C

Vmax3S4
Km3S4+C

ka·F

Vmax2S1
Km2S1+C

Vmax2S2
Km2S2+C

Vmax2S3
Km2S3+C

Vmax2S4
Km2S4+C

5’–DFCR
carboxylesterase

cyd deaminase

5’–DFUR
dThdPase

5–FU

DPD

blood

liver

GI tract

tumor

NET

CLr,u

Tsukamoto et al., Pharmaceutical Research. 2001. Vol. 18, Iss. 8; pg. 1190
Drug Delivery System

DDS is a transport system for delivering drugs to the in vivo targeting site properly, at the right time, and in appropriate amount for requirements. ‘Courier for Drugs’

Controlled Release
Improved absorption
Targeting

† Cited from Dr. M. Morishita, Department of Pharmaceutics, Hoshi University
Time Course of Plasma Concentration after Treatment of Controlled Release-Type Formulation

† Cited from Dr. M. Morishita, Department of Pharmaceutics, Hoshi University
New time controlled medication, in accordance with the concept of “chrono-pharmacotherapy” has been established. Midnight medication is avoidable.

‡ Cited from Dr. M. Morishita, Department of Pharmaceutics, Hoshi University
Do patients occasionally need medication during a certain period of time?

**Benefit for patients**
- Symptoms at night or dawn are suppressible.
- With no disturbance of sleep
- No need to go up to take medicine in the middle of night.

‡ Cited from Dr. M. Morishita, Department of Pharmaceutics, Hoshi University
Metabolism and Efficacy of Drugs

Substances acting to body

Alcohol

Drug

Action

Intoxication

Efficacy

Isn’t medication easy to work in the fast metabolizer?

e.g. Antiulcer Omeprazole (Gastric Secretion inhibitor)
Difference between Mono- and Di-Zygotic Twin in Plasma Half Life of Antipyrin and Bisdihydroxycoumarine

‡ Cited from Professor T. Kamataki (Hokkaido University) (Vesell, 1975)
Metabolism of Antiulser Omeprazole

Drug metabolizing enzyme CYP2C19
Main metabolic pathway

Omeprazole

Drug metabolizing enzyme CYP3A4

5-hydroxyomeprazole (inactive)

Omeprazole sulfone (inactive)
CYP2C19 gene

Rapid metabolizer: RM
Individuals with no mutation in both CYP2C19 alleles

Intermediate metabolizer: IM
Individuals with mutation in one CYP2C19 allele

Poor metabolizer: PM
Individuals with mutation in both CYP2C19 alleles
**Ethnic Difference of CYP2C19 Genotype**

Ethnic difference in ‘Poor Metabolizer (PM)’ percentage

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2.5%</td>
</tr>
<tr>
<td>White (EU)</td>
<td>3.0%</td>
</tr>
<tr>
<td>Black (US)</td>
<td>2.0%</td>
</tr>
<tr>
<td>Zimbabwean</td>
<td>4.8%</td>
</tr>
<tr>
<td>Chinese (Han people)</td>
<td>19.5%</td>
</tr>
<tr>
<td>Korean</td>
<td>12.6%</td>
</tr>
<tr>
<td>Japanese</td>
<td>18.0-22.5%</td>
</tr>
</tbody>
</table>

CYP2C19 Genotype and Plasma Omeprazole Concentration

Omeprazole, 20mg treatment

Plasma concentration of omeprazole (ng/ml)

Time after treatment (hr)

Comparison of AUC

- Poor metabolizer (PM)
- Intermediate metabolizer (IM)
- Rapid metabolizer (RM)

CYP2C19 Genotype and Pharmacological Effects of Omeprazole

Time after treatment (hr)

<table>
<thead>
<tr>
<th>pH</th>
<th>Poor metabolizer (PM)</th>
<th>Intermediate metabolizer (IM)</th>
<th>Rapid metabolizer (RM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0</td>
<td>▲</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>4.0</td>
<td>▲</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>2.0</td>
<td>▲</td>
<td>□</td>
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</tr>
<tr>
<td>1.0</td>
<td>▲</td>
<td>□</td>
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</tr>
</tbody>
</table>

CYP2C19 Genotype and Decolonization of H. pylori by Omeprazole.

Eradication rate of H. pylori

Omeprazole, 20mg & Amoxicilin, 2000mg
Treatment for 2 weeks