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Review

Antibiotics: Pharmacokinetics, toxicity, resistance and multidrug efflux pumps

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ABSTRACT

The discovery of penicillin followed by streptomycin, tetracycline, cephalosporins and other natural, semi-synthetic and synthetic antimicrobials completely revolutionized medicine by reducing human morbidity and mortality from most of the common infections. However, shortly after they were introduced to clinical practice, the development of resistance was emerged. The decreasing interest from antibiotic industry in spite of rapid global emergence of antibiotic resistance is a tough dilemma from the pointview of public health. The efficiency of antimicrobial treatment is determined by both pharmacokinetics and pharmacodynamics. In spite of their selective toxicity, antibiotics still cause severe, life-threatening adverse reactions in host body mostly due to defective drug metabolism or excessive dosing regimen. The present article aims at updating current knowledge on pharmacokinetics/pharmacodynamics concepts and models, toxicity of antibiotics as well as antibiotic resistance mechanisms, resistome analyses and search for novel antibiotic resistance determinants with special emphasis given to the-state-of-the-art regarding multidrug efflux pumps and their additional physiological functions in stress adaptation and virulence of bacteria. All these issues are highly linked to each other and not only important for most efficient and prolonged use of current antibiotics, but also for discovery and development of new antibiotics and novel inhibitors of antibiotic resistance determinants of pathogens.

Contents

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1. Introduction

The identification of penicillin by Alexander Fleming in 1928 [1] is the cornerstone discovery in the history of the 'antibiotic era'. Still, the efforts of Paul Ehrlich and his co-workers to establish a systematic screening approach for discovery of antimicrobials took place much earlier and introduced the 'magic bullet' Salvarsan [2,3]. Salvarsan remained the most populously prescribed drug against syphilis till the first use of penicillin in 1941 [3,4]. Prontosil as the first sulfa drug was next discovered by the use of same approach [5] and followed by discovery of streptomycin which was the first antibiotic used for the treatment of tuberculosis [6]. In 1945, the fungus *Cephalosporium acremonium* was shown to produce an "antibiotic principle" effective against staphylococcal, streptococcal infections, typhoid fever and brucellosis [7]. Later on, the principle was demonstrated to represent a group of natural compounds called cephalosporins, and N-phenylacetyl derivative of cephalosporin C being the most effective against *Staphylococcus aureus* [8,9]. These investigations led to the production of new generation cephalosporin compounds and saved many lives as the former ones. However, resistance has eventually appeared for nearly all antibiotics, shortly after they were introduced to clinical practice [10].

According to the estimates of Bérdy (2012) as based on Bioactive MICrobial Metabolite Database of his own, of 60–80 thousand natural metabolites produced by microbes, 47% exhibit bioactivity [11]. On the other hand, when it comes to the total number of drugs in market for use in human therapy, there are ca. 3500 such compounds 200–220 of which include antibiotics made up of direct natural products, more than 250 being semisynthetic/modified derivatives of them, and synthetic antimicrobials (especially quinolones and oxazolidinones) do also have a role in the antimicrobial market. As headed by the problem of increasing resistance to antibiotics creating clinical and economic burden, the search for novel antibiotics (from nature, combinational biosynthesis, hybrid antibiotics, discovery of new molecular targets, screening of unculturable microorganisms, combinatorial chemistry as well as computerized drug design) should constitute a very hot research area for finding new antibacterial drugs. Indeed, in between late 1960s and mid 1980s, the pharmaceutical industry introduced many new antibiotics to solve resistance problem, but since then there appears only a very limited number of new antibiotics reported. To exemplify, some new antibiotics including synthetic (e.g. besifloxacin, doripenem, radezolid), and semi-synthetic (e.g. cethromycin; derived from erythromycin A) compounds were recently approved by FDA or in clinical trials [12]. In a recent study, Ling and his co-workers (2015) announced the discovery of a new class of natural antibiotic namely teixobactin which inhibits cell wall synthesis by a novel mechanism after the screening of a previously uncultured bacterium namely *Eleftheria terrae* [13]. Another research group suggested a new antimicrobial agent called lugdunin produced by *Staphylococcus lugdunensis* which is an inhabitant of human nares. They demonstrated the potential killing effect of lugdunin against many Gram-positive bacteria including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) isolates [14]. Also, a team at Harvard University proposed a new platform for the production of new macrolides which is based on the synthesis of different compounds that cannot be produced by traditional semi-synthetic methods [15]. The novel targets in different bacterial processes such as quorum sensing (QS) and biofilm formation are being investigated for development of new antibacterial agents mainly by academia [16]. The Infectious Diseases Society of America (IDSA) provided a platform called 'the 10×20 initiative' for development of ten new antibacterial drugs including new chemical classes and modified versions of current classes till 2020 [17]. 'Return On Investment' considerations and challenging regulatory requirements unfortunately restricted the attempts of antibiotic industry to discover and develop novel classes of agents against pathogenic bacteria which instead preferred to focus on altering existing ones or development of antiviral agents [18,19]. Thus, the decreasing interest from antibiotic industry in spite of worldwide rapid emergence of antibiotic resistance is a tough dilemma from the pointview of public health. Maintaining and prolonging the useful life span of existing antibiotics must have a high priority under these circumstances [20]. In this respect, computer-aided screening to identify potential inhibitors of the antibiotic resistance and also preferentially quorum sensing and virulence has received great attention in recent years [21].

Pharmacokinetic properties of antibiotics are mainly based on their chemical structure which absolutely affects their bioavailability, half-life, tissue penetration, distribution, degradation and elimination [22]. For each class of antibiotics, dosage application and duration of exposure have been critical issues to obtain optimum outcomes in patients while minimizing the risk of resistance development and toxicity. Expanding knowledge on the interaction between antibiotic pharmacokinetics, toxicity and resistance provided better understanding of individualized therapy [22,23]. Pharmacodynamic factors include antimicrobial activity against the pathogen, drug stability in the case of resistance and absence of organ toxicity [24]. The present article aims at overviewing pharmacokinetics/pharmacodynamics concepts and models, toxicity of antibiotics as well as antibiotic resistance mechanisms with special emphasis to multi-drug transporters, all of which are highly linked to most efficient and prolonged use of antibiotics.

2. Pharmacokinetics/pharmacodynamics and toxicity of antibiotics

2.1. Pharmacokinetics/pharmacodynamics concepts and models

Since the emergence of antibiotic resistance is mostly attributed to drug overuse, inappropriate prescribing and suboptimal dosing, certain measures must be taken for dose optimization of current antibiotics [25]. Optimization of antibiotic usage requires well-understood criteria that can be simplified as the relationships between concentration, dose and both desirable and side effects. This requirement has emerged a well established and authorities-recognized field called pharmacokinetics/pharmacodynamics (PK/PD) that basically studies the interactions between host, pathogen and drug in that infection/immune response, pharmacodynamics/drug susceptibility, pharmacokinetics/toxicity couples forming the edges of an equilateral triangle [25,26]. PK/PD concepts were originally described by Eagle et al. [27] who revealed time-dependent, concentration-dependent and mixed patterns of these for different antibiotics including penicillin and streptomycin and re-emerged by the effort of Craig (1998) [27,28]. "The optimal dosage regimen" is to be determined before the drug receives regulatory approval and should be a function of the correct dose and dosing interval rather than the duration of treatment [26]. After administration of an antibiotic to a patient, it goes through some processes in body known as ADME (Absorption, Distribution, Metabolism and Excretion). PK is after 'what the body does to the drug' with certain parameters like total body clearance, volume of distribution, bioavailability and protein binding [26]. When drug goes to the action site (i.e. pathogenic bacterium), it develops desirable effects as well as undesirable ones, the topics studied by PD which can be defined as 'what the drug does to the body' [29]. In other words, PK deals with the time course of serum level of antibiotics in body, thus its parameters