What can pharmacokinetic modelling do for you? Rational design and interpretation of clinical studies

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October 21, 2024

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Acknowledgements: We are grateful for funding from the EDCTP2 programme supported by the European Union (grant number RIA2016MC-1606-VirTUAL) and Wellcome Trust Clinical Research Career Development Fellowship awarded to Catriona Waitt. 222075_Z_20_Z which enabled the establishment of the Uganda Chapter of Pharmacometrics Africa.

Conflict of Interest: The authors declare no conflict of interest

Data availability statement: Not applicable

Integration of data, including patient and treatment characteristics, along with drug exposure to optimize treatment has been possible for more than fifty years.[1] Quantitative pharmacology (QP) models combine information from biology, *in-vitro* systems, drug exposure, clinical data, and statistical methods to characterise how drugs behave after administration and to describe the relationship between drug exposure and treatment outcomes.

As diverse mathematical concepts are increasingly incorporated into QP, its application has expanded across various data types, including continuous, categorical, and count data, enabling different kinds of models/analyses including pharmacokinetic-pharmacodynamic modelling, time to event analyses, disease progression modelling, and tumour growth models. The need to optimize therapies for biologically complex patients—such as infants, the elderly, pregnant and breastfeeding women, obese or malnourished individuals, and those with organ dysfunction—alongside the growing complexities of clinical situations, including multiple comorbidities, polypharmacy, and rising drug resistance, has driven the diversification of QP methods.

The advancement of QP is closely linked to pharmacometric methodologies, particularly nonlinear mixed-effects modelling. Pharmacometrics is the science of developing and applying mathematical and statistical methods to characterise, understand, and predict a drug's pharmacokinetic (PK), pharmacodynamic (PD), and biomarker-outcomes behavior as well as the relationships between each of these variables (PK, PD and biomarkers).[2] The growth of pharmacometrics has been supported by the exponential rise in affordable, accessible computational power supporting complex analyses, particularly nonlinear mixed-effects modeling.

This themed issue showcases a range of scenarios in which pharmacometrics was applied to answer diverse questions in drug development or clinical application of drugs.

A distinctive insight into the evolution of QP is offered by Dunn and Gobburu.[3] The core of QP is intimately connected to the principles of PK-what the body does to the drug and PD-what the drug does to the body.[3] The adaptation of PK-PD principles to incorporate the effects of time on drug action ultimately gave rise to *pharmacometrics* as a distinct field. Since its inception, this field has transitioned through several phases: from 1960 to 1990, it underwent both inception and growth, along with periods of implementation and hesitation; from 1990 to 2010, it saw legitimization and acceptance, leading to reliance; and from 2010 to the present, it has been marked by expansion and a deepening role in drug development and clinical practice. Physiologically-Based Pharmacokinetic (PBPK) modeling and quantitative systems pharmacology are being

increasingly utilized to address critical questions in both drug development and clinical practice, and are increasingly part of new drug submissions to regulatory authorities such as the US Food and Drug Administration (FDA).[3] The evolutionary path of pharmacometrics includes, among other things, the integration of big data and its application to real-world scenarios.

The pharmacokinetics of tacolizumab was evaluated in patients with COVID-19 induced cytokine storm syndrome (Css), followed by exploration of alternative dosing strategies.[4] A population pharmacokinetic model was developed to describe the plasma disposition of tacolizumab. Model-based evaluation of alternative fixed tacolizumab doses identified a 400 mg daily dose as sufficient to provide adequate concentration cover over the 1µg/mL threshold, with significant reduction in costs and drug exposure levels during treatment in contrast to the reference weight-based dosing.

Zou Y et al., undertook population pharmacokinetic modelling for comparative biovalability assessment of two oral formulations of delamanid.[5] This example specifically highlights the suitability of model-based bioavailability assessment for drugs with a long half-life and also showcases more broadly the possible application of pharmacometrics in bioavailability evalaution.

One specialized area of pharmacometrics focuses on optimizing treatment for complex and often under-researched pediatric populations. Infants are frequently excluded from early-phase clinical trials, which hampers the ability to make informed dosing decisions in clinical settings. A case scenario illustrates how pharmacometrics can be used to optimise antimalarial treatment in resource-limited environments.[6] In this review physiological attributes associated with complex pharmacokinetics in infants are discussed, laying the groundwork for pharmacokinetic-pharmacodynamic dose optimisation. The limited application of pharmacometrics in optimisation of antimalarial treatment is summarised, highlighting current gaps in this field, such as rapid age-related physiological changes and small sample sizes. The discussion also emphasizes the potential of additional methodologies, including PBPK modeling and machine learning.

Five articles illustrate the diversity of PBPK modeling and its application. Two pregnancy models were developed for the long-acting injectable (LAI) antiretrovirals cabotegravir and rilpivirine[7], and for sertraline[8]. These models aimed to characterise the maternal and fetal disposition of the drugs and to assess the effects of different dosing regimens on drug exposure. Key model-based predictions suggest that monthly dosing of LAI cabotegravir provides adequate antiretroviral coverage during pregnancy, while bimonthly dosing maintains efficacy for most patients by week

12.[7] Additionally, fetal exposure to sertraline was estimated to be 30-40% of maternal levels.[8] Two PBPK models developed by Ezuruike U *et al*.,[9] and Chao C *et al*.,[10] provide a mechanistic evaluation of genetic polymorphisms in drug metabolism of lansoprazole and fluorouracil exposure, respectively, whereas Ng TM *et al*.,[11] characterised the pharmacokinetics of nirmatrelvir/ritonavir in COVID-19 patients with renal impairment.

Underpining the evolution in methodologies for model-based analysis, a small data paradigm, combining the pharmacometric item response theory modelling with Bayes factor analysis is presented to evaluate the efficacy of blacarmasine in Rett's syndrome.[12] Small data approaches leverage different strategies to understand dynamic, multicausal and idiosyncratically manifesting phenomena, which can help to make these complexities more manageable. Whereas a sample size <100 patients may be considered small for a typical randomised control trial, in rare diseases, for example Rett's syndrom with a prevalence of 1:10000, these numbers are seldom attainable. Authors present an efficacy evaluation of blacarmasine based on twenty-five (n=25) patients from a drug development program, which provides insight into how clinical trials can be conducted in other rare conditions.

The field of pharmacometrics continues to expand, with applicability across a diverse range of medical conditions and complex patient scenarios. In the past, strict eligibility critieria meant that trial populations often did not reflect the patient group in whom therapeutic agents were to be used. As well as being innacurate, this also contributed to inequity. The status quo is being challenged, supported by the FDA's 2024 Diversity Action Plan,[13] and pharmacometric approaches support further mechanistic understanding. A case-scenario from the VirTUAL project highlights the integration of diverse modelling methodologies (PBPK and population analysis) to optimise clinical trial design and data analysis in a complex and understudied HIV/TB-infected population.[14,15] By drawing together key exemplars illustrating the use of several pharmacometric approaches, we aim to showcase this methodology and excite the reader that the time is coming when all individuals are able to access individualised guidance on the safest, most effective use of medications.

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