British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2016) **82** 900–902 900

EDITORIAL

Therapeutic drug monitoring in the era of precision medicine: opportunities!

Correspondence Dr Serge Cremers PharmD, PhD, Associate Professor of Pathology and Cell Biology and Medicine, Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY 10027, USA. Tel.: +1 212 305 9287; E-mail: sc2752@columbia.edu

Received 16 June 2016; **accepted** 16 June 2016

Serge Cremers[1], Nishan Guha[2] and Brian Shine[2]

[1]Departments of Pathology & Cell Biology and Medicine, Columbia University Medical Center, New York, NY, USA and [2]Department of Clinical Biochemistry, John Radcliffe Hospital and Nuffield Department of Clinical Laboratory Sciences, University of Oxford, Oxford, UK

Introduction

Bioanalytical assays are available for virtually all drugs used in humans, partly because of the regulatory requirements to characterize a drug's pharmacokinetic properties during its preclinical and clinical development. However, only a few drugs are subject to routine therapeutic drug monitoring (TDM) in patients, including several immunosuppressive drugs, antibiotics, antiepileptics, antidepressants, digoxin and methotrexate. Major reasons for this relatively small number of drugs include a lack of a straightforward relationship between serum/blood levels and effect, a wide therapeutic window and an unfavourable balance between intra- and interpatient and intra- and interoccasion variability in pharmacokinetics [1, 2]. Moreover, there are surprisingly few prospective randomized data available to demonstrate a true beneficial effect of routine TDM, especially when looking at defined outcome parameters. Instead, most published data rather suggest that TDM might benefit patients [2–8].

Another important reason for the relatively low number of drugs for which levels are monitored routinely might be that interpretation of drug levels may be perceived to be complicated. TDM data are often used to adjust dose regimens using fairly challenging pharmacokinetic calculations, or even using population pharmacokinetic models and Bayesian forecasting embedded in sophisticated software packages [9, 10]. Although deemed useful by most clinical pharmacologists, and for some even a 'raison d'être', this relatively complicated use of data tends to scare off clinicians, minimizing the use of TDM. In our opinion, straightforward, easy-to-use TDM will result in its much broader use by the average clinician, which can be achieved by implementing user-friendly information technology tools, but can also be achieved by returning to user-friendly sampling strategies, such as the use of trough levels wherever possible and by considering alternative matrices such as saliva or dried blood spots [11, 12]. Broader application is further supported by the rapidly developing field of pharmacogenetics, which makes it possible to identify patients who might benefit from higher or lower doses of some drugs without even having to determine a drug level [13]. However, despite being able to explain some variability in the pharmacokinetics of some drugs, some aspects relevant for drug exposure are simply not covered by pharmacogenetics such as ontogeny in paediatric patients, poor adherence, and drug–drug and drug–food interactions, which can easily be monitored adequately by measuring trough levels for most drugs [14–17].

A more practical but also important reason for the relatively small number of drugs for which levels are measured routinely is the limited availability of drug assays with turnaround times adequate for patient care. Most drug assays available in routine clinical chemistry and toxicology laboratories are automated immunoassays, which are fairly easy to perform and have a relatively short turnaround time. Other methodologies to determine drug levels are mostly chromatography based, such as high-performance liquid chromatography combined with ultraviolet detection (HPLC-UV) and liquid chromatography combined with mass spectrometry (LC-MS). While usually having a longer turnaround time and needing specialized technologists to perform them, these methods are much more versatile than automated assays and allow the development of assays for individual drugs by clinical laboratories themselves, so-called 'laboratory-developed tests' (LDTs) or 'in-house' assays. The recent growth in the number of LC-MS instruments in many clinical laboratories around the world could, therefore, produce enormous growth in quantitative 'in house' assays for TDM but this has not happened yet.

The discrepancy between the increased availability of instruments and the relatively modest number of TDM assays may be because, for most drugs, levels are requested only rarely, which makes it difficult to cover the costs of developing, validating and maintaining a clinical assay for such a drug, even for large reference laboratories, and even though

DOI:10.1111/bcp.13047

developing and validating chromatographic assays are much easier and cheaper than for most immunoassays. This situation might be a 'catch 22' as it is likely that some drug levels are not requested, for the simple reason that an assay for it does not exist, or is not easily accessible.

In summary, the limited availability of drug assays, the lack of strong data demonstrating a positive effect on clinical outcome, and logistical sampling and interpretive challenges all contribute to underutilization of TDM. Expanding the number of drug assays, improving access to these assays, and simplifying blood sampling and data interpretation will not only improve the current status of TDM, but also better position TDM in the era of precision medicine.

Precision medicine

Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle. A near consequence of precision medicine, especially with the inclusion of a systems biology approach, is the selection of drugs entirely tailored to a specific patient and her or his disease. This could mean prescribing according to the label, but it could also involve off-label use, such as using an antidiabetic drug to treat breast cancer or using an antibiotic to treat a specific form of childhood epilepsy. Although this practice is expanding into all disease areas, most headway has been made in oncology. Indeed, an incredibly exciting therapeutic approach that is currently entering the clinic is the treatment of cancer patients with (combinations of) drugs based on a systems biology analysis of tumour gene expression data in the absence and presence of pharmacological perturbation; this identifies relevant pathways, master regulator genes and actionable proteins, and optimal combinations of compounds that target these [18]. This approach, which is currently being tested in various settings, will revolutionize pharmacotherapy, in oncology as well as other disease areas, and TDM can be of immense value to advance this novel way of treating patients. One example involves treating a patient with prostate cancer with a combination of the well-known mechanistic target of rapamycin (mTOR) inhibitor, rapamycin, and an experimental drug, DP0325901, which together optimally target the Forkhead box protein 1 / Centromere protein F (FOXM1/CENPF) pathway that was identified using a systems biology analysis of tumour expression data in the absence and presence of pharmacological perturbation [18]. In this example, both drugs would be taken orally and it is not known if there is any interaction between the two drugs, or between the experimental drug and other drugs that are concomitantly prescribed to patients with prostate cancer. Measuring circulating levels of both drugs would help to characterize the pharmacokinetics of these drugs in this particular combination, in this particular patient population. Measuring levels of both drugs might also directly benefit this patient. Pharmacokinetic data are available for both rapamycin and DP0325901, so from the literature a preliminary estimate could be made regarding what levels to expect and, perhaps, even when to adjust the dose [19].

TDM in precision medicine

Recently, a few perspectives and mini-reviews have described the opportunities for TDM in the era of precision medicine [20, 21]. Although positive in nature, the scope of all of these papers was mostly restricted to reviewing drugs that are currently already monitored, although a recent editorial by Martin *et al*. in the *British Journal of Clinical Pharmacology* expanded this to more experimental drugs, by calling for more clinical pharmacology in the era of personalized medicine [22]. The above-mentioned example of rapamycin and DP0325901 identifies additional tremendous opportunities for clinical pharmacologists, (bio-)chemists, pharmacists and pathologists who are active in the TDM field. Systems biology-driven selection of combinations of drugs will lead to unforeseen off-label use of registered drugs, as well as an increasing number of experimental drugs used to treat patients who are not part of a clinical study protocol. To some extent, this practice will take place within the grey area of combining patient care and clinical research. This research would benefit from generating pharmacokinetic data in patient groups for whom such data do not yet exist. Simultaneously, however, individual patients might benefit from dose adjustments based on rapidly determined drug levels that are compared with the scarce pharmacokinetic data available. In a sense, laboratories would, therefore, simultaneously generate both drug development and TDM data.

This exciting and novel application of TDM requires extensive assay development and validation, easy access to the validated assays, and rapid turnaround times so that assays can be used for drug development and individual patient care. Such an endeavour would entail a new set of bioanalytical, regulatory, interpretive and financial challenges. The development and validation of these new assays require collaboration between individual laboratories, national and international clinical chemistry societies, and industry. In addition, each new assay needs assessment and approval by the respective national regulatory/accreditation services. Finally, optimal interpretation of the scarce data requires significant input from national and international medical, pharmacology and pharmaceutical societies, including the British Pharmacological Society and the International Association for Therapeutic Drug Monitoring and Clinical Toxicology.

This new and exciting era of precision medicine has created never-before-seen opportunities for TDM in support of drug development and patient care. All that is required to seize these opportunities is tenacity, creativity, flexibility and collaboration.

References

1 Holford NH, Buclin T. Safe and effective variability – a criterion for dose individualization. Ther Drug Monit 2012; 34: 565–568.

2 Bardin C, Veal G, Paci A, Chatelut E, Astier A, Leveque D, *et al*. Therapeutic drug monitoring in cancer – are we missing a trick? Eur J Cancer 2014; 50: 2005–2009.

3 Tseng A, Seet J, Phillips EJ. The evolution of three decades of antiretroviral therapy: challenges, triumphs and the promise of the future. Br J Clin Pharmacol 2015; 79: 182–194.

4 Krasowski MD, McMillin GA. Advances in anti-epileptic drug testing. Clin Chim Acta 2014; 436: 224–236.

5 Shipkova M, Hesselink DA, Holt DW, Billaud EM, van Gelder T, Kunicki PK, *et al*. Therapeutic drug monitoring of everolimus: a consensus report. Ther Drug Monit 2016; 38: 143–169.

6 Wallerstedt SM, Lindh JD. Prevalence of therapeutic drug monitoring for antidepressants and antipsychotics in Stockholm, Sweden: a longitudinal analysis. Ther Drug Monit 2015; 37: 461–465.

7 Mann K, Hiemke C, Schmidt LG, Bates DW. Appropriateness of therapeutic drug monitoring for antidepressants in routine psychiatric inpatient care. Ther Drug Monit 2006; 28: 83–88.

8 Wilbaux M, Fuchs A, Samardzic J, Rodieux F, Csajka C, Allegaert K, *et al*. Pharmacometric approaches to personalize use of primarily renally eliminated antibiotics in preterm and term neonates. J Clin Pharmacol 2016; (In press).

9 Cremers S, Schoemaker R, Bredius R, den Hartigh J, Ball L, Twiss I, *et al*. Pharmacokinetics of intravenous busulfan in children prior to stem cell transplantation. Br J Clin Pharmacol 2002; 53: 386–389.

10 Hahn A, Frenck RW Jr, Zou Y, Vinks AA. Validation of a pediatric population pharmacokinetic model for vancomycin. Ther Drug Monit 2015; 37: 413–416.

11 Wilhelm AJ, den Burger JC, Swart EL. Therapeutic drug monitoring by dried blood spot: progress to date and future directions. Clin Pharmacokinet 2014; 53: 961–973.

12 Patsalos PN, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs by use of saliva. Ther Drug Monit 2013; 35: 4–29.

13 Deneer VH, van Schaik RH. Evidence based drug dosing and pharmacotherapeutic recommendations per genotype. Methods Mol Biol 2013; 1015: 345–354.

14 Blassmann U, Roehr AC, Frey OR, Koeberer A, Briegel J, Huge V, *et al*. Decreased linezolid serum concentrations in three critically ill patients: clinical case studies of a potential drug interaction between linezolid and rifampicin. Pharmacology 2016; 98: 51–55.

15 Taguchi K, Kouroki M, Ohmura T, Jono H, Endo F, Saito H. Carbamazepine-imatinib interaction in a child with chronic myeloid leukemia. Pediatr Int 2014; 56: e33–e66.

16 Stiehl SR, Squires JE, Bucuvalas JC, Hemmelgarn TS. Tacrolimus interaction with dexmedetomidine – a case report. Pediatr Transplant 2016; 20: 155–157.

17 Outeda Macias M, Salvador Garrido P, Elberdin Pazos L, Martin Herranz MI. Management of everolimus and voriconazole interaction in lung transplant patients. Ther Drug Monit 2016; 38: 305–312.

18 Mitrofanova A, Aytes A, Zou M, Shen MM, Abate-Shen C, Califano A. Predicting drug response in human prostate cancer from preclinical analysis of *in vivo* mouse models. Cell Rep 2015; 12: 2060–2071.

19 LoRusso PM, Krishnamurthi SS, Rinehart JJ, Nabell LM, Malburg L, Chapman PB, *et al*. Phase I pharmacokinetic and pharmacodynamic study of the oral MAPK/ERK kinase inhibitor PD-0325901 in patients with advanced cancers. Clin Cancer Res 2010; 16: 1924–1937.

20 Jang SH, Yan Z, Lazor JA. Therapeutic drug monitoring: a patient management tool for precision medicine. Clin Pharmacol Therapeut 2016; 99: 148–150.

21 Clarke NJ. Mass spectrometry in precision medicine: phenotypic measurements alongside pharmacogenomics. Clin Chem 2016; 62: 70–76.

22 Martin JH, Phillips E, Thomas D, Somogyi AA. Adding the 'medicines' back into personalized medicine to improve cancer treatment outcomes. Br J Clin Pharmacol 2015; 80: 929–931.