INCREASING RESISTANCE TO SOME ANTIBIOTICS. USE OF CEPHALOSPORINS.

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SUMMARY

Resistance to chemotherapeutic agents is the adaptation of bacteria to changes in their environment. The introduction of a novel antibacterial agent will inevitably lead to the emergence of resistant organisms. In the present short review the ways of transferring of antibiotic resistance in bacteria are described as well as the most important molecular and biochemical mechanisms responsible for the development of antibiotic resistance. Due to changed circumstances many cephalosporins have got an important role in the treatment of some STDs e.g. gonorrhoea or chancroid. A short overview of the use of cephalosporins is given.

KEY WORDS

antibiotic resistance, molecular mechanisms, biochemical mechanisms, cephalosporins in STD

INTRODUCTION

Bacterial and some fungal STDs have been successfully treated in the last four decades due to antibacterial and antifungal drugs. However many of these drugs lost their effectiveness because many of microorganisms developed resistance to them. Unchanged sensitivity of Treponema pallidum to pencillin is rather an exception (1). Resistance to chemotherapeutics can seriously constrain the options available for the medical treatment of many bacterial infections (2).

Resistance to chemotherapeutic agents can develop to particular drug or group of drugs. Particular bacterial genera or environments develop particular mechanisms of resistance.

In most cases the resistance is apparently acquired rather than intrinsic. The rapidity with which resistance often appears after introducing of a new drug is astonishing (3).

GENETIC DETERMINANTS OF ANTIBIOTIC RESISTANCE

Chromosomal determinants: mutations

Although spontaneous mutation is an important mechanism for the evolution of resistance it is not of great clinical relevance, possibly because mutants often have reduced pathogenecity (2,3). It is important in mycobacterial infections, particularly tuberculosis (and leprosy) (2).

Mobile genetic elements: plasmids and transposons

Plasmids are extrachromosomal genetic elements that can replicate on their own and can carry genes coding for resistance to antibiotics (r genes) from one bacterium to another (2,3).

The main method of transfer of r genes from one bacterium to another is conjugation. Conjugative plasmids can cause the bacterium to make a connecting tube between bacteria, through which the plasmid itself (and other plasmids) can pass (2).

A less common method of transfer is by transduction. This is the transmission of a r-gene-carrying plasmid into a bacterium by a bacterial virus (phage) (2).

The third way of transfer, clinically not very important, is transformation. The bacterium incorporates naked DNA - coming from a cell belonging to the same strain or a strain very closely related to the host bacterium - into its genome by the normal cross-over mechanism (2).

Transposons are stretches of DNA that can be transposed from one plasmid to another, and also from plasmid to chromosome and vice versa. They are not able to replicate on their own. Transposition is a continuous process in bacterial population and is a powerful mechanism for generation and dissemination of resistance determinants (2,3).

BIOCHEMICAL MECHANISMS OF RESISTANCE TO ANTIBIOTICS

Production of enzymes that inactivate the drug

Some microorganisms e.g. staphylococci, and some Gram-negative organisms produce ß-lactamases, which inactivate ß-lactam antibiotics (e.g. penicillins, cephalosporins, semisynthetic broad-spectrum ß-lactam antibiotics) by cleaving their ß-lactam ring (2,4).

Resistant strains of both Gram-positive and Gram-negative organisms produce acetyltrasferases, which inactivate chloramphenicol (2,5).

Enzymes for phosphorylation, adenylation or acetylation which inactivate aminoglycosides have been found in both Gram-negative and Gram-positive organisms (2,6).

Alteration of drug-sensitive site or drug-binding site

These mechanisms may provoke the resistance to aminoglycosides, erythromycin, rifampicin, penicillins (2,3).

Decreased drug accumulation in the bacterium

Energy dependent efflux (due to inducible "resistance" proteins) of tetracyclines in both Gram-positive and Gram-negative bacteria results in a common type of resistance. Resistance to some hydrophylic antibiotics and to ampicillin is based on altered permeability of the outer membrane of bacteria. The accumulation of aminoglycosides, ß-lactams, chloramphenicol, peptide antibiotics and tetracyclines is changed by mutations affecting envelope components of bacteria (2).

The development of an alternative pathway that bypasses the reaction inhibited by the antibiotic

Some strains of staphylococci have developed alternative pathways to bypass the reactions inhibited by the antibiotics, and have become multiple resistant to virtually all current antibiotics: methicillin, streptomycin, aminoglycosides, trimethoprim, sulphonamides, rifampicin, fusidic acid. This resistance is transferred by transposons and/or plasmids (2).

Due to mentioned and other mechanisms the antibiotic therapy of many STDs has changed. Azithromycin, roxythromycin, cephalosporins, cephamycins as well as quinolones and fluoroquinolones are frequently used in the treatment of some STD. Fortunately, resistance to the newer macrolides, cephalosporins, fluoroquinolons remains uncommon in most settings, although fluoroquinolone resistance of Neisserria gonorrhoeae in some geographic areas represents a growing problem (7).

In the present work we wish to elucidate the use of cephalosporins and cephamycins in some STDs.

BASIC PHARMACOLOGY OF CEPHALOSPORINS AND THEIR USE IN SOME STDs

Cephalosporins and cephamycins are chemically and pharmacologically closely related to each other. Both agents are bactericidal antibiotics, inhibiting bacterial cell-wall synthesis similarly as does penicillin: they interfere with peptidoglycan synthesis after binding to the ß-lactam antibiotic binding proteins (2,8).

Resistance:

As with penicillins, resistance occurs if an organism generates enzymes that cleave the ß-lactam ring (although penicillinase-producing staphylococci may be susceptible to cephalosporins) or if it has an outer membrane that prevents penetration of the

drug. The cephalosporins and cephamycins are not readily attacked by the plasmid-encoded ß-lactamases, but there are reports of resistance due to mutations involving the binding-site proteins (9).

Classification

Development of new cephalosporins during past decade led to different classifications. The well-accepted system of classification by "generations" is based on general features of antimicrobial activity (8): The first-generation cephalosporins (e.g. cephalotin and cefazolin) have good activity against Gram-positive bacteria and relative modest activity against Gram-negative microorganisms. The second-generation cephalosporins (e.g. cephamandole, cefuroxime) have somewhat increased activity against Gram-negative microorganisms but are much less active than the third-generation agents. Third-generation cephalosporins (e.g. cefotaxime, cefmenoxime, ceftriaxone, cefixime) are generally less active than first-generation agents against Gram-positive cocci, but they are more active against Enterobacteriaceae, including β-lactamase-producing strains. The newer cephalosporins cefepime and cefpirome have been described by some as forth-generation because of their broad spectrum of activity (8).

The semisynthetic cephamycins (e.g. cefoxitin, cefmetazole, cefotetan, cefbuperazone, cefminox) are generally classified with the second-generation cephalosporins, but are more active against some anaerobic bacteria (8).

Use of cephalosporins in gonorrhoea

Combined results of several studies showed that following cephalosporins can cure anogenital infections with N. gonorrhoeae:

- 2nd generation: cefuroxime (1 g, single oral dose, with probenecid 1 g orally (7,8,10); prodrugs of cefuroxime are cefuroxime-axetil and cefuroxime-sodium).
- 3rd generation: cefixime 400 mg, single oral dose (7,8); cefmenoxim 2-12 g, i.m. (11); cefotaxime 1 g, single dose i.m. (10); its active metabolite is desacetylcephotaxime, cefpodoximeproxetil 200 mg, single oral dose (7,8); ceftazidim 1,5-6 g, i.m. (11,12), ceftizoxime 500 mg i.m. (7,8,10); similar properties as cefotaxime, no active metabolites, ceftriaxone 250 mg, single dose i.m.
- 4th generation: cefepime (in the state of studies).

According to certain recommendations all regimens should be accompanied by doxycycline 100 mg orally 2 times a day for 7 days, except in pregnant women, for whom erythromycin base 500 mg orally 4 times a day for 7 days should be substituted (10).

For disseminated gonococcal infection ceftriaxone 1 g i.m. or i.v. daily, ceftizoxime 1 g i.v. 3 times a day, cefotaxime 1 g i.v. 3 times a day are considered equivalent. Duration of treatment is ranging from 3 to 10 days (10).

CONCLUSIONS

Due to development of antibiotic resistance as well as to the introduction of novel antibacterial agents the treatment of many STDs has changed over time. Cephalosporins are used (besides some other chemotherapeutics, e.g. ampicillin, spectinomycin, doxycycline, azithromycin, fluoroquinolons or erythromycin, which are not the subject of the present review) in the treatment of gonorrhoea and chancroid (10,11,12).

In the treatment of STDs some important clinical pharmacological principles should be considered:

Single-dose therapy should be used whenever possible. Therapeutic compliance is a problem in all patients, even more when symptoms are mild or the patient does not fully understand the long-term consequences of infection (7).

The antimicrobial susceptibility patterns of some STD pathogens are geographically variable and fluctuate over time, sometimes rapidly. Clinicians should be aware of local patterns and treatment recommendations (7).

In general the minimum effective dose should not be used, especially for gonorrhoea or chancroid. Using higher doses probably delays the selection of antibiotic-resistant strains (7).

REFERENCES

1. Lukehart SA. Pathogenesis of syphilis. Update in sexually transmitted diseases. V. American Euro Date 1994; 25: 18-21.

2. Rang HP, Dale MM. Pharmacology, 2nd ed., Edinburgh: Churchill Livingstone, 1991; 765-780.

3. Hayward CMM, Griffin GE. Antibiotic resistance: the current position and the molecular mechanisms involved. Br J Hosp Med 1994; 52: 473-478.

4. Madeiros AA. ß-lactamases. Br Med Bull 1984; 40: 18-27.

5. Shaw WV. Bacterial resistance to chloramphenicol. Br Med Bull 1984; 40: 36-41.

6. Phillips I, Shannon K. Aminoglycoside resistance. Br Med Bull 1984; 40: 28-35.

7. Handsfield HH. Recent developments in treatment of bacterial STDs. Update in sexually transmitted diseases. V. American Euro Date 1994; 25: 62-64.

8. Martindale, The extra Pharmacopoeia, 30th ed., Reynolds JFE, Parfitt K, Parsons AV. Sweetman SC eds. London: The pharmaceutical press, 1993: 79-141.

9. Mandell GL, Sande MA. Antimicrobial agents. Penicillins, cephalosporins, and other beta-lactam antibiotics. "In": Gilman AG, Rall TW, Nies AS, Taylor P eds. Goodman and Gilman's The pharmacological basis of therapeutics, 8th ed., Toronto, MacMillan, 1990: 1065-1097.

10. The Merck manual of diagnosis and therapy, 16th ed., Berkow R, Fletcher AJ eds. Rahway, N.J., USA.: Merck Res Lab, div. Merck & Co., 1992: 256-257.

11. Marolt-Gomišček M. Antibiotiki in kemoterapevtiki v vsakdanji praksi. Tabelarični prikaz, Ljubljana: Tangram, 1992.

12. Korting HC. Cephalosporin-Therapie der Gonorrhoe, Basel: Karger 1987.

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