EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
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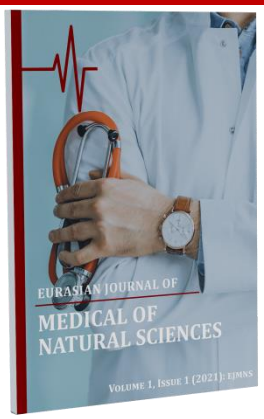

CLINICAL PHARMACOLOGICAL APPROACH TO THE USE OF ANTIBIOTICS IN CHILDREN

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https://doi.org/10.5281/zenodo.14228194

ARTICLE INFO

Received: 22th November 2024
Accepted: 26th November 2024
Online: 27th November 2024

KEYWORDS

Children, pharmacokinetics, antibiotics, pharmacodynamics, dosing.

ABSTRACT

Knowledge of the pharmacokinetic and pharmacodynamic profile of an antibacterial drug is critical for optimizing the dosage regimen. The strategy of individual selection of the dosage regimen taking into account the principles of pharmacokinetics and pharmacodynamics can be especially effective in patients with expectedly altered pharmacokinetic parameters and in infections caused by bacterial strains with low sensitivity to antibiotics. The review presents current concepts of the pharmacokinetic and pharmacodynamic profile of antibacterial drugs most frequently used in pediatrics and their relationship with the clinical efficacy of the therapy.

INTRODUCTION

More than 100 years ago, Dr. Abraham Jacobi, the founder of American pediatrics, emphasizing the need for a special approach to pharmacotherapy in children, wrote: “Pediatrics does not deal with “little” men and women who require “mechanical” dose reduction” [3]. Indeed, when choosing an antibacterial drug and its dosage regimen in children, it is necessary to rely on the age characteristics of pharmacokinetic processes, taking into account the degree of maturity of the distribution, metabolism and excretion systems of the drug [4]. In addition, in pediatrics, special attention should be paid to pharmacotherapy of patients with severe infections, cystic fibrosis, immunocompromised patients (HIV infection, oncological diseases, including hemoblastoses, solid organ or stem cell transplantation, asplenia, congenital immunodeficiencies), when standard antibacterial therapy regimens may be ineffective.

MATERIALS AND METHODS

For antibiotics, unlike other groups of drugs, it is more difficult to determine the correlation between the concentration of the drug in the blood plasma or body tissues and the clinical effect. The effectiveness of an antibacterial drug is determined by the value of the minimum inhibitory concentration (MIC) - the lowest concentration of the antibiotic that can suppress the visible growth of a microorganism in vitro. During the development of an

infectious process in the human body, the pharmacodynamics of antibacterial agents can be influenced by the following factors: localization of the infection, pH of the environment at the site of infection, the magnitude of the microbial load [5]. In this regard, when assessing the effectiveness of antibacterial drugs in vivo, they are guided by such pharmacokinetic parameters as the ratio of the maximum (peak) concentration to the MIC (Cmax/MIC), the ratio of the area under the pharmacokinetic curve to the MIC (AUC0–24/MIC), and the time during which the concentration of the drug in the blood plasma exceeds the MIC (T > MIC) [2].

RESULTS AND DISCUSSION

Antibacterial drugs whose activity depends on plasma concentration and post-antibiotic action demonstrate maximum effectiveness when high concentrations are reached, providing the possibility of increasing the intervals between administrations [2]. Among the antibiotics of this group, aminoglycosides are most frequently used in pediatrics [1].

Aminoglycosides

Aminoglycosides have been used in pediatric practice for over 60 years. The most studied representative of this group in pediatric practice is gentamicin. The bactericidal action of aminoglycosides is achieved by forming covalent bonds with bacterial ribosome proteins and disrupting their synthesis, and the degree of their activity depends on the maximum (peak) concentration in the blood serum [5]. R. Moore et al. were the first to describe the relationship between achieving a favorable clinical outcome in adult patients with an infectious process of gram-negative nature and a Cmax/MP ratio of 8–10 [3].

This range is used as a target when selecting an individual dosage regimen for children [4]. Despite the fact that the instructions for medical use of aminoglycosides traditionally include daily multiple dosing regimens, strategies for prescribing aminoglycosides in high doses at extended intervals (once a day) are considered optimal. Such extended dosing intervals have advantages in terms of the dose-dependent activity of aminoglycosides, clinically manifested by the development of a significant post-antibiotic effect, an increase in leukocyte activity [2], and minimization of bacterial growth when the concentration of the antibiotic in plasma falls below the MIC level [3]. Prolonging the intervals between administrations of aminoglycoside drugs is also justified from the point of view of the pharmacodynamic effect known as adaptive resistance, when bacteria develop reversible resistance to the action of antibiotics. Increasing the interval between administrations allows for the complete removal of the antibiotic from the plasma, thus providing a sufficient time interval for bacteria to restore sensitivity and reducing the risk of complications associated with the development of resistance to aminoglycosides [4]. Physicians' concerns about the development of nephro- and ototoxicity seriously limit the use of aminoglycoside antibiotics in the treatment of severe infections, including those caused by multidrug-resistant pathogens. Nephrotoxic effects are associated with the accumulation of aminoglycosides by nephrocytes [5]. Constant low concentrations of aminoglycosides in plasma are associated with more active accumulation of drugs in the kidneys than when using high doses, but with an increased interval [4]. Ototoxicity of aminoglycosides is associated with the production of free oxygen radicals that damage cochlear and hair cells of the vestibular apparatus [2]. Ototoxicity is irreversible in most cases; nephrotoxicity, on the contrary, is reversible in the vast majority of cases, but both side effects lead to prolongation of hospitalization and, as a

consequence, a significant increase in treatment costs [1]. Individualization of the aminoglycoside dosing regimen using pharmacokinetic data helps to significantly reduce the development of nephrotoxic effects [2].

The dosage regimen of aminoglycosides in premature infants should be determined taking into account the pharmacokinetic parameters of the antibiotic. Given the reduced renal function in such children, the expected period of drug elimination increases from the standard 2–3 hours to 8–12 [3]. Thus, in our opinion, the standard dosage regimen with a high degree of probability can lead to the development of toxic effects in premature infants. Premature infants also have reduced peak concentrations of aminoglycosides due to an increased volume of distribution (the ratio of the total content of the drug in the body to its serum concentration, Vd), which indicates the need to use high doses of aminoglycosides with an increased dosing interval (24–48 hours) in premature infants [3]. When using gentamicin in the treatment of neonatal sepsis, the target peak concentration should be more than 8–10 μg/ml with microorganism sensitivity to MIC less than 1 μg/ml, the target concentration before the administration of each subsequent dose of gentamicin should be less than 0.5–1 μg/ml [4]. This example demonstrates the possibilities of personalizing antibacterial therapy for neonatal sepsis based on the pharmacokinetic profile of gentamicin [4]. In many cases, in order to determine the steady-state concentration of the drug in plasma, blood is taken in the interval between the administration of the third and fourth dose [2]. However, in the case of aminoglycosides, a delay in determining the plasma concentration can lead to a delay in changing the dosing regimen and, as a consequence, the development of toxic effects [3].

Patients with cystic fibrosis may also benefit from aminoglycosides administered at extended dosing intervals. High doses of aminoglycosides are indicated in cystic fibrosis to combat gram-negative organisms, particularly Pseudomonas aeruginosa, for three reasons: decreased susceptibility of the organisms to antibiotics; patients with cystic fibrosis have increased total clearance (Cl) and volume of distribution (Vd), requiring higher doses to achieve peak concentrations; and higher doses of antibiotics are required to achieve high concentrations in the lung tissue. Extended dosing intervals when prescribing high doses of aminoglycosides allow achieving high peak concentrations and, as a result, maximum efficacy, including in infections with organisms with low susceptibility to antibiotics. On this basis, this strategy was recommended by the Cystic Fibrosis Foundation (USA) as a priority.

Antibacterial drugs whose activity depends on the duration of action

Antibacterial drugs whose activity depends on the duration of action demonstrate maximum efficiency with prolonged exposure at concentrations exceeding the MIC [3]. Since such antibiotics do not have a pronounced post-antibiotic effect, bacterial growth at the site of infection can be observed immediately after the concentration of the drug falls below the MIC. Achieving maximum efficiency for this category of antibacterial drugs is possible by increasing the duration of infusion or frequency of administration.

Beta-lactams

Beta-lactams (penicillins, cephalosporins, carbepenems) are often used in pediatric practice as first-choice drugs due to their high safety profile. Acute otitis media and bacteremia can be considered as examples of the use of pharmacokinetic and pharmacodynamic principles to optimize antibiotic therapy.

Linezolid

Linezolid has an inhibitory effect on protein synthesis by microorganisms, has a bacteriostatic effect, and is the drug of choice for the treatment of infections caused by multidrug-resistant gram-positive cocci [2]. Currently, linezolid is widely used in pediatric practice worldwide due to the growth of infections caused by MRSA (with intermediate sensitivity to vancomycin) and VRE (vancomycin-resistant enterococci) [3]. Linezolid is characterized by time-dependent efficacy with post-antibiotic effects of medium duration, depending on the magnitude of the excess of the MIC [4]. The study by C. Rayner et al. demonstrated a relationship between AUC0–24/MIC 80–120, T > MIC > 85%, and favorable outcome in the treatment of bacteremia in lower respiratory tract infections and soft tissue infections in adult patients [5].

CONCLUSION

Information on the pharmacokinetic/pharmacodynamic profile of a particular antibacterial drug is key when choosing a dosing regimen in children, especially with severe infections, as well as in special categories of patients with expectedly altered pharmacokinetic parameters. Although standard dosing regimens are suitable for most children, it is very important to identify populations that require personalized approaches to choosing an antibacterial therapy strategy. In addition, pediatricians now often deal with infections caused by resistant pathogens.

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