ISSN: 2710-0588

Analysis of Macrolide Antibiotics Administration and Discontinuation Methods

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Abstract

Macrolide antibiotics are highly antimicrobial and have a wide range of applications, such as azithromycin and roxithromycin, which are both widely used over-the-counter antimicrobials. But in use, it was gradually found to have the characteristics of slow metabolism in vivo, and drug resistance was gradually developed in use. This article discusses macrolide use and discontinuation, with the aim of reducing endoresistance in cases where the greatest value of this class of antibiotic is achieved.

Keywords

Macrolide Antibiotics; Medication Methods; Research Progress.

1. Introduction

The nomenclature for macrolide antibiotics is derived from the nomenclature used to classify antibiotic structures, as the main body structures of this class of antibiotics are often named because they have a lactone structure of a 14 -, 15 -, or 16 membered ring (Fig1). Macrolide antibiotics are very common in daily life, including roxithromycin, azithromycin, and so on, and are usually effective for diseases caused by bacterial infections with susceptible mycoplasmas. But there are often disagreements between this class of antibiotic use and the timing of discontinuation that are involved in daily medication, such as the statement stop four with three, that is, use three days followed by four days off.

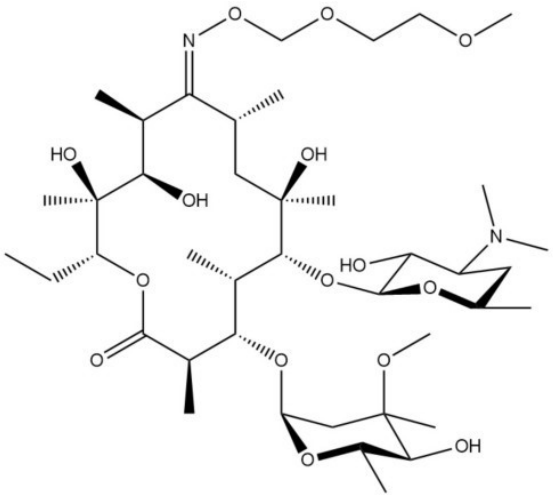

Fig. 1 Roxithromycin structural formula

2. Mechanisms of Resistance

First we want to give an introduction to the scope and treatment principles of this class of antibiotics. The antibacterial spectrum of this class of antibiotics is narrow, and first generation agents have potent antibacterial activity mainly against most gram positive bacteria,

ISSN: 2710-0588

anaerococci, and some gram negative bacteria, including Neisseria, Haemophilus, and Corynebacterium diphtheriae, but also against Legionella pneumophila, mycoplasma, chlamydia, and atypical mycobacteria, among others, against β- Lactamase resistant staphylococci and methicillin-resistant Staphylococcus aureus (MRSA) also have some antibacterial activity. The second generation of macrolide antibiotics expanded the antimicrobial range, increasing and improving antibacterial activity against gram negative bacteria. Generally bacteriostatic, high concentrations are bactericidal. Macrolide antibiotics achieve their bacteriostatic purpose mainly by inhibiting bacterial protein synthesis. This mechanism irreversibly binds to the target site of the 50S subunit of the bacterial ribosome, blocking peptide acyl t-RNA translocation and thereby affecting the synthesis of the bacterial ribosomal peptide chain. Studies have demonstrated that there are also macrolides that can bind to L2 and L22 proteins on the 50S subunit and promote the dissociation of peptidyl t-RNA from the ribosome, thereby inhibiting protein synthesis. Structurally, chloramphenicol, clindamycin, and lincomycin are identical to or close to macrolides on the 50S subunit of bacterial ribosomes and are antagonistic when used. Also since bacterial ribosomes are 70s composed of 50s and 30s subunits, while mammalian ribosomes are 80s composed of 60s and 40s subunits, there is no effect on mammalian ribosomes.

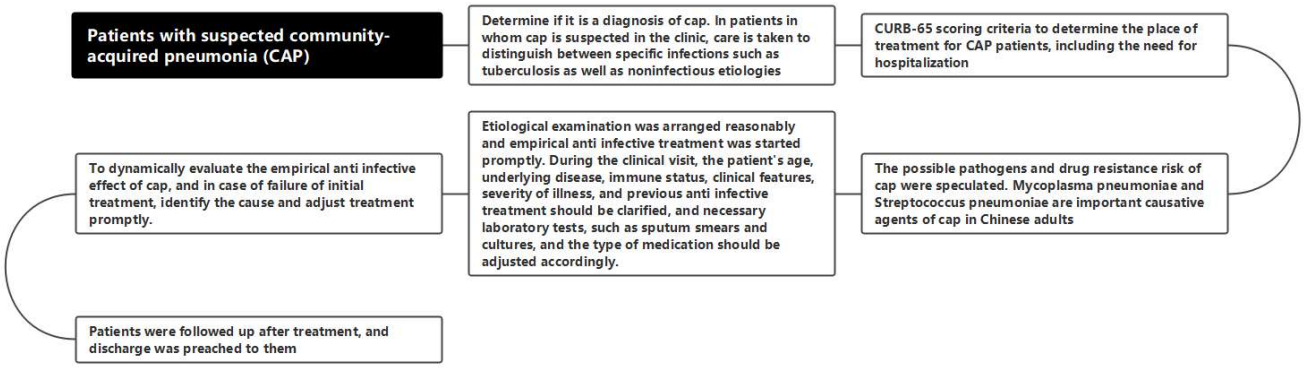

Fig. 2 Process of admission to clinic for patients with suspected CAP

3. Clinical Features

Often patients are not highly adherent to their antibiotic medications, and there are frequent instances in which they are taken autonomously when antibiotics are not required and in case of premature discontinuation of medications for reasons such as symptom relief while taking them. A subset of patients perceive macrolide antibiotics such as azithromycin to have a long in vivo half-life when using macrolide antibiotics such as azithromycin. For example, clarithromycin, because its metabolite 14 hydroxyclarithromycin in the body is also pharmacologically active, reaching a half-life of more than 30 h with a single administration according to individual differences, would be discontinued after three days for consideration of damage such as liver and kidney function and continued for several days.

Drug resistance performance can be measured by the mic value, which is the minimum inhibitory concentration of a bacteriostatic component, and an increase in the mic value can respond to a certain extent to a decline in the sensitivity of bacteria to bacteriostatic drugs. Experiments have shown that MIC values increase over time during a single azithromycin application. Analysis of data from further clinical studies may reveal that there exists a clear advantage of intermittent dosing over continuous dosing when administered in hospital in terms of increased drug resistance. This article lists two clinical studies that have been

ISSN: 2710-0588

conducted in our country. In a 2017 study, 94 patients with mycoplasma pneumonia from the same hospital between 2015 and 2017 were selected, and the samples were randomly divided into observation and control groups, in which the control group was treated with azithromycin continuously, and the observation group was treated with azithromycin intermittently, and the efficacy and resistance of the two groups were observed and compared.

Table 1. Selected from the guidelines for the diagnosis and treatment of community-acquired pneumonia in adults in China (2016 Edition)

Diagnostic criteria for community acquired pneumonia
1. Community onset
2. Pneumonia related clinical manifestations: (1) newly developed cough, expectoration, or aggravation of original respiratory disease symptoms with or without purulence, chest pain, dyspnea, and hemoptysis; (2) Fever; (3) Signs of lung consolidation and (or) audible and wet rales; (4) $>10x10^9$/L or $<4x10^9$/L in peripheral blood leukocytes with or without left shift of nuclei.
3. Chest imaging revealed emerging patchy infiltrative opacities, leaf or segment consolidation, ground glass opacities, or interstitial changes with or without pleural effusion.
4. Clinical diagnoses were established after meeting any 1 of 1, 3 and 2 criteria and after exclusion of tuberculosis, lung neoplasm, noninfectious interstitial lung disease, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration and pulmonary vasculitis.

Results the overall response rate of treatment in the observation group was 93.62%, which was higher than the 85.11% in the control group. At 6 and 9 days of drug administration treatment, the MIC values of in vitro susceptibility testing in both groups rose to different degrees, but the rise was larger in the observation group [1]. One hundred and twenty patients with mycoplasma pneumonia, 80 of whom were treated with intermittently administered azithromycin, were enrolled in a study at the people's Hospital of Jinghong, Yunnan, in 2013 and placed in an observation group; Forty patients received continuous administration of azithromycin and served as a control group. The minimum inhibitory concentration (MIC) values after treatment were compared with those before treatment, on days 4, 8, and 12; Recurrence rates at 1, 3, and 6 months after treatment. Results in terms of basic treatment, the overall response rate was 96.3%, the response rate was 40.0%, the response rate was 56.3%, and the non response rate was 3.7% in the observation group; In the control group, the overall response rate was 85.0%, the response rate was 45.0%, the development rate was 40.0%, and the non response rate was 15.0%. In terms of the changes in the minimum inhibitory concentration values, the minimum inhibitory concentration values of both groups showed an upward trend after 4, 8, and 12 days, but the increase in the control group was significantly higher than that in the. Observation group, the control group was already above the blood concentration value at 12 days. In terms of recurrence rate, the cumulative total number of recurrences after 6 months of treatment in the observation group was 6 (7.5%); 10 cases in the control group, 22.5%. Overall, the observation group had better efficacy, better drug resistance, and the emergence of drug resistance was slower. [2].

From the mechanism of drug resistance generation, bacteria develop resistance to macrolide antibiotics mainly in the following ways:

Several inactivating enzymes have been isolated from macrolide antibiotic induced bacteria, including esterase, phosphorylase, methylase, glycosidase, acetyltransferase, and nucleotidyltransferase, Inactivate macrolide antibiotics or hydrolyze or phosphorylate or methylate or acetylate or nuclear camp; Some bacteria alter the structure of the target site. These bacteria can develop resistance genes to macrolide antibiotics, thereby synthesizing

ISSN: 2710-0588

methylases that methylate the drug binding site of the ribosome to produce resistance; Some bacteria reduce macrolide antibiotic intake. These macrolide resistant bacteria can have altered membrane composition or the emergence of new components, leading to a decrease in the entry of macrolide antibiotics into the bacteria, but the affinity between the drug and the ribosome remains the same. For example, a 6 kDa protein produced from the S. epidermidis pne24 plasmid confers resistance to 14 membered erythromycin. Resistance of macrolide antibiotics to G-bacteria is caused by the outer membrane barrier of bacterial lipopolysaccharide, making it difficult for drugs to enter human bacteria; There are some bacteria with increased efflux of macrolide antibiotics. These bacteria can produce efflux pumps by gene coding that can specifically pump out macrolide antibiotics. For example, MEF in Streptococcus, MSR in Staphylococcus, and Enterococcus faecalis are energy dependent active efflux systems that confer resistance to 14 and 15 membered macrolides.

Resistance situation examinations for infecting bacteria in patients should therefore be increased for conditional situations, such as the rational use of macrolide antibiotics and the decision on the use of combined potentiators if only mutant forms created by inactivating enzymes are available.

4. Conclusion

In conclusion, conducting a suitable dosing to discontinuation interval under the guidance of professionals within the hospital can reduce the emergence of drug resistance and protect liver and kidney function to a certain extent.

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