Outline

• Introduction
• The Scientist
  • Contributions to Pharmacology
• The Professor
• The Human
• Dr. Derendorf received his B.S. (1976) and Ph.D. (1979, summa cum laude) in Pharmacy from the University of Münster, Germany. He then joined the University of Florida (UF), first as a Postdoctoral Fellow (1981/82) and later (1983) as a faculty member, teaching Biopharmaceutics, Pharmacokinetics and Clinical Pharmacokinetics.

• He expected to stay in Gainesville two years, but he fell in love with UF and met the love of his life, his wife, Kerry, ’82. She was pursuing her own Ph.D. in pharmaceutical sciences. They raised two sons, Kevin, BSME ’08, (Ph.D. from Washington University in St. Louis) and Karsten, MACC ’13, who also went on to graduate from the University of Florida. Hartmut would proudly refer to them as “a Gator family.”

Meet Dr. Derendorf

• Hartmut was among an elite group of faculty at UF to be awarded the title of Distinguished Professor and spent over three decades serving the college, including more than 25 years as chair of the Department of Pharmaceutics.
The Scientist

- Over 500 publications, with an h-index (Scopus) of 61, over 900 presentations at meetings throughout the world.
- Editor (or Associate Editor) of the Journal of Clinical Pharmacology, International Journal of Clinical Pharmacology & Therapeutics, International Journal of Antimicrobial Agents and Die Pharmazie, and served on the Editorial Board of several other Journals.
- Ten textbooks published in English and German.
- Hartmut was a pioneer for studying tissue concentrations of antibiotics in humans and animals using microdialysis, and held a patent (Issued 2005) for Microdialysis Probes and Methods of Use.
Books
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- Ten textbooks in English and German.
- Prof. Derendorf served as President of ACCP (American College of Clinical Pharmacology) in 2006/08 and President of ISAP (International Society of Anti-infective Pharmacology) in 2004/06, and as the PK/PD modeling Chair for ISSX.
- He was a fellow of ACCP and AAPS and a former review panel member of the NASA Human Research Program.
- He also served as an advisor to FDA and an expert consultant to the pharmaceutical industry.
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• He was a fellow of ACCP and AAPS and a former review panel member of the NASA Human Research Program.
• He also served as an advisor to FDA and an expert consultant to the pharmaceutical industry.
• His research interests included the pharmacokinetics and pharmacodynamics of corticosteroids, analgesics and antibiotics as well as drug interactions.
• One of the fathers of modern pharmacokinetics and pharmacometrics.
• Hartmut was a pioneer for studying tissue concentrations of antibiotics in humans and animals using microdialysis, and held a patent (Issued 2005) for Microdialysis Probes and Methods of Use.
Pharmacokinetics
conc. vs time
what the body
does to the drug

Pharmacodynamics
conc. vs effect
what the drug
does to the body

PK/PD
effect vs time

what the body
does to the drug

what the drug
does to the body
Clearance
Quantifies Elimination

CL is the volume of body fluid cleared per time unit (L/h, mL/min)

\[ CL = Q \cdot E \]

- \( Q \): Blood Flow
- \( E \): Extraction Ratio

**Eliminating Organ**

\[ Q \]

\[ C_i \rightarrow C_o \]

\[ E = \frac{C_i - C_o}{C_i} \]

\[ CL = Q \cdot E \]

Well-stirred model

\[ CL = \frac{Q \cdot \frac{f_u}{1-f_u} \cdot CL_{int}}{Q + \frac{f_u}{1-f_u} \cdot CL_{int}} \]
High-extraction drugs

Well-stirred model

\[ CL = \frac{Q \cdot f_u \cdot CL_{int}}{Q + f_u \cdot CL_{int}} \]

Q \ll f_u \cdot CL_{int} \Rightarrow CL = Q

Low-extraction drugs

Q \gg f_u \cdot CL_{int} \Rightarrow CL = f_u \cdot CL_{int}
Volume of Distribution

\[ Vd = \frac{X}{Cp} \]

- Quantifies \textit{DISTRIBUTION}
- Relates drug concentration (Cp) to amount of drug in the body (X)
- Gives information on the amount of drug distributed into the tissues
Half-Life

Time it takes for the concentration to fall to half of its previous value

\[ t_{1/2} = \frac{0.693 \cdot Vd}{CL} \]

\[ t_{1/2} = \frac{\ln 2}{k} = \frac{0.693}{k} \]

\[ CL = k \cdot Vd \]
Bioavailability (F)

Rate and extent to which an active compound is absorbed from a drug product and becomes available at the site of action

\[ F = \frac{AUC_{po}}{AUC_{iv}} \]

- quantifies ABSORPTION

F is the fraction of the administered dose that reaches the systemic circulation
Bioavailability

First-Pass Effect

High- and low-extraction drugs, oral administration

\[ F = 1 - E = \frac{Q}{Q + f_u \cdot CL_{int}} \]
\[ Cp_{ss} = \frac{F \cdot D}{CL \cdot \tau} = \frac{D}{f_u \cdot CL_{int} \cdot \tau} \]
\[ Cp_{ss\ free} = \frac{D}{CL_{int} \cdot \tau} \]

Assumption: Presystemic and systemic extraction ratios are equal
"Free, active concentrations should be measured in the test system instead of correcting for literature protein binding values."

Contributions to Pharmacology
Protein Binding

Effect of Protein Binding on the Pharmacological Activity of Highly Bound Antibiotics

Stephan Schmidt,1 Katharina Röck,1 Martina Sahre,1 Olaf Burkhardt,1,2 Martin Brunner,3 Maximilian T. Lehmann,4 and Hartmut Derendorf1

Significance of Protein Binding in Pharmacokinetics and Pharmacodynamics

Stephan Schmidt,1,2 Daniel Gonzalez,1 Hartmut Derendorf1

MINIREVIEW
Protein Binding: Do We Ever Learn?

Markus A. Zeitlinger,1 Hartmut Derendorf,2 Johan W. Mouton,3 Otto Cars,4 David Andes,5 and Ursula Theuretzbacher6

LESSONS LEARNED
When is Protein Binding Important?*

Jules Heuberger, Stephan Schmidt, Hartmut Derendorf
Department of Pharmaceutics, University of Florida, Gainesville, Florida

Received 28 February 2013; revised 31 March 2013; accepted 2 April 2013
Published online 6 May 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23559
Protein Binding

- **reversible** vs. **irreversible**
- **linear** vs. **nonlinear**
- **rapid** equilibrium

The free (unbound) concentration of the drug at the receptor site should be used in PK/PD correlations to make predictions for pharmacological activity.
Contributions to Pharmacology
Tissue Distribution

- Early 1980s: Drug concentrations in saliva as a proxy of free tissue concentrations and analgesic efficacy
- Late 80s-90s: Target tissues: joints, brain, and local treatment strategies (pulmonary delivery via inhalation)
- 1990s: Technological breakthrough achieved by adopting microdialysis technique to access unbound concentrations in the tissue interstitial space
- 1990s-2000s: Application of microdialysis to measure free extracellular concentrations at various target sites in combination with a target based pharmacokinetic pharmacodynamic (PK/PD) modeling and simulation in various tissues, in animals and humans
  - Microdialysis for large molecules
  - Regulatory impact

“Dr. Derendorf’s work...led to an entirely new understanding of tissue PK principles, with major impact in clinical pharmacology.”
vascular space

plasma protein binding

blood cell binding,
diffusion into blood cells,
binding to intracellular biological material

extravascular space

binding to extracellular biological material
tissue cell binding,
diffusion into tissue cells,
binding to intracellular biological material
The Street Light Effect

I'm looking for my quarter. I dropped it here?

No, I dropped it two blocks down the street!

Then why are you looking for it here?

Because the light is better here!

DID YOU DROP IT HERE?

NO, I DROPPED IT TWO BLOCKS DOWN THE STREET!

THEN WHY ARE YOU LOOKING FOR IT HERE?

BECAUSE THE LIGHT IS BETTER HERE!

?
Microdialysis has opened the door for the experimental measurement of extracellular drug concentrations, both in humans and in animals.
In Vitro Microdialysis

- Syringe pump
- Sample vial
- Magnetic heating stirrer
- Probe
Contributions to Pharmacology: PK/PD modeling for Rational Dose Selection

“Refinement of dosages and dosing schedules will benefit from a PK/PD modeling approach”
MIC
The Current Paradigm

MIC is poison for the mind.

H. Mattie (1994), after a long after-dinner discussion
Why MIC is poison for the mind
Why Target Site Concentrations-Based Kill Curves are Better Predictors than MIC-based PK/PD Indices

Why MIC is poison for the mind
Why Target Site Concentrations-Based Kill Curves are Better Predictors than MIC-based PK/PD Indices

Time above MIC

AUC_{24}/MIC

PK

PD

Serum

MIC
Cefpodoxime PK
(400 mg oral dose, n = 6)

Cefixime PK
(400 mg oral dose, n = 6)

Mean ± SD
Kill Curves
Unbound Tissue Concentrations

Immediate Release

\[ C_T = \frac{Ff_u/Dk_{am}}{(k_{am} - k_e)Vd} (e^{-k_e(t-t_{lag})} - e^{-k_{am}(t-t_{lag})}) \]

Modified Release

\[ C_T = \frac{XTf_uF}{Vd_{ss} - V_c} \]

PK/PD Simulations

Time-kill curves

“The interest of the scientific and medical community in space keeps growing, and the technology is there. It is time to harness space for identifying new drug targets, generate novel formulations, and even produce drugs in space.”
The Professor

- Mentored over 70 graduate students and 40 postdoctoral fellows from several different countries.
- **Teaching awards**: UF Teaching Improvement Award, HHMI Distinguished Mentorship Award, UF Research Foundation Professorship, CVS Pharmacy Endowed Professorship, International Educator of the Year Award and UF Doctoral Advisor/Mentoring Award.
- UF Alumni Association’s 18th Distinguished Alumni Professor (2015)
- More than 900 national and international presentations.
The Professor

Global Gators Düsseldorf 2017
The earlier $t_{\text{max}}$, the faster the absorption
Absorption half-life 4h

Figure 1a. Serum concentration-time profile of FP after a single dose of 500 μg inhaled via the Diskus® dry-powder device. The closed circles represent experimental data (mean of n = 14, SD) and the solid line represents the fitted concentrations based on a two-compartment body model with first order absorption.

Figure 2. Absorption profile of FP after a single inhalation of 500 μg via the Diskus® dry-powder device, as determined using the Loo-Riegelman method. The profile is based on a three-compartment disposition model after i.v. administration. Calculations were based on average parameters obtained after i.v. administration of 1000 μg [Mackie et al. 1996] and median inhalation data obtained in the present study.
Don’t Judge Too Quickly

Link to video: Don’t Judge Too Quickly #1
This effect of protein binding is most significant with drugs that are highly protein-bound (>95%) and have a low therapeutic index, such as warfarin. A low therapeutic index indicates that there is a high risk of toxicity when using the drug. Since warfarin is an anticoagulant with a low therapeutic index, warfarin may cause bleeding if the correct degree of pharmacologic effect is not maintained. If a patient on warfarin takes another drug that displaces warfarin from plasma protein, such as a sulfonamide antibiotic, it could result in an increased risk of bleeding.
Warfarin-Phenylbutazone

$1+1=2$ ?

1 Phenylbutazone decreases warfarin plasma protein binding, increasing warfarin’s unbound fraction.

1 When co-administered, phenylbutazone causes bleeding in otherwise well-controlled patients on warfarin. This is clearly a clinically relevant drug interaction.

$1+1$ The mechanism of the phenylbutazone-warfarin drug interaction is displacement of warfarin from plasma proteins, leading to increased unbound warfarin concentrations.

Is this true?

Hint: Warfarin is a low-extraction drug
Warfarin-Phenylbutazone

A change in protein binding for a low-extraction drug changes the fraction unbound by a change in the total concentration. The unbound concentration, and therefore the pharmacological effect, do not change significantly.

Hence, displacement from protein binding sites cannot explain this interaction.

There is something else going on: Phenylbutazone inhibits warfarin metabolism, decreasing intrinsic clearance.

Enzyme inhibition is the mechanism for the clinically observed drug interaction between warfarin and phenylbutazone.
Don’t Judge Too Quickly

Link to video: Don’t Judge Too Quickly #2
Right on target

Link to video: Right on Target
The Human

• Teacher, Mentor, Colleague, Friend
• Citizen of the world
• Avid traveler
• Inclusive and welcoming
• Family Man
• Soccer Fan
• Music lover
• Car aficionado
Dr. Derendorf’s Pearls of Wisdom, never expressed in words... all by example!
A Pharmacokinetic-Pharmacodynamic First- and Last-Generation Model to Characterize Circadian Variations and Non-linear Binding of Endogenous Gatorsol and Circulating Gainesvillocytes Using Microdialysis During Space Travel

Hartmut Derendorf, PhD
University of Florida
1. Be a learner, always...
2. Work hard to create safe spaces for risk taking!
3. Build Networks

Collaborative problem solving is the only way!
4. Take your work seriously ....

But not yourself....
5. Welcome Everyone
6. Care – Be available over the long haul
7. There is no problem too big!
Acknowledgements

Kerry Estes
Sriram Krishnaswami
Stephan Schmidt
Teresa Dalla Costa
Bernd Meibohm
Markus Müller
Nelamangala Nagaraja
Julie Johnson

ISSX Modeling and Simulation Focus Group
Nita Patel
Zoë Fuller