Some PK relationships

dA/dt = -Ke * A, where A = amount, Ke = rate constant
Let volume be V.
Concentration = A/V
Clearance (Cl) = Ke*V, and Ke = Cl/V
V has units of Liters, for example
Ke has units of 1/hours, for example
So Clearance has units of L*1/hour, which is L/hr. Only the rate of volume cleared is perceived, and the true information about the rate of drug movement is obscured.
V and clearance or V and Ke?

Clearance comingles V and Ke, and obscures info of both volume and drug movement.

Ke is the parameter giving direct information about movement from one compartment to another, or excretion from the body.

For unstable ICU patients, who often have problems with fluid balance (V), and changing renal function (CCr) it is useful clinically to separate V and Ke.
Clearance is an unnecessary parameter

• Clearance is a combination of V and Ke. It adds nothing new to the information from V and Ke. The contributions of V and Ke are comingled and obscured.

• V and Ke contain all the necessary information.

• Separating V and Ke permit better understanding and management of fluid balance (V) and drug elimination (Ke).
Chr dialysis pt with sepsis. Doses of zero during dialysis, add 50 CCr

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Analysis with population PK model
Fitted data
Lessons from this patient.

1. Physicians and pharmacists need a common minimum knowledge base in order to be able to communicate at all. Medical students currently get no clinically meaningful education in pharmacokinetics.

2. One can include episodes of dialysis or other forms of renal replacement therapy as described here.
A very unstable patient
Predicted versus measured levels

R-squared: 0.77, mean error: 1.11, mean squared error: 3.41
Y = 0.80X - 0.13
No parameter changes allowed
Interacting Multiple Model Methods in Target Tracking: A Survey.

E. MAZOR Technion, Israel Institute of Technology
A. AVERBUCH Tel Aviv University
Y. BAR-SHALOM, Fellow, IEEE University of Connecticut
J. DAYAN Technion, Israel Institute of Technology

IEEE TRANSACTIONS ON AEROSPACE AND ELECTRONIC SYSTEMS VOL. 34, NO. 1
JANUARY 1998

“The main purpose of a tracking system for air traffic control or air defense is the estimation of target trajectories in the controlled area and their prediction into the near future”.

The IMM analysis
IMM predicted - measured

R-squared: 0.96, mean error: 0.06, mean squared error: 0.36
Y = 0.97X + 0.05
Change probability 1.00000 [%]
IMM – changing V and Ke
Back to the first patient, now with IMM
Changing V and Ke in this patient
Putting it all together,

1. Get samples of SCr and the drug concentration at start and end of dialysis or RRT, and peaks and other times.
2. Use D-optimal or MM-opt monitoring strategies.
3. Use nonparametric (NP) models,
4. Use NP Bayesian analysis of individual patient data,
5. Use multiple model (MM) maximally precise dosage design, and
6. Use Interacting MM (IMM) clinical software as described in the two cases presented.
Estimation of CCr

\[ C = \frac{(U \times V)}{P} \]

Or, \( P \times C = U \times V \)

SCR response to decrease in CCr
Estimation of changing SCr

Change in C in body = Production - Excretion

$0.4W(C_2 - C_1) = P - C_{avg} \times C_{Cr} \times 1440$

• Where
  
  $P$ is daily creatinine production (see article)
  $C_1$ and $C_2$ are SCr in mg/100ml,
  $W$ is weight (in hundreds of grams), and
  $C_{Cr}$ is creatinine clearance (in hundreds of ml/min).

Then adjust for 1.73 M$^2$ BSA
Estimation errors in CCr

CV of serum creatinine = ± 5%
CV of urine creatinine = ± 8%

Then if collect 24 hr urine with CV = ± 5%,

\[ 5^2 = 25 \text{ twice } = 50, \text{ plus } 8^2 = 64, = 114. \]

\[ \sqrt{114} \approx 11 \]

So the GOLD STANDARD CCr has a CV = ± 11%,
or 95% conf limits of ± 22%
Estimated vs Measured CCr
Optimize TDM protocols

Do not just spot check. Instead, sample to learn drug behavior. Think before you sample.

Do **NOT** wait to get steady state trough levels.

Start right with the **very first dose**.

Use, for example, D-optimal or MM-opt design. There is an optimal time to sample for each patient, given a certain dosage regimen format.

Often, get a **peak** and a sample at about **1/3 the peak**.

Do **NOT** waste money, effort, and patient care with poor designs. The TDM community can do a MUCH BETTER job here. Better info, better care, shorter stays, **less** cost.
For a constant assay error, the greatest change in serum conc when volume of dist changes is at the true peak, not later. **Samples near the peak are most informative about Vd.**
The greatest change in serum conc from a change in the Kel is when the serum conc is 36% of the original peak value. **Samples near 1.44 half-times are most informative about Kel.**
What is the IDEAL Population Model?

• The correct **structural** PK/PD Model.
• The collection of each subject’s **exactly known** parameter values for that model.
• Therefore, **multiple discrete individual models**, one model from each subject.
• Usual continuous statistical summaries can also be obtained, but usually will **lose** info.
• **Unconstrained Parameter Distribution (UPD)** models **best approach** this unattainable ideal.
A UPD Population Model Unconstrained Parameter Distribution, made by Alain Mallet
Individualizing Drug Therapy:

Developing **maximally precise** dosage regimens for each patient, using

1- Nonparametric (NP-UPD) PK/PD models, using V and Ke, not V and clearance.
2- Multiple Model (MM) maximally precise dosage design,
3- Estimates of CCr from pairs of changing SCr’s,
4- D-Optimal or MM-opt TDM protocols,
5- IMM Bayesian adaptive control tools
6- Entering dialysis data as described

Optimize learning about the patient while treating at the same time.
Continuous IV Vanco. Predictions when regimen based on parameter means is given to all support points
Vanco, continuous IV. Predictions when MM regimen is given to all support points
Then, after starting TDM and making an individualized model for the patient,

- Exact knowledge of GFR is no longer needed.
- But you need to track CCr from changing serum creatinines, not just a single sample.
- Then you have **locked in** the relationships between dosage, serum concentrations, and the changing serum creatinines. Your patient's empirical individualized model is complete.
- Control this model, especially with IMM, and MM dosage design, and you dose to control the patient’s serum concentrations most precisely.
- Use V to help with fluid management.
To do this, you need optimal software and a trained dosing service.

- Pierre Marquet in France has a large transplant dosing service in Limoges, providing dosage recommendations for much of France by web.

- Anders Aasberg in Oslo, for all transplants in Norway. They now dose tacrolimus more precisely than their experienced transplant physicians.
Dear all,

Statistics from the French Agency of Biomedicine have just been known: we (IHOP) are the best pediatric bone marrow transplantation center in France, with the lowest transplantation-related mortality and the highest one-year overall survival. Although these results are attributable to a multidisciplinary team work, the contribution of drug dosage regimens individualization is evident: busulfan, antibiotics, voriconazole, antiviral agents and immunosuppressive agents. Moreover, I guess that we have the best disease-free survival in the world for children transplanted for leukemia, thanks to Bayesian monitoring of cyclosporine (paper to come).

All these good results are also yours. A special thanks to Roger and Pascal for having spread drug individualization methods and having trained people, Michael, Sylvain and Laurent for continuing the job.

A special thanks to all the residents who participated at building PK models and applying Bayesian monitoring in Debrousse Hospital and now IHOP...

Hope the youngest of us (Michael and co) will go on, and improve the outcome of patients suffering from other pathologies!

Best regards

Nathalie
References (1)


References (2)


References (3)


• Jelliffe R: Commentary - Optimal Methodology is Important for Optimal Pharmacokinetic Studies, Therapeutic Drug Monitoring, and Patient Care. Clinical Pharmacokinetics; (DOI) 10.1007/s40262-015-0280-4mplpin
References (4)


