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# Translation of Central Nervous System Occupancy from Animal Models: Application of Pharmacokientic/Pharmacodynamic Modeling

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Translational aspects of neuroimaging and target engagement.

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## List of abbreviations and terms in equations:

5-HT: 5-hydroxytryptamine (serotonin),

*a*: first drug or process coefficient ,

*b*: second drug or process coefficient,

*C*: drug concentration at the biophase,

CNS: central nervous system,

SERT: serotonin transporter,

$EC_{50}$: sensitivity parameter representing the drug concentration producing 50% of $E_{max}$,

$E_{max}$: maximum drug effect,

$K_i$: inhibition constant corresponding to plasma concentration required for half-maximum receptor occupancy,

$k_{off}$: first-order association rate constant, $k_{on}$: second-order association rate constant,

PBPK: physiologically-based pharmacokinetic,

PET: positron emission tomography,

PK/PD: pharmacokinetic/pharmacodynamics,

*RC*: concentration of the receptor-ligand complex,

$R_{tot}$: maximum receptor concentration,

*W*: body weight (animal or human),

γ: Hill coefficient, shape factor or slope term that reflects the steepness of the effect concentration curve,

θ: pharmacokinetic parameter

## Abstract

Translation of central nervous system receptor occupancy from animal models to humans has been elusive for many theraprutic targets. However, this may represent a valuable link to clinical efficacy of drugs acting within the brain and spinal cord. The introduction of positron emission tomography (PET) has marked a significant noninvasive advance in determination of target engagement in the central nervous system. Pharmacokinetic/ pharmacodynamic (PK/PD) modeling represents a valuable tool to translate *ex vivo* receptor occupancy from relevant animal models to humans. While PK properties usually are reasonably scaled across species using standard allometric principles, PD properties related to receptor occupancy are usually species-independent. The translational value and applicability of PK/PD approaches is more directly evident when comparable modeling assumptions and mathematical model structures are employed across experiments and analyses. The purpose of this letter is to review the basic principles of PK/PD analysis of receptor occupancy determined using noninvasive PET imaging, and first principles of allometric PK scaling and PD prediction based on animal data. We also provide a case study of PK/PD analysis showcasing the importance of PK/PD model assumptions in predicting receptor occupancy in humans based on data from animal models using data from the area of pain management.

## Introduction:

Quantitative characterization of the relationship between drug exposure and target occupancy at its site of action (biophase) is essential in drug development. Without such information, the probability for under- or overdosing becomes higher. Consequently, patients risk being exposed to less than optimal therapy or suffer unnecessary adverse effects. Pharmacokinetics (PK) quantitatively describe the processes controlling the time course of drug concentrations in relevant biological fluids and biophases. PK is the driving force for subsequent pharmacological/pharmacodynamic and, in most cases, toxicological effects. Pharmacodynamics (PD) quantitatively describe the mechanism(s) of drug action, such as target occupancy by the therapeutic agent in the brain. Data on the drug PK and PD are required to fully understand the relationships between drug dose and clinical effects, both desirable (efficacy) and adverse (toxicity) (Holford et al., 1981).

Molecular neuroimaging has been used to study the exposure–occupancy relationships relevant to treatment of central nervous system (CNS) conditions (de Greef et al., 2011;Lim et al., 2007; Fischman et al.,2002; Howes et al., 2009; McGuire et al., 2008; Pien et al., 2005; Willmann et al., 2008). Positron emission tomography (PET) is an extremely powerful imaging technique for making PK and PD measurements in a variety of tissues. If a suitable ligand is labeled with a positron or γ emitter and administered to humans, the distribution of receptors in the human body can be visualized and quantified with a positron or γ camera. In 1983 several groups demonstrated that it was

possible to produce images of the distribution of dopamine receptors (Baron, 1983; Crawley, 1983; Wagner, 1983) and of dopaminergic nerve terminals (Garnett, 1983) in the human brain.

Receptor occupancy in the brain and related drug affinity to these receptors has been related to drug efficacy or probability of adverse effects. While ultimately the appropriate dose ranges should be determined in terms of clinical response, receptor occupancy often enables identification of the likely dose ranges to be studied, consequently reducing the risk of under- or overdosing in clinical trials. The affinity of antipsychotic drugs for dopamine $D_2$ receptors closely parallels their clinical potency (Seeman et al., 1975), and antipsychotic dopamine $D_2$ receptor occupancy *in vivo* predicts both the clinical response of patients and the risk of side effects during antipsychotic treatment (Kapur et al., 2000). Similarly 5-hydroxytryptamine transporter (5-HTT) occupancy is used as one of the indices for the evaluation of antidepressants such as selective serotonin reuptake inhibitors (Takano, 2007). There is evidence that efficacy is generally associated with a minimum serotonin transporter (SERT) occupancy of ≥ 80% in the treatment of major depressive disorders. This is evident at the clinically efficacious doses of various selective 5-HT reuptake inhibitors and tricyclic antidepressants (Suhara et al., 2003; Meyer et al., 2001, 2004). Collectively, such findings suggest that receptor occupancy is a meaningful PD biomarker for understanding the drug-receptor interaction that underlies a clinical effect and is useful for predicting the potential dose ranges for a given drug candidate.

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In this article, we briefly review the basic tenets of PK/PD analysis of receptor occupancy determined using noninvasive PET imaging, and first principles of interspecies PK scaling and PD prediction based on animal data. Additionally, we provide a case study of PK/PD analysis showcasing the importance of PK/PD model assumptions in predicting receptor occupancy in humans based on data from animal models using data from the area of pain management.

## Relevant Principles of Receptor Occupancy

The drug concentration at the site of action governs the interaction with the pharmacological target. Ariens et al. applied the law of mass action to the limited concentration of pharmacological targets at the biophase. This is often manifested as a nonlinear, capacity-limited system (Ariens, 1954). In such systems, the rate of change in drug-receptor complex concentrations (RC) can be defined as:

$$\frac{dRC}{dt} = k_{on} \cdot (R_{tot} - RC) \cdot C - k_{off} \cdot RC \qquad (1)$$

where, $R_{tot}$ is the maximum receptor concentration, $C$ is the drug concentration at the biophase, and $k_{on}$ and $k_{off}$ are the second-order association and first-order dissociation rate constants. At equilibrium, this mathematical relationship can be rearranged to yield the following general binding equation:

$$RC = \frac{R_{tot} \cdot C}{K_D + C} \qquad (2)$$

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where $K_D$ is the equilibrium dissociation constant ($k_{off}/k_{on}$). From the classic theory of receptor occupancy, the stimulus or drug effect ($E$) can be directly proportional to the fraction of bound receptors, which results in the widely used Hill equation or simple direct sigmoid $E_{max}$ model (Alvan, 1999):

$$E = \frac{E_{max} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \qquad (3)$$

where $E_{max}$ is the maximum effect, γ (or Hill coefficient) is a slope term that reflects the steepness of the effect concentration curve, and the $EC_{50}$ is a sensitivity parameter representing the drug concentration producing 50% of $E_{max}$.

While it is necessary to characterize both the PK and PD behavior of a drug to fully predict its action *in vivo* and determine its dosing (Meibohm et al., 1997), most studies of CNS-active agents have simply applied the Hill model to characterize the relationship between plasma concentration and receptor occupancy (Grunder et al., 2008; Mamo et al., 2004; Remington et al., 2006; Vernaleken et al., 2008; Takano et al., 2006, Euitae et al, 2012). Indirect or effect compartment models (Jusko et al., 1971, Sheiner et al., 1979; Sharma, 1996; Mager et al., 2003) may be more appropriate than direct models to describe the relationship between occupancy and plasma concentration and may lead to more accurate predictions of the steady-state relationship for drugs that exhibit delayed brain penetration and/or target PD (Abanades et al., 2011). However, for many centrally active agents, establishing the link between plasma drug concentration and target engagement or occupancy has been the conventional practice. A more detailed

discussion of the need to understand the relationship between plasma PK (time course of concentration in plasma) and the receptor occupancy is provided in the next section.

## Extrapolation to Humans from Animals

Translation of target occupancy from preclinical species to humans represents a viable strategy for the prediction of clinical efficacy for novel therapeutics. This is particularly important when the relationship between target occupancy and clinical effect has been or can be established. This approach relies on an understanding of the relationship between drug concentrations in the plasma and CNS biophase that result in specific levels of target occupancy. The majority of studies that examine this relationship rely on single time-point determinations of target occupancy following a single dose administration of the drug (Hughes et al., 2005; Liu et al., 2009). These single time-point investigations usually fall short in determining the true relationship between plasma drug concentration and CNS target occupancy. This is especially true in cases in which the drug distribution from the plasma to the CNS is relatively slow or the rates of drug binding to the target are slow. Following drug administration, a relatively richly sampled time course of drug in plasma and the corresponding time course of target occupancy allow for a more complete characterization of the PK/PD relationships.

In general, the common practice uses allometric scaling principles to extrapolate systemic PK properties from compartmental models from animals to humans (Dedrick,

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1973). Many physiological processes and organ sizes ($\theta$) are thought to obey a power law as related to body size measures (Adolph, 1949):

$$\theta = a \cdot W^b \quad (4)$$

where $W$ is body weight, while $a$ and $b$ are drug or process coefficients. The theory behind allometric scaling assumes that the exponent, $b$, tends to be around 0.75 for clearance processes, 1.0 for organ sizes or physiological volumes, and 0.25 for physiological times or the duration of physiological events (e.g., heartbeat, breath duration and turnover times of endogenous substances or processes) (Boxenbaum et al., 1982). Using nonlinear mixed effects modeling, empirical models (nonstandard fixed exponents) have also been used, separately or along with allometric relationships, to improve the scalability of such empirical models (Cosson et al., 1997; Proost et al., 2006). Different allometric scaling methodologies of key PK parameters yield different predictions. In a published comparative assessment (Ring et al., 2011), 29 different scaling methods based on *in vivo* animal and/or *in vitro* data were used to scale/predict intravenous clearance estimates for 19 drugs. The different methods yielded different estimates of clearance in humans with predictions falling within 10-fold, 3-fold, and 2-fold error of observed estimates. Moreover, commonly used prospective measures of allometric scaling success, including correlation coefficient and allometric exponents, failed in many cases to discriminate between successful and failed allometric predictions (Ward et al., 2004), The success of scaling PK parameters depend on the

mix of species used for scaling schemes, the drug properties, routes of elimination and species-specific characteristics (i.e, transporters and targets).

While measuring the drug concentration near the biophase may be of more relevance to PK/PD relationships (de Lange, 2013), it is not always feasible in both humans like it is in animals. Additionally, the scalability of tissue PK parameters becomes more challenging due to possible interspecies differences in tissue affinities and transporter involvement.

In contrast to compartmental PK models, the structure of physiologically-based pharmacokinetic (PBPK) models (Rowland et al., 2011) renders them highly amenable for interspecies scaling based on differences in tissue blood flow, partitioning tissue binding properties, transporter involvement, and target distribution characteristics. Using PBPK models, and taking into consideration tissue-specific and species-specific differences in tissue blood flow, protein binding, tissue binding affinity and transporters, tissue drug concentrations may be predicted in humans based on pharmacologically relevant animal models.

While the general expectation is that the drug PK can be predicted across species using allometric scalingwith standard exponents, the plasma drug concentration required to elicit a certain intensity of action is often similar in experimental animals and humans with no scaling needed (Levy, 1993). Thus, capacity ($E_{max}$) and sensitivity ($EC_{50}$) parameters tend to be species-independent (Mager et al., 2009). While interspecies

differences in relative receptor affinity and plasma protein binding can be evident (Chien et al., 2005), there are several examples that show reasonable agreement of such properties between rats and humans for chemically-related series of drugs. Quinn and colleagues were amongst the first to examine some PK/PD properties across species, revealing interspecies differences in PK properties between different species (namely duration of action and biological half-life), but close similarity in plasma concentrations on awakening (a concentration that can be analogous to an $EC_{50}$), following hexobarbital administration (Quinn et al., 1958). A linear relationship existed between the logarithm of $K_D$ values of benzodiazepines in rat and human cerebral cortex tissue over several orders of magnitude (Ito, 1997). Cox and coworkers also showed good agreement for the $EC_{50}$ values of four synthetic opioids between different species (Cox, 1999).

However, other studies have shown interspecies differences in apparent *in vivo* affinity to targets within the CNS. For example, TPA023, a $GABA_A$ receptor compound, has been shown to have similar *in vivo* affinity at central benzodiazepine receptor sites in several preclinical species. However, TPA023 was found to be slightly more potent in humans (Atack et al., 2010). Such interspecies difefrences in the *in vivo* affinity were not predictable from the inhibition rate constant ($K_i$ equivalent to $EC_{50}$) values in rat and human $GABA_A$ receptors determined *in vitro* (Atack et al., 2006). The 5-$HT_{1A}$ receptor antagonist NAD-299 has shown approximately 10-fold higher *in vivo* affinity in cynomolgus monkeys (Farde et al., 2000) than in human subjects (Andrée, 2003). Such

a difference may be attributed to a 10-fold higher unbound fraction of NAD-299 in monkeys compared to human plasma (Andrée et al., 2003). These last few examples illustrate that, although studies in preclinical species are mostly useful for predicting initial clinical doses, human studies are warranted to confirm the concentration-occupancy relationships established in preclinical experiments.

## Case Study: PK/PD Model Assumptions in Predicting Human Duloxetine SERT Occupancy from Rat Models

Duloxetine (Cymbalta; Eli Lilly & Co., Indianapolis, IN) is a dual inhibitor of the serotonin and norepinephrine transporters and is used for the treatment of major depressive disorders (Dhillon, 2013), generalized anxiety disorder (Piero, 2011), and various chronic pain conditions (Skljarevski et al., 2011; Smith et al., 2012). Brain SERT occupancy of > 80% was observed at dose levels that successfully demonstrated efficacy in depression (Takano et al., 2006). In chronic pain conditions, duloxetine exhibits efficacy at similar dose levels. Despite the fact that the site of action in humans is still unclear, the analgesic effects are likely due to SERT inhibition located both spinally and supraspinally (Iyengar et al., 2004; Mixcoatl-Zecuatl et al., 2011).

Bourdet et al. reported the translation of CNS receptor occupancy from animals to humans using PK/PD modeling (Bourdet et al., 2012). The group suggested that the preclinical modeling approach was capable of predicting $EC_{50}$ occupancy of SERT in the human CNS (Bourdet et al., 2012). The authors provided a strong foundation supporting the hypothesis that occupancy of SERT by duloxetine is a translatable biomarker between rats and humans, while emphasizing the value of translational PK/PD modeling approaches.

Bourdet et al. compared the parameter estimates from their modeling efforts of SERT occupancy in rats to those reported for humans in two literature reports (Takano et al., 2006; Abanades et al., 2011). . While the authors concluded that the estimates of duloxetine sensitivity parameter were similar, the estimated $EC_{50}$ in humans was significantly higher than that observed in rats. The mean estimate of $EC_{50}$ reported by Takano et al. in humans was 60% higher (3.70 ng/ml) than the mean estimates in humans reported by Abanades et al. (2.29 ng/ml), and in rats reported by Bourdet et al. (2.32 ng/ml). These differences appear to be a consequence of an inconsistent approach to data analysis and PK/PD modeling assumptions between the three reports. While a simple Hill model was used in all three reports to describe SERT occupancy data, Takano et al. assumed a maximal achievable SERT occupancy ($E_{max}$) of 100%. In comparison, Abanades et al. and Bourdet et al. estimated the maximal SERT occupancy in humans and rats, respectively. The mean estimates of $E_{max}$ were 84.0% and 85.6% in humans and rats, respectively. This difference in model assumptions

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(fixing the capacity versus estimating it) led to an inappropriate comparison of $EC_{50}$ between the three reports.

To illustrate the importance of using consistent model assumptions across studies and analyses, we attempted a similar analysis of the human duloxetine SERT occupancy data that were reported by Takano et al. The human receptor occupancy data (in Figure 1b of the published study) was digitized using the image digitizing software Engauge. A sigmoid $E_{max}$ function was then fit to the digitized human data using the nonlinear mixed effects modeling software NONMEM® (Beal, 2009). The resulting mean estimates of $E_{max}$ and $EC_{50}$ were 88.8% and 2.31 ng/ml, respectively. The mean $EC_{50}$ estimates were 2.32 ng/ml and 2.29 ng/ml as reported by Bourdet et al. and Abanades et al., while $EC_{50}$ was estimated to be 2.31 ng/ml from our *ad hoc* analysis of the human data reported Takano et al. These findings suggest that a better agreement between the duloxetine SERT occupancy parameters in rats and in humans existed. This also highlights the better translatability of receptor occupancy PD parameters and the value of consistent modeling assumptions.

In summary, CNS receptor occupancy has been related to clinical efficacy and risk of adverse events. The scaling of receptor occupancy parameters relies heavily on the ability to predict and integrate the fundamental processes controlling drug exposure (PK), drug action (pharmacology and/or PD), and interactions with physiological systems. Preclinical data can be very valuable to decipher such properties and processes, especially as key PD aspects tend to be species-independent. However, it is

of extreme importance that measurements of drug effects are verified and meaningful across species. Despite their limitations, power laws of allometric relationships have proven useful in scaling physiological turnover and drug PK properties from animals to humans. Animal studies can provide preliminary data for the development of mechanism-based PK/PD models, which will continue to evolve toward efficient descriptions of pharmacological systems. While PK properties are often scalable across species using allometric scaling, PD measures of capacity and sensitivity tend to be species-independent. The translational value and applicability of PK/PD approaches is more directly evident when comparable modeling assumptions and mathematical model structures are employed across experiments and analyses.

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