Precision dosing to avoid adverse drug reactions

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***Abstract*:** Adverse drug reactions (ADRs) have traditionally been managed by trial and error, adjusting drug and dose selection reactively following patient harm. With an improved understanding of ADRs, and the patient characteristics that increase susceptibility, precision medicine technologies enable a proactive approach to ADRs and support clinicians to change prescribing accordingly. This commentary revisits the famous pharmacology–toxicology continuum first postulated by Paracelsus 500 years ago and explains why precision dosing is needed to help avoid ADRs in modern clinical practice. Strategies on how to improve precision dosing are given, including more research to establish better precision dosing targets in the cases of greatest need, easier access to dosing instructions *via* e-prescribing, improved monitoring of patients with novel biomarkers of drug response, and further application of model-informed precision dosing.

Keywords: adverse drug reactions, medication safety, model-informed precision dosing, precision dosing, precision medicine

Introduction

Alle Dinge sind Gift, und nichts ist ohne Gift, allein die Dosis macht dass ein Ding kein Gift ist. This famous quote from the 'Father of Toxicology' is 500 years old and translates into English as, 'All things are poison, and nothing is without poison, but the dose alone makes it so a thing is not a poison.' (Paracelsus, 1493/1494–1541). With the rise of 'precision medicine', that is, the use of novel technologies such as genetic testing to individualize patient treatment,[1] this simple principle is as important today as ever. In contrast to correct drug selection based on improved diagnostic certainty, the role of correct dose selection has received less attention in the debate on precision medicine.[2] 'Precision dosing' has been defined recently as dose selection by a prescriber for an individual patient at a given time.[3] The definition covers initial dose selection, which occurs following the decision to commence a particular drug, and ongoing dose selection, which occurs after assessment of the benefit: risk of continuing drug treatment. The drug, disease and patient characteristics that define the need for precision dosing

have been described in detail.[4] In principle, the greatest clinical benefit for precision dosing comes from patients taking narrow therapeutic index drugs who are intrinsically difficult to dose, such as those at the extremes of age. Health economic benefits are also gained by reducing the waste of high-cost drugs.[5] This commentary describes eight reasons why precision dosing is needed to help avoid adverse drug reactions (ADRs) in modern clinical practice. Strategies are then given on how precision dosing can be improved.

Reasons why precision dosing is important to avoid ADRs

(1) Drugs are still a leading cause of patient harm. Despite the development of new drugs that resemble more closely 'magic bullets', and countless initiatives designed to improve medication safety,[6] the problem of ADRs has increased rather than decreased in the new millennium. Indeed, harm from drugs now costs about US $42 billion per annum globally.[7] Errors

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leading to ADRs can occur at any point in the medication management cycle, from medication history taking (e.g. previous medications, doses, durations of treatment, responses) to dose administration and the monitoring of response, but prescribing errors, including inappropriate dose selection, are potentially the most serious.[8,9]

(2) Most ADRs are a predictable extension of a drug's pharmacology (Type A or 'Augmented' ADRs).[10] As understood by Paracelsus, the pharmacology–toxicology continuum means that considering dose is essential when evaluating the benefit: risk of any drug therapy. Importantly, this balance is patient- and time-dependent. Unacceptable risk for one patient may not apply for another. For example, the risk of postsurgical respiratory depression with opioids in an old patient with chronic obstructive lung disease is much greater than for a young patient with no chronic medical conditions. Regarding time, a patient who previously tolerated a drug may become intolerant. Examples include; acute deterioration in health leading to poor drug clearance (e.g. acute kidney injury), new treatment regimens causing drug-drug interactions (e.g. added anticholinergic burden), and when patients change their mind about the acceptability of adverse effects (e.g. irretraceable nausea from chemotherapy in light of cancer progression).

(3) The pharmaceutical industry outwardly projects a 'one-dose fits all' culture for commercial reasons. This perceived devaluing of dosing options can filter through to prescribers. This most often leads clinicians to believe that 'This dose is in the prescribing information (PI) so it must be effective and safe'. Poor vigilance in monitoring for potential ADRs is partly explained by underestimating the degree of between patient variability in drug responses at the approved dose. Introduction of the direct oral anticoagulants (DOACs) is an example, where the initial promotion of easy dosing with no laboratory monitoring of response gave unrealistic expectations about low bleeding rates.[11,12]

(4) The primary evidence for dose comes from randomized controlled trials (RCTs). These studies have tight inclusion criteria to find supporting p-values for regulatory applications and marketing, so patients in RCTs often differ significantly from those in the real-world.[13] Approved doses are therefore used routinely in patient types for which established efficacy and safety data are absent, such as at the extremes of age. That is, prescribers are literally in a dosing 'black hole'.[14] The foundation of modern medical training and practice is evidence-based medicine (EBM), defined as 'the conscientious explicit and judicious use of current best evidence in making decision about the care of individual patients'.[15] However, the caveat of EBM for drug therapy is that the evidence, at least in the initial stages of a drug's life, is from industry-sponsored RCTs not designed usually to account for large between patient variability in drug exposure. A prime example is drug development in oncology, where early clinical studies based on the maximum tolerated dose (MTD) approach are geared to select one dose to move development forward into larger studies. Therefore, blind faith in EBM for drug therapy may act as a barrier to precision dosing and the treatment of patients dissimilar to those in RCTs.

(5) Patients are older, have more comorbidities, and are taking more drugs than ever before. Such patients are intrinsically more difficult to dose compared with the 'average' patient because of physiological, pathophysiological and extrinsic factors that significantly alter pharmacokinetics or pharmacodynamics. Examples include the frail elderly, the morbidly obese, patients with significant organ dysfunction and those with multiple chronic conditions who are on polypharmacy (often defined as taking more than five drugs).[16] These are independent risk factors for ADRs and add to the challenge of modern clinical practice.[17]

(6) Clinical care has become increasingly fragmented. It is well recognized that medical specialties apply clinical practice

guidelines in isolation causing unanticipated ADRs.[18] This is particularly pertinent for older patients with multiple comorbidities who attend numerous specialty clinics in addition to their general practice. In these cases, doctors are often reluctant to question the prescribing of their colleagues out of professional courtesy. The hierarchical structure of medicine also means that junior doctors are less likely to question senior colleagues about drug-related problems caused by their prescribing. Since fragmented clinical care is expected to continue,[1] it is harmful to assume that the drug dose has been evaluated in the context of the latest patient presentation.

(7) Clinical pharmacology education in medical schools and the number of doctors choosing clinical pharmacology as a specialist career has declined since the 1990s. One consequence of this is less opportunities for on-the-job learning by junior doctors on how to translate clinical pharmacology principles into practice, for example, dosing in renal impairment when no guidance is available in the PI or drug monograph. Doctors who are less familiar with the discipline may lack knowledge about the importance of dose and lack confidence to make changes beyond approved doses and their experience. This is a well-recognized barrier to precision dosing.[19]

(8) Clinical workflows are fast and precision dosing may take time for some patients, even with a team member dedicated to help, such as a clinical pharmacist. Drug-related problems are frequently 'solved' by ceasing the potential offender quickly and starting a new drug from the same ('me-too') or closely related therapeutic class. The opportunity for 'fine-tuning' and its potential clinical benefits are lost, replaced by a new therapeutic trial ($n = 1$) which can take time and may introduce different clinical problems. This happens frequently in patients with chronic mental health conditions, who often receive a merry-go-round of psychotropic drugs due to poor efficacy or ADRs.[20]

Strategies to improve precision dosing to avoid ADRs

Given that inappropriate dose can cause ADRs, strategies to improve precision dosing have considerable clinical and health economic potential. Above and beyond the standard suggestions of 'more cross-disciplinary research', 'better education and training', and 'greater team-work in healthcare',[19] what else is needed to improve precision dosing?

(1) Establishing superior precision dosing 'targets'. As described in the Introduction, precision dosing has the greatest benefit for patients taking narrow therapeutic index drugs that are difficult to dose. However, this covers many clinical cases, some of which still require further understanding of dose-exposure-response relationships and the factors that impact these relationships. For example, the best plasma concentration range of everolimus is currently unclear for infants <2 years of age who suffer seizures due to tuberous sclerosis complex.[21] Establishing robust dose-, exposure- or biomarker-targets in the cases of greatest clinical need is an essential step to improve precision dosing. Sometimes, precision dosing targets are found in clinical development but their translation into clinical practice is poor. Sometimes, the basic research to find a dosing 'sweet spot' is still needed after a drug is marketed, particularly if the patient population changes, such as when a drug for adults is used off label in paediatrics. Once a dosing target is accepted, prospective studies of precision *versus* standard dosing are then possible to investigate whether any benefits of the extra effort are worthwhile.

(2) Easier access to precision dosing instructions *via* electronic prescribing (e-prescribing) modules that are now part of most electronic health records (EHRs). This is an example of where information is already available, yet better tools and a framework for broader implementation are required. For some drugs, the major patient characteristics known to influence exposure or response (age, weight, renal function, pharmacogenomics etc.) are identified during drug development and accounted

for by having several approved doses. For example, the dose of apixaban to prevent emboli in patients with atrial fibrillation is reduced by half in patients who satisfy two of the following three criteria: weight <60 kg, age >80 years, and serum creatinine >133 μmol/L.[22] Guidance may also be available on how to adjust doses based on patient characteristics that may impact benefit: risk but do not justify the extra work required for an alternative approved dose. Changing from paper-based prescribing to e-prescribing improves access to drug information sources with precision dosing instructions that are familiar to most prescribers, for example, PI and commercial or independent drug monographs. Electronic systems also have automated allergy and ADRs alerts, drug–drug interaction warnings, and dose range checking.[3] Recent data suggest that e-prescribing decreases prescribing errors by 50% or more compared with paper-based systems.[9] Importantly, prescribing software can effectively 'deliver' to the bedside or clinic specialized precision dosing initiatives, such as quantitative pharmacokinetic modelling and simulation (see point 4 below on model-informed precision dosing),[23] tailored deprescribing schedules or bespoke institutional dosing protocols.[24]

(3) Initiatives that improve the monitoring of drug responses. Precision dosing using the empirical approach, that is, starting treatment and then adjusting dose according to a biomarker of response,[3] can be improved relatively easily by superior patient monitoring and documentation. Interventions that help prescribers achieve this are many and varied, incorporating simple examples such as correct blood pressure measurement in triplicate for patients on antihypertensives, the recording of pain and sedation scores after opioid administration, and the questioning of patients about medication adherence. A standout example in this domain is when close collaboration occurs between doctors and clinical pharmacists at the point of care.[25,26] Dedicated clinical pharmacy services dramatically improve the accuracy of medication histories in relation to ADRs, and give prescribers the detail necessary to make superior dosing decisions. Another example is the expected benefits to patient care that will result from the proliferation of novel molecular biomarkers of drug response. Prescribers will need to learn how these biomarkers can be useful for dose selection, for example, plasma factor Xa activity to identify patients on long-term DOACs who are at high risk of bleeding on the approved dose, thus warranting a lower dose.[27]

(4) Greater application of model-informed precision dosing (MIPD), which is biosimulation in health care to predict the best dose for an individual patient.[28] The proof of concept for MIPD dates back to the 1970s with digoxin,[29] but rapid advances in our understanding of drug action, made possible by affordable '-omics' technologies (genomics, proteomic and metabolomics), in analytical capabilities from biological fluids, and in computer processing power, have accelerated MIPD to the point that broader clinical application is occurring.[30] Recent examples of successes include the dosing of antibiotics in critically ill patients who are haemodynamically unstable,[31] treatment of invasive fungal infections with voriconazole in immunocompromised patients,[32] busulfan in paediatrics prior to haemopoetic stem cell transplantation,[33] and targeted pharmacotherapy in haematology and oncology.[34] Because MIPD considers how many covariants simultaneously determine exposure–response, including covariants that are novel and unfamiliar (e.g. estimates of drug metabolizing enzyme and transporter abundances),[35] MIPD allows prescribers to be 'pro-active' in avoiding ADRs rather than 'reactive' using trial and error.

In conclusion, this commentary revisits the simple 16th century principle that all drugs are poisons dependent on dose. Reasons are given to emphasize why precision dosing to avoid ADRs is as important today as ever. Strategies to improve precision dosing include establishing better precision dosing targets, easier access to dosing instructions, improved monitoring of patient responses, and further application of MIPD. Precision

dosing for each patient can help avoid ADRs, and should be part of routine prescribing rather than as an afterthought following patient harm.

Conflict of interest statement
TMP and ARH are employed by Certara, a company that develops and supplies modelling and simulation software and services to the pharmaceutical industry. CMJK has no conflicts of interest to declare.

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References
1. Jameson JL and Longo DL. Precision medicine – personalized, problematic and promising. *N Engl J Med* 2015; 372: 2229–2234.

2. Peck RW. Precision medicine is not just genomics: the right dose for every patient. *Annu Rev Pharmacol Toxicol* 2018; 58: 105–122.

3. Polasek TM, Shakib S and Rostami-Hodjegan A. Precision dosing in clinical medicine: present and future. *Expert Rev Clin Pharmacol* 2018; 11: 743–746.

4. Darwich AS, Ogungbenro K, Vinks AA, *et al.* Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. *Clin Pharmacol Ther* 2017; 101: 646–656.

5. Ogungbenro K, Patel A, Duncombe R, *et al.* Dose rationalization of pembrolizumab and nivolumab using pharmacokinetic modeling and simulation and cost analysis. *Clin Pharmacol Ther* 2018; 103: 582–590.

6. Polasek TM, Ambler K, Scott HS, *et al.* Targeted pharmacotherapy after somatic cancer mutation screening. *F1000Res* 2016; 5: 1551.

7. World Health Organization. *Medication without harm – global patient safety challenge on medication safety*. Geneva: World Health Organization, 2017.

8. Bates DW, Boyle DL, Vander Vliet MB, *et al.* Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995; 10: 199–205.

9. Al-Sarawi F, Polasek TM, Caughey GE, *et al.* Prescribing errors and adverse drug reaction documentation before and after implementation of e-prescribing using the enterprise patient administration system. *J Pharm Pract Res* 2019; 49: 27–32.

10. Rawlins MD and Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM (ed) *Textbook of adverse drug reactions*. Oxford: Oxford University Press, 1977, pp.10–31.

11. Tritschler T, Kraaijpoel N, Le Gal G, *et al.* Venous thromboembolism: advances in diagnosis and treatment. *JAMA* 2018; 320: 1583–1594.

12. Forbes HL and Polasek TM. Potential drug–drug interactions with direct oral anticoagulants in elderly hospitalized patients. *Ther Adv Drug Saf* 2017; 8: 319–328.

13. Masters JC and Wiernik PH. Are we ready to include organ-impaired patients in oncology trials? A clinical pharmacology perspective on recent recommendations. *J Clin Pharmacol* 2018; 58: 701–703.

14. Polasek TM, Mina K and Suthers G. Pharmacogenomics in general practice – the time has come. *Aust J Gen Pract* 2019; 48: 100–105.

15. Sackett DL, Rosenberg WMC, Gray JAM, *et al.* Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312: 71.

16. Snyder BD, Polasek TM and Doogue MP. Drug interactions: principles and practice. *Aust Prescr* 2012; 35: 85–88.

17. Scott IA, Hilmer SN, Reeve E, *et al.* Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015; 175: 827–834.

18. Boyd CM, Darer J, Boult C, *et al.* Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. Implications for pay for performance. *JAMA* 2005; 294: 716–724.

19. Polasek TM, Rostami-Hodjegan A, Yim DS, *et al.* What does it take to make model-informed precision dosing common practice? Report from the 1st Asian symposium on precision dosing. *AAPS J* 2019; 21: 17.

20. Fabbri C and Serretti A. Is pharmacogenetics useful in antidepressant treatment? *Clin Pharmacol Ther* 2019; 106: 916–918.

21. Franz DN, Lawson JA, Yapici Z, *et al.* Everolimus dosing recommendations for tuberous

sclerosis complex-associated refractory seizures. *Epilepsia* 2018; 59: 1188–1197.

22. Rossi S, Hurley E and Sutcliffe A. *Australian medicines handbook*. 19th ed. Adelaide: The Royal Australian College of General Practitioners, the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, and the Pharmaceutical Society of Australia; 2018.

23. Abdel-Rahman SM, Breitkreutz ML, Bi C, *et al*. Design and testing of an EHR-integrated, busulfan pharmacokinetic decision support tool for the point-of-care clinician. *Front Pharmacol* 2016; 7: 65.

24. Fischer S and Rose A. Responsible e-prescribing needs e-discontinuation. *JAMA* 2017; 317: 469–470.

25. Kaboli PJ, Hoth AB, McClimon BJ, *et al*. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med* 2006; 166: 955–964.

26. Polasek TM, Rowland A, Wiese MD, *et al*. Pharmacists in Australian general practice: an opportunity for expertise in precision medicine. *Ther Adv Drug Saf* 2015; 6: 186–188.

27. Chin PKL and Doogue MP. Long-term prescribing of new oral anticoagulants. *Aust Prescr* 2016; 39: 200–204.

28. Polasek TM, Rayner CR, Peck RW, *et al*. Toward dynamic prescribing information: codevelopment of companion model-informed precision dosing tools in drug development. *Clin Pharmacol Drug Dev* 2019; 8: 418–425.

29. Peck CC, Sheiner LB, Martin CM, *et al*. Computer-assisted digoxin therapy. *N Engl J Med* 1973; 289: 441–446.

30. Vinks AA. From molecule to patient and ways to get the dose precisely right. *Clin Pharmacol Ther* 2019; 105: 534–537.

31. Tängdén T, Ramos Martin V, Felton TW, *et al*. The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections. *Intensive Care Med* 2017; 43: 1021–1032.

32. Hope WW, Vanguilder M, Donnelly JP, *et al*. Software for dosage individualization of voriconazole for immunocompromised patients. *Antimicrob Agents Chemother* 2013; 57: 1888–1894.

33. Abdel-Rahman SM, Casey KL, Garg U, *et al*. Intravenous busulfan dose individualization - impact of modeling approach on dose recommendation. *Pediatr Transplant* 2016; 20: 443–448.

34. Rowland A, van Dyk M, Mangoni AA, *et al*. Kinase inhibitor pharmacokinetics: comprehensive summary and roadmap for addressing inter-individual variability in exposure. *Expert Opin Drug Metab Toxicol* 2017; 13: 31–49.

35. Rowland A, Ruanglertboon W, van Dyk M, *et al*. Plasma extracellular nanovesicle (exosome)-derived biomarkers for drug metabolism pathways: a novel approach to characterize variability in drug exposure. *Br J Clin Pharmacol* 2019; 85: 216–226.