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Intravenous or oral antibiotic therapy: Sophie's choice?

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Abstract

Antibiotics are one of the most important medicines of the 21st century. Due to the emergence and spread of multidrug resistant (MDR) bacteria, the therapy of infectious diseases may be jeopardized. The possible routes for the administration of the antimicrobials principally depends on the bioavailability of these drugs *in vivo*. There have been several clinical studies and meta-analyses on comparing the efficacy of intravenous and oral antimicrobial therapy in various types of infections. None of these studies found oral therapy inferior to intravenous administration, therefore, if possible, this route should be primarily used. By definition, antibiotics with >90% bioavailability (including a few exceptions), are interchangeable/equivalent in intravenous and oral antibiotic therapy and they are candidates for sequential therapy. The relevance of sequential antibiotic therapy is highlighted and encouraged in the era of prudent antibiotic use and antimicrobial stewardship. The aim of this mini-review is to provide a concise overview of the topic of different routes of antibiotic administration in the clinical practice.

Antibiotics are one of the most important medicines of the 21st century [1]. Due to the emergence and spread of multidrug resistant (MDR) bacteria, the therapy of infectious diseases may be jeopardized, leading to sequelae, decreased quality of life and excess mortality [2]. The spread of MDR pathogens is a major public health issue, which requires global action of an intersectoral nature, involving prudent use and prescribing, development of novel drug candidates, clinical trials and government action and financial support [3]. From the standpoint of antimicrobial drug resistance, the so-called "ESKAPE" pathogens (E: *Enterococcus faecium*, S: *Staphylococcus aureus* or recently *Stenotrophomonas maltophilia*, K: *Klebsiella pneumoniae* or recently C: *Clostridioides difficile*, A: *Acinetobacter baumannii*, P: *Pseudomonas aeruginosa*, E: *Enterobacter* spp., or recently *Enterobacteriaceae*) are the most concerning [4-6]. In the clinical practice, in addition to the susceptibility of the bacteria, other factors also influence the choice of antimicrobial drugs, such as the age (infants, children), pregnancy/lactation or the general state of the patient [7]. Several drugs may be useful is almost all conditions (e.g., beta-lactams or macrolides if allergy is not detected), while other may not be administered due to their dose-limiting side effects or teratogenicity (fluoroquinolones, tetracyclines), further limiting therapeutic options [8]. Another important factor to consider is the administration route of the antimicrobials: this may occur orally (*per os*) or parenterally (*i.v.* or *i.m.*). The possible routes for the administration of the antimicrobials principally depends on the bioavailability of these drugs *in vivo*.

In pharmacology, bioavailability represents the fraction of an administered dose of unchanged drug reaching the systemic circulation [9]. As a general rule, intravenous administration represents 100% bioavailability, while if a medication is administered via other routes (e.g., *per os*), its bioavailability is generally lower, due to incomplete absorption, first-pass metabolism (FPM) in the liver and additional factors; therefore, bioavailability may vary from patient to patient [9]. Drug–drug interactions (inducing or inhibiting various cytochrome P450 enzymes; predominantly the CYP3A4, CYP2C9 and CYP2D6 isoenzymes), should also be considered during the choice of therapy, as they affect therapeutic response by modulating the degradation of medicinal drugs [10]. Bioavailability should always be included during dose calculations in the clinical practice. In addition, the tissue penetration of drug molecule should also be adequate to attain therapeutic concentrations in including peripheral parts of the body (i.e. in infected sites that are hard-to-reach and that have specific physico-chemical characteristics, like the central nervous system [CNS], bone tissue, abscesses) [11]. During drug design and development, Lipinsky's Rule of Five (RO5) is generally used as an indicator of drug-likeness. Based on these rules (1. ≤ 5 hydrogen bond donors, 2. ≤ 10 hydrogen bond acceptors, 3. molecular mass < 500 Da, 4. octanol-water partition coefficient (clogP) < 5), it can be assumed that the most orally administered drugs are relatively small and moderately lipophilic molecules [12]. From the standpoint of pharmaceutical technology and formulations, the compounds should also be Class I molecules in the Biopharmaceutical Classification System (BCS) [13].

There have been several clinical studies and meta-analyses on comparing the efficacy of intravenous and oral antimicrobial therapy in various types of infections. None of these studies found oral therapy inferior to intravenous administration, therefore, if possible, this route should be primarily used [14-16]. There are several advantages to oral antibiotic therapy: it is cheaper (no need for needles, diluents, IV pumps, equipment) there is no need for an intravenous access or a central catheter (e.g., CVC), there are no associated complications (e.g., phlebitis, thrombosis, bloodstream infections), there is less concern regarding changes in the fluid balance of the patient (e.g., sulfamethoxazole/trimethoprim needs to be administered in a large volume *i.v.*) and it is more comfortable for the patients. On the other hand, for oral therapy, the patient needs to be conscious and has to have an intact gastrointestinal tract (not manageable in patients with swallowing difficulties, vomiting and absorption disorders), the onset

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of clinical effects may take up to 30 minutes to 6 hours and some of the administered dose is lost to FPM in the liver [9]. In contrast, the dose of antimicrobial administered intravenously (through a drip or a bolus injection) ensures a rapid distribution and clinical response in the patient, and the bioavailability is 100% as the entire dose reaches the bloodstream (no FPE). Intravenous administration is also useful in cases where the patient is not able to take oral drugs, or an urgent effect is needed. In addition, for critically ill patients and in several indications (e.g., osteomyelitis, septic arthritis, sepsis/bacteremia, endocarditis, CNS/ocular infections), intravenous administration is still the preferred route of drug entry. There are several cases where the required therapeutic doses can only be reached through *i.v.* dosing; finally, some bacteria (especially in the therapy of MDR infections) can only be treated with antibiotics that are available in *i.v.* formulation only (e.g., ceftaroline-fosamil, daptomycin) or the therapeutic choices are limited to these drugs based on the antibiogram [17,18].

According to the data from the United States, more than 80% of drugs in current clinical use are orally administered (although this report was not limited to antibiotics) [19]. As previously mentioned, intravenous (IV) administration should only be utilized, if it is justified by the medical condition of the patient or the resistance trends associated with the pathogen. By definition, antibiotics with > 90% bioavailability (trimethoprim-sulfamethoxazole, metronidazole, doxycycline, minocycline, clindamycin, metronidazole, linezolid, tedizolid, rifampin, clindamycin, most of the fluoroquinolones and the antifungal drugs fluconazole and voriconazole) are interchangeable/equivalent in intravenous and oral antibiotic therapy and they are candidates for sequential therapy (IV-to-PO switches) [4]. The relevance of sequential antibiotic therapy is highlighted and encouraged in the era of prudent antibiotic use and antimicrobial stewardship [20]. Exceptions include ciprofloxacin (~70% bioavailability) and azithromycin (~40% bioavailability), as they still manage to achieve the therapeutic levels, when taken orally. Additionally, most of the beta-lactam antibiotics are administered parenterally (iv. or im. injections and infusions), where instead of bioavailability, the main limiting issues are physico-chemical characteristics (e.g., degradation due to acid sensitivity) [21]. Clinicians should be aware of the advantages/disadvantages and relevance of intravenous and oral antibiotics, and use them appropriately, based on the clinical situation, which needs to be evaluated on a case-by-case approach [22,23]. This topic should be further highlighted in university curricula and during continuous professional development (CPD) [22]. Clinical pharmacists have a pivotal role in advising clinicians towards the appropriate choice of antibiotics and formulations [24,25].

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