Model antibiotic use to improve outcomes

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Traditional approaches to antibiotic administration in key infective indications are being challenged. Last year saw the publication of two important trials, both in the New England Journal of Medicine (NEJM), describing the non-inferiority of oral (or partial oral) treatment of osteomyelitis and left-sided endocarditis compared to standard intravenous administration.[1] These build on a growing literature that supports the use of prolonged antibiotic infusions over classical bolus dosing in the critical care setting for patients with sepsis: a recent meta-analysis demonstrating that infusions lead to a higher cure rate and lower hospital mortality.[2]

Improving our use of exisiting antibiotics has clear benefits at both the individual and societal level. For a given patient, potential advantages may include treatment efficacy, a preferable route of administration, shorter duration of therapy and associated length of hospital stay (with attendant cost and risks), along with a reduced rate of side effects. More broadly, it is expected that optimised therapy designed to promote compliance with treatment and pathogen clearance will form one part of a comprehensive antimicrobial stewardship programme to limit the development of antibiotic resistance.

Generating the evidence to support modification of antibiotic prescription is however not simple. Antimicrobial drugs are used in a number of different clinical contexts and situations. These include prophylactically (e.g. of urinary tract infections or in the peri-operative period), reactively in the treatment of localised and systemic infections, empirically when the causative pathogen is unknown or in a targeted manner when it is, and often in special situations and patient populations. 'Established', antibiotic dosing and duration of treatment for each indication frequently varies between practitioners and centres. Despite large variation between patients (e.g. severity of infection, causative pathogen, renal and hepatic function, comorbidities and co-prescriptions), and in the absence of widespread availability of therapeutic drug monitoring of plasma and tissues antibiotic concentrations, the efficacy of pragmatic standardised doses is commonly assumed for certain pathologies or in predescribed settings.

Given this complex landscape, an explicit explanation of the underlying pharmacological rationale of a proposed novel antibiotic strategy, ideally supported by pharmacometric data, is crucial to our ability to judge comparative efficacy and safety.[3] Too often this is absent from reports. Clearly a suggested dosing strategy must additionaly integrate the intended context in which an antimicrobial will be used, as well as the patient population involved.

An antibiotic's concentration in the host in relation to time is described by its pharmacokinetics (PK), while its concentration and time dependent interactions with bacteria in the host are described by its pharmacodynamics (PD). Based on their effect on bacteria, antibiotics can be divided into two major groups - bactericidal and bacteriostatic – although classification may vary dependent on bacterial strain and *in vitro* determined bacterial minimum inhibitory concentration (MIC). Based on their PD, antibiotics can therefore be divided into two categories: those with time-dependent (e.g. beta-lactams, cephalosporins, vancomycin) and those with concentration-dependent (e.g. aminoglycosides, fluoroquinolones) bactericidal effect.[4] Maximizing the duration of exposure to time-dependent active antibiotics can be achieved via three methods: dose increase, prolonging the infusion time or shortening the dosing interval. This is also true of concentration-dependent antibiotics, although route of administration may additionally exert a significant impact.

In the case of beta-lactam antibiotics (penicillins, cephalosporins), optimal bactericidal effect is achieved depending on the time through which drug concentrations in the host are kept above the MIC of the bacteria causing the infection. Usually, the aim is to maintain the antibiotic concentrations at 2 to 4 times over the MIC across 40 to 60 percent of the dosing interval. For concentration-dependent bactericidal antibiotics, increased antibacterial activity is accomplished with increased drug concentration in the host. The efficacy of the antibiotics is determined based on their peak concentration and the area under the concentration curve.[5] Typically, antibiotic concentrations of up to 10 times over the MIC are required for best antibacterial activity.[6]

Exeplifying integration of these fundamental principles and the value of applied PK/PD modelling to a targeted population, several recent articles in the British Journal of Clinical Pharmacology have sought to optimise antibiotic administration – specifically cefuroxime – in the context of surgical prophylaxis.

Gertler el al, in their 2018 article, elegantly employed a two-compartment model to examine the PK of cefuroxime in a niche but clearly vulnerable population: infants and neonates undergoing cardiac surgery incorporating cardiac bypass. Whilst routine bolus dosing appeared sufficient for prophylaxis, continuous infusion of cefuroxime was demonstrated to provide a higher percentage of ƒT > bacterial MIC. [7] Similar findings were reported by Skhirtladze-Dworschak et al, who showed that higher cefuroxime concentrations were achieved in plasma - and importantantly, subcutaneously - over a prolonged period of time when cefuroxime was administered to adult patients undergoing elective cardiac surgery via infusion rather than standard bolus dosing. [8] Finally, Rimmler et al used a physiologically based pharmacokinetic model (PK-Sim ® /MoBi ®) to investigate unbound plasma concentrations of cefuroxime following pre-operative administration in the context of thoracic surgery. They found that, whilst a traditional 1.5 g bolus dose every 2.5 hours reached the PK/pharmacodynamic (PD) target for *Staphylococcus aureus,* it was insufficient for *Escherichia coli* prophylaxis, this only being achieved via a 1.5 g bolus dose immediately followed by a continuous infusion of 3 g of cefuroxime over 3 hours.[9]

Whilst none of these studies incorporates a clinical endpoint (e.g. reduction in surgical site infection), they illustrate the importance of integrating pharmacometrics and provide the rationale and safety data to support further work. Equally, given the inevitable difficulties in conducting prospective pivotal studies for the vast range of antibiotic/infection indications and clinical populations, they may be able to inform practice directly given the known safety of these commonly employed drugs.

What seems clear from the NEJM trials is that there is scope to improve our use of exisiting antibiotics and that superior antibiotic dosing strategies can be identified via appropriate use of predictive models of clinical response based on pharmacodynamic targets. Such models can be run with different kind of data pertaining to the dose, interval and infusion time in order to evaluate the likelihood of reaching target antibiotic concentrations over MIC. Moreover, they can be adjusted even further to account for specific patient populations' characteristics, patterns of antibiotic resistance, as well as local bacterial MIC spreads. A recent workshop and related publication by the National Institute of Allergy and Infectious Diseases outlines best practice in dose selection and clinical PK/PD for the development of *new* antimicrobial agents.[10] We believe the same rigour and principles need to apply to all studies exploring novel uses of, or approaches to administering established agents. This should maximise the chances of success, permit greater understanding of unexpected or 'negative' clinical results and hopefully facillitate translation and further advances across drug classes, pathogen type and tissue site.

Reliance on and exposition of pharmacological principles in studies seeking to re-purpose or optimise antimicrobial use is vital. Today, preclinical PK and PD data, as well as clinical PK data can be used for predictive PD modelling in order to establish dosing regimens with a greater chance of achieving in vivo PK/PD targets that will lead to best treatment outcomes. The future of PD modelling will likely take into account PK extremes across the population, such as renal and hepatic function, body weight as well as characteristics of paediatric population. There are clear limitations to a pharmacometric approach, especially at the individual level – a lack of assays for all drugs, when the dose-concentration-response relationship is uncertain[11] – however it is anticipated that a better understanding of an antimicrobial's pharmacology through dose modelling and focused clinical study will both enhance future trial protocols and influence practice directly. Most importantly, we hope that optimised, pharmacologically driven antibiotic dosing will lead to further demonstrable improvement in outcomes for patients as well as help reduce the development of antimicrobial resistance.

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