PK/PD - General Concepts and Advanced Material

Workshop on September 07-08, 2004

PK / PD General Concepts Workshop Program
(Beginner – Intermediate Level)

Tuesday, September 07th, 2004

Time	Topic
8:30	**PK 1 Basic Principles - Michael Weiss** Structure of the body, administration and sampling sites Transport processes Clearance, volume of distribution, half-life
9:30	**PD 1 Ligand Binding and Receptors - Nick Holford** Receptors and binding sites Specific binding and non-saturable binding Occupancy, stimulus and response models
10:30	Coffee
11:00	**PK 2 Processes - Michael Weiss** Hepatic and renal elimination Absorption and bioavailability Plasma protein and tissue binding
12:00	**PD 2 Immediate Drug Effects - Nick Holford** The E_{max} and Sigmoid E_{max} models of drug action Time course of drug effect Duration of drug effect
13:00	Lunch
14:00	**PK 3 Data Analysis I - Michael Weiss** Compartmental and noncompartmental models
14:45	**Population Data Analysis - Nick Holford** Individual vs population methods Why understanding fixed and random effects is important Sources of PK and PD variability
15:30	Coffee
16:00	**Common Parallel Session – Discussion (PK and PD) by Nick Holford & Michael Weiss**
16:30	End

PK / PD General Concepts Workshop Program (Beginner – Intermediate Level)

Wednesday, September 08th, 2004

Time	Topic
	PK / PD General Concepts
8:30	**Advanced PK 4 - Michael Weiss** Multiple dosing Designing dose regimens Nonlinear PK
9:30	**PD 3 Delayed Drug Effects - Nick Holford** Distribution delay and the effect compartment Physiological delay and the turnover model family Thiopentone, digoxin, warfarin, anti-depressants
10:30	Coffee
11:00	**Advanced PK 5 Data Analysis II - Michael Weiss** Oral administration Metabolite PK
12:00	**PD 4 Exposure Response - Nick Holford** What does exposure mean? Cumulative effects and schedule dependence Diuretics and anti-cancer agents
13:00	Lunch

Parallel sessions	**PK / PD General Concepts Workshop**
14:30 – 16:30	**Physiologically Based PK - Michael Weiss** Recirculatory modeling (initial distribution) PK in isolated organs and destructive sampling Allometric up-scaling (Including general discussion)
14:30 – 16:30	**Clinical Pharmacology = Disease Progression + Drug Action** **Nick Holford** Introduction to the concepts of disease progression modeling Application to clinical pharmacology and drug development Alzheimer's disease and Parkinson's disease (Including general discussion)
14:30 – 17:00	**Applications in Anticancer Drug Therapy** **Charlotte Kloft**, Berlin: Pharmacokinetics of high-molecular anticancer agents **Ulrich Jaehde**, Bonn: Surrogate parameters in cancer chemotherapy **Rüdiger Port**, Heidelberg: Tissue pharmacokinetics with non-invasive measurements

PK/PD Modeling Methods and Clinical Applications

(Intermediate – Advanced – Expert Level)

Faculty:

Roger Jelliffe, MD
Irina Bondareva, Ph.D.
George Drusano, MD
Rüdiger Port, MD
Alexander Vinks, Ph.D.

Target Participants:

This workshop, using minimal math, starts at a beginning level and progresses to an advanced level over 2 intensive days. It is intended for physicians, pharmacists, clinical chemists and biomedical scientists who have an interest in clinical therapeutic drug monitoring and optimal individualization of drug therapy for patient care and in population pharmacokinetic and pharmacodynamic research modeling techniques. Participants will be introduced to the USC*PACK software which can be used both for therapeutic drug monitoring as well as for parametric and nonparametric population PK/PD and physiological modeling.

Objectives and Expectations:

After this workshop, the participant should:

1. Be able to describe basic pharmacokinetic behavior of drugs in patients.
2. Be able to design optimal initial individualized dosage regimens of drugs to hit selected target goals most precisely.
3. Be able to enter and store patient data of doses, TDM serum concentrations, etc., and to make an individualized model of drug behavior in that patient.
4. Be able to develop an adjusted dosage regimen based on the patient's individualized model.
5. Understand how to apply these techniques to therapy with Vancomycin, Digoxin, anticonvulsants, and drugs for AIDS, cancer, and transplants.
6. Understand the basic ideas (not the math) behind parametric and nonparametric population PK/PD modeling.
7. Know how to determine the error polynomial for a drug assay, to fit each data point by an optimal measure of its credibility.
8. Understand Monte-Carlo simulation and its applications to clinical situations.
9. Understand the basic concepts of multiple model dosage design.

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(Intermediate – Advanced – Expert Level)

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8:30	**Beginning-Intermediate Clinical PK 1** The basic PK model – **Roger Jelliffe** Its parameters: Ka, Kel, Vol, Clearance, Kcp, Kpc, T1/2 Dose individualization using target concentration strategy An example for discussion: tracking drug behavior in unstable patients, with changing doses, changing renal function, and ad-lib serum samples. Basic PK building blocks Evaluating renal function, especially in unstable patients Evaluating lab assay errors, and then acting on them! Evaluating other environmental errors
9:30	**Beginning-Intermediate Clinical PK 2** Ways of fitting data - **Roger Jelliffe** Linear regression on logs of data Weighted nonlinear least squares Maximum Aposteriori Probability (MAP) Bayesian fitting The basic MAP Bayesian scenario When to get data best - **Alexander Vinks**
10:30	Coffee
11:00	**Beginning-Intermediate Population Modeling** Parametric, iterative 2 stage Bayesian (IT2B) population modeling - **Roger Jelliffe** Strengths and weaknesses of parametric models
11:45	*Nonparametric Population Modeling* - **Roger Jelliffe** Its strengths and weaknesses Unified approaches to population modeling
12:30	*Multiple Model Dosage Design* - **Roger Jelliffe**
13:00	Lunch
14:30	**Intermediate PK – Tissue Distribution** Modeling diffusion in endocardial vegetations - **Roger Jelliffe** Modeling bacterial growth and kill, and post-antibiotic effect
15:30	How to describe and build PD relationships for anti-infective drugs - **George Drusano**
16:00	Erythropoetin therapy in childhood renal anemia - **Rüdiger Port**
16:30	End

PK/PD Modeling Methods and Clinical Applications

(Intermediate – Advanced – Expert Level)

Wednesday, September 07th, 2004

Time	Topic
8:30	**Advanced PK 3** Modeling linear and nonlinear antiepileptic drug models - **Irina Bondareva**
9:00	Outcome and costs of a goal-oriented, model-based, active TDM service – **Alexander Vinks**
9:45	Combination chemotherapy - Monte-Carlo simulation: from PK/PD Relationships to clinical applications - **George Drusano**
10:30	Coffee
11:00	**Applied Clinical PK 4** Getting Nonparametric Bayesian Posteriors – **Roger Jelliffe** Multiple Model (MM) versions Interacting Multiple Model (IMM) versions for very unstable patients The structure of MM Bayesian dosage individualization and adjustment
12:00	Aminoglycoside ototoxicity - **Roger Jelliffe**
12:30	Introduction to Clinical Cases - **Roger Jelliffe** Planning initial MM aminoglycoside therapy Normal and reduced renal function
13:00	Lunch
14:30	**Advanced Clinical PK 5** More clinical case histories - **Roger Jelliffe** Planning initial vancomycin therapy Planning initial digoxin therapy A gentamicin patient with changing renal function A tobramycin patient with changing renal function and changing clinical status Digoxin and atrial fibrillation Why the literature says it is no good for conversion Why the literature is probably wrong Four interesting digoxin cases
16:30	End