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Registered Nurse

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How to Predict Human CNS PK/PD: Preclinical Experiments and Advanced Mathematical Modelling

Elizabeth CM de Lange
Professor in Predictive Pharmacology, LACDR,
Leiden University, The Netherlands
ecmdelange@lacdr.leidenuniv.nl
Given patients having the same diagnosis and same drug prescription:

What is the most important reason for differences in effects among the patients?

A) Not all patients take the drug according to the instructions with regard to when and how to take the drug

B) Not all patients take the drug according to the instructions with regard to the amount: they take too little or too much

C) Not all patients are the same. Rate and extent of body processes differ, so do the drug effects

D) It is still unknown what the reason is for interindividual differences of drug effects between patients
Given patients having the same diagnosis and same drug prescription:
What is the most important reason for differences in effects among the patients?

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Outline

Interrelationships of body processes
Factors in CNS drug effects
Need for knowledge on unbound CNS conc-time profiles
Microdialysis as key technique
Mastermind Research Approach
Drug vs. systems properties
Prediction of the PKPD of a CNS drug in human
Prediction of human CNS PK for a single drug
Prediction of human CNS PK for multiple drugs
CNS PK prediction for any small drug without the need for in vivo data?
Interconnections and Relationships

Driver + Car = Car Performance

Interconnections and Relationships

Drug + CNS Drug Effect = CNS Drug Effect
Factors in CNS Drug Effects

- Dose
- Plasma PK
- Target tissue (site) distribution
- Target binding kinetics
- Cellular response & homeostatic feedback
- Body response & body homeostatic feedback

The Blood-Brain Barrier (BBB)
BBB transport of drugs depend on:

A) The drug’s properties

B) BBB transport just generally restricts transport of drugs into the brain

C) The BBB characteristics

D) Combination of drug properties and BBB characteristics

E) None of the above
Factors in CNS Drug Effects

Blood-Brain Barrier - Modes of Transport

Factors in CNS Drug Effects

Blood-Brain Barrier - Simple Diffusion
Factors in CNS Drug Effects

Blood-Brain Barrier - **Facilitated Diffusion**

Factors in CNS Drug Effects

Blood-Brain Barrier - **Active Transport**
Factors in CNS Drug Effects

Blood-Brain Barrier - **Vesicle Based Transport**

**BLOOD (Luminal face)**
- Influx transport
- Paracellular diffusion
- Efflux transport
- Facilitated diffusion

**BRAIN (Abluminal face)**
- Transcellular diffusion
- Receptor Mediated endo/transcytosis
- Adsorptive Mediated endo/transcytosis
- Pinocytosis

Factors in CNS Drug Effects

Blood-Brain Barrier - **Modes of Transport**

**BLOOD (Luminal face)**

BBB transport of a drug is the result of the combination of drug properties and BBB characteristics.

**BRAIN (Abluminal face)**
Factors in CNS Drug Effects

Drug concentrations at (off) targets drive the effects of the drug

Factors in CNS Drug Effects

Simulations on plasma_u and brain_u PK

BBB transport – simple cases

Model for simulations

Hammarlund-Udenaes, Paalzow, & De Lange, Pharm Res (1997)

CL_in = CL_out

Varying: 1.0 - 0.01

CL_out = 0.5

Varying CL_in: 0.5 - 0.01
Factors in CNS Drug Effects

Simulations on plasma_u and brain_u PK

BBB transport – simple cases

Model for simulations

\[ CL_{in} = CL_{out} \]

Varying: 1.0 - 0.01

\[ CL_{in} = CL_{out} \]

Varying: 0.5 - 0.01

We need to have information on (unbound) brain concentrations

Experimental Approach

Microdialysis: a key technique

Microdialysis probe - semipermeable membrane

Reflection of unbound Extracellular tissue concentrations
Prediction of CNS Drug Effects in Human

Differences in:
- rate of PK and PD processes
- sizes, and surfaces of physiological compartments, and flows

Drug vs. CNS Systems Properties

Pharmacokinetics
- Plasma kinetics
- Barrier transport
- Intratissue distribution

Drug Characteristics:
- Molecular weight
- LogP / logD
- pKa / charge at pH 7.4
- PSA (polar surface area)
- H-bond donor / acceptor
- P-gp / MRP (etc) substrate
- Receptor affinity
- etc

Systems Parameters:
- Blood flow
- Barrier permeabilities
- Transporter / enzyme function
- Volumes (intra- / extracellular)
- Blood / tissue pH
- Capillary surface area
- Receptor density
- Signal transduction
- Homeostatic feedback

Pharmacodynamics
- Target occupancy
- Efficacy

Drug Characteristics:
- Drug Dependent

Pharmacokinetics vs. Pharmacodynamics
Drug vs. CNS Systems Properties

**Pharmacokinetics**
- Plasma kinetics
- Barrier transport
- Intractissue distribution

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**Drug vs. CNS Systems Properties**

**Pharmacokinetics**
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- Volumes (intra- extracellular)
- Blood / tissue pH
- Capillary surface area
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- Signal transduction
- Homeostatic feedback

---

*We need to explicitly distinguish between drug and systems parameters*
De Lange. The mastermind approach to CNS drug therapy: translational prediction of human brain distribution, target site kinetics, and therapeutic effects. Fluids Barriers CNS. 2013

Mastermind Research Approach

To crack the code:
need for an integrated systems approach

- Move away from reductionism and face complexity
- Obtain connected data at multiple levels
- Reveal interactions & interdependency

Apply
- Cross-compare designed studies
- Advanced mathematical modeling
to dissect contributions of individual mechanisms in animals to provide information that can be used for extrapolation to the human situation.
**1. Prediction of PKPD of a CNS Drug in Human**
Prolactine as a translational biomarker of the dopaminergic system

**Prediction of Human PKPD of a CNS Drug**

Pituitary lactotrophs release prolactin into blood

- Dopamine high → inhibition of release of prolactin
- Dopamine low → induction of release of prolactin (~ use of DA antagonist)

**Prediction of Human PKPD of a CNS Drug**

Remoxipride plasma and brain PK in the rat

**Remoxipride plasma**

**Remoxipride brainECF**

**Prolactin plasma**

Intravenous administration

- Remoxipride = Dopamine D2 antagonist → Induces Prolactin Release

Stevens et al. Systemic and Direct Nose-to-Brain Transport PK Model for Remoxipride after IV and IN Administration. DMD 2011
Rat plasma PRL concentrations (+/-SEM) after different interval dosing regimens of 3.8 mg/kg REM IV (IV, 30 min)

**Prediction of Human PKPD of a CNS Drug**

**Remoxipride PD in the rat**

*Insight into rate of synthesis of prolactin in lactotrophs in rats*

Rat plasma PRL concentrations (+/-SEM) after different interval dosing regimens of 3.8 mg/kg REM IV (IV, 30 min)

*Movin-Osswald and Hammarlund-Udenaes. Prolactin release after remoxipride by an integrated PKPD model with intra- and interindividual aspects. JPET, 1995*

**Prediction of Human PKPD of a CNS Drug**

**PK-PD Model Remoxipride in rat**

*Brain unbound concentration = target site concentration*

\[ E_{max} \times \frac{C(t)}{EC50 + C(t)} \]

**Prolactin plasma concentrations increase synthesis rate of prolactin**
Translation on species:
Prediction of PKPD relationship of REM in human
Prediction of Human PKPD of a CNS Drug

POP-PK Model of remoxipride in rat versus human

Observed (o) and predicted (-----) remoxipride plasma concentrations in human

Time (hours)

PRL human – data and translational model prediction

Observed (o) and predicted (-----) prolactine plasma concentrations in human

Time (h)

Stevens et al. MBPKPD model for the prolactin biological system response following acute dopamine inhibition challenge: quantitative extrapolation to humans. JPKPD 2012
Prediction of Human PKPD of a CNS Drug

PRL human – data and translational model prediction

Stevens et al. MBPKPD model for the prolactin biological system response following acute dopamine inhibition challenge: quantitative extrapolation to humans. JPKPD 2012

IN: Brain Distribution enhancement

IV: Same model for rat and human

Rat: unbound brain PK of REM = linked to the effect

Human: In vitro values + allometric scaling give prediction of human plasma PRL concentrations
Use of CSF to predict CNS target site PK?

Which concentration in the human brain is most representative to the brain target site concentration?

What CNS sites in human are accessible to obtain information about brain PK?

De Lange. Utility of CSF in translational neuroscience. JPKPD. 2013

Audience Challenge Question

Answer the question on blue screen in one moment

For prediction of human CNS target site PK for a target that is facing the brainECF:

A) CSF concentrations can be used as it is in quick equilibrium with brainECF

B) We can use in vitro and animal data to build a mathematical model by which we can calculate brainECF concentrations

C) We can make direct use brainECF concentrations as measured in animals

D) CSF concentrations can be used, if taken from the ventricles in the brain, as CSF in the brain ventricles is the closest to the brainECF

E) We can make use of brainECF concentrations measured in humans

- CSF = cerebrospinal fluid
- BrainECF = brain extracellular fluid
For prediction of human CNS target site PK for a target that is facing the brainECF:

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De Lange. Utility of CSF in translational neuroscience. JPKPD. 2013

CNS Properties

Physiological brain compartments, flows, membranes, active transporters, metabolic enzymes, subcellular compartments, pH values, targets
Experimental Approach

Overview - How to Predict CNS PK?

Animal experiment

Westerhout et al. PBPK Modeling to Investigate Regional Brain Distribution Kinetics in Rats. AAPSJ. 2012
Overview - How to Predict CNS PK?

Animal experiment → Animal PK profiles

Animal PBPK model

Westerhout et al. PBPK Modeling to Investigate Regional Brain Distribution Kinetics in Rats. AAPSJ. 2012
Overview- How to Predict CNS PK?

Animal experiment

Animal PK profiles

Animal PBPK model

Translation to human model

Westerhout et al. PBPK Modeling to Investigate Regional Brain Distribution Kinetics in Rats. AAPSJ. 2012

Overview- How to Predict CNS PK?

Animal experiment

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Translation to human model

Westerhout et al. PBPK Modeling to Investigate Regional Brain Distribution Kinetics in Rats. AAPSJ. 2012

Validation on human data

Overview - How to Predict CNS PK?

Animal experiment  →  Animal PK profiles  →  Animal PBPK model

Validation on human data

Observed (Bannwarth et al. Br j Clin Pharmacol. 1992) and predicted human acetaminophen concentrations in plasma (●, ...) and CSF (○, ...).

Translation to human model

Westerhout et al. PBPK Modeling to Investigate Regional Brain Distribution Kinetics in Rats. AAPSJ. 2012

3. Prediction of Human CNS PK for Multiple Drugs
CNS target site concentration-time profiles (PK) depends on:

A) BBB permeability (rate of crossing the BBB)

B) BBB permeability and all aspects of intra-brain distribution

C) BBB permeability and cellular accumulation (brain binding)

D) The ratio between unbound plasma and brain PK
Generic Drug Modeling Approach

Individual drug translational models

Generic drug translational model (mult. drugs with distinctive phys-chem properties)

Overview Data Modeling

Prediction: Human CNS Morphine


Pedriatic TBI patients

Patient 1 (Focal TBI)

Patient 2 (Focal TBI)

Patient 4 (Focal TBI)

Patient 5 (Focal TBI, only 2 blood samples)

Patient 6 (Diffuse TBI)
4. CNS PK prediction for *any* small drug without the need for in vivo data?
### Prediction without in vivo data?

- Animal experiment
- Animal PK profiles
- Human prediction

#### Animal experiment

- Animal PK profiles

#### Human prediction

#### Translation to human model

### Full PBPK CNS Model

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Predicted Human Acetaminophen Concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>120</td>
<td>1000</td>
</tr>
<tr>
<td>240</td>
<td>10000</td>
</tr>
<tr>
<td>360</td>
<td>100000</td>
</tr>
</tbody>
</table>

- Plasma observed
- CSF (SAS) observed
- Plasma predicted
- SAS (CSF) predicted
- Brain ECF predicted
- LV
- CM

### Full PBPK CNS Model Diagram

- Diagram of the Full PBPK CNS Model showing various compartments and flows.

---

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Simulations and Actual Data

Human PBPK CNS Model

Yamamoto et al, EJPS, 2018
Human PBPK CNS Model

Simulations – systems changes

Simsimulations and Actual Data

Phenyltoin
General Conclusions (1)

Can we use animal data on brainECF, and CSF and/or human CSF PK to predict human brainECF (off) target PK?

Relation between drug concentrations and their time course in brainECF, CSF in lateral ventricles, CSF in cisterna Magna, and CSF in lumbar region are

- Drug dependent
- Species dependent
- Time dependent

General Conclusions

- We need to distinguish between drug properties and system (CNS) characteristics for being able to translate between species and/or conditions
- Inter-relationships between PK and PD processes of drugs can be revealed by mathematical modelling if experiments using in individual animals include
  - Measurements with time-resolution (multiple time-points)
  - Measurements that reflect different processes within one single animal (multi-level measurements)
- Such information from animals should be stored in mathematical models, so that it provides knowledge, and reduces the need for animals in research.
Final Food for Thought

• Reductionists approaches will not bring us further ....
• We should face the complexity of processes in the living body, and design our experiments accordingly in order to unravel interrelationships for true understanding and translation
• Medicinal chemist need to realize that many PK processes govern CNS target site PK- it is not only “BBB permeability”
• Thus, for optimization of drug properties, all aspects need to be considered
• The CNS PBPK model provides a very useful tool for investigating the relationship between drug properties and drug distribution into and within the CNS

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Elisabeth CM de Lange
Professor in Predictive Pharmacology, UL, Leiden University

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Michelle Nadeau
Registered Nurse


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