DRUG EVALUATION IN PEDIATRICS USING K-PD MODELS: PERSPECTIVES

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USES OF MODELS

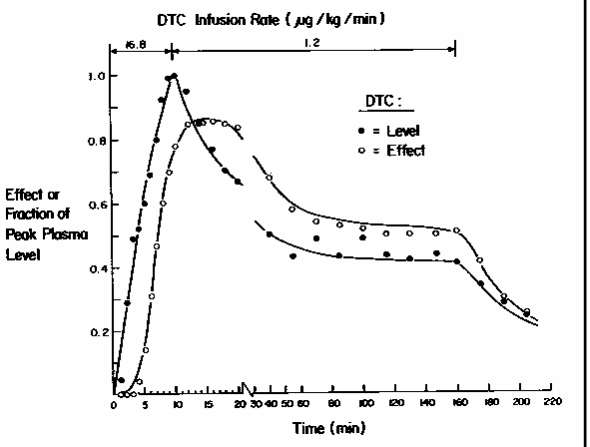
- Describe quantitatively drug kinetics.
- Simulate and predict.
- Plan and design clinical trials.
- Bayesian adaptation of drug dosing.

DRAWBACKS OF PK-PD MODELS

- Invasiveness:

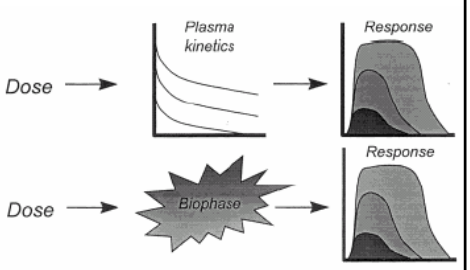
  blood samples for PK.

- Logistic and cost associated with samples and measurements



A SOLUTION: THE K-PD MODEL

- Kinetic – Pharmaco-Dynamic model
- Drug concentrations are not measured
- Only the kinetics of response is measured.
- A simple model is used to describe drug concentration kinetics.



LESS INVASIVE MEASUREMENTS OF THERAPEUTIC RESPONSE

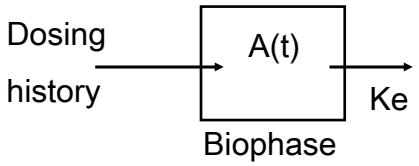
- Body temperature, heart rate, blood pressure, respiratory peek flow …
- Scores for depression (HAMD,…), pain (VAS), …
- Frequency of seizures, emesis, …
- ECG, EEG
- Bone density, tumor size, …

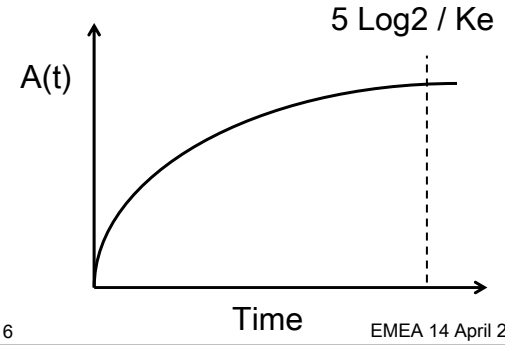
COMPONENTS OF A K-PD MODEL (1)

- Simplified PK model:

  variable of interest: Input Rate (t) in mg/h

  IR(t) = Ke.A(t)



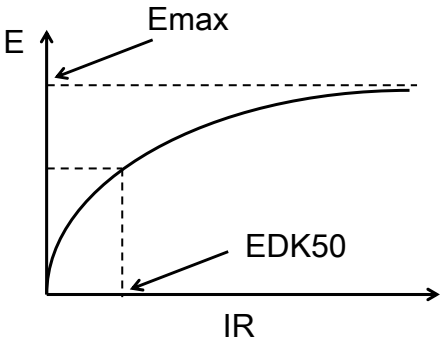


COMPONENTS OF A K-PD MODEL (2)

- Effect model: links IR(t) to E(t)

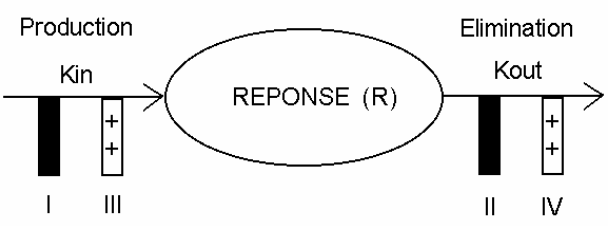
$$E(t) = \frac{Emax.IR(t)}{EDK_{50} + IR(t)}$$

EDK_{50} = $CL.CE_{50}$ in mg/h



COMPONENTS OF A K-PD MODEL (3)

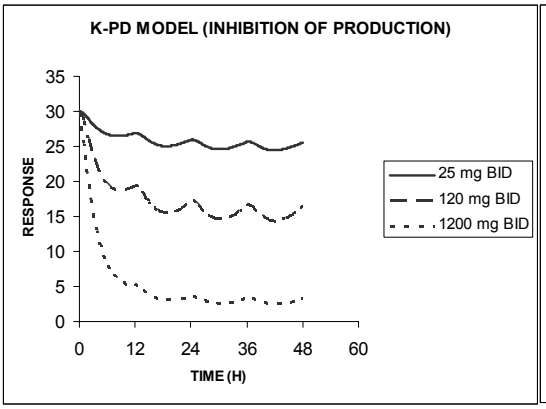
- Model for a continuous response: links E(t) to R(t)

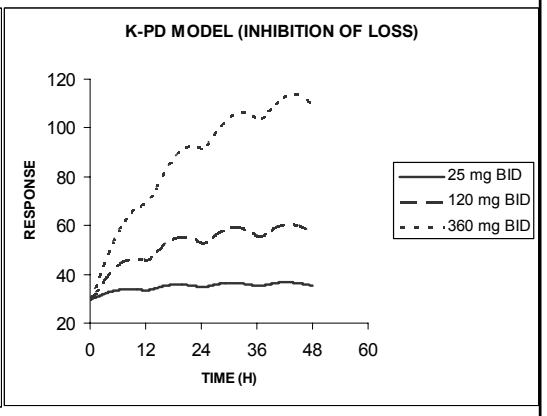


Example: inhibition of production

$$\frac{dR(t)}{dt} = Kin.(1 - \frac{Emax.IR(t)}{EDK_{50} + IR(t)}) - Kout.R(t)$$

TYPICAL CURVES OF 2 K-PD MODELS





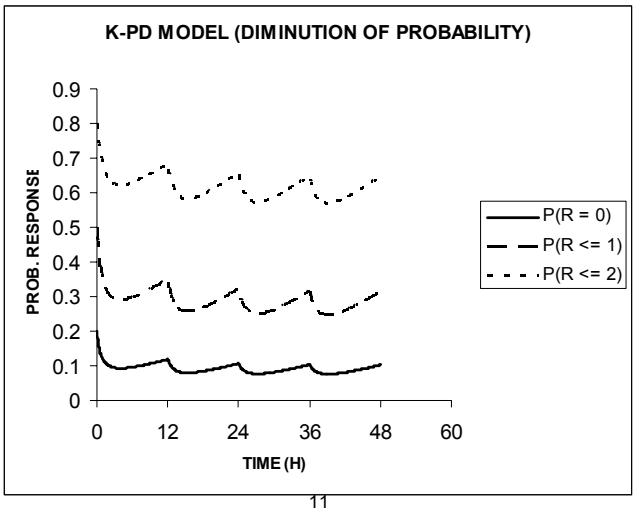
COMPONENTS OF A K-PD MODEL (4)

- Model for categorical response: links E(t) to probability to observe score k of response R(t)

$$\text{logit}[P(R(t) \le k)] = B_k \pm \frac{E\max . IR(t)}{EDK_{50} + IR(t)}$$

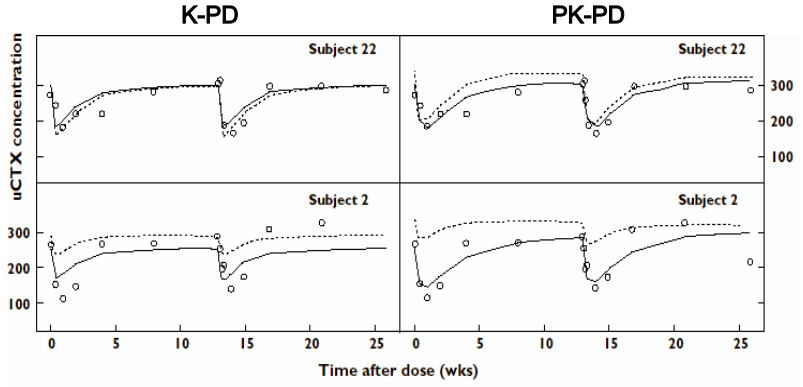
TYPICAL CURVES FOR A K-PD MODEL OF CATEGORICAL RESPONSE

Score from 0 to 3



K-PD versus PK-PD MODELS

A semimechanistic and mechanistic population PK–PD model for biomarker response to ibandronate, a new bisphosphonate for the treatment of osteoporosis. *G. Pillai, 2004*

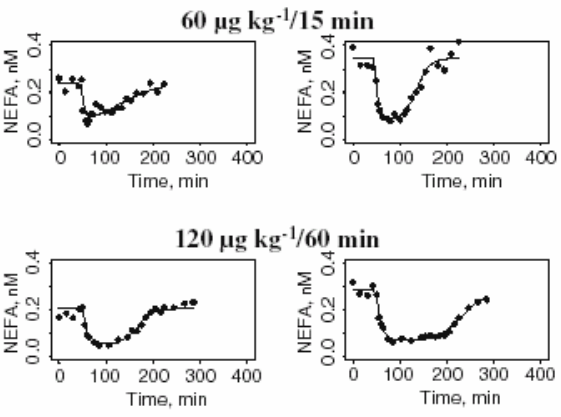


Typical fits for the K-PD and the PK-PD models in arbitrarily chosen subjects. Observation (o), individual prediction (——), population prediction (----)

K-PD MODEL: continuous response

Modelling Response Time Profiles in the Absence of Drug Concentrations: Definition and Performance Evaluation of the K–PD Model.
P. Jacqmin et al.
J. Pharmacokin Pharmacodyn 2007

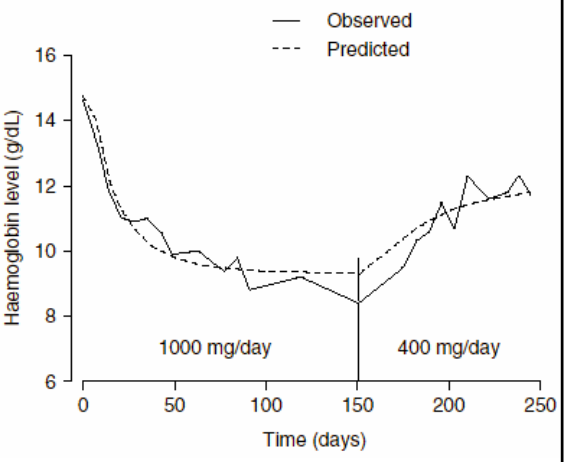
NEFA plasma concentration–time profiles after IV infusion of *N*6-(*p*-sulfophenyl) adenosine in Wistar rats.



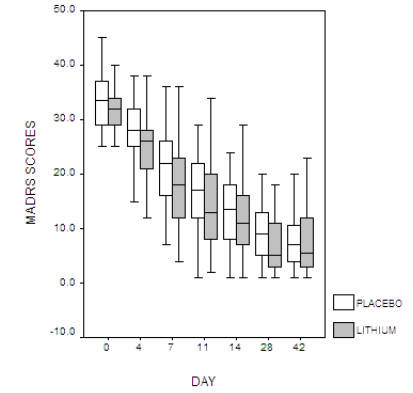
K-PD MODEL: continuous response

Pharmacokinetic/Pharmacodynamic and Time-to-Event Models of Ribavirin-Induced Anaemia in Chronic Hepatitis C
M. Tod et al.
Clin. Pharmacokinet. 2005

Prediction of the K-PD model for a typical patient.



K-PD SET-POINT MODEL (1)

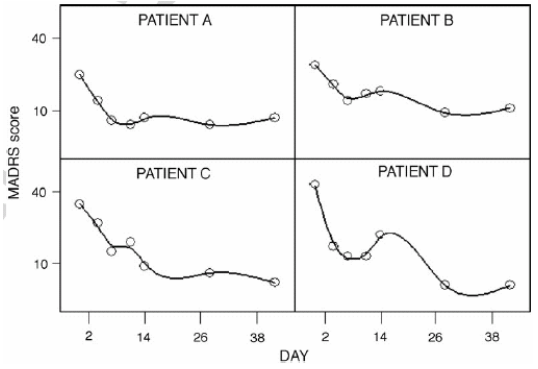


Box-plot of MADRS scores of patients treated with clomipramine and placebo or lithium. (clinical data)

A kinetic-pharmacodynamic model for clinical trial simulation of antidepressant action: Application to clomipramine–lithium interaction.
B. Gruwez et al., Contemp Clin Trials, 2007.

Non-invasive measurements …

K-PD SET-POINT MODEL (2)



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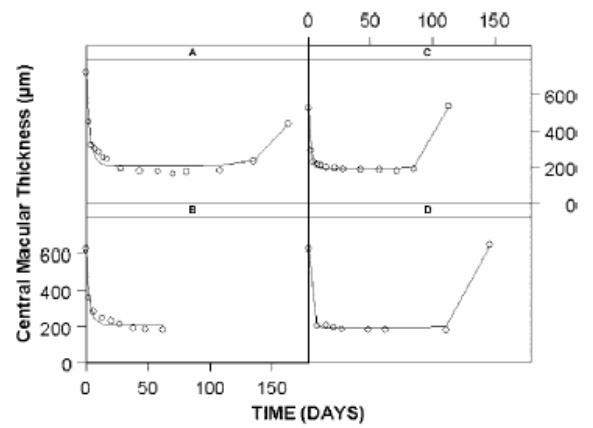
B.Gruwez et al., Contemp Clin Trials, 2007.

Oscillating profile…

KPD MODEL: biphasic kinetics

PKPD Modeling of the Effect of Triamcinolone Acetonide on Central Macular Thickness in Patients with Diabetic Macular Edema
F. Audren et al.,
Invest Ophthalmol Vis Sci. 2004

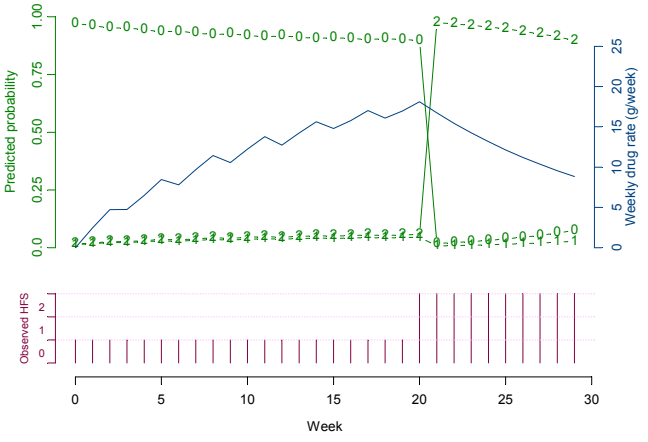
Non-invasive measurements …



Examples of individual central macular thickness (CMT) curves calculated from individual CMT values (*circles*).

K-PD MODEL: catégorical data

A predictive model of Hand-and-Foot Syndrome dynamics in patients receiving capecitabine.
E. Hénin et al, 2007



Evolution with time of observed HFS scores, weekly drug rate and predicted probabilities of grade 0, 1 and ≥2 predicted by the model in a patient.

LIMITS OF THE K-PD MODEL

- The drug PK in biophase is handled as monocompartmental:

- PK is actually monocompartmental, or :
- Effect kinetics is slow compared to drug kinetics (Kout < Ke)

- Complicated response models may be handled if correctly specified.
- K-PD models for drug-drug interaction are merely identifiable.

CONCLUSIONS

- K-PD models have been useful for modelling animal or human data in adults.
- Well suited if effect kinetics is rate limiting
- Might be used in pediatrics to reduce experimental workload.
- More useful if coupled with a minimally invasive measurement of response.