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EDITORIAL

Precision dosing in clinical medicine: present and future

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1. The 'problem' of variability in drug response

There are four potential outcomes when a patient commences a new drug and its effects are assessed at the correct time. First, the new drug provides no clinical benefits and gives the patient intolerable adverse effects (negative benefit: risk). Second, clinical benefits occur but the adverse effects are so severe that the drug must be ceased (negative benefit: risk). Third, there are no clinical benefits or adverse effects because meaningful pharmacological activity is absent in that patient, including any interaction with the immune system (zero benefit: risk). Finally, the patient experiences clinical benefits with little or no adverse effects and treatment continues, ideally with ongoing monitoring of efficacy and vigilance for potential toxicities (positive benefit: risk). Unfortunately, failed drug therapy occurs widely in clinical medicine, i.e. outcomes 1–3. The financial costs to healthcare are considerable, with a recent analysis by the World Health Organization estimating that the cost of medication-related harm globally is about US $42 billion per annum [1]. No data are available to quantify the cost of ineffective treatment with medication, which is likely to be considerable. This 'problem' exists because drug response is highly variable between different patients who take the same dose (inter-individual variability), and because drug response changes in the same patient taking the same dose over time (intra-individual variability). Assuming a correct diagnosis and complete adherence by the patient to the drug regimen, the causes of drug response variability are either pharmacokinetic and/or pharmacodynamic. Pharmacokinetic variability occurs when drug concentration at the site of action differs between patients or changes with time resulting in different responses. Pharmacodynamic variability occurs when pharmacological activity following molecular target binding differs between patients or changes with time at the same drug concentration [2].

There is incongruity between drug development and clinical medicine in how to tackle variability in drug response. Drug development has a one-dose-fits-all culture because it is impractical and cost prohibitive to study too many different doses and too many different types of patients. There are no regulatory requirements to find the best dose, rather, only a safe and effective dose at the study population (not the individual) level. Clinical trials therefore limit the number of doses studied. Participation in clinical trials is also homogenized by tight inclusion criteria. This decreases response variability and improves the chances of success. For example, many cancer patients are excluded from clinical trials due to age (>65 years old), significant organ dysfunction, prior or concurrent malignancies, comorbidities, and potentially interacting concomitant medications [3]. Clinical trials therefore limit the types of patients studied. Drug therapy fails in the 'real world' because limited doses are approved, and because drugs are given to patient types for which established efficacy and safety data are lacking, i.e. a 'black hole' in Professional Drug Information (PI)/Summary of Product Characteristics. Prescribers attempt to counteract these difficulties by selecting drugs with fewer or less severe adverse effects, by selecting drugs with lower variability in response, and hence more predictable clinical outcomes, and by individualizing dose. The latter option is 'precision dosing,' defined as dose selection by a prescriber for an individual patient at a given time. Importantly, there are examples where the approved dose is no longer used in clinical practice, with safer and more effective dosing having evolved with real world experience, e.g. sunitinib.

2. Current precision dosing

Precision dosing in clinical medicine is needed for drugs with a narrow therapeutic index (TI) and for patients who belong to 'special populations.' Therapeutic classes with narrow TI drugs include the antiarrhythmics, anticoagulants, antiepileptics, antineoplastics, aminoglycoside antibiotics, and immunosuppressants. Patients in the special populations are at increased risk of medication-related harm compared to other groups – pediatrics, the elderly, those with renal or hepatic impairment, the infant who is breastfeeding, and patients taking concomitant medications that cause pharmacokinetic or pharmacodynamic drug–drug interactions [4]. The most compelling cases for precision dosing are when a narrow TI drug is essential for a patient in one or more of the special populations.

2.1. Professional drug information/summary of product characteristics and drug monographs

The PI is a regulatory approved document from the manufacturer. Drug monographs (DMs) are contained in commercial and independent drug information resources [5]. Both are used for precision dosing when no robust biomarker is

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available to allow empirical dosing (see below), e.g. direct oral anticoagulants. Recommended doses come directly from clinical studies (e.g. a dedicated renal impairment study), or indirectly via population pharmacokinetic ± pharmacodynamic analyses (pop PK ± PD) of large clinical datasets. These approaches identify covariates driving inter- and intra-individual variability in exposure or response, including age, gender, weight, body surface area, ethnicity, and renal and hepatic functions (note that some of these covariates correspond to the special populations listed above). The recommended dose is dependent on the value of one, sometimes two, of these covariates for a given patient [6]. For example, the recommended dose of apixaban for stroke prevention in non-valvular atrial fibrillation is halved to 2.5 mg twice daily in patients with at least two of the following characteristics: age ≥80 years, total body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. However, PI/DM are difficult to apply to patients who have multiple covariates known to influence drug exposure or response, i.e. the unique combination of their covariates has not been studied in clinical trials or addressed by pop PK ± PD analyses so a 'black hole' exists in PI/DM. Sticking with the apixaban example, it is difficult to choose a dose for an 85-year-old patient who has renal impairment (serum creatinine = 1.7 mg/dL), ischemic heart disease, hypertension, and osteoarthritis, and is taking verapamil, a drug that increases apixaban exposure by inhibiting cytochrome P4503A4 and p-glycoprotein, and ibuprofen, a drug with anti-platelet action that increases the risk of bleeding [7,8].

2.2. Empirical approach

An initial dose is selected and then adjusted based on exposure or response (as measured clinically or through a biomarker, e.g. warfarin and the international normalization ratio, INR). Since there is prescriber feedback and room to move with dose, prescribing requires greater thought than with PI/DMs that stipulate a fixed dose based on a patient covariate. With the empirical approach, the intensity of monitoring and frequency of dose-titration depends on the nature of the medical condition (acute vs. chronic), the TI of the drug (narrow or wide), and the robustness of the biomarker(s) of exposure or response (correlation to clinical outcomes). This is well done in acute settings, such as immunosuppression following whole organ transplantation, and is improving in primary care with automatic reminders to monitor biomarkers of chronic diseases, such as blood HbA1c concentration in patients on anti-diabetics. Whilst the empirical approach allows some dose flexibility, potentially useful drugs are ceased often prematurely due to limited dose options. Indeed, there may be legal ramifications if things go wrong on a dose outside the approved range, and this range may be narrow from the clinical trials.

2.3. Genetic testing (pharmacogenomics)

Germ line and somatic mutations are increasingly important in explaining variability in drug response. The main utility of pharmacogenomics, however, is for drug selection. Examples include the choice of targeted pharmacotherapy after molecular diagnoses in oncology (e.g. dabrafenib in patients with malignant melanoma harboring *BRAF V600* mutations [9]), or to warn prescribers about unfavorable risks of toxicity (e.g. abacavir hypersensitivity in HIV patients with the *HLA-B*5701* genotype [10]). The case for pharmacogenomics is less clear for dose selection. Some practical guidance is available for polymorphisms in drug metabolizing enzymes and transporters (DMET) [11,12]. For example, a dose reduction of 50% is recommended when initiating several selective serotonin re-uptake inhibitor antidepressants in patients who are cytochrome P4502C19 and cytochrome P4502D6 poor metabolizers [13]. There are early indications that DMET testing has economic value in high-risk patients (e.g. the elderly on polypharmacy [14]), and several large prospective studies of preemptive DMET genotyping on health and economic outcomes are underway in the United States and Europe [15].

2.4. Model-informed

Biosimulation in 'high-impact' cases predicts the dose for a given patient that is most likely to improve efficacy and/or lower toxicity based on their unique values of covariates known to influence drug response [6]. This niche is limited to academic-hospital centers with strong clinical pharmacology expertise, and to trained healthcare providers with access to specialized software and guidelines that typically require a therapeutic drug monitoring service (TDM). Algorithms based on pop PK ± PD models are available for the initiation of warfarin, although empirical dosing via the INR takes over once treatment has started. For other narrow TI drugs, biosimulation is applied after initiating drug treatment, with a Bayesian approach using pop PK ± PD models to predict subsequent doses from personalized inputs to the model that include a recent drug concentration. This approach is more powerful than dose recommendations in PI/DMs because it combines the flexibility of empirical dosing via biomarker feedback whilst accounting for multiple patient covariates that determine variability in drug response [16]. Examples include model-informed precision dosing (MIPD) of antibiotics in the critically ill [17], the use of models to suggest metformin dose in patients with renal impairment [18], and MIPD of immunosuppressants and chemotherapy in serious pediatric illnesses [19,20].

3. Future precision dosing

Precision dosing is set to become more sophisticated. Affordable omics technologies (genomics, transcriptomics, proteomics, and metabolomics), improved medical imaging, rapid pathology testing, characterization of the gut microbiome, superior analysis of biological samples, and powerful computational tools to analyze 'big data' are all important factors in advancing precision dosing. Our understanding of inter-individual and intra-individual variability in drug response now goes beyond simple patient covariates (e.g. age, gender, weight, etc.) to include the 'hidden' physiological and molecular determinates of pharmacokinetics and pharmacodynamics – organ sizes, blood flows, DMET activities, inflammatory status, gut microbiome,

genetics of molecular targets, etc. [21,22]. An improved understanding of disease heterogeneity as a source of pharmacodynamic variability is also increasingly recognized, e.g. doses of the IgE-specific monoclonal antibody omalizumab are determined by age, weight, and pretreatment serum plasma IgE concentration in moderate to severe allergic asthma [23].

Capitalizing on the complexity of inter-related patient information to predict dose is only possible with biosimulation. In addition to pop PK ± PD models linked to TDM, physiologically based (PB) PK ± PD models and quantitative systems pharmacology (QSP) approaches will become important tools for precision dosing. These allow generation of a patient's virtual twin based on their unique physiological and molecular characteristics, including pharmacogenomics. In theory, prescribers could predict drug response prior to treatment, as concomitant drugs change, and as medical conditions progress or improve [16]. Model-informed approaches are now revolutionizing drug development [24,25], and efforts are underway to repurpose PBPK ± PD and QSP for clinical application [26–30]. Importantly, the model-informed approach is a way to distill large quantities of drug-related and patient-related information into relatively simple dosing instructions. For example, a recent study identified abundance of hepatic cytochrome P4503A4 as the major driver of axitinib exposure, accounting for >90% of inter-individual variability (Dr Andrew Rowland, personal communication). When the technology becomes available, a blood test result of this single covariate may be sufficient to predict an axitinib dose that improves the chances of survival for a patient with metastatic renal cell carcinoma prior to treatment and/or when TDM is unavailable [31].

Economic incentives that encourage precision dosing in drug development will improve precision dosing in clinical medicine. Value-based or outcome-based pricing is when a drug is paid for only if it works, i.e. outcome 4. Compared to fixed-pricing, there would be greater incentive for manufacturers to find the best dose and to find the types of patients that benefit the most. Exposure-controlled clinical trials and response-controlled clinical trials may be needed to generate this evidence, although these are expensive and logistically more challenging than current trial designs. However, the provision of lower doses for certain patient populations would lower manufacturing costs, whilst patients who fail drug therapy could be treated successfully at a higher dose [2].

In conclusion, this editorial outlines why variability in drug response occurs in clinical medicine and describes the current precision dosing strategies to address the problem. Model-informed approaches that incorporate the unique physiological and molecular characteristics of individual patients will become increasingly important for precision dosing in the era of precision medicine.

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Declaration of interest

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