THERAPEUTIC DRUG MONITORING

Prof.dr.C.Neef
University Hospital Maastricht
Dept Clinical Pharmacy & Toxicology

Summer course Gent 2007
THERAPEUTIC DRUG MONITORING

Program

- Introduction
- Pharmacokinetic principles
- TDM practice
- cases

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Therapeutic drug monitoring is defined as the measurement made in the laboratory of a parameter which, with appropriate interpretation, will directly influence prescribing procedures. Commonly the measurement is in a biological matrix of a prescribed xenobiotic, but it may also be of an endogenous compound prescribed as replacement therapy in an individual who is physiologically or pathologically deficient in that compound.
Therapeutic drug monitoring is a system of quality assurance of a drug management system, aiming that the right drug is given to the right patient in the right dose in order to obtain the right effect.

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subjects (1)

- Classic pharmacokinetics
- Logarithmes and other estimation methods
- Standard deviations
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subjects (2)

- Estimation of the creatinin clearance
- range in the laboratory numbers
- assay error pattern
- non-pharmacokinetic sources of variation of the outcome:
  - attributions of the nurses, the pharmacy, the lab

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Classic Pharmacokinetics

- compartmental kinetics
- \( C_t = C_0 \times e^{-kt} \)
- volume of distribution
- elimination rate constant
- clearance

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- Fitting a Pharmacokinetic Model to the Drug Concentrations found
  - linear regression on logarithms of the serum levels
  - least squares estimation (nonlinear regression)
  - Likelihood estimation
  - Bayesian estimation
Logarithms

- Sawchuk en Zaske: lineair least squares regression method
- 3 disadvantages:
  - Information from a single dosing interval
  - Assay error is a constant percentage of the measured serum concentration
  - Method does not take into account the population data of a drug

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The Estimation Problem and Methods

Model (\(\alpha\) unknown) \[\Rightarrow\text{Data}\]

\(\alpha\)=collection of all model parameters

Estimation Method

Estimate of \(\alpha\) (state of nature)

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Likelihood Estimation

Model (\( \alpha \) unknown) \rightarrow Error \rightarrow Maximum likelihood Estimator \rightarrow Data

\[ \text{Estimate of } \alpha \text{ (state of nature)} \]

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FISHER INFORMATION INDEX

$$FII = \sum \frac{C}{(sd^2)}$$

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Reverend Thomas Bayes

1702 - 1761

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Bayes Theorema

Essays toward solving a problem in the doctrine of chances

Thomas Bayes
Postuum 1763

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Bayesian Estimation

Prior \( p(\alpha) \)

Information

Data \( z(t_j) \)

Error

Model

Bayesian Estimator

Estimate posterior \( p(\alpha|z) \)
Rule of Bayes

- Posterior odds = prior odds $\times$ likelihood ratio
CREATININE CLEARANCE

- Cockroft - Gault: $Cl = \frac{(140\text{-}age) \times \text{W} \times 88.3}{72 \times C_{cr}}$

- Schwartz - children: $Cl = \frac{0.55 \times \text{BH} \times 88.5}{C_{cr}}$

- Jelliffe 1 en 2

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Creatinine clearance
Traynor et al. BMJ 2006

4-variable MDRD

\[ 186.3 \times \left( \frac{S_{Cr}}{88.4} \right)^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}) \]

where \( S_{Cr} = \) serum creatinine in \( \mu \text{mol/l} \), and age is expressed in years

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Estimation of the creatinin clearance
variability in de lab results
assay error pattern
non-pharmacokinetic sources of variability of the results:
- cooperation of the nursing staf, the pharmacy, the lab

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assay pattern
\[ y = 0.568 - 0.171X + 0.022X^2 \]

<table>
<thead>
<tr>
<th>serum level (mg/L)</th>
<th>assay sd (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>5.0</td>
<td>1.0</td>
</tr>
<tr>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>10.0</td>
<td>2.0</td>
</tr>
<tr>
<td>12.5</td>
<td>2.5</td>
</tr>
<tr>
<td>15.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

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- THERAPEUTIC / TOXIC RANGE
FIG. 2. Serum digoxin concentrations in patients without (left) and with (right) digoxin toxicity, as found by Doherty (1), redrawn with permission. Note the great overlap between therapeutic and toxic concentrations, and the fact that approximately half the patients with serum levels of 3.0 ng/mL or more tolerated that level and were not toxic. Also note that the incidence of toxicity is very low for levels up to 1.0 ng/mL, moderate (though significant) for levels of 1.0 to 2.0, and still only approximately 50% for levels of 3.0 ng/mL or greater.
Therapeutic Range

![Graph showing the therapeutic range between drug efficacy and drug toxicity as a function of increasing serum concentration. The graph illustrates the optimal concentration range for therapeutic effects while minimizing toxicity.]
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- ADAPTIVE CONTROL
- Bayes theoreme
- Fisher Information Index
- Optimal sampling times

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- MAP Bayesian Fitting

- maximum aposteriori probability Bayesian fitting procedure
  - population parameter values + SD and serumlevels and SD

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Goal oriented - Model based dosing

- Patient data
- PK model
- Target concentration
- PK dosing
- Patient
QUANT BAYES' THEOREM:
1. DETERMINE ASSAY ERROR EXPLICITLY.
2. USE IN CURRENT BAYESIAN OBJ FUNCTION

\[
\text{MINIMIZE } \sum \frac{(Cobs-Cmod)^2}{SD^2 \text{Cobs}} + \sum \frac{(Ppop-Pmod)^2}{SD^2 \text{Ppop}}
\]

<table>
<thead>
<tr>
<th>PRIOR PROB</th>
<th>NEW INFO</th>
<th>CONSIDER PRIOR+NEW</th>
<th>POST PROB</th>
<th>THERAPY GOALS</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>POP MODEL</td>
<td>SERUM CONC'S</td>
<td>OBJ FUNCT</td>
<td>INDIV MODEL</td>
<td>LOOK AT PT, THINK</td>
<td>CALC DOESES</td>
</tr>
</tbody>
</table>
When do we take our samples?

- Optimal sampling times
- Distribution volume at the end of the infusion
- Elimination rate constant at 1.44 x T1/2
- The trough level is the less reliable level (if T1/2 < dosing interval)

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Fig. 5. Optimal strategies for monitoring serum drug concentrations. A change in the volume of distribution (Vd) causes the greatest change in the concentration (S) when the latter is at its highest (the true peak). This is a D-optimal time for a 1-compartment model with intermittent intravenous therapy. Abbreviation: $k_{el}$ = elimination rate constant.
VARIATION IN ELIMINATION RATE CONSTANT

Fig. 6. Optimal strategies for monitoring serum drug concentrations. A change in the elimination rate constant ($k_{el}$) causes the greatest change in concentrations ($S$) 1.44 half-lives after the end of an intermittent intravenous infusion. This is also a D-optimal time for a 1-compartment model when such therapy is used. *Abbreviation:* Vd = apparent volume of distribution.
FIGURE 3.13. Illustrating the value of waiting to draw the second level (29). Intramuscular gentamicin therapy of 80 mg every 8 hr in a simulated patient with $C_{cr} = 100$. Vertical: the index of the amount of information contained in a specimen drawn at that time. Horizontal: time into the regimen. There is an optimal time to draw the level in each dose interval. With each succeeding dose interval, the information contained in the specimen increases, up until a steady state is reached (after about the fourth dose interval).
TDM of aminoglycosides

FORGET THE TROUGH LEVEL
It gives you a false feeling of safety!!!!
Factors influencing TDM process

A simulation study of factors affecting aminoglycoside therapeutic precision

- dose, pharmacy (ward) accuracy
- dose administration, start and stop
- precision laboratory assay
- precision phlebotomy service


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- factors affecting therapeutic precision
  - good
  - pharmacy dose +/- 4 mg
  - phlebotomy serv +/- 6 min
  - ward care iv start +/- 6 min
  - ward care iv stop +/- 6 min
  - smart pump start +/- 0.6 min
  - smart pump stop +/- 0.6 min
  - poor
    - pharmacy dose +/- 16 mg
    - phlebotomy serv +/- 24 min
    - ward care iv start +/- 18 min
    - ward care iv stop +/- 12 min

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• factors affecting therapeutic precision

<table>
<thead>
<tr>
<th>group</th>
<th>clinical scenario</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>all factors good</td>
<td>24.1</td>
</tr>
<tr>
<td>2</td>
<td>poor flebotomy service</td>
<td>29.6</td>
</tr>
<tr>
<td>3</td>
<td>poor lab</td>
<td>27.3</td>
</tr>
<tr>
<td>4</td>
<td>poor pharmacy</td>
<td>43.5</td>
</tr>
<tr>
<td>5</td>
<td>poor ward care</td>
<td>84.8</td>
</tr>
<tr>
<td>6</td>
<td>all poor</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>all poor with smart pump</td>
<td>21.9</td>
</tr>
</tbody>
</table>
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- factors affecting therapeutic precision

<table>
<thead>
<tr>
<th>group</th>
<th>clin. scenario</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>all poor smart pump</td>
<td>21.0</td>
</tr>
<tr>
<td>8</td>
<td>all good smart pump</td>
<td>3.6</td>
</tr>
</tbody>
</table>

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Prediction of future serum concentrations:
- data collected by nurses vs trained pharmacy residents
- percent of serum levels accurately predicted (within +/- 20%), MAP Bayesian 1-comp model:
  - Res.Coll.Data : 80%   peak levels accurately predicted
  - Nur.Coll.Data : 20%   peak levels accurately predicted (p<0.01)
  - trough levels N.S. different

B. Charpiat e.a. Ther.Drug Mon. 16; 1994:166-173

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Impact of goal oriented and model based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis

Nicolette AEM van Lent-Evers, Ron AA Mathot, William P Geus, Ben A van Hout, Alexander ATMM Vinks,

Therapeutic Drug Monitoring 1999; 21: 63-73

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n=127 vs 105
mean 26.3 ± 2.9 vs 20.0 ± 1.4 days
p=0.045
deceased patients

% of patients

controls
intervention

deceased patients

Time in hospital (days)

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Patients with suspected or proven Gram(-) infection

n=62 vs 48
mean 18.0 ± 1.4 vs 12.6 ± 0.8 days
p = 0.0007

deceased patients

% of patients
controlls
intervention

Time in hospital (days)

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PHARMACODYNAMICS

Concentration - Effect model

\[ \frac{dN}{dt} = (\lambda - F(C(t))) \cdot N \]

\[ C(t) = C(0) \cdot e^{-k_e \cdot t} \]

\[ F(C) = \frac{E_{\text{max}} \cdot C^\gamma}{C_{50}^\gamma + C^\gamma} \]

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Tobramycin pharmacodynamics

\[
\text{N}_{\text{discrete}} & \quad \text{N}_{\text{continuous}}\quad \text{TOBRAMYCIN}
\]

\[
\text{C}_{\text{discrete}} & \quad \text{C}_{\text{continuous}}\quad \text{TOBRAMYCIN}
\]

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TDM of Ciclosporine using the AUC method

Daan Touw
Hospital Pharmacy Haagse Ziekenhuizen

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TDM ciclosporin therapeutic targets

- Minimalise rejection
- Minimalise side effects
Development TDM ciclosporin

- After introduction of ciclosporin: AUC based on many datapoints
- Years ‘90: only trough levels based on relation AUC - throughlevel
- From 2000: AUC based on optimally chosen samples
  - Research from Leiden University Medical Center

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DOI: 10.1093/ndt/gfg065

Original Article

A compartmental pharmacokinetic model of cyclosporin and its predictive performance after Bayesian estimation in kidney and simultaneous pancreas–kidney transplant recipients

Serge C. L. M. Cremers¹, Eduard M. Scholten², Rik C. Schoemaker³, Eef G. W. M. Lentjes⁴, Pieter Vermeij¹, Leendert C. Paul², Jan den Hartigh¹ and Johan W. de Fijter²

¹Department of Clinical Pharmacy and Toxicology, ²Department of Nephrology, ³Centre for Human Drug Research and ⁴Department of Clinical Chemistry, Leiden University Medical Center, Leiden, The Netherlands

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Model building ((n=20))</th>
<th>KTA recipients ((n=20))</th>
<th>SPKT recipients ((n=20))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>13/7</td>
<td>12/8</td>
<td>13/7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 ± 15</td>
<td>70 ± 13</td>
<td>75 ± 16</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>173 ± 9</td>
<td>169 ± 11</td>
<td>175 ± 9</td>
</tr>
<tr>
<td>GFR (ml/min)(^a)</td>
<td>46 ± 19</td>
<td>52 ± 18</td>
<td>59 ± 25</td>
</tr>
<tr>
<td>Cause of renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Unknown, other</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>KTA/SPKT</td>
<td>12/8</td>
<td>20/0</td>
<td>0/20</td>
</tr>
</tbody>
</table>

\(^a\)Cockcroft and Gault. GFR, glomerular filtration rate.
## Ciclosporine pop. parameters

### Table 2. CsA pharmacokinetics in renal transplant recipients (n = 20)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{lag}}$ (h)</td>
<td>0.576 (0.485)</td>
</tr>
<tr>
<td>$F$</td>
<td>0.5 (fixed)</td>
</tr>
<tr>
<td>$K_a$ (h$^{-1}$)</td>
<td>0.741 (0.273)</td>
</tr>
<tr>
<td>$V_1$ (l/kg)</td>
<td>0.491 (0.135)</td>
</tr>
<tr>
<td>$K_{\text{elm}}$ (h$^{-1}$)</td>
<td>0.559 (0.045)</td>
</tr>
<tr>
<td>$K_{12}$ (h$^{-1}$)</td>
<td>0.567 (0.215)</td>
</tr>
<tr>
<td>$K_{21}$ (h$^{-1}$)</td>
<td>0.149 (0.114)</td>
</tr>
</tbody>
</table>

$t_{\text{lag}}$, lag time; $F$, oral availability; $K_a$, absorption rate constant; $V_1$, apparent volume of distribution of the central compartment; $K_{\text{elm}}$, elimination rate constant from the central compartment; $K_{12}$ and $K_{21}$, distribution rate constants between the central and peripheral compartment.
Fig. 1. CsA blood concentration time curve according to the population model (dashed line), the actual measured CsA blood concentrations at $t=0, 2$ and $3$ h (open circles) and $t=1, 4, 6, 8$ and $12$ h (closed circles) and the CsA blood concentration time curve according to the model (solid line) after fitting the population parameters to the measured concentrations at $t=0, 2$ and $3$ h (open circles) after administration, in a 45-year-old female 1 year after renal transplantation. Dose $= 225/200$ mg.
## Optimal sampling

<table>
<thead>
<tr>
<th>Time-points blood sampling (h)</th>
<th>MPE (%)</th>
<th>(95% CI)</th>
<th>MAPE (%)</th>
<th>(95% CI)</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (trough)</td>
<td>-</td>
<td>-</td>
<td>23</td>
<td>(17; 30)</td>
<td>0.78</td>
</tr>
<tr>
<td>0 (with model)</td>
<td>-9</td>
<td>(-21; 4)</td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>-8</td>
<td>(-17; 1)</td>
<td>16</td>
<td>(11; 22)</td>
<td>0.80</td>
</tr>
<tr>
<td>3</td>
<td>-13</td>
<td>(-22; -4)</td>
<td>19</td>
<td>(13; 25)</td>
<td>0.82</td>
</tr>
<tr>
<td>0, 2</td>
<td>-1</td>
<td>(-6; 4)</td>
<td>9</td>
<td>(6; 11)</td>
<td>0.96</td>
</tr>
<tr>
<td>0, 3</td>
<td>-9</td>
<td>(-16; -1)</td>
<td>15</td>
<td>(11; 20)</td>
<td>0.90</td>
</tr>
<tr>
<td>0, 1, 2</td>
<td>3</td>
<td>(-1; 7)</td>
<td>8</td>
<td>(5; 10)</td>
<td>0.97</td>
</tr>
<tr>
<td>0, 1, 3</td>
<td>-1</td>
<td>(-0; 3)</td>
<td>6</td>
<td>(3; 9)</td>
<td>0.98</td>
</tr>
<tr>
<td>0, 2, 3</td>
<td>-3</td>
<td>(-9; 2)</td>
<td>11</td>
<td>(7; 14)</td>
<td>0.96</td>
</tr>
<tr>
<td>0, 1, 2, 3</td>
<td>0</td>
<td>(-3; 3)</td>
<td>5</td>
<td>(3; 7)</td>
<td>0.99</td>
</tr>
<tr>
<td>0, 1, 2, 3, 4</td>
<td>-1</td>
<td>(-4; 2)</td>
<td>5</td>
<td>(3; 6)</td>
<td>0.99</td>
</tr>
<tr>
<td>0, 1, 2, 3, 4, 6, 12</td>
<td>-3</td>
<td>(-4; -1)</td>
<td>3</td>
<td>(2; 4)</td>
<td>1.00</td>
</tr>
<tr>
<td>LSM (1, 3) [7]</td>
<td>-3</td>
<td>(-8; -1)</td>
<td>7</td>
<td>(4; 11)</td>
<td>0.95</td>
</tr>
<tr>
<td>LSM (2, 6) [6]</td>
<td>-1</td>
<td>(-5; 3)</td>
<td>7</td>
<td>(5; 10)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

CI, confidence interval.

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Correlation

Trapezium rule  \( C_0 \) and \( C_2 \)  \( C_0, C_2 \) and \( C_3 \)

<table>
<thead>
<tr>
<th>A</th>
<th>15000</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>10000</td>
</tr>
<tr>
<td>C</td>
<td>5000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AUC_{0-2h} (h*μg/L)</th>
<th>( C_{trough} ) (μg/L)</th>
<th>( r^2 = 0.69 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>5000</td>
<td>5000</td>
<td>10000</td>
</tr>
<tr>
<td>15000</td>
<td>15000</td>
<td>15000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AUC_{0-12h 0+2h} (h*μg/L)</th>
<th>( C_{trough} ) (μg/L)</th>
<th>( r^2 = 0.72 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>5000</td>
<td>5000</td>
<td>10000</td>
</tr>
<tr>
<td>15000</td>
<td>15000</td>
<td>15000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AUC_{0-12h 0+2+3h} (h*μg/L)</th>
<th>( C_{trough} ) (μg/L)</th>
<th>( r^2 = 0.93 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>5000</td>
<td>5000</td>
<td>10000</td>
</tr>
<tr>
<td>15000</td>
<td>15000</td>
<td>15000</td>
</tr>
</tbody>
</table>

Fig. 2. (A) Relationship between \( C_{trough} \) and AUC calculated with the trapezium rule (golden standard). Relationship between the AUC calculated according to the compartment model with blood concentration time points taken at 0 and 2 h (B) and 0, 2 and 3 h (C) and the golden standard AUC. All relationships are shown for 20 KTA (closed circles) and 20 SPKT (open circles) recipients. The \( r^2 \) is based on all 40 patients.

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proposal dept nephrology:

- TDM by AUC method
- Patiënt stays at maximum 0,5 day in outpatient department
- AUC estimation by 3 samples at optimal times
- Clinical pharmacist calculates AUC
- Clinical pharmacist calculates a new dosage regimen if necessary
- Clinical pharmacist proposes the time for the next plasmasample
Optimal sampling ciclosporin

- 1 sample:
  - 3 hours after ingestion ($r^2 = 0.82$)

- 2 samples:
  - Before ingestion and 2 hours after ingestion ($r^2 = 0.96$)

- 3 samples:
  - Before ingestion and two of the samples 1, 2, 3 hours after ingestion ($r^2 = 0.97$)

Bron: Cremers NDT 2003
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AUC method protocol

- Patiënt takes the normal dose the evening before
- Patiënt skips the morning dose
- Patiënt visits the hospital in the morning
- Lab takes a trough plasmalevel (t=0)
- Patiënt takes the morning dose
- Lab takes a sample 2 hours after ingestion
- Lab takes a sample 3 hours after ingestion
- Pharmacy lab analyses and interprets the results
Case

- woman, born 1937, 70 kg, renal transplant, treatment ciclosporin b.i.d 125 mg at 08.00 and 20.00 hrs.
- 10-11-03, 09.00 hrs: level 120 mcg/L
- 10-11-03, 09.30 hrs: dose 125 mg
- 10-11-03, 11.30 hrs: level 1084 mcg/L
- 10-11-03, 12.30 hrs: level 521 mcg/L
- target AUC: 3250 mcg*h/L
- What will be the new dosing regimen?

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TDM procedure:

- Ciclosporin: calculated AUC at b.i.d. 125 mg = 4150 microg*h/L
- target AUC: 3250 microg*h/L
- New advise: b.i.d. 100 mg

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Advice

- calculation AUC for the present dosing regimen
- compare AUC with target value
- Calculate new dosing regimen for target AUC
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Phenytoin

farmacogenetic and kinetics of phenytoin

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Kinetics of phenytoine

- Lineair and non lineair kinetics
- largely non lineair kinetics
- Non lineair kinetics according to Michaelis Menten (Km & Vmax)
- Therapy & adverse effects are conc. dependet: C ther. 8 – 20mg/l
The effect of genetic polymorphism of cytochrome P450 CYP2C9 on phenytoin dose requirement.

Van der Weide J, Steijns LS, van Weelden MJ, de Haan K.

Department of Clinical Chemistry, St Jansdal Hospital, Harderwijk, The Netherlands. j.vander.weide@stjansdal.nl
Inheritance of poor phenytoin parahydroxylation capacity in a Dutch family

The mode of inheritance of insufficient phenytoin \( p \)-hydroxylation was studied in the family of a patient who had previously suffered from a phenytoin intoxication caused by insufficient metabolism of this drug. This family was compared with a control group. The rate of phenytoin metabolism was derived from the phenytoin/metabolite ratio in serum 6 hours after an oral test dose of 300 mg phenytoin. The postinus, a brother and a sister, were very slow metabolisers of phenytoin, with a metabolic ratio of approximately 20. In the other individuals, 22 family members of the second generation and 37 control subjects, a metabolic ratio of \( 4.7 \pm 2.2 \) (mean \( \pm SD \); \( n = 59 \)) was found. When comparing the members of the second generation (\( F_2 \)) with the control group, two statistically significantly different groups appear to exist: \( F_2 \), with a metabolic ratio of \( 6.6 \pm 1.7 \) (mean \( \pm SD \); \( n = 22 \)), and the control group, with a metabolic ratio of \( 3.7 \pm 1.8 \) (mean \( \pm SD \); \( n = 37 \)) (\( p < 0.001 \)). Based on these results the mode of inheritance of this defect seems to be autosomal recessive. (Clin Pharmacol Ther 1988;44:588-93.)

P. Vermeij, PhD, M. D. Ferrari, MD, O. J. S. Buruma, MD, PhD, H. Veenema, MD, and F. A. de Wolff, PhD, Leiden, The Netherlands

Inherited insufficient \( p \)-hydroxylation as a cause of phenytoin (PHT) toxicity was described for the first time by Kutt et al.\(^1\) in 1964. In spite of the widespread use of this drug, it was not before 1980 that this phenomenon was confirmed by others.\(^2\) In 1983 we described a patient who developed a severe phenytoin intoxication most probably the result of a drug-metabolizing enzyme deficiency.\(^3\) The formation of \( p \)-hydroxyphenylphenylhydantoin (\( p \)-HPPH), the main metabolite of phenytoin,\(^4\) expressed as the \( p \)-HPPH ratio in urine, was strongly reduced in this patient in comparison with reference values obtained in a group of outpatients receiving phenytoin monotherapy. Characterization of the metabolic drug capacity in general showed that this patient was an extensive metabolizer of debrisoquin. He also had a high antipyrine clearance and selective enzyme induction for \( 4 \)-hydroxyantipyrine formation. These findings led to the conclusion that the reduced metabolizing capacity demonstrated for PHT was specific for this drug in comparison with the test substances used. Acquisition of the deficiency, although not impossible, was deemed to be unlikely in this patient. Assuming an inherited nature, the mode of inheritance of the insufficient PHT \( p \)-hydroxylation was studied in the family of the patient described before.\(^3\)

SUBJECTS

The patient (aged 72 years) had five brothers and 0 three sisters; four brothers and two sisters were already deceased at the onset of the study. The patient and his brother and sister still alive were studied, as well as 22 family members of the second generation.

Thirty-seven healthy volunteers were studied for establishing reference values.

All persons studied were white and apparently in good health. The reference group was comprised of a number of partners of the family members to obtain similar environmental conditions as much as possible, but otherwise environmental conditions were not controlled. Alcohol consumption and smoking habits of each individual were recorded. Most probands were moderate alcohol consumers and nonsmokers. Caffeine consumption was not recorded. Drug use was recorded and was equivalent in the family member group and the control group. Drugs used were oral contraceptives (three in the control subjects and four in the second-generation family) and a number of other drugs, mainly
Metabolism phenytoin

- CYP2C9 & CYP2C19 are involved in metabolism of phenytoin
- CYP2C9 & CYP2C19 are genetically polymorphic
  - CYP2C9(*2,3)  CYP2C19(*2,3,4,5)
- Mutant allele influences Km & Vmax
- To less data for Km & Vmax
- What influence on Vmax?

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# Genotype v.s. phenotype

<table>
<thead>
<tr>
<th>genotype</th>
<th>phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT/WT</td>
<td>Ext. met.</td>
</tr>
<tr>
<td>WT/MUT</td>
<td>Inter mediate met.</td>
</tr>
<tr>
<td>MUT/MUT</td>
<td>Poor met.</td>
</tr>
<tr>
<td>nX WT (n&gt;2)</td>
<td>Ultra rapid met.</td>
</tr>
</tbody>
</table>

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Article Jan van der Weide

- 60 mentally retarded patients get an estimated dose of phenytoin during 6 months.
- After 6 months within two hours before dosing time 2 blood samples are drawn: one for phenytoin estimation, one for genotyping.
- Article describes the relation between dosing and genotype.

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Relation phenytoine daily dose & genotype

- wildtype CYP2C9 (n=37)
- drager van tenminste een mutant CYP2C9 allele (n=23)
Dosing advice

- Means of all patients
- WT/MUT: 199 mg/day (sd39)
- WT/WT: 287 mg/day (sd81)
- Means of patients where C = ther.
- WT/MUT: 199 mg/day (sd43)
- WT/WT: 314 mg/dag (sd61)
  - (for dose>300mg all pat. WT/WT.)

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Results dataset (1/2)

Vmax als functie van (deel)populatie

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Relevant mutation

- CYP2C9mut relevant
- CYP2C19mut not relevant
- WT/WT significantly different from the total population
Results dataset (2/2)

Vmax als functie van (deel)populatie

- fenylall: 60, 14.35
- fenylwt/wt: 31, 16.47
- fenylwt/mut: 18, 11.55
- fenyl2c19: 6, 14.27

Type mutatie

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Conclusion

- Genotyping may be useful by tuning the individual dose
## Conclusion

Use a population model related to a genotype:

<table>
<thead>
<tr>
<th>Model</th>
<th>wt/wt</th>
<th>overall</th>
<th>2C9<em>2of</em>3</th>
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<tbody>
<tr>
<td>Vd</td>
<td>0,53</td>
<td>0,53</td>
<td>0,53</td>
</tr>
<tr>
<td>Km</td>
<td>5,0</td>
<td>5,0</td>
<td>5,0</td>
</tr>
<tr>
<td>Vmax</td>
<td>16,47</td>
<td>14,35</td>
<td>11,55</td>
</tr>
</tbody>
</table>

**pat. 70kg, creat 70 mmol/l en spiegel 14mg/l**

<table>
<thead>
<tr>
<th>Dosis</th>
<th>316</th>
<th>275</th>
<th>220</th>
</tr>
</thead>
</table>

**Art. vd Weide:**

<table>
<thead>
<tr>
<th>Dosis</th>
<th>314</th>
<th>199</th>
</tr>
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</table>

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Therapeutic drug monitoring is a system of quality assurance of a drug management system, aiming that the right drug is given to the right patient in the right dose in order to obtain the right effect.