How to organize a therapeutic drug monitoring service

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What is Therapeutic Drug Monitoring?

- TDM corresponds to a multi-disciplinary service aiming to individualize/optimize drug treatment (efficacy/side effects)
- Requires excellent communication with prescribers
- Requires competencies in pharmacology/toxicology
  - Pharmacodynamics/biomarkers of activity-toxicity
  - Variations in drug disposition: pharmacokinetics/drug metabolism
  - Pharmacogenetics
- Requires competencies in drug analysis
  - Preanalytical phase
  - Analytical phase
    - Chromatographic methods/Immunoassays
How individualize drug treatment?

*Example of immunosuppressive drugs*

**Pharmacokinetics**
- Drug exposure
- Drug interactions
- Distribution
- Metabolism
- Elimination
- Pharmacogenetics (CYP3A5, P-gp, ...)

**Pharmacodynamics**
- Action on receptors
  - IL2
- Lymphocytes CD+4
- Cylex assay
- Pharmacogenetics, Proteomic, metabolomics...

**Adverse events**
- Nephro-, neurotoxicity
- Hypercholesterolemia
- Overimmunosuppression

**Treatment efficacy**
- Acute rejection
- Chronic rejection
- Tolerance

**Methods**
- Immunoassays
- LC-MSMS
- Analytical performances (specificity, sensitivity, ...)
- Dry spot analysis,...

**CLINIQUES UNIVERSITAIRES SAINT-LUC**
What is not Therapeutic Drug Monitoring?

• TDM should not be « reduced to a simple » drug measurement from any blood specimen
  – Time-dependent concentrations
  – In absence of known expertise from the prescriber
  – In absence of accurate information allowing adequate interpretation
  – In absence of contact/dialogue with the prescriber or his staff
What are the criteria to justify TDM?

- Critical dose drugs (small therapeutic index)
  - Drugs with unpredictable PK (non linear PK) or unstable pathological status (intensive care, oncology, elderly, etc…)
  - Drugs with side effects possibly misinterpreted by disease progress or symptoms
  - Absence of pharmacodynamic markers
  - Chronic treatment with risk of non compliance

- Pharmacoeconomic and cost-effective reasons
  - Shorter treatment
  - Shorter hospital stay
Basic assumption for TDM

• Since the ’70 it was recognized that plasma drug concentrations were better related to effects than the amount of drug administered

• Successful applications for digoxin, theophylline, aminoglycosides, antiepileptics, immunosuppressants…
  – Low therapeutic index, variable PK, effect difficult to quantify,…

• Largely contributes to the principles of « personalized medicine » (PK variability)
  – Identification of drug interactions
  – Identification of high or low drug clearance (accumulation)
  – Identification of non-compliance
  – …
What drugs?

• « Old » drugs with proved interest
  – Aminoglycosides and glycopeptides (gentamicin, vancomycin..)
  – Cardiac glycosides (digoxin)
  – Antiepileptics (carbamazepine, valproic acid, phenytoin..)
  – Methotrexate
  – Theophylline
  – Immunosuppressive drugs (cyclosporine, tacrolimus, everolimus, sirolimus, MPA..)
  – Some antiarrhythmic agents (amiodarone)
  – Some antidepressive agents (Lithium, TCA ?)
What drugs?

• « New » drugs of interest
  – Newer antiepileptics (levetiracetam, oxcarbazepine, lamotrigine..)
  – Some antiretrovirals (efavirenz, lopinavir,..)
  – Some cephalosporins (cefepime, meropenem..)
  – Some antifungals (posaconazole, itraconazole, voriconazole..)
  – Some cytotoxic agents (imatinib, irinotecan, tamoxifen, L-asparaginase, ..)

• Drugs with limited interest (?)
  – Benzodiazepines
  – SSRI
TDM challenges and issues

• But…limitations of TDM
  – Sometimes poor relationship between trough drug concentration ($C_0$) and clinical outcome
  – High dependency of sampling time accuracy
    • Difficulty to get reliable data from nursing (times, dose, interval,…)
• Difficulty to get real consensus for therapeutic ranges
  – Maybe as a consequence of erratic blood sampling, variable analytical methods,…
• As a consequence: limited and still debated success in some applications
  – Mycophenolate, antiretrovirals, cytotoxics, antidepressants,…
TDM: search for better PK-PD markers
the « quest of the GRAAL »

- Since the years ’70, permanent search for optimal marker of efficacy/toxicity e.g.:
  - Plasma, whole blood, free vs total fraction
  - Bioassay (MLC, RRA, EA, MIC,…)
  - Sampling time: C₀, C₂, Cₘₐₓ, full AUC …

- Single blood sampling: easy but sometimes weak for predicting effects (e.g. C₀,…)
  - Pharmacokinetic reasons
    - Drug ≠ endogenous analyte (e.g. creatinine)
    - Logistic issues (accuracy in routine setting)
    - Sometimes lack of good relationship between C₀ and AUC
  - Pharmacological reasons
    - Concentration- or time-related effects e.g. antibiotics
    - Blood conc not well related to target (intra-cellular) site conc,…
Evolution in Laboratory Medicine

- Important economic pressure and progress in technology
- Trend to « industrialize » laboratory testing
  - Increased automation
  - Consolidation, laboratories merging
  - Reduction of test production costs
- Need to increase the Medical expertise and the « value-added » for any laboratory tests
  - Need to optimize the value of any laboratory result
  - Knowledge service
  - Better interpretation
  - Guidance in prescription
  - Evidence based …
How to organize a TDM service?
Step 1
Scientific background

• Acquire a strong background and knowledge in pharmacology, toxicology and pharmacokinetics
  – University programmes (MD, pharmacy, clinical chemistry, …)
  – Continuous education
  – eLearning (Webcast, Podcast,…)
  – Spend some time abroad in an experienced laboratory
  – IATDMCT…
Causes for variability in drug response

• Non compliance
• Underlying disease (kidney and liver function)
• Age, gender
• Drug-drug interactions
• Environmental factors (smoking, diet,…)
• Genetics factors (pharmacokinetics and pharmacodynamics)
Drug disposition and interactions

- Absorption
- Distribution
- Metabolism
- Excretion
- Transport proteins
- Biotransformation enzymes

F
Example of immunosuppressive drugs

- Blood concentrations are regulated by PK and PG
  - Bioavailability (first pass effects)
  - Distribution ($f_{u,\ldots}$)
  - Drug transporters (P-gp,\ldots)
  - Biotransform enzymes (CYP3A\ldots) and clearance
  - Drug interactions

- Typical time-conc profile
Drug Area Under the time-concentration Curve (AUC)

- Better relationship with drug effects than $C_0$
- Direct access: possible but difficult
  - 8-12 blood sampling
  - Medical issue, costs, time,…
- Indirect access: prediction through mathematical approaches
  - Limited sampling strategies (LSS): 2-3 blood samples with equations adapted to specific populations: OK (need strict blood sampling times compliance)
  - Population pharmacokinetics with Bayesian estimates: OK (allow more flexibility in sampling times)
Pharmacodynamic biomarkers

• Antibiotics:
  – MIC, peak/MIC, Time above MIC, AUIC…

• Immunosuppressives
  – Lymphocytes proliferation (Proliferating Cell Nuclear Antigen)
  – Expression of surface antigens of T-cell
  – IFN-γ ELISPOT assay
  – Quantification of intracellular IL-2 in CD8+T cells
  – Measure of the ATP production from stimulated T-cells (Cylex ImmuKnow assay)
  – Specific enzymes activity (IMPDH, calcineurin,…)

• Antiretrovirals
  – Viral load,
  – CD4,
  – RNA-HIV,…
Genetic factors

Adapted from Lindpaintner
**Genotype**

**Drug Metabolism (Degradation)**

- **WT/WT**
  - AUC = 100
  - Concentration over time

- **WT/V**
  - AUC = 200
  - Concentration over time

- **V/V**
  - AUC = 400
  - Concentration over time

**Drug Receptor (Efficacy)**

- **Efficacy**
  - Response over AUC
  - Toxicity over AUC

<table>
<thead>
<tr>
<th>Metabolism genotype</th>
<th>Receptor genotype</th>
<th>Efficacy</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>65%</td>
<td>Low (5%)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>32%</td>
<td>Low</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>9%</td>
<td>Low</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>79%</td>
<td>Moderate (15%)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>40%</td>
<td>Moderate</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>10%</td>
<td>Moderate</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>80%</td>
<td>High (80%)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>40%</td>
<td>High</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>10%</td>
<td>High</td>
</tr>
</tbody>
</table>
Goals of a pharmacogenetic approach

1. Help choosing the most appropriate drug for each individual, taking into account PK and PD aspects

2. Select an optimal dose

3. Identify those at risk from atypical adverse drug reactions or lack of efficacy
   CYP3A, CYP2D6, CYP2C, CYP1A2, P-gp, MRP2, etc…
Step 2
Prescribers and care units

• One of the most important step is to have well informed, motivated and trained prescribers and nursing staff
• Identify key prescribers (e.g. infectious disease, transplantation, paediatry, neurology/psychiatry etc…)
• Need to convince them of the utility of well performed TDM in order to assure appropriate sampling and information provided…
Prescribers and care units

• Develop/reinforce collaboration through a series of seminars/staff meeting/lectures
  – Most of prescribers have weak knowledge of drug disposition and causes of PK variability, laboratory and preanalytical constraints…
  – Teach them basis of PK/PD

• A large proportion of TDM issues results from mistakes during preanalytical phase, sampling and (lack of) data provided
  – « Understand why doing something in order to do it properly »
  – Relatively heavy task so… risk to drop out
Prescribers and care units

• Ideally electronic prescription with mandatory « fields » to fill out
• If not, « paper » request form with information regarding:
  – Patients biometric data (age, weight, size,…)
  – Pathology involved (e.g. cystic fibrosis, orthopedic surgery, transplantation, hematologic disorder, sepsis,…)
  – Clearance-organs status (kidney or hepatic function…)
  – Information regarding dose/interval, hours of dosing and sampling…
• Potential role of clinical pharmacists or PharmD in the care unit
Step 3
Analytical methods

- Identify the analytical environment and possibilities
  - Equipment available
  - Analytical expertise
- Before to decide what to do and invest in chromatography or immunoanalysis, need to develop a « business plan »
  - What drugs (chemical structure) ?
  - Expected number of assays ?
  - Funding sources (social security, insurance, patient,...) ?
  - Staff needed and costs ?
  - Maintenance and back up, etc…
Analytical methods improvement and standardization

• Apparent simple matter… In fact full of questions
• Large domination of immunoassays (IA) until recently, alternative methods appearing
  – Variety of IA: (RIA, FPIA, ELISA), MEIA, EMIT, ACMIA, CMIA, CEDIA
  – HPLC-UV, LC-MS users 2% (1999) → >25% (2011)
• Choice between IA or LC-MS(MS)?
  – Depends on each lab characteristics (n samples, staff qualif, costs)
• Existence of significant differences between methods
  – Important concern when performing PK studies or when comparing clinical trials, outcome studies or target ranges
  – Need to describe properly the method and understand the differences among methods
Analytical methods improvement and standardization

- Immunoassays
  - Routine analyzer, robust, fast TAT, lab technician flexibility,…
  - Reproducibility, and/or calibration bias issues
  - Interfering compounds
    - Cross-reactivity with metabolites e.g. cyclosporine,…
    - Endogen interfering compounds e.g. digoxin, tacrolimus,…
    - Heterophilic antibodies,…

- Chromatographic based methods (UV, MS)
  - Expected to be more specific
  - Most are « home-brew » sometimes lacking of rigorous validation
  - Need technical expertise
  - Reproducibility and/or calibration bias issues (certified kits?)
  - Interferences
    - Carry-over,
    - Ion-suppression,…
Analytical methods improvement and standardization

• Clinicians need consistent results
• Need of international standardization
  – To limit calibration bias occurring both with IA and LC-MSMS
  – To limit interferences with endogenous compounds or metabolites
  – To improve outcome studies comparison
• Need to improve automation and robustness of IA and LC-MSMS
  – Automated preanalytical phase
  – Deuterated IS
• Methods need to follow any change in therapeutic ranges
• Mandatory to participate to Proficiency Testing Schemes
Cyclosporine International Proficiency Testing Scheme, UK, PT329 August 2011

- Cyclosporine: 459 participants
What method(s) use?

• Probably mixture of different IA and HPLC methods
• Several large analyzers in laboratory medicine can measure a few drugs (e.g. antiepileptics, digoxin, immunosuppressive drugs…)
• Many drugs can be measured by HPLC-UV or -MS (cheaper in terms of reagents, but equipment costs?)
• Need reasonable turn-around-time (TAT): ideally within the 24h to be useful
What method(s) use?

• Should the service be separated from the Core- or Central Laboratory?
  – Definitely yes, for the biomedical expertise (need specific competencies)
  – Perhaps no, for the analytical measurements but depends on the size of the laboratory and equipment involved
    • Separated plateforms for large automated analyzers and chromatographic equipments
Step 4
Pharmacokinetics softwares

- Implement pharmacokinetics softwares or even better population pharmacokinetics models in order to better predict AUC and reduce the number of sampling
- Commercial or public PK softwares
  - Direct online access to international webserver with/without login
  - ABIS/ISBA
  - Applications for iPhone, Palm, and other PDA
  - Pharmonitor II
  - USC*PACK software
  - PharmaCalc
  - SAAMII
  - ATM, etc…
Cliniques Universitaires Saint-Luc

PharMonitor - Analysis file

- **Last Name**: OKUZA
- **First Name**: Philippe
- **Date of birth**: 10/02/1958
- **Date of calculation**: 20/03/2009
- **Prescriber**: CRATCUD
- **Name**: AMIKACIN OD
- **Target Cp min (µg/mL)**: 2.000
- **Target Cp max (µg/mL)**: 50.000

**Curve concentrations**

- **Weight (kg)**: 70.0
- **Height (cm)**: 183
- **Creatinine (mg/dL)**: 0.90
- **CL creat. (mL/min/1.73m²)**: 82.05
- **Urea (mg/dL)**: 30.00
- **MIL (µg/mL)**: 1.50

**Date/time start of perfusion**: 12/12/2008 / 08:30
**Date/time end of perfusion**: 12/12/2008 / 09:06
- **First dose**: ?
- **Administered dose (mg)**: 1000.00
- **Dosage interval (h)**: 24

**Date of blood drawing**:
- **12/12/2008**: 10:55, 29.000 µg/mL
- **12/12/2008**: 15:00, 10.000 µg/mL
- **20/03/2009**: 00:00, 0.000 µg/mL

- **Calculated Cp max (µg/mL)**: 47.796
- **t1/2 (h)**: 2.67
- **AUC (mg.h/L)**: 135.24
- **Calculated Cp min (µg/mL)**: 0.108
- **ke (h)**: 0.2591
- **CL antibiotic (mL/min/kg)**: 1.21
- **Vd (L/kg)**: 0.28

- **Calculated dose (mg)**: 1011.37
- **Calculated interval (h)**: 12.92

- **Proposed dose (mg)**: 1010.00
- **Proposed interval (h)**: 12.00

- **Cp max (µg/mL)**: 50.429
- **Cp min (µg/mL)**: 2.562

- **Creatinine Clearance**: Cockcroft Gault (BSA - Boyd [1.8757 m²])
- **20/03/2009 20:45:10**

- **Analysis identifier**: 09E00013
- **Encoded by**: ADM
- **Encoded on**: 20/03/2009
- **Modified by**: ADM
- **Modified on**: 20/03/2009

- **Comments**: Proposition de maintien le même schéma posologique

- **Sign and print the protocol**: Signer et imprimer le protocole
- **View the last protocol**: Voir le dernier protocole
- **Generate the protocol**: Générer le protocole
- **Print a proposition**: Imprimer une proposition
- **Validate**: Valider
- **Cancel**: Annuler
Dear Colleagues,

Please find below the results of the tests required for your patient OKUZA Philippe born on 10/02/1958.

**Current treatment**
Antibiotic administered: AMIKACIN OD
Regimen (dose/interval) administered: 1000 mg / 24 h

<table>
<thead>
<tr>
<th>Desired conc. (target)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmin : 2.000 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Cmax : 50.000 µg/mL</td>
<td></td>
</tr>
</tbody>
</table>

**Results of the therapeutic**

<table>
<thead>
<tr>
<th>Measured conc. (quantified)</th>
<th>Calculated conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9 h after adm.</td>
<td>29.000 µg/mL</td>
</tr>
<tr>
<td>6.0 h after adm.</td>
<td>10.100 µg/mL</td>
</tr>
</tbody>
</table>

**Calculated PK parameters**

- Vd : 0.28 (L/kg)
- CL : 1.21 (mL/min/kg)
- t1/2 : 2.67 h
- AUC : 196.25 (mg.h/L)

**Protocol and proposed treatment**

Regimen (dose interval) administered: 1000 mg / 24 h

**Comments:**
Proposons de maintenir le même schéma posologique

<table>
<thead>
<tr>
<th>Predicted conc. (expected)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmin : 0.108 µg/mL</td>
<td></td>
</tr>
<tr>
<td>Cmax : 47.796 µg/mL</td>
<td></td>
</tr>
</tbody>
</table>

Conc. concentration ; Cmin, minimum concentration ; Cmax, maximum concentration, adm., administration ; Vd, volume of distribution ; CL, total clearance ; t1/2, elimination half-life ; AUC, Area under curve.

Protocol generated by: Administrateur Administrateur

(version n° 8)
Access portal to the websites of routine and clinical trials of the Limoges University Hospital laboratory of Pharmacology

<table>
<thead>
<tr>
<th>Access</th>
<th>TDM - Modalities</th>
<th>Available tools</th>
<th>ISBA Newsletters</th>
<th>Publications</th>
</tr>
</thead>
</table>

Please identify yourself

Login: [Input field]
Password: [Input field]

[Link: You lost your identifier and/or your password]

[Buttons: Delete, Enter the Websites]

[Link: Registration on ISBA website]
### Therapeutic Drug Monitoring of Mycophenolate-mofetil

**Identification**

- **Identification code:** [Redacted]
- **Renal transplantation (Adult)**
- **Cyclosporine HPLC**

- **Transplant Date:** 07/06/2008
- **Date of sampling:** 21/08/2008

**Informations about applicant**

- **Email:** [Redacted]
- **Comments:**

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**Context of the request**

- **Non-diabetic patient**

**Concentration data**

<table>
<thead>
<tr>
<th>Time of sampling n1 (min)</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration n1</td>
<td>5.01 mg/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time of sampling n2 (min)</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration n2</td>
<td>13.21 mg/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time of sampling n3 (min)</th>
<th>160</th>
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</thead>
<tbody>
<tr>
<td>Concentration n3</td>
<td>4.71 mg/L</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Time of sampling n4 (min)</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration n4</td>
<td>[Blank]</td>
</tr>
</tbody>
</table>

**Results interpreted by:** Dr J. Debord - 06/08/2003 - 06:17:34

- **Delay between graft and dosage:** 14 days
- **Trough estimated by Bayesian method:** 0.95 mg/L
- **C max estimated by Bayesian method:** 16.73 mg/L

---

**AUC (0-12h) estimated by Bayesian method**: 37.32 h.mg/L

**Dose estimated for AUC = 45 h.mg/L**: 1250 mg

**Current dosage (by dose)**: 1000 mg

- **Dose estimated for AUC = 30 h.mg/L**: 750 mg
- **Dose estimated for AUC = 60 h.mg/L**: 1500 mg
- **Number of doses per day**: 2

- **AUC estimated par multilinear regression**: 41.17 h.mg/L
Bayesian modelling of mycophenolate mofetil concentration data, measured in patients.

### Graph 1

**C (mg/L)**

<table>
<thead>
<tr>
<th>t (h)</th>
<th>C (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
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<tr>
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<tr>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

### Graph 2

Review of the estimated AUC values in patient.

**AUC h mg/L**

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose</th>
<th>AUC h mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/08/2008</td>
<td>2 x 1000 mg</td>
<td>30</td>
</tr>
<tr>
<td>21/08/2008</td>
<td>2 x 1000 mg</td>
<td>45</td>
</tr>
</tbody>
</table>

The review is limited to the last 5 estimated AUC values over a period of 2 years.
Step 5
Politics and concept of « knowledge service »

• Set forth benefits of TDM to public health authorities highlighting potential costs saving resulting from a well organized TDM service
  – Need to demonstrate clinical utility and cost-effectiveness
  – Obtain better reimbursement
• Develop partnership with diagnostic companies or instruments manufacturers
• Promote alliance and networks to reduce costs
  – Consolidation
Politics and concept of « knowledge service »

• Promote the concept of « knowledge service »
  – Several drug adjustments could be obtained by simple « knowledge » with minimal or (even absence of) blood sampling and drug measurements
  – Avoiding drug interactions
  – Anticipating drug accumulation
  – Reaching effective concentrations
  – Interpretating unexpected drug concentrations
  – Planning rational frequency of drug monitoring and limiting the number of useless analyses

• Bring a real « value added » to the TDM service
Conclusions

• The organization of a TDM service could be obtained through several steps
  – Acquisition of a strong clinical pharmacology and pharmacokinetics background
  – Development of a good communication with prescribers
  – Identify the best analytical approach based on each individual laboratory characteristics
  – Implement PK software to better predict AUC
  – Development of a true « knowledge service » demonstrating the cost effectiveness of the activity
Thank you for your attention