

Population pharmacokinetic analysis of TDM in optimising therapy

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- C.Neef has nothing to declare
- This presentation is a compilation of PP-pharmacokinetics presentations from D.Touw, J.H.Proost and C.Neef

- Estimation methods
- Bayesian estimation
- Population models
- Inter and intra individual variability

Population Pharmacokinetics

- › Description of pharmacokinetic behaviour of a drug in a population
- › Pharmacokinetic model
- › Statistical model
 - parameter distribution
 - residual error

Goal

- › Characterization of PK
- › Influence of patient characteristics on PK
- › MAP Bayesian parameter estimation
 - for dose adjustment in individual patient (TDM)

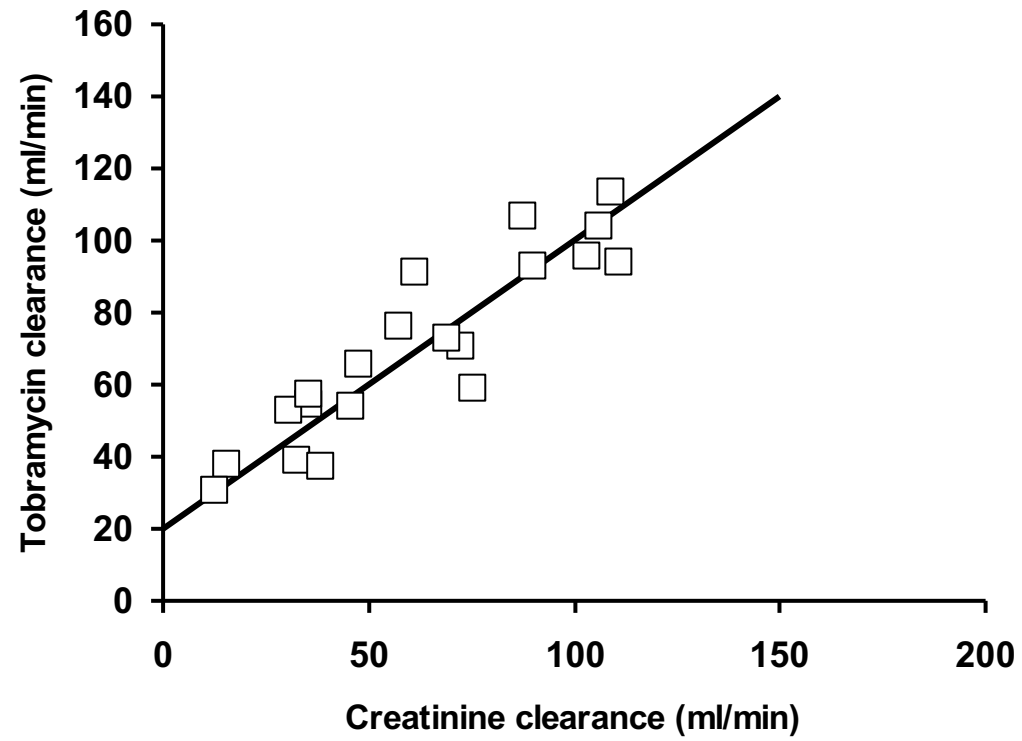
Model parameters

- › Model parameters
 - Measure of central tendency ('mean value')
 - Measure of inter-individual variability ('sd')
 - Covariance between parameters (often ignored!)
 - Assessment of covariates

Covariates

- › Descriptors related to a pharmacokinetic parameter, e.g.
 - creatinine clearance for renal clearance
 - BSA for (metabolic) clearance
 - LBMc for volume of distribution
 - age
 - gender

$$CL = CL_m + fr \cdot CL_{cr}$$



Parameter distribution

- › Parametric methods require assumptions, e.g.
 - normal distribution
 - log-normal distribution
- › Nonparametric methods

Residual Error

- › Analytical error
 - accounted for by appropriate weighting
- › Errors in dosing and time
- › Model misspecification

Residual Error

- › Assumptions on residual error required for appropriate weighting of measurements, e.g.
 - independent of concentration
 - proportional to concentration
 - log-normal distribution (use logarithmic transformation)
 - assay error related to concentration by a polynomial
$$SD(C) = s_0 + s_1 \cdot C + s_2 \cdot C^2 + s_3 \cdot C^3$$

Residual Error

- › Fixed residual error (related to concentration)
- › Residual error parameters estimated during the population analysis

Data (measurements)

- › Rich data
- › Sparse data

Rich data

- › Large number of blood samples from each subject
 - › Small number of subjects
 - › Experimental environment
 - › Healthy volunteers
-
- › Aim: model identification

Sparse data

- › Small number of blood samples from each patient
 - › Large number of subjects
 - › Clinical environment
 - › Patients
-
- › Aim: Identification of model parameters and covariates for TDM

Methods

- › Naive pooling
- › Standard Two-Stage (STS)
- › Mixed-Effect modeling (eg: NONMEM)
- › Nonparametric methods (eg: NPEM)
- › Iterative Two-Stage Bayesian (ITSB)

Naive Pooling

- › Data of all patients pooled
- › Inter-individual variability ignored
- › No information on inter-individual variability obtained

Standard Two-Stage

Step 1

Data of each patient analysed separately

Step 2

Mean and SD of model parameters

Standard Two-Stage

+

- Conceptually and computationally simple

-

- Inter-individual variability overestimated
- Not applicable to sparse data
- Problems with 'non-fittable' patients

Mixed-Effect Modeling

> NONMEM

+

- Statistically sophisticated
- Generally accepted (FDA)

—

- 'Black box'

Nonparametric methods

> NPEM, NAG

+

- No assumptions on distribution of parameters within the population required
- Detection of typical distribution patterns, e.g. bimodal
- Suited for 'Multiple Model Approach'

-

- Conversion to parametric distribution required for application in MAP Bayesian fitting
- Not well documented in public area

Iterative Two-Stage Bayesian

- › KinPop (MwPharm)
- › IT2B (USC*PACK)

+

- Conceptually and computationally simple

—

- Results may be less precise and/or less accurate for sparse data

Iterative Two-Stage Bayesian

- › Assume a reasonable set of population data (e.g. from STS)
 - means \pm sd
 - covariance matrix (usually zero)
 - residual error (e.g. assay error pattern)

Iterative Two-Stage Bayesian

- › Step 1: Perform Bayesian analysis on each subject separately
 - Estimate PK parameters using Maximum *A Posteriori* Bayesian feedback
 - Pharmacokinetic population parameters (*a priori* information)
 - Observed plasma concentrations (measurements, actual information)

Iterative Two-Stage Bayesian

- › Step 1: Perform Bayesian analysis on each subject separately
- › Step 2: Calculate new set of population data
 - means \pm sd
 - covariance matrix
 - residual error

Iterative Two-Stage Bayesian

- › Repeat step 1 and step 2 until convergence is reached, i.e.

stable values for:

- means \pm sd
- covariance matrix
- residual error

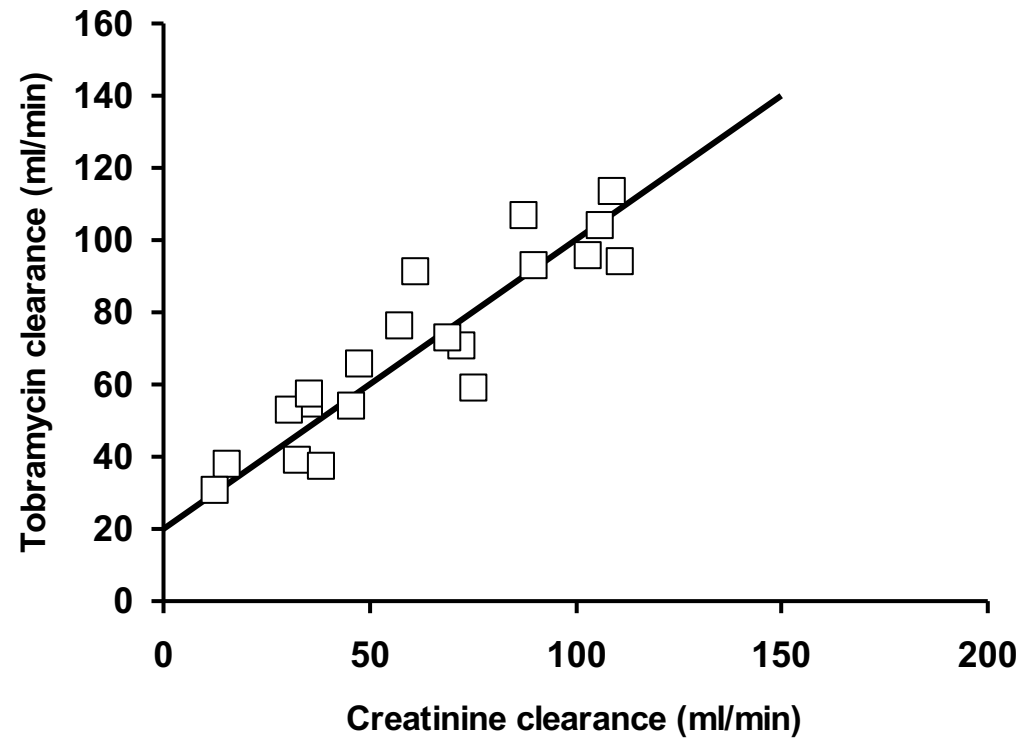
Iterative Two-Stage Bayesian

- › **Steimer et al.**
Drug Metab Rev 1984; 15: 265-292
- › **Mentré and Gomeni**
J Biopharm Stat 1995; 5: 141-158
- › **Bennett and Wakefield**
J Pharmacokinet Biopharm 1996; 24: 403-432
- › **Proost and Eleveld**
Pharm Res 2006; 23: 2748-2759 (+ Pharm Res 2007; 24: 1599)
- › **Proost et al.**
Biopharm Drug Dispos 2007; 28: 455-473

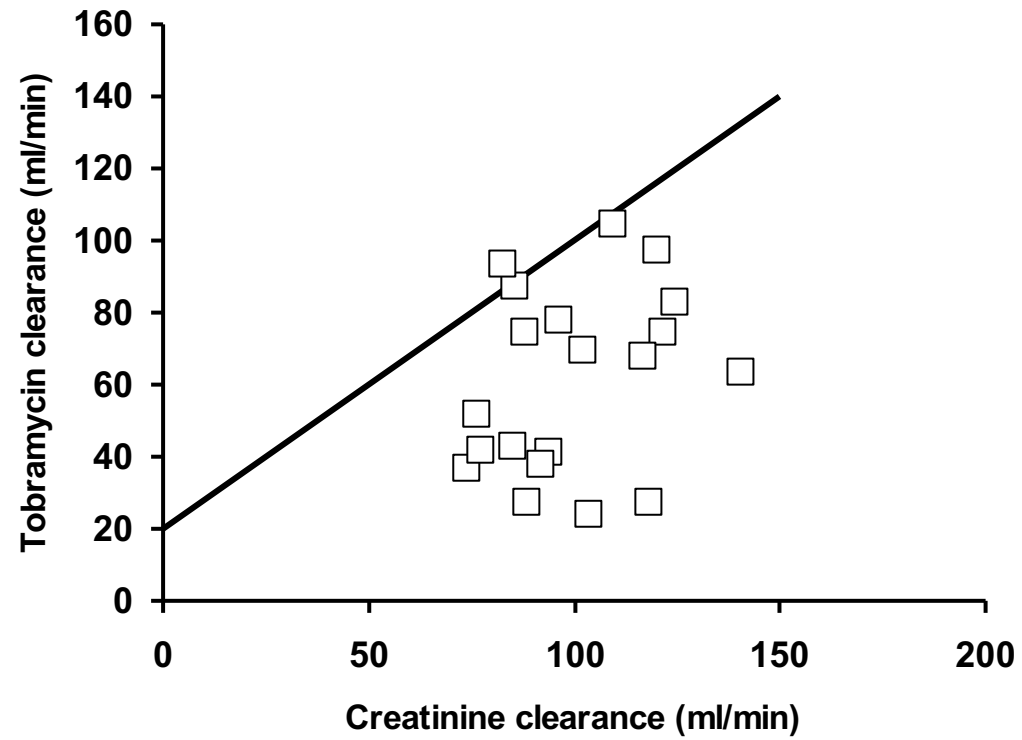
APPLIED PHARMACOKINETICS

- 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

$$CL = CL_m + fr \cdot CL_{cr}$$

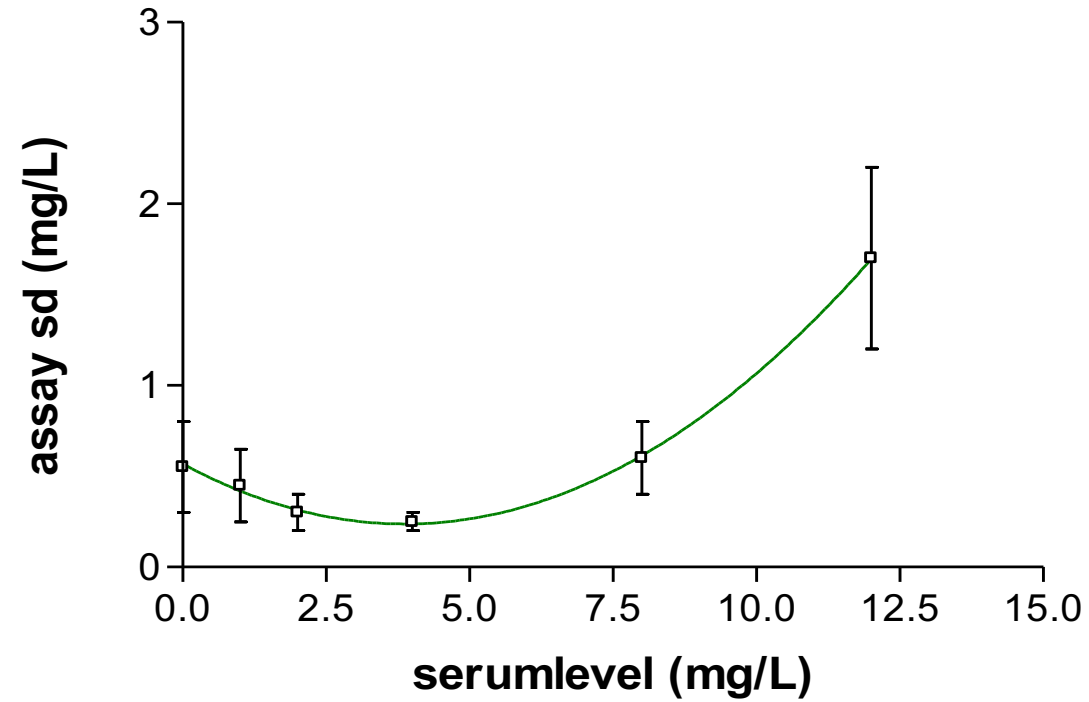


$$CL = CL_m + fr \cdot CL_{cr}$$



APPLIED PHARMACOKINETICS

assay pattern
 $y = 0.568 - 0.171X + 0.022X^2$



APPLIED PHARMACOKINETICS

- THERAPEUTIC / TOXIC RANGE

SERUM DIGOXIN LEVELS

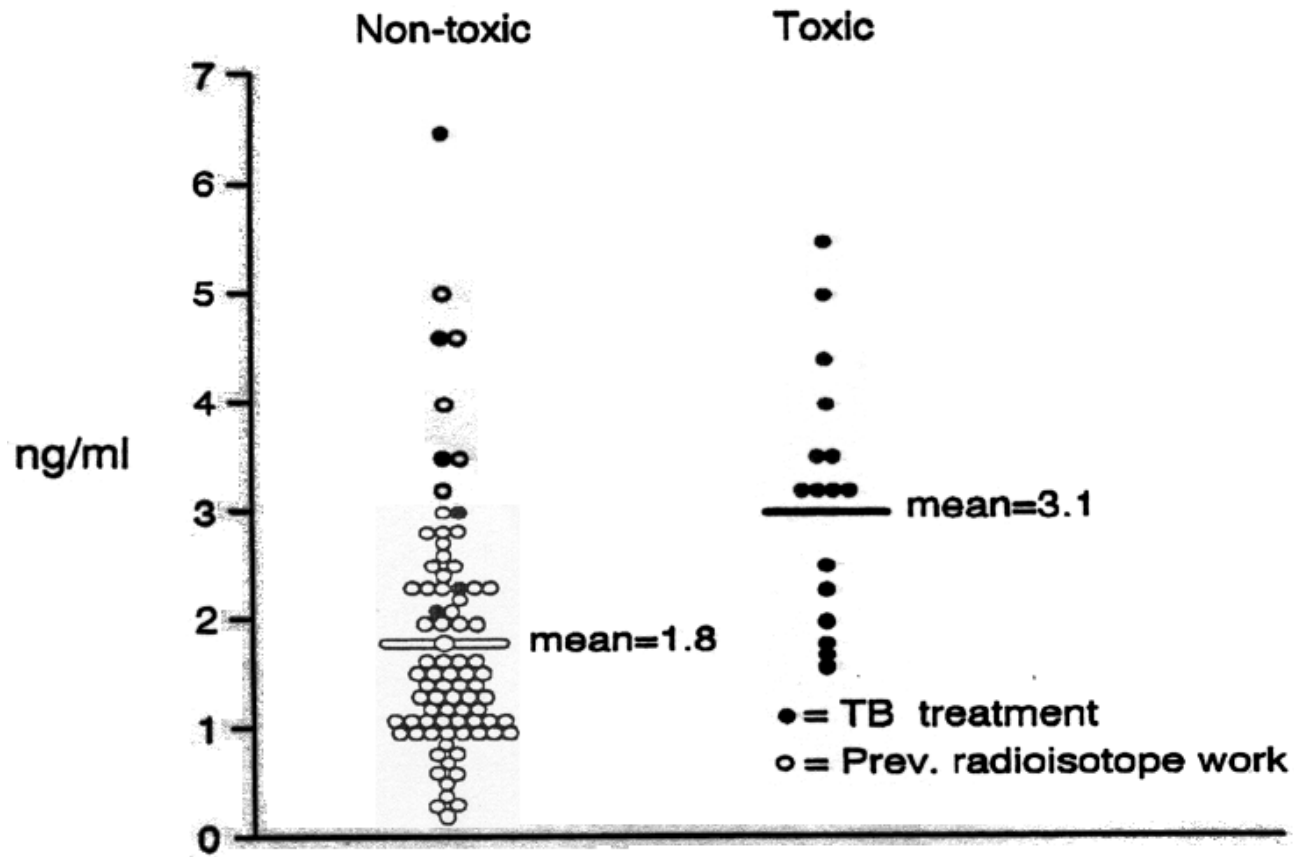
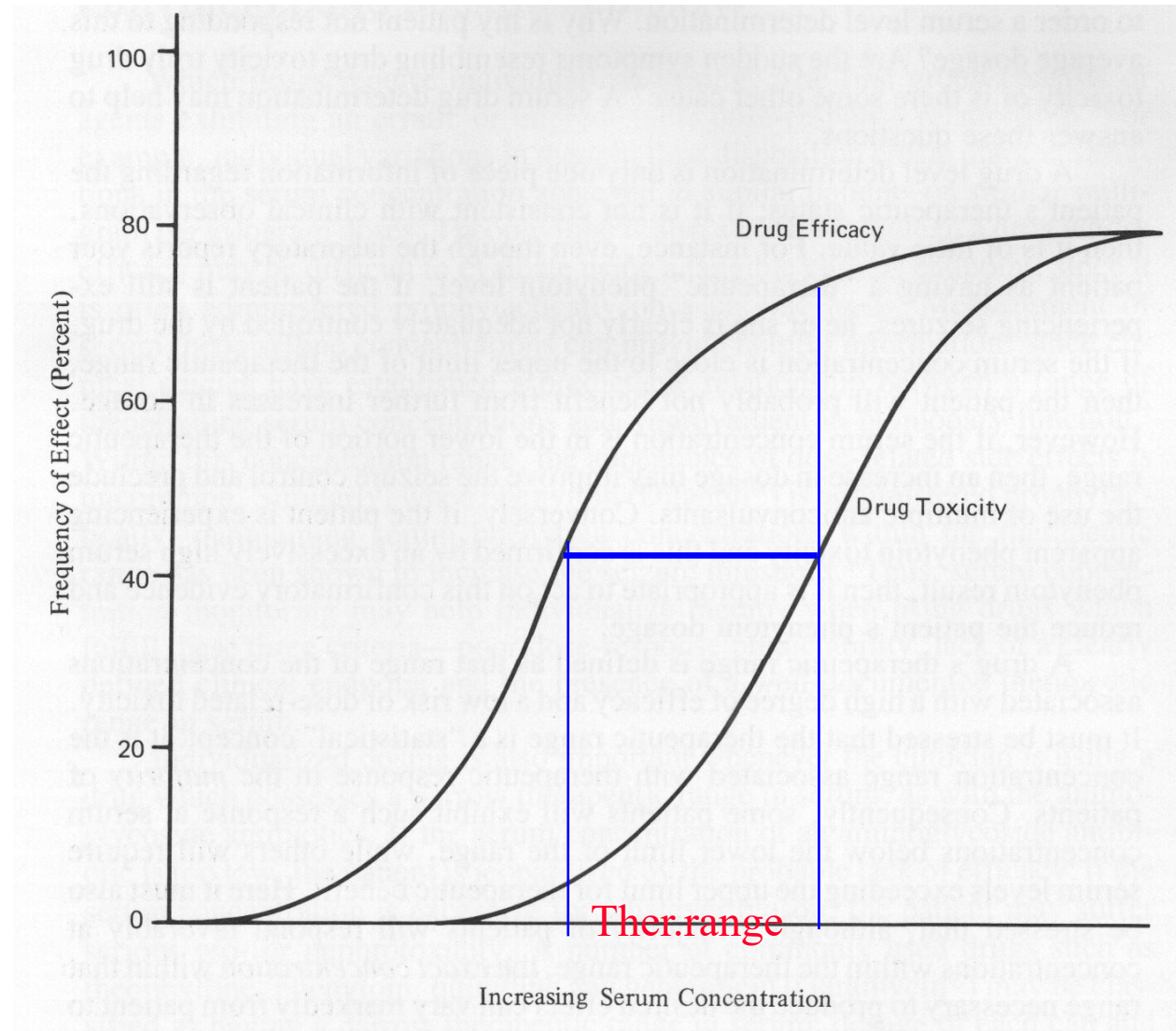


FIG. 2. Serum digoxin concentrations in patients without (left) and with (right) digoxin toxicity, as found by Doherty (1), redrawn with permission. Note the great overlap between therapeutic and toxic concentrations, and the fact that approximately half the patients with serum levels of 3.0 ng/mL or 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.

Bloodlevel - effect - toxicity



APPLIED PHARMACOKINETICS

- **ADAPTIVE CONTROL**
 - Bayes theoreme
 - Fisher Information Index
 - Optimal sampling times

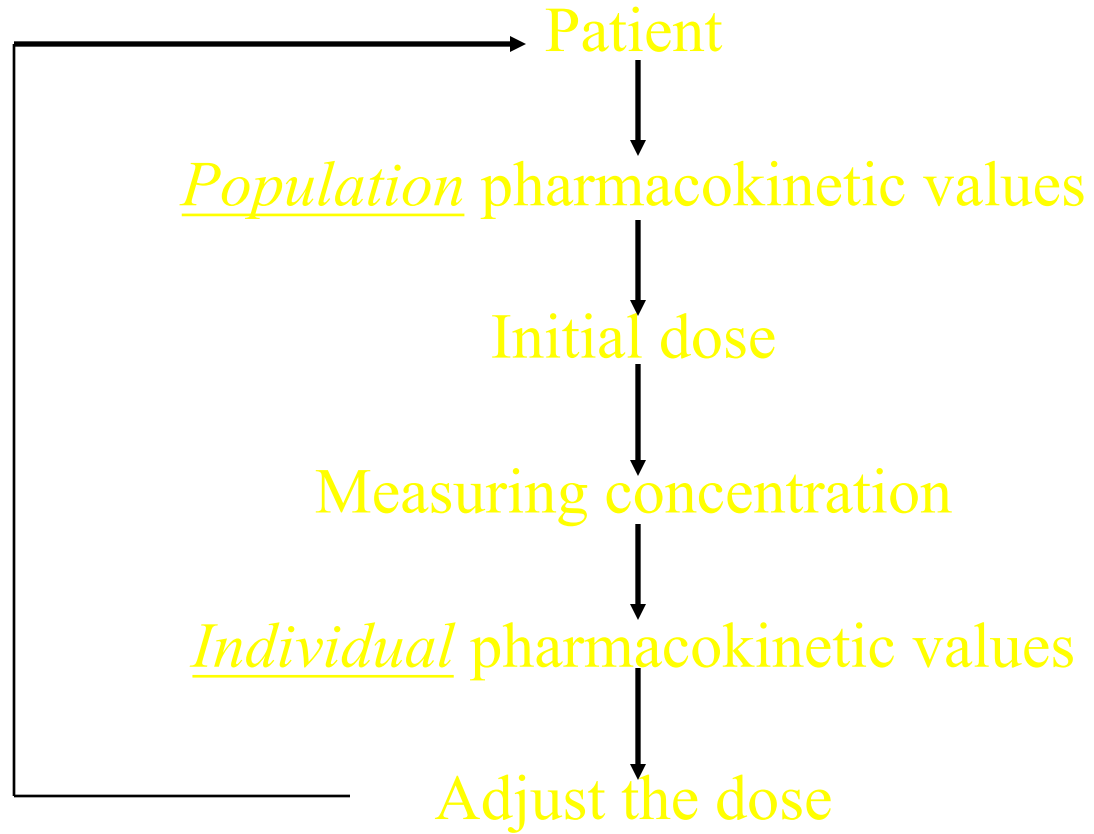


Charlie Toorop 1935-38

APPLIED PHARMACOKINETICS

- ADAPTIVE CONTROL
- dose-individual patient data (1-4 samples) - PK-data - populationdata - standard dose - plasmalevels - Bayesian parameter estimation - relate expected (Bayesianse) to the estimated parameters - individualise the dose

ADAPTIVE CONTROL

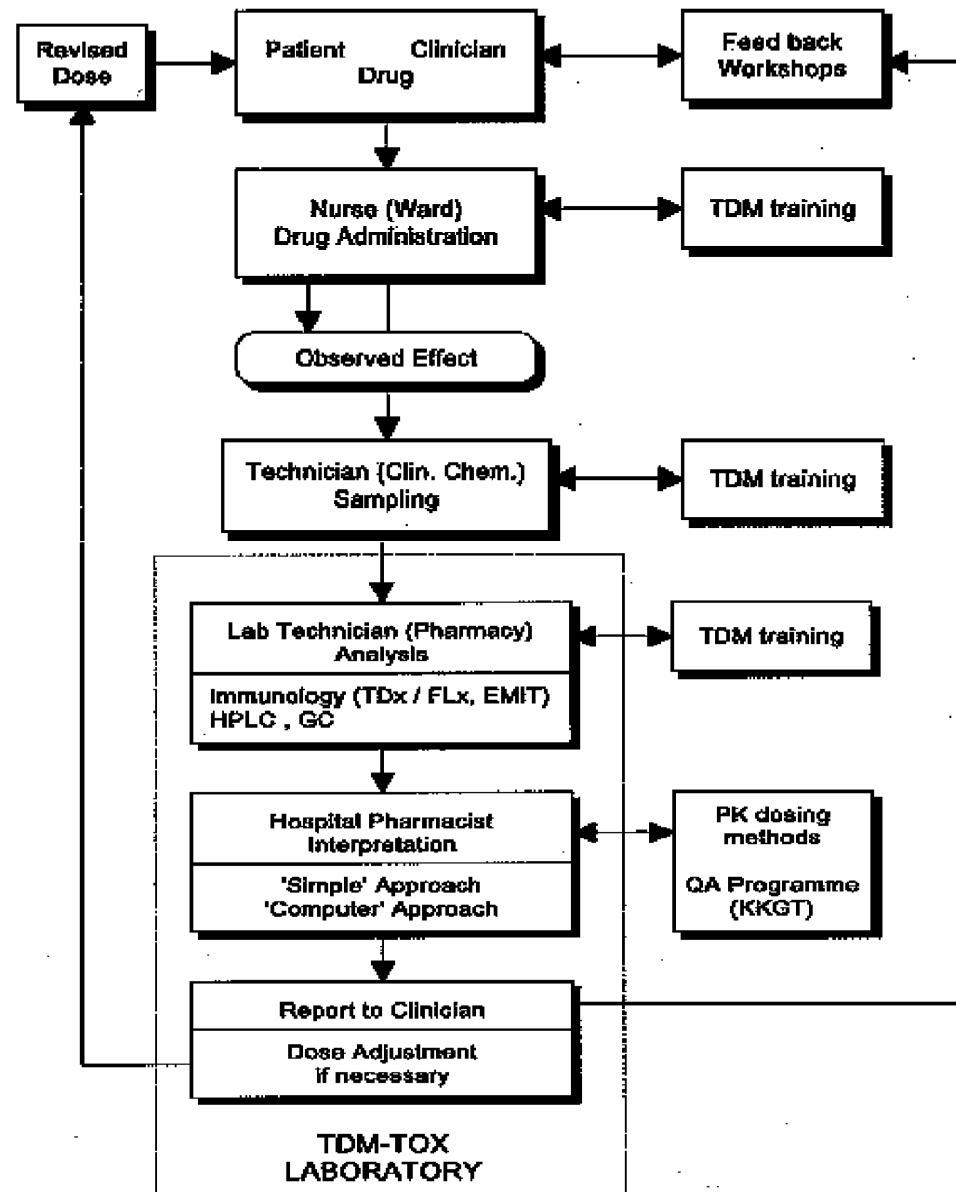


APPLIED PHARMACOKINETICS

- MAP Bayesian Fitting
- maximum a posteriori probability Bayesian fitting procedure
 - population parameter values + SD and serumlevels and SD

THERAPEUTIC DRUG MONITORING

EDUCATION



QUANT BAYES' THEOREM:

1. DETERMINE ASSAY ERROR EXPLICITLY.
2. USE IN CURRENT BAYESIAN OBJ FUNCTION

$$\text{MINIMIZE SUM } \frac{(\text{Cobs} - \text{Cmod})^2}{\text{SD}^2 \text{Cobs}} + \text{SUM } \frac{(\text{Ppop} - \text{Pmod})^2}{\text{SD}^2 \text{Ppop}}$$

| PRIOR PROB | NEW INFO | CONSIDER PRIOR+NEW | POST PROB | THERAPY | |
|---------------|-----------------|-----------------------|----------------|----------------------|---------------|
| | | | | GOALS | CONTROL |
| POP MODEL | SERUM CONC'S | OBJ FUNCT | INDIV MODEL | LOOK AT PT, THINK | CALC DOSES |

APPLIED PHARMACOKINETICS

- Optimal sampling times
- distribution volume at the end of the infusion
- elimination rate constant at $1.44 \times T_{1/2}$
- the trough level is the less reliable level

APPLIED PHARMACOKINETICS

- Optimal sampling strategy
- D - optimal sampling
 - D-optimality is a design criterium that, if minimalised, finds the sampletimes where the overall variance of the estimated parameter values are minimalised

APPLIED PHARMACOKINETICS

- Optimal sampling strategy
- in D - optimal design the determinant of the inverse Fisher Information matrix is taken as criterium to be minimalised

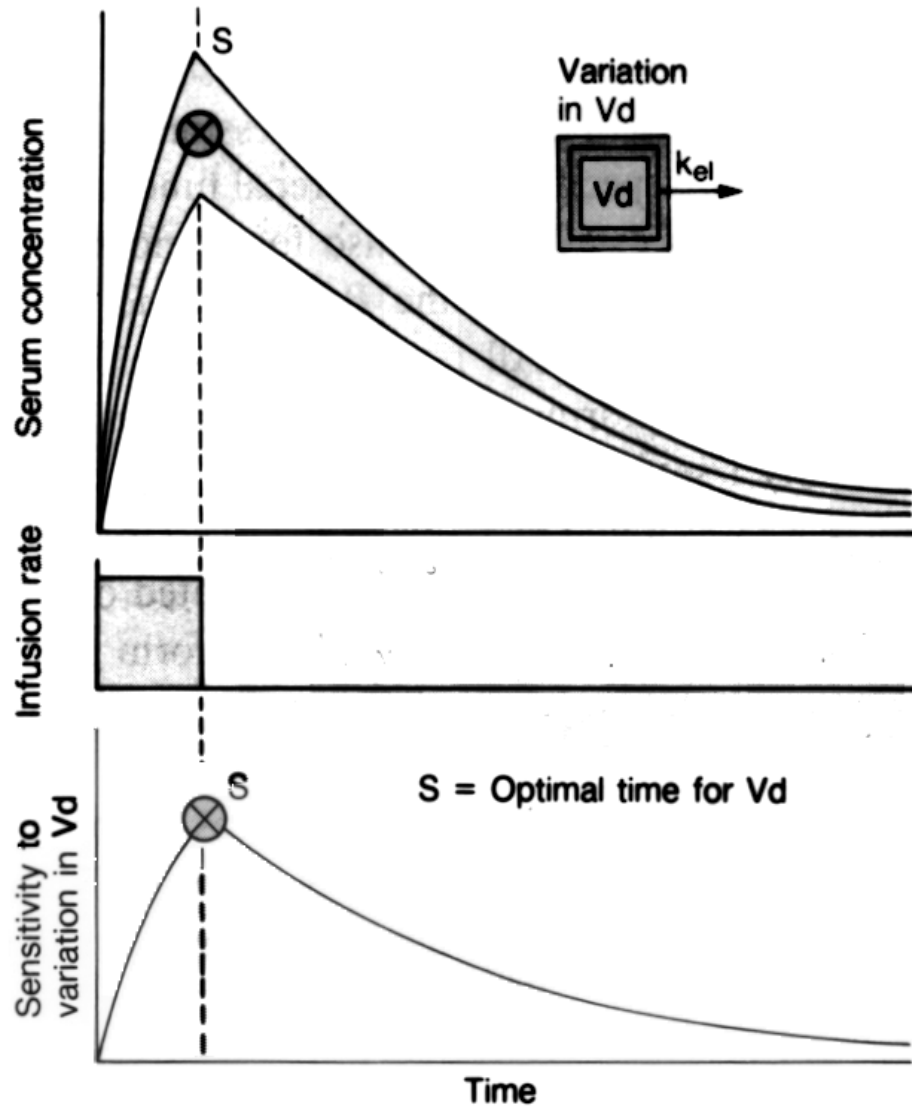
APPLIED PHARMACOKINETICS

- FISHER INFORMATION INDEX

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

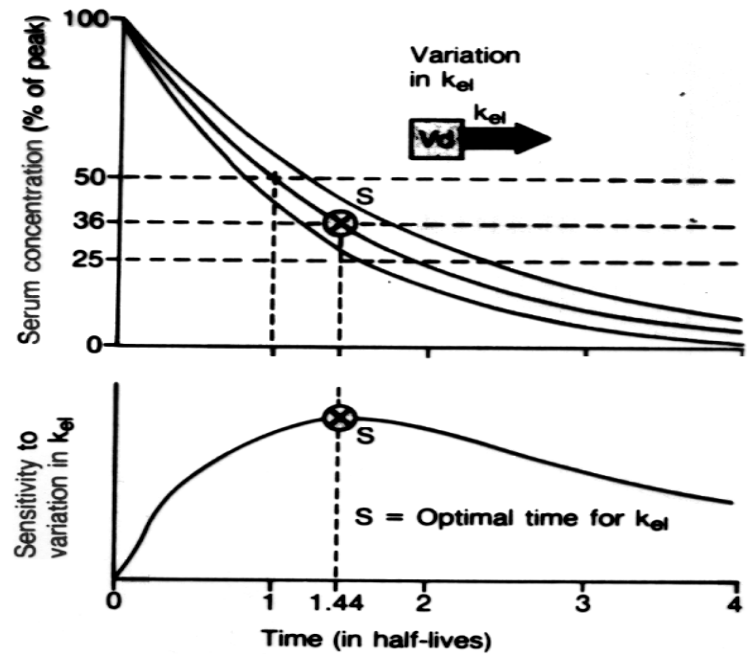


▲ Ronald Aylmer Fisher, de aartsvader van de statistiek, stelde een grens tussen bruikbare en onbruikbare resultaten voor.



VARIATION IN DISTRIBUTION VOLUME

Fig. 5. Optimal strategies for monitoring serum drug concentrations. A change in the volume of distribution (V_d) 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.

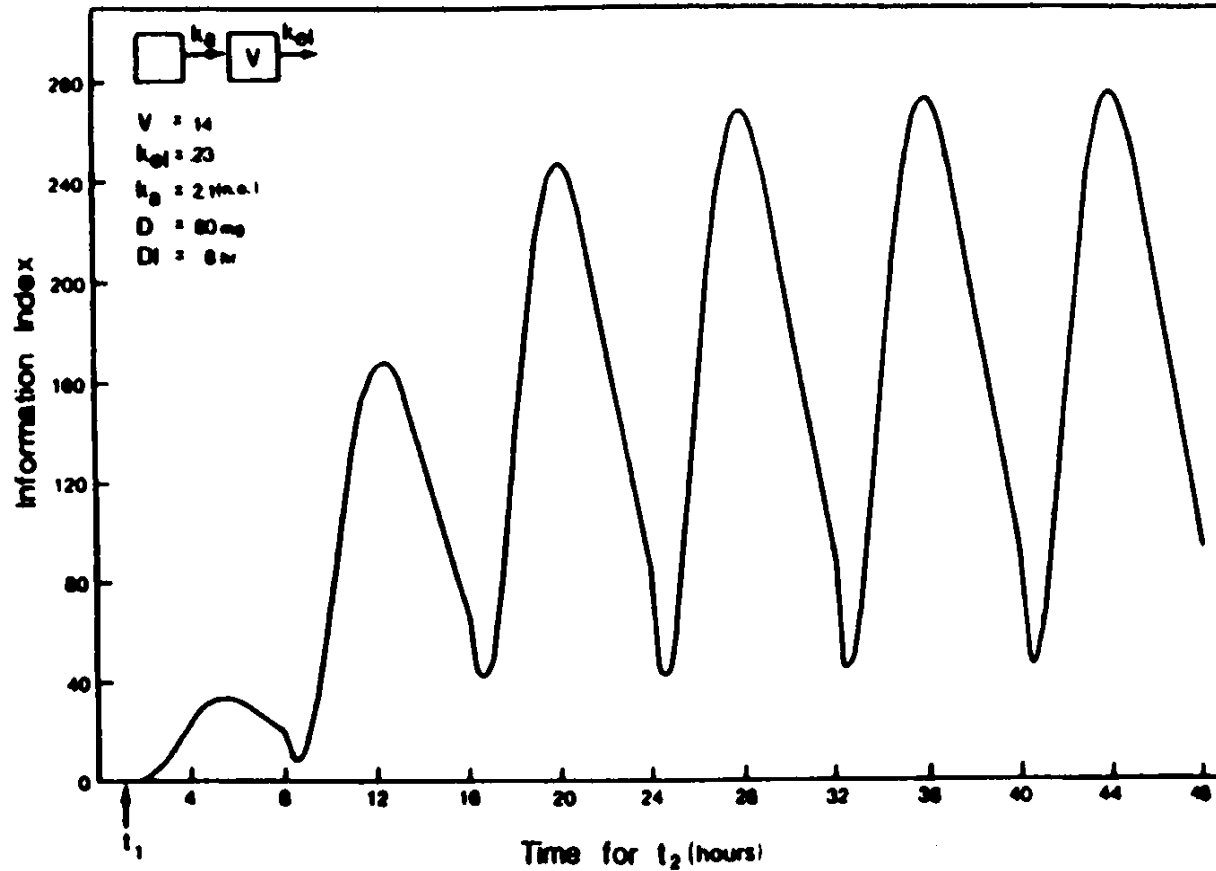


FIGURE 3.13. Illustrating the value of waiting to draw the second level (29). Intramuscular gentamicin therapy of 80 mg every 8 hr in a simulated patient with $C_{Cr} = 100$. Vertical: the index of the amount of information contained in a specimen drawn at that time. Horizontal:

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).

INFORMATION CURVE and BAD RENAL FUNCTION

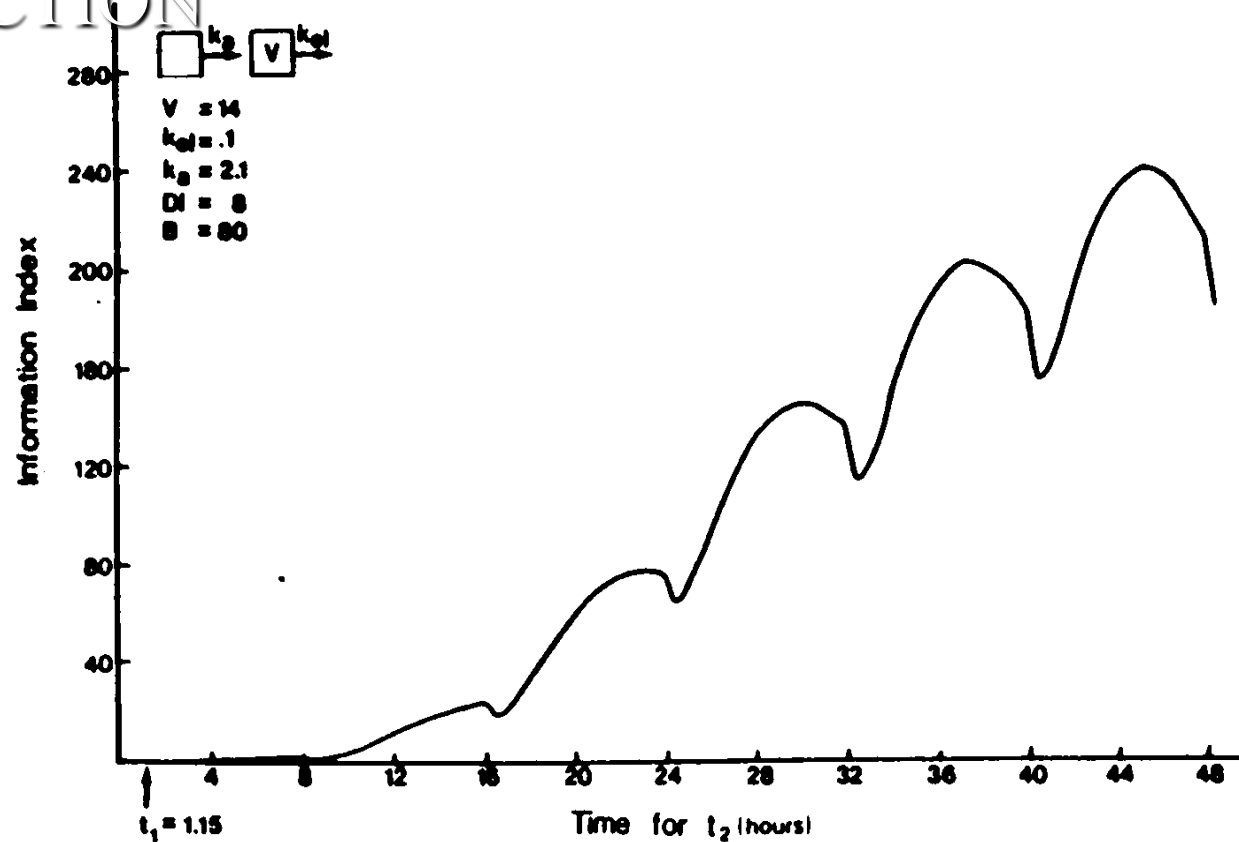


FIGURE 3.14. Illustrating the value of waiting to draw the second level (29). Intramuscular gentamicin therapy of 80 mg every 8 hr in a simulated patient with reduced renal function ($C_{Cr} = 40$). Vertical: the index of the amount of information contained in a specimen drawn at that time. Horizontal: time into the regimen. Much less information is contained in early samples from this

patient compared to the patient with normal renal function in Figure 3.13, because his half-time is longer. Almost no additional information is obtained, for example, by drawing the second level in the same dose interval as that of the peak level, drawn at time t_1 , at lower left in both Figures 3.13 and 3.14.