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Population pharmacokinetics meets microdialysis: Benefits, pitfalls and necessities of new analysis approaches for human microdialysis data

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ABSTRACT

Pharmacokinetic (PK) data originating from human microdialysis studies have by now most commonly been analysed using noncompartmental analysis or the standard two-stage population approach. During the last decades, additional modelling strategies for PK data have been developed, which also seem apt for the analysis of microdialysis data. The present opinion article gives an overview of the three approaches of nonlinear mixed-effects (NLME) modelling, physiologically-based pharmacokinetic (PBPK) modelling and a combined population PBPK modelling approach (PPBPK) as well as their application within the field of microdialysis in humans. Potential benefits and pitfalls of the different approaches will be outlined and exemplified, complemented by modelling prerequisites to be met on the part of principal investigators, bioanalysts and documentalists involved in a microdialysis study.

In summary, the combination of microdialysis as the method of choice for measuring unbound drug concentrations in peripheral tissues and the presented modelling strategies seems a promising way to enhance the understanding of drug disposition at the target site of drugs and might thus contribute to a more rational use of medicines.

1. Introduction

In the last decade, microdialysis has emerged as the technique of choice for measuring unbound concentrations of both drugs and endogenous biomarkers in peripheral tissues (Plock and Kloft, 2005). Several approaches are available to determine parameters characterising the pharmacokinetics (PK) of a drug in the tissue of interest. A systematic literature research in Pubmed on the topic of microdialysis in antibiotic research (MeSH-terms "antiinfectives", "microdialysis" and "human") revealed that noncompartmental and two-stage (TS) approaches were predominantly used for the analysis of human microdialysis data (Table 1). However, more modern modelling strategies such as nonlinear mixed-effects (NLME), physiologically-based PK (PBPK) and population physiologically-based PK (PPBPK) modelling offer some important advantages over the NCA and the TS approach. The aim of the present article is to provide an overview of these modern modelling approaches, to demonstrate their benefits and pitfalls and to state which type of data serve as the base and are thus indispensable for the model development process.

2. Three so far unexploited modelling strategies in microdialysis data analysis: Benefits and pitfalls

2.1. The nonlinear mixed-effects (NLME) modelling approach

NLME modelling is a population-based data analysis method for typically pharmacokinetic/pharmacodynamic data to describe a course of observations (e.g. drug concentrations in plasma and in tissue interstitial space fluid (ISF), resultant drug effects or responses) by a mathematical function (model). The term 'nonlinear mixed-effects' refers to the fact that the model function depends on its model parameters in a nonlinear manner and both fixed- and random-effects form part of ("are mixed" in) the model. Whereas *fixed-effects* represent measured components (e.g. time, dose, weight) and can be quantified independently from the observations (e.g. drug concentrations), *random-effects* quantify the variation across the population (Beal, 1984; Pillai et al., 2005; Tornøe et al., 2004).

All pharmacokinetic NLME models exhibit a hierarchical structure and consist of three components (Fig. 1): The *structural submodel* describes the typical concentration–time profile in the plasma and tissue ISF in the population of interest, whereas the *stochastic model* quantifies different sources of variability as a function of random-effects. Thereby, inter-individual, intra-individual and residual variability can be distinguished, the latter

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Table 1
Results of a systematic literature search in Pubmed. Overall, after rejection of reviews, 70 publications were considered (references available upon request).

Criterion	Item	Outcome
Number of investigated participants per study	Mean	8
	Standard deviation	4
Measurement time of drug concentrations (after single vs. multiple dose)	Single dose	52
	Multiple dose	15
	Both	3
Data analysis approach	NCA	42
	TS	24
	NLME	1
	No data analysis	3
Reference matrices for microdialysis measurements	Plasma	51
	Serum	17
	Ultrafiltrate	1
	No reference matrix	1
Investigation of covariates	Yes	0
	No	70
Software	Kinetica®	33
	WinNonlin®	8
	Scientist®	6
	NONMEM®	2
	Other	15
	Not stated	6

NCA: noncompartmental analysis, TS: two stage approach, NLME: nonlinear mixed-effects approach.

of which also covers uncertainty linked to the measurement method.

Thirdly, observed discrepancies within patients or subgroups of a population are aimed to be explained by the *covariate submodel*. For instance, by modelling microdialysis data, patient characteristics influential on drug tissue distribution, whether demographic factors or disease status, may be identified and consequently more rational and individual dose recommendations be given.

2.1.1. Benefits of the NLME modelling approach

NLME modelling offers several advantages over more traditional approaches of data analysis (Table 2). In contrast to the TS approach, in which at first individual PK parameters for drug concentration–time profiles are estimated and in a second step summary statistics for the PK parameters are calculated to describe variability across the population in one overall value, the NLME approach acknowledges different sources of variability, thus avoiding overprediction of otherwise only one overall variability. As a result, patient- and study-related variability can be estimated more accurately and separately from variability due to the method of microdialysis. Within the latter, microdialysis- and retrodialysis-related residual variability are further distinguishable.

NLME modelling represents a single-stage approach, thus considers all measured drug concentrations of all individuals simultaneously. Hence, not all individuals of a population need to provide data sufficient to characterise a complete individual concentration–time profile, but also sparse data situations and incomplete individual profiles, e.g. due to clotting of microdialysis probes over the course of a sampling interval, can be considered. Moreover, data stemming from different microdialysis studies with possibly unbalanced and heterogeneous designs and diverse sampling schedules, as frequently encountered in clinical study protocols, as well as single measurements, e.g. resulting from routinely performed therapeutic drug monitoring, can be analysed concurrently.

As within the field of microdialysis, studies commonly do not involve more than 10 participants (mean number of participants = 8, Table 1), a joint "pooled" analysis of several studies seems advantageous in contrast to one-by-one analysis, also because it paves the way for systematic covariate analysis to identify patient-related factors influencing drug tissue distribution. By

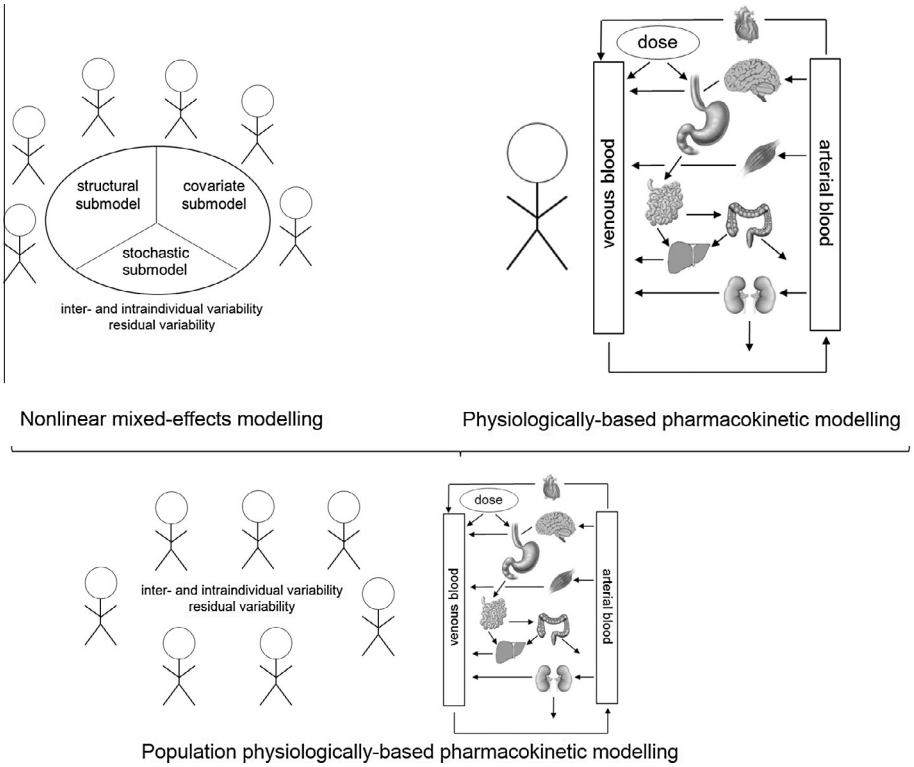

Fig. 1. Schematic depiction of the three outlined modern data analysis approaches.