Adjustment of dosing of antimicrobial agents for bodyweight in adults

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Advances in molecular biology have given rise to the disciplines of pharmacogenomics and pharmacoproteomics and have created the appealing possibility of individual patient-tailored drug therapy.[1] The consideration of body size characteristics of patients is essential for the optimisation of drug therapy in specialties such as oncology, haematology, anaesthetics, critical care, and paediatrics. However, for most widely used antimicrobial agents, dosing recommendations in adults do not take into account adjustment to body size measures. Even when such recommendations are made for an agent, the degree of their application in routine clinical practice can be inadequate.[2]

In the era of globalisation and international travel, the variability in body size characteristics of patients encountered in routine clinical practice can be substantial. For example, a hypothetical male patient with community-acquired pneumonia who weighs 90 kg and is 1·90 m tall has a calculated lean body mass twice that of a female patient who weighs 56 kg and is 1·50 m tall,[3] even though they both have a body-mass index of 24·9 kg/m², within the healthy weight range. However, according to present treatment guidelines, these patients would both receive the same dosage of antibiotics.[4] Additionally, obesity has become a modern epidemic, particularly in more developed countries, with prevalence rates exceeding 30% and 20% in adults in the USA and several European countries, respectively.[5,6] Patients who are obese can no longer be regarded as a small group, and merit special consideration with respect to the appropriate dosing of antimicrobial agents.

Regulatory rules for new antimicrobial drug development require the demonstration of average population effectiveness.[7] Special pharmacokinetic studies are required for children, elderly people, and patients with renal or hepatic impairment, but not for individuals with body size and composition characteristics deviating from average.[7] As a result, this group is generally underrepresented in pharmacokinetic studies and clinical trials done during new drug development, and data on the appropriate dosing and effectiveness of most antimicrobial agents is scarce for these patients.[8]

There is evidence, however, that some drug pharmacokinetic indices differ with respect to body size and composition. Several physiological alterations reported in obesity can affect the processes of distribution, protein binding, metabolism, and clearance of antimicrobial agents.[8] Particularly for tissue distribution, the degree of this process depends on the hydrophilic or lipophilic properties of a drug, among other factors.[9] The panel presents a classification of antibiotics into hydrophilic and lipophilic agents. Hydrophilic antibiotics do not dissolve well in adipose tissue, but they can have a substantially higher volume of distribution in the presence of obesity. The explanation for this finding is that roughly 30% of adipose tissue is water, and that patients who are obese tend to have higher lean bodyweight than their normal-weight counterparts on the basis of height and sex.[3] Plasma volume, likewise, correlates positively with bodyweight.[10] These factors can lead to lowered serum concentrations of hydrophilic drugs in obesity. For lipophilic drugs, the volume of distribution, adjusted for bodyweight, generally increases in obesity because of adipose-tissue binding.[9] However, exceptions to this rule have been noted. The pharmacokinetics of highly lipophilic drugs in obesity are not accurately predictable, because they depend on variables such as the degree of protein binding, relative binding in adipose and lean tissues, blood flow to adipose tissue, and even the metabolic activity of adipose tissue.[11]

The degree of drug absorption through the gastrointestinal tract does not seem to differ between non-obese and obese patients.[11] However, obesity can change the degree of protein binding of some drugs in serum. This change is related to increased serum concentrations of the α1-acid glycoprotein, which can bind some alkaline antibiotics,[12] or to alterations in the expression of serum lipoproteins, which can compete with drugs for binding to albumin.

Body size and composition characteristics can also affect several metabolic drug processes. Liver and kidney volume and function correlate with lean body mass.[13] Furthermore, the hepatic clearance of some drugs can increase in obesity, through phase I metabolic reactions (oxidation, hydrolysis, and reduction) and, particularly, phase II reactions (mainly glucuronidation and sulphation).[11] Obesity can also be associated with liver changes, including steatosis, steatohepatitis, and fibrosis. For kidney function, obesity is related to a state of glomerular hyperfiltration, which resembles that seen in early-stage diabetic nephropathy.[14] Thus, the renal clearance of some antibiotics can increase in obesity.

Available data support the notion that antimicrobial agents, such as several β-lactams, vancomycin, fluoroquinolones, macrolides, linezolid, sulphonamides, and fluconazole, which are approved as flat dosing regimens, should be given in higher doses to patients with large body size to better attain pharmacodynamic targets.[8] Moreover, specific antimicrobial agents have been approved for clinical use at dosages in adults that should be related to bodyweight. These agents are mainly those with a narrow therapeutic window (such as amino-

Panel: Hydrophilic and lipophilic classes of antibiotics*

Hydrophilic
- β-lactams
  - Penicillins
  - Cephalosporins
  - Monobactams
  - Carbapenems
- Glycopeptides
- Aminoglycosides
- Polymyxins
- Fosfomycin

Lipophilic
- Fluoroquinolones
- Macrolides
- Lincosamides
- Tetracyclines
- Tigecycline
- Co-trimoxazole
- Rifampicin
- Chloramphenicol

*Degree of hydrophilicity/lipophilicity can differ between agents of each class.

glycosides, daptomycin, colistin, and amphotericin B), as well as agents given at high doses for specific indications (such as co-trimoxazole, metronidazole, and aciclovir). However, for most antimicrobial agents, the interaction between drug pharmacokinetics and body-size indices is complex, and the most accurate size descriptor that should be taken into consideration for dosage calculation has not been firmly established. Several relevant indices exist, including total, adjusted, ideal, or lean bodyweight, body surface area, and body-mass index.[9] Additional adjustments might need to be made for patients at the extremes of body-mass index, since the correlation of pharmacokinetic indices to body-size descriptors might have a particular pattern in this group.[15]

For specific agents, data suggest that the dosage of aminoglycosides in obese patients should be related to adjusted bodyweight, which is calculated by the addition of a fraction (in this case about 40%) of the excess bodyweight (ie, total minus ideal bodyweight) to the ideal bodyweight.[8,16] Similar dosing adjustments could also be required for patients who are underweight.[16] Additionally, there is evidence that the initial dosing regimen of vancomycin should be calculated as a function of total bodyweight, although subsequent adjustments for patients with obesity[8] and, particularly, morbid obesity,[15] should be made according to monitored serum drug concentrations. No conclusive recommendations can be made, however, on the basis of pharmacokinetic data, for the precise dosing regimen in patients with obesity and morbid obesity of additional antibacterial agents, such as daptomycin and quinupristin/dalfopristin, or of specific antifungal, antituberculous, and antiviral agents.[8] Notably, the use of total bodyweight for adjustment of the dosage of these agents in obesity could carry the risk of overdosing and development of adverse events.[17]

The development of appropriate dosing strategies of antimicrobial agents to adjust for differences in body size and composition characteristics of individual patients should include the consideration of relevant pharmacokinetic and pharmacodynamic principles. From a pharmacokinetic perspective, dosing adjustments for differences in volume of distribution or systemic clearance rate can involve modifications in the loading or maintenance doses of antibiotics, respectively.[8,9] From a pharmacodynamic perspective, dosing adjustments for agents that show a concentration-dependent or a time-dependent profile of antimicrobial activity can be made through modification of the dose given or the duration of the dosing interval, respectively.[8] Of note, the attainment of pharmacodynamic targets of drug therapy is also important for the prevention of emergence of antimicrobial drug resistance. The association of pharmacodynamic indices with the likelihood of resistance development has been suggested for a range of antimicrobial agents—for example, fluoroquinolones used against *Streptococcus pneumoniae*.[18]

We believe that tailoring the dosing of antimicrobial agents in adults to the physical characteristics of individual patients could be an important way to achieve maximum effectiveness and safety of antimicrobial therapy. This goal seems more important than ever, considering the increasing proportion of patients seen in clinical practice who have various risk factors for acquisition of infection or impaired immunological mechanisms for response to infection.[19] Moreover, the decreasing susceptibility of most common pathogens to various antimicrobial agents substantially restricts the clinician's armamentarium of potentially active agents.[20] Some agents might also have reduced effectiveness for the treatment of infections caused by pathogens with high minimum inhibitory concentrations, as some investigators have suggested for vancomycin in *Staphylococcus aureus* infections.[21] Additionally, achieving appropriately high serum concentrations could be important to overcome relative antimicrobial drug resistance, as exemplified by amoxicillin use against penicillin non-susceptible *S pneumoniae* infections.[4] Last but not least, use of the highest acceptable antibiotic dose is regarded as a means to prevent the emergence and selection of resistant pathogens during therapy.[18] The suppressive effect of antibiotics on the normal bacterial flora, which provides protection against colonisation by resistant pathogens, should also be considered in this respect.[22]

Individual patient-tailored dosing of antimicrobial agents should help to reduce dose-dependent drug toxicity. Notably, this approach has led to the revival of daptomycin and polymyxins, which are valuable antimicrobial agents that were once practically abandoned

because of concerns about toxic effects on skeletal muscle and the kidneys, respectively.[23,24]

Substandard dosing of antimicrobial agents could also be a factor contributing to the increased likelihood for development of infection noted in several studies of obese patients receiving perioperative antibiotic prophylaxis.[25] Moreover, some evidence suggests that the outcome of patients with infections is worst in the presence of obesity.[26]

Considerations about appropriate antibiotic dosing for adult patients might also be necessary for children, as the proportion of children who are overweight increases in the general population.[5] Even though a mg/kg antibiotic dosing strategy is routinely used in children, greater attention to pharmacokinetic and pharmacodynamic indices might be required for optimum dosing of some antimicrobial agents in paediatric patients.[27] Careful use of antibiotics in children is also warranted, in view of the high rate of community-acquired infection by resistant pathogens reported in this population.[28]

We suggest that available published or unpublished pharmacokinetic data be re-assessed with the aim of identifying the most appropriate dosage adjustments needed for the administration of antimicrobial agents to adults at the highest and lowest ranges of the distribution of bodyweight. Simulation studies based on pharmacokinetic models might also aid in this respect,[7] although further clinical trials could be needed to clarify the issue. We suggest that the identification of dosage adjustments needed with respect to body size and body composition should be an integral part of the process of new antimicrobial drug development. These issues especially pertain to the regulatory authorities on drug use, which need first to provide guidance for any change in antibiotic dosing strategies. The time appears right. The US Food and Drug Administration has recently stated that modernisation of the drug development process is crucial and has generated a relevant initiative.[29]

Implementation of these ideas in routine clinical practice will entail substantial effort and cost, especially because clinicians' longstanding attitudes towards prescription of antimicrobial agents will have to change.[2] To commit to memory elaborate dosing regimens, potentially including mathematical formulas, for a vast array of antimicrobial agents would be difficult. Dosing errors could become more common. Time constraints in everyday clinical practice might not allow for appropriate dosage calculations to be made. Furthermore, clinicians might be reluctant to give higher doses of antimicrobial agents than are typically used for fear of toxic effects. These difficulties could be overcome, however, with the use of novel technologies such as personal digital assistants or the aid of computerised pharmacy dosing systems. These systems are increasingly used in hospitals, mainly for dosing antibiotics with a narrow therapeutic index, such as aminoglycosides and vancomycin.[30] However, such modalities might not be routinely available in primary health care, the setting in which a substantial proportion of antibiotics are prescribed. Nevertheless, the routine dosing of antibiotics on a mg/kg basis in children suggests that similar strategies cannot be a far-fetched goal for adults.

We believe that the one-size-fits-all strategy for prescribing antimicrobial agents to adults is outdated in the era of increasing antimicrobial drug resistance. The individual body size and composition characteristics of patients could substantially affect pharmacokinetic indices and clinical effectiveness of several antimicrobial agents. Appropriate studies are needed to provide guidance to clinicians on the common clinical question of how to achieve optimum effectiveness and safety of antimicrobial therapy for patients whose physical characteristics deviate from average.

Contributors

MEF had the idea of writing the Viewpoint. Both authors contributed to writing of the report and to the final version.

Conflicts of interest

MEF is on the advisory board of Bayer and has received speaker's honoraria from Merck, Wyeth, Astra-Zeneca, Astellas, Cipla, and Grunenthal. DEK declares that he has no conflicts of interest.

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