Therapeutic drug monitoring in the past 40 years of the JAC

David Reeves[1], Andrew Lovering[1] and Alison Thomson[2]*

[1]Antimicrobial Reference Laboratory, Severn Infection Sciences Partnership, Southmead Hospital, Bristol BS10 5NB, UK
[2] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, UK

Corresponding author. Tel +44-117-4148468;Fax+44-117-3238332; Email: Andrew.lovering@nbt.nhs.uk

Summary

Since the Journal was first published in 1975, papers addressing therapeutic drug monitoring (TDM) have been a regular feature. Initially they focused on laboratory aspects of drug concentration measurement then they changed more to the application of TDM in a clinical setting. Over its history, the Journal has provided its readership with the latest technological and scientific advances in TDM and has helped to drive changes in TDM that have directly impacted on patient care. These have varied from improvement in the quality of antimicrobial measurements through better identification of dosage regimens and TDM targets that help predict outcome and adverse events. Despite these advances in our understanding of the science and practice of TDM, there still remain many areas of uncertainty. As we move into the next 40 years, it is clear that the Journal will continue to provide the readership with the latest science and opinion in this important area.

Article

In the 40 years since the Journal was first published, the papers within it have reflected the cutting edge of therapeutic drug monitoring (TDM) in the field of antimicrobial chemotherapy and provide a fascinating 'roadmap' illustrating how the science underpinning it has developed.

While TDM has traditionally been thought of as a process to help reduce the risk of adverse events in patients receiving toxic drugs, increasingly it is being recognised as important for optimising therapeutic outcomes, either in terms of cure or resistance suppression. However, irrespective of objectives, TDM relies on the rapid, and accurate, determination of drug levels in a patient with adjustment of dose if these are not consistent with the expected, or target, concentration ranges.

In the early years of the Journal, there was a clear focus around practical aspects of therapeutic drug monitoring and laboratory support for the clinical use of antimicrobials[1]. This was largely driven by the increasing use of the aminoglycosides and during the first decade of the Journal's publication there were frequent reports of methodological advancement. While early reports addressed developments of bioassays to shorten turnaround times and prevent interference from other agents, within a few years' new approaches started to be reported. Initially, these were based around either bacterial enzymes (transferase assay) or growth (bioluminescence), but by the early 1980s immunoassay reports dominated the publications[2]. These started with simple descriptions of the methods but very quickly shifted to publications reporting comparisons between the different assay systems as it became clear that these assays were highly specific, accurate and rapid[3]. While some of the assays reported in the early 1980s are no longer relevant, those based around homogeneous reactions largely remain in use to the current date. In the main, this change was driven by technological advances and commercial factors, but publications in the Journal highlighting the relative performance of such methods in external quality assessments certainly advanced the withdrawal of those methods that performed poorly[4].

During these early years, although there were significant advancements in the technology supporting delivery of TDM services, understanding of the targets and objectives for TDM largely lagged behind. Aminoglycosides had long been known to have to have the potential for oto- and nephrotoxicity and during the early years of the Journal there were many studies reporting the incidence of toxicity of aminoglycosides[5]. These concerns over toxicity dominated TDM approaches for both aminoglycosides and other less toxic classes of antimicrobial[6] and persist to the present day, However, although the first report of once daily administration of gentamicin appeared in the Journal in 1978[7], it wasn't really until the late 1990s that TDM objectives became clearer thanks to the increasing volume of information coming from PK/PD analysis[8].

Immunoassay methods and liquid chromatography were introduced almost contemporaneously into the microbiology laboratory[9]. This was initially reflected in the Journal publications by methodological papers reporting assay conditions to measure different agents but rapidly developed during the early 1980s to reflect the application of these methods in a TDM setting. This started with reports describing their use in plasma pharmacokinetics of existing and the rapidly increasing number of new agents, but by the mid-1980s the focus had expanded to include studies of antimicrobial penetration into extra vascular sites[10]. While some of these studies addressed surrogates of penetration, such as the blister fluid or implanted thread methods, as frequently reported by Wise and colleagues[11], increasingly the focus changed to penetration into tissues recovered during routine operations; particularly bone[12]. Most of the published studies reported data for low subject numbers (typically 5-10 subjects) and rarely presented information to support validation of the assay system. In the absence of any higher quality information, these penetration studies helped inform TDM and dosing approaches for non-vascular sites[13]. However, and especially in the case of the penetration studies, in more recent years the quality of some of the findings reported during this period has been questioned[14].

During the early 1980s, there was an increasing recognition that antimicrobial concentrations at the site of infection are important for outcome as well as the recognition that measures of free-drug rather than whole drug better predicted activity[15]. This led to an increasing number of papers describing the protein binding of antimicrobials; principally conducted in healthy volunteers using ultrafiltration under non-physiological conditions. Such was the extent of this work, that by the mid-1990s there was a general consensus that protein binding was understood and it would be a further 10-15 years before this was challenged[16]. Here, thanks to the work of Roberts and others[17], who have highlighted the impact of sepsis on protein binding and the general potential for under dosing in those with severe sepsis, protein binding is again topical and important in dose optimisation strategies based on TDM[18].

From the mid-1990s, traditional approaches to antimicrobial TDM began to change. For aminoglycosides, discussions focused on the need to achieve high *Cmax*/MIC ratios to optimise efficacy and low troughs to reduce the risk of toxicity. Traditional 8 hourly dosage regimens were replaced by "high dose, extended interval" regimens and peak and trough monitoring by single, mid-dose concentration measurements interpreted using a nomogram.[8] The value of measuring peak vancomycin concentrations was questioned and new dosage guidelines reflected a change in the target range for trough concentrations.[19]

During the 1990s, PK studies and reviews rarely reported data from healthy volunteers but instead examined the influence of clinical characteristics, such as renal replacement therapy,[20] on drug handling and dose requirements. Over time, studies using population pharmacokinetic (PopPK) methodology, which could handle "sparse" concentration data from many patients, began to replace traditional PK studies that involved taking multiple blood samples from a small number of patients.

This enabled research to be conducted using TDM data[19] and in patients who were often excluded from traditional PK studies, such as paediatric patients and patients with renal impairment, liver disease, critical illness, burn injury, cystic fibrosis and malignant disease.

From the mid-2000s to the present day, new laboratory techniques, such as liquid chromatography tandem-mass spectroscopy (LCMS), provided increased assay sensitivity and facilitated the quantification of free drug concentrations in plasma and interstitial fluid. Microdialysis techniques began to replace studies based on tissue homogenates and have led to a greater understanding of how clinical characteristics, such as obesity[21], influence the distribution of antimicrobial agents.

While papers continued to describe challenges associated with aminoglycoside and glycopeptide therapy, the paucity of new antibiotics and the development of resistant organisms stimulated the resurgence of older antimicrobial agents, such as colistin and polymyxin B. This led to the development of new assays to support PK studies designed to fill knowledge gaps around how best to use these agents.[22] There was also an increase in research related to the TDM of other antimicrobial agents, particularly the beta-lactams, due to concerns about underdosing in critically ill patients.[23] An increasing use of TDM for antifungal agents in clinical practice prompted to the publication of consensus guidelines in 2014.[24]

Data analysis techniques have also progressed in recent years. While early PopPK studies focused on estimating PK parameters and identifying the clinical factors that influence these parameters, later studies used PopPK models to design dosage regimens for clinical use.[19] More recently, PopPK models are being combined with Monte Carlo simulations to determine the antimicrobial dosage regimens with the highest probability of target attainment (PTA) or cumulative fraction of response (CFR) to achieve $fT_{>MIC}$, *fCmax/*MIC or $AUC_{0\text{-}24}$/MIC targets. The results of such studies have indicated that higher doses or prolonged infusions of beta lactam antibiotics are more likely to reach PKPD targets than traditional doses administered by bolus injection.[25,26]

In the last 20 years we have witnessed a remarkable increase in the availability of new antiviral agents, in marked contrast to other antimicrobials, leading to major improvements in the management of HIV and hepatitis B and C infections. While initial studies tried to link efficacy or toxicity with trough concentrations of single agents,[27] recent studies have considered the challenges of combination therapy[28]. These include using ritonavir to optimise therapy and reduce costs by boosting concentrations of protease inhibitors, and managing the complex interactions that arise with drug combinations used in the management of HIV positive patients co-infected with HCV/HBV,TB or malaria.[29] Such challenges have enhanced international collaborations leading to high quality research being conducted in Africa and South East Asia, where large populations of patients suffer the burden of these diseases.

Over the last 40 years, new drug assay and data analysis techniques have led to major improvements in our understanding of how to use antimicrobial agents effectively. With the current lack of economic incentives to develop new antibiotics, such methods are key to ensuring optimal use of both current and new antimicrobial agents. Future developments in this field are likely to incorporate pharmacogenetic data and physiologically based PK modelling techniques to improve the prediction of human outcomes from in vitro and animal data.

Transparency Declarations
None to declare

References

1. Waterworth PM. Which gentamicin assay method is the most practicable? J Antimicrob Chemother. 1977; **3**:1-3.
2. Shaw EJ. Immunoassays for antibiotics. J Antimicrob Chemother. 1979; **5**:625-8.
3. White LO, Scammell LM, Reeves DS. An evaluation of a gentamicin fluoroimmunoassay kit; correlation with radioimmunoassay, acetyl transferase and microbiological assay. J Antimicrob Chemother. 1980; **6**:267-73.
4. Reeves DS, Bywater MJ. Quality control of serum gentamicin assays--experience of national surveys. J Antimicrob Chemother. 1975; **1**:103-16.
5. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity - a review of clinical studies published between 1975 and 1982. J Antimicrob Chemother. 1984; **13** Suppl A:9-22.
6. Wenk M. Concepts for aminoglycoside serum level monitoring. J Antimicrob Chemother. 1982; **9**:168-9.
7. Reiner NE, Bloxham DD, Thompson WL. Nephrotoxicity of gentamicin and tobramycin given once daily or continuously in dogs. J Antimicrob Chemother. 1978; **4** Suppl A:85-101.
8. Freeman CD, Nicolau DP, Belliveau, PP *et al*. Once-daily dosing of aminoglycosides: review and recommendations for clinical practice. *J Antimicrob Chemother* 1997; **39:**677-686.
9. White LO. HPLC in clinical microbiology laboratories. J Antimicrob Chemother. 1981; **8**:1-3.
10. Wise R. Protein binding of beta-lactams: the effects on activity and pharmacology particularly tissue penetration. II. Studies in man. J Antimicrob Chemother. 1983; **12**:105-18.
11. Findlay CD, Wise R, Allcock JE et al. The tissue penetration, as measured by a blister technique, and pharmacokinetics of cefsulodin compared with carbenicillin and ticarcillin. J Antimicrob Chemother. 1981; **7**:637-42.
12. Rolinson GN. Tissue penetration of antibiotics. J Antimicrob Chemother. 1984; **13**:593-602.
13. Golledge CL, McKenzie T. Monitoring vancomycin concentrations in CSF after intraventricular administration. J Antimicrob Chemother. 1988; **21**:262-3.
14. Mouton JW, Theuretzbacher U, Craig WA et al. Tissue concentrations: do we ever learn? J Antimicrob Chemother. 2008 **61**:235-7.
15. Rolinson GN. The significance of protein binding of antibiotics in antibacterial chemotherapy. J Antimicrob Chemother. 1980; **6**:311-7.
16. Burkhardt O, Kumar V, Katterwe D et al. Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. J Antimicrob Chemother. 2007; **59**:277-84.
17. Huttner A, Harbarth S, Hope WW *et al*. Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother. 2015; **70**:3178-83.
18. McKenzie C. Antibiotic dosing in critical illness. J Antimicrob Chemother. 2011; **66** Suppl 2:ii25-31.
19. Thomson AH, Staatz CE, Tobin CM, *et al*. Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations. *J Antimicrob Chemother* 2009; **63**: 1050-1057.
20. Cotterill S. Antimicrobial prescribing in patients on hemofiltration. *J Antimicrob Chemother* 1995; **36**:773-780.
21. Brill MJE, Houwink API, Schmidt S, *et al*. Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. *J Antimicrob Chemother* 2014;69:715-723.
22. Theuretzbacher U, Van Bambeke F, Cantón R, *et al.* Reviving old antibiotics *J. Antimicrob. Chemother* 2015; **70:** 2177-2181.
23. Wong AF, Brinkman G, Benefield A *et al*. An international, multicentre survey of -lactam antibiotic therapeutic drug monitoring practice in intensive care units. *J. Antimicrob. Chemother* 2014; **69:** 1416-1423.

24. Ashbee HR, Barnes R, Johnson EM, *et al*. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology *J. Antimicrob. Chemother* 2014; **69**:1162-1176.
25. Roberts JA, Kirkpatrick CMJ, Roberts MS, *et al*. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. *J. Antimicrob. Chemother* 2009; **64**:142-150.
26. Zelenitsky SA. Ariano RE, Zhanel GG. Pharmacodynamics of empirical antibiotic monotherapies for an intensive care unit (ICU) population based on Canadian surveillance data. *J. Antimicrob. Chemother*. 2011; 66:343-349.
27. Morello J, Rodriguez-Novoa Sonia, Jimenez-Nacher I, *et al*. Usefulness of monitoring ribavirin plasma concentrations to improve treatment response in patients with chronic hepatitis C. *J. Antimicrob. Chemother* 2008; **62**:1174-1180.
28. Roos JF, Bulitta J, Lipman J *et al*. Pharmacokinetic-pharmacodynamic rationale for cefepime dosing regimens in intensive care units. *J. Antimicrob Chemother*. 2006 ;**58:**987-993
29. Seden K, Merry C, Hewson R *et al*. Prevalence and type of drug-drug interactions involving ART in patients attending a specialist HIV outpatient clinic in Kampala, Uganda. *J. Antimicrob. Chemother* 2015; **70**:3317-3322