An important determinant of clinical outcome of a LRTI may be sterilisation of the infected lung, which is dependent on sustained antibiotic concentrations achieved in the lung. For this reason, recently, there has been increased interest in measuring the concentration of antimicrobial agents at different potential sites of infection in the lung. In patients with acute bronchitis, acute exacerbation of chronic bronchitis, bronchiectasis or cystic fibrosis, the infection develops within the airway lumen on the surface of mucus cells and in the mucosa itself. In patients with bacterial pneumonia, the site of infection is in the alveolar spaces or in the pulmonary interstitium. This article, adapted from the European Respiratory Society (ERS) School Course on “New perspectives in pneumonia treatment and prophylaxis”, held at the 2005 ERS conference in Glasgow, discusses the pharmacokinetics and pharmacodynamics of antibiotics with respect to clinical and microbiological outcomes.

Summary

An important determinant of clinical outcome of a LRTI may be sterilisation of the infected lung, which is dependent on sustained antibiotic concentrations achieved in the lung. For this reason, recently, there has been increased interest in measuring the concentration of antimicrobial agents at different potential sites of infection in the lung. In patients with acute bronchitis, acute exacerbation of chronic bronchitis, bronchiectasis or cystic fibrosis, the infection develops within the airway lumen on the surface of mucus cells and in the mucosa itself. In patients with bacterial pneumonia, the site of infection is in the alveolar spaces or in the pulmonary interstitium. This article, adapted from the European Respiratory Society (ERS) School Course on “New perspectives in pneumonia treatment and prophylaxis”, held at the 2005 ERS conference in Glasgow, discusses the pharmacokinetics and pharmacodynamics of antibiotics with respect to clinical and microbiological outcomes.
Levels of antimicrobials are now measured in bronchial mucosa, epithelial lining fluid (ELF) and alveolar macrophages, as well as in sputum. Penicillins and cephalosporins only reach marginal concentrations in sputum and bronchial secretions (their sputum or bronchial secretion to simultaneous serum ratios vary 2–25%, although the percentages for the extent of penetration of piperacillin and tazobactam, as defined by the bronchial secretion/serum area under the curve (AUC) ratio, has been calculated to be 35.70 and 78.42%, respectively), whereas fluoroquinolones have been shown to achieve high concentrations (their concentrations are 0.8–4.0-

times greater than those in the bloodstream). Macrolides exhibit a variable penetration, between 5 and 500%. However, penetration ratios >500% have been found with azithromycin and dirithromycin.

Unfortunately, sputum is now considered an unsuitable fluid for pharmacokinetic studies, as its lack of homogeneity, its dilution by saliva pooling within the respiratory tract and, in addition, the instability of some antimicrobial agents in sputum have led to methodological and interpretational problems.

The penetration of different antibiotics into bronchial mucosa is relatively high. This is also true for β-lactams, although their tissue levels never reach blood concentrations. The members of this class of antibiotic accumulate in the bronchial mucosa at concentrations up to 35–60% of the level attained in serum. The penetration of fluoroquinolones and macrolides is higher: for example, the levels of fluoroquinolones at this site are 1.5–3-fold greater than those in the bloodstream, whereas the concentrations of macrolides are 1.7–8-times greater than those in the blood. Drugs that show a high intracellular accumulation in vitro present higher concentrations in bronchial mucosa. Many antibiotics are capable of accumulating in cells, with the exception of β-lactams and aminoglycosides. Antimicrobials penetrate less into ELF than into bronchial mucosa, but fluoroquinolones appear to concentrate more in alveolar lavage than in bronchial mucosa, probably because they possess additional mechanisms that allow the crossing of the membrane, as compared to the simple process of passive diffusion that occurs with β-lactam antibiotics.

The hydrophilic nature of β-lactams leads to poor penetration into the relatively impermeable alveolar space and the ELF, with levels only reaching 12–50% of the serum concentration. Macrolides have been found to concentrate in the ELF, with azithromycin showing a 7-fold and clarithromycin a 5.7-fold increase compared with serum levels. The concentration of the ketolide telithromycin, a semi-synthetic derivative of the 14-membered ring macrolides, in ELF is 8-times higher than in serum. β-Lactams diffuse into, but do not accumulate in, phagocytes, probably because of their acidic character, with the exception of clavulanate, which is detectable in macrophages. In any case, their activity at this site is negligible due to low pH. Aminoglycosides are too polar to pass across membranes and are, therefore, only taken up slowly by endocytosis. Lincosamides, macrolides and fluoroquinolones all accumulate in phagocytes. Levels of azithromycin are up to 23-times and clarithromycin ~70-times higher than in serum, whereas levofloxacin shows an 8-fold, gatifloxacin a 35-fold and moxifloxacin a 50-fold increase compared with serum levels.

**Minimal inhibitory concentration**

It has been suggested that experimentally determined “total tissue concentrations” are not good indicators of activity, since they represent average values, including unspecifically bound drug, and not the actually present concentrations at the site of action. For the same reason, the concept of
New antibiotics in paediatric clinical practice

The current concept on the aetiology of paediatric community-acquired pneumonia (PCAP) is mainly based on serological studies. The treatment is empirical and the recommendations are based on aetiological findings, not on clinical trials. On average, 35% of PCAP cases are caused by viruses alone, 25% by bacteria alone and 30% of PCAP cases are mixed viral–bacterial infections. Viral aetiologies are common in infants and young children. Mycoplasmal aetiology is common from the age of 5 years and chlamydial aetiology from the age of 10 years onwards. Most mycoplasmal and chlamydial PCAP cases are treated at home. Pneumococcus is the most important agent at all ages, and in both ambulatory and hospital settings. Pneumococcus must always be considered in the treatment of PCAP.

When high and intermediate levels are combined, the worldwide prevalence of pneumococcal penicillin resistance is >30%. Likewise, the worldwide prevalence of pneumococcal macrolide resistance is >30%, with large variations between different countries. At age <24 months, daycare at a centre and repeated antibiotic courses are the main risk factors for antibiotic resistance problems.

The new amoxicillin–clavulanate ratio (1:14) allows the use of high amoxicillin doses, i.e. 80–90 mg·kg−1·day−1. Even in the case of highly resistant strains, pneumococcal penicillin susceptibility is dose dependent, and >90% of pneumococcal strains are susceptible to amoxicillin at high doses. Amoxicillin–clavulanate is effective against β-lactamase-producing bacteria, which are common in ear and sinus infections, but are only occasionally causative agents in PCAP.

In paediatrics, fluoroquinolones are only allowed for restricted use due to potential cartilage toxicity. New group-4 compounds, moxifloxacin, gatifloxacin and gemifloxacin, are effective against Gram-positive and atypical bacteria, and, thus, have a broad spectrum for respiratory infections. Oral bioavailability and tissue penetration are both good. Their use in adults is rapidly increasing, and it is likely that pneumococcal resistance, based on the clonal spread of multiresistant strains, will be faced in the near future. Currently, nearly all pneumococcal strains, including penicillin- and macrolide-resistant strains, are susceptible to new fluoroquinolones. There are no dose recommendations for children. http://www.mayo.edu/proceedings/2003/sep/7809r1.pdf

Ketolides are semisynthetic erythromycin derivatives, and telithromycin is approved for >12-year-old children in Europe. Ketolides are effective against Gram-positive and atypical bacteria, and, as such, have a broad spectrum for respiratory infections. Currently, all pneumococcal strains, including macrolide-resistant strains, are susceptible to ketolides.

Telithromycin seems to induce resistance less than macrolides. In adults, the use of telithromycin is rapidly increasing, and the first telithromycin-resistant pneumococcal strains have been isolated.

Oxazolidinones are new synthetic antibiotics and have no relationship with other older antibiotics. Linezolid is registered for severe Gram-positive infections and it is effective against pneumococci, including both penicillin- and macrolide-resistant strains. Linezolid has no effect against atypical intracellular bacteria. Oral bioavailability and tissue penetration are good. There have been two controlled studies on linezolid in pneumonia in children, and the efficacy was >90% in PCAP. The dose of linezolid is 30 mg·kg−1·day−1 (in three divided doses). The drug is indicated only in severe/complicated pneumonia cases that are treated in hospital.

The misuse of antibiotics, such as the prescription of antibiotics for viral upper respiratory infections and the overuse of antibiotics due to false diagnoses of bacterial otitis media or bacterial sinusitis, increases antibiotic resistance in the community. Correspondingly, the cornerstone of PCAP treatment are correct diagnoses, preferably by chest radiographs, and the monitoring of pneumococcal antibiotic resistance in the area.

The selection of antibiotics to PCAP depends on the pneumococcal antibiotic resistance in the area. If both penicillin and macrolide resistance are low, the drug of choice for PCAP is penicillin or amoxicillin by conventional doses in <5-year-old children and macrolides for >5-year-old children. If pneumococcal penicillin resistance is common, high-dose amoxicillin should be used, i.e. 90 mg·kg−1·day−1. If pneumococcal macrolide resistance is common, the drug of choice is penicillin or amoxicillin using conventional doses for all ages. Macrolides can be combined with β-lactams, but they should not be used as the sole medication.

Suggested further reading

Jacobs M. Worldwide trends in antimicrobial resistance among common respiratory tract pathogens. Pediatr Infect Dis J 2003; 22: Suppl. 8, S109–S119. A review on antimicrobial resistance problems, based mainly on the Alexander Project and national surveillance studies in different countries, and focusing clearly on the problems faced in paediatric practice.

Felmingham D, Farell D, Reinert R, Morsey I. Antibacterial resistance among children with community-acquired respiratory tract infections (PROTEKT 1999–2000). J Infect 2004; 48: 39–55. A thorough review on antimicrobial resistance problems, based on the paediatric samples of the worldwide PROTEKT study. Although mainly aimed to monitor telithromycin susceptibility in respiratory bacteria, the project offers useful information for all groups of antibiotics.

Schito G, Marchese A. The impact of antibiotic resistance in the management of lower respiratory tract infections. Eur Respir Mon 2004; 28: 131–145. A useful discussion about the development of antibiotic resistance and its impact in clinical practice. Useful basic data, although paediatric experiences are not presented.
“tissue partition coefficients” is inadequate, since it implies homogenous tissue concentrations. It is the aqueous unbound concentration at the site of infection in the tissue that is most relevant for the magnitude of antibiosis. In any case, there is growing consensus on the opinion that neither blood nor tissue levels are of primary importance and that the tissue/blood ratio is equally scarcely important. More important, instead, is the correlation between blood or tissue concentrations of the drug and the minimal inhibitory concentration (MIC) values for the infectious agent.

The results of several studies seem to indicate a good correlation between pulmonary concentrations of a drug and the MIC for the pathogens; however, they have only associated MIC values with the peak concentration at the site of infection. In vivo, bacteria are not exposed to constant antibiotic concentrations, as they are constantly changing, with peaks and troughs. Therefore, pathogens are exposed to a gradient of antibiotic concentration, according to the pharmacokinetics of the antibiotic, even at the pulmonary site of infection.

Pharmacodynamics

The addition of bacteriological characteristics to in vivo pharmacokinetic studies has triggered a "pharmacodynamic approach". Pharmacodynamic parameters integrate the microbiological activity and pharmacokinetics of an anti-infective drug by focusing on its biological effects, in particular growth inhibition and killing of pathogens. Being a major component of the antibiotic-bacterium interaction system, pharmacodynamics, when properly integrated with the pharmacokinetics established for the antibiotic, allow better evaluation of the dosage regimen in conjunction with its clinical response.

From concentrations greater than zero up to twice the MIC, all antibacterials kill bacteria more rapidly as concentrations increase. After 2–4-times MIC, the mechanisms of killing diverge. β-Lactam agents, vancomycin, clindamycin and the macrolides kill bacteria in a time-dependent fashion. The aminoglycosides, fluoroquinolones and metronidazole are concentration-dependent killers.

Assessing antibiotic efficacy

Pharmacodynamic parameters used to assess efficacy in β-lactam antibacterials are the length of time that the serum concentration exceeds the MIC (t >MIC) and area under the curve for the time interval that the concentrations are above the MIC divided by the MIC value (AUIC). This is also known as AUC/MIC. Time-dependent killing is characterised by maximum efficacy of an antimicrobial at 2–4-times the MIC, an exposure profile achieved when 80–100% of the concentrations are above the MIC. This also coincides with an AUC24/MIC ratio of 125 (where AUC24 is the AUC to 24 h). Further increases in concentration above these values do not kill bacteria more rapidly. A previous study has shown a significant correlation between AUIC, t >MIC and time to eradication. Further analysis of the data revealed that an AUIC >125 also correlated with microbiological response.

Quinolones and aminoglycosides show a concentration-dependent bactericidal effect for most bacteria. Thus, the ratio maximum concentration (Cmax)/MIC should be the parameter that correlates most closely with efficacy. A value of Cmax/MIC of 8-times the MIC for quinolones predicts a satisfactory outcome. However, it has been found that AUIC is the best predictor of efficacy for fluoroquinolones in clinical practice. In any case, the Cmax/MIC, t >MIC and AUIC are all linked to a positive clinical outcome for fluoroquinolones and aminoglycosides.

Impact on antibiotics administration

It is extremely difficult to define the real impact of the interrelationship between pulmonary pharmacokinetics and pharmacodynamics on clinical and microbiological outcomes. The
majority of studies have, in fact, only examined the interrelationship between serum pharmacokinetics and pharmacodynamics in patients with lower respiratory tract infections (LRTIs), probably because it is easier and ethical to sample blood rather than sputum, bronchial mucosa or ELF. Since β-lactams exert a dose-dependent bactericidal effect on bacteria and do not possess a significant post-antibiotic effect, their levels at the sites of infection should be above MIC for the entire length of treatment. A significant linear correlation exists between $t > \text{MIC}$ and time to eradication of bacteria from respiratory secretions. Nevertheless, the magnitude and duration by which concentrations must exceed the MIC remain controversial.

Experimental research has shown that cephalosporins exert an in vivo bacteriostatic effect, even when their concentrations are above MIC for only 40% of the time between administrations, whereas maximal bactericidal effect is obtained when concentrations are above MIC for 60–70% of time. Therefore, the aim for a highly effective dosing regimen would be to provide levels above the MIC for at least 70% of the dosing interval. Although these data are intriguing, it must be noted that it is always better to administer high concentrations of the drug, particularly when treating patients hospitalised in intensive care units, because studies on β-lactam tissue kinetics show evidence of a decline in antibiotic tissue levels parallel to serum concentrations.

**Resistance**

It must also be highlighted that there is a close link between antibiotic dosing and antibiotic resistance. As the number of really active antibiotics is declining rapidly, it is now becoming imperative to manage resistance by managing the dosing and usage patterns of the remaining agents. With all β-lactams, which have a slow, time-dependent antibacterial effect, the aim must be to keep the antibiotic level above the MIC for the duration of therapy. Consequently, if the drug has a long life, single doses at long intervals can be given. However, if the half-life is short, the antibiotic should be given frequently, thus ensuring that the β-lactam is maintained at concentrations above MIC at all times in infected tissues. However, at least for β-lactams, some studies question the role of pulmonary pharmacodynamics, and seem to indicate that the correlation between clinical and microbiological outcomes and serum concentration is better than that between the outcomes and pulmonary levels of the antibiotic, probably because serum concentration better reflects interstitial fluid concentration.

Conversely, drugs that penetrate well and remain for long periods of time at the pulmonary site of infection often induce therapeutic responses greater than expected on the basis of in vitro data. Thus, fluoroquinolones, which concentrate in pulmonary tissues and fluids reach levels that are sufficient to overcome a good percentage of cases of infective processes caused by *Streptococcus pneumoniae*, which presents high MICs toward these antibiotics.

Several macrolides, such as azithromycin and dirithromycin, which are capable of penetrating massively into cells and interstitial fluid, and remaining there for long periods of time causing sustained high tissue concentrations for many hours following the last administration of the drug, are unexpectedly effective against *Haemophilus influenzae* in the treatment of acute exacerbations of chronic bronchitis and community-acquired pneumonia. A high efficacy in respiratory infections caused by *H. influenzae* has been shown for clarithromycin and this is probably due to its excellent lung penetration.

**During inflammation**

In conclusion, antimicrobials show considerable variation in their ability to penetrate pulmonary tissues. Nonetheless, lung penetration is considered, in part, to be predictive of efficacy in the treatment of LRTIs. Unfortunately, most studies are performed during the steady state in uninfected individuals. This could result in bias, because the pharmacokinetics of antibiotics may be altered in individuals with an infection.

In order to provide the greatest insight into
the utility of these agents for different pathogens causing LRTIs, it is important to examine the penetration in the presence of the pathological process for which they are being employed. The presence of LRTIs will have significant inflammation attendant to them. It is likely that this inflammation will alter penetration in a time-dependent way. The inflammation is likely to peak early in the process, with a maximal effect on tight junctions and penetration occurring in the first few days after introduction of the drug. As the agent starts the resolution process, it is further likely that penetration will decrease. These issues need to be adequately studied if we are to gain the fullest understanding of drug penetration and its effect on the pathological process of LRTIs. It is also possible that tissue penetration at steady state differs from that after a single dose. Consequently, several doses may be needed to achieve the steady state, which may also affect tissue penetration. Continued research is warranted to determine the best method of assessing respiratory tract concentrations and prediction of clinical response.

**Educational questions**

1. The concentration of β-lactams is highest in:
   - [ ] sputum  [ ] bronchial secretion  [ ] bronchial mucosa  [ ] ELF  [ ] alveolar macrophages

2. Which class of antimicrobials presents the highest penetration into alveolar macrophages:
   - [ ] β-lactams  [ ] macrolides  [ ] aminoglycosides  [ ] fluoroquinolones

3. Which classes of antimicrobials are concentration-dependent:
   - [ ] β-lactams  [ ] macrolides  [ ] aminoglycosides  [ ] fluoroquinolones

4. Which is the best PK/PD parameter predictive of bacteriological efficacy for antimicrobials with time-dependent killing and prolonged persistent effects:
   - [ ] peak/MIC  [ ] time of dosing interval above MIC  [ ] AUC/MIC

5. Cephalosporins exert an in vivo bacteriostatic effect even when their concentrations are above MIC for at least:
   - [ ] 20% of the time between administrations
   - [ ] 40% of the time between administrations
   - [ ] 50% of the time between administrations

6. The role of pulmonary pharmacodynamics is questioned for:
   - [ ] antimicrobials with concentration-dependent killing and prolonged persistent effects
   - [ ] antimicrobials with time-dependent killing and minimal-moderate persistent effects
   - [ ] antimicrobials with time-dependent killing and prolonged persistent effects

**References**

1. Bergogne-Bérzin E. New concepts in the pulmonary disposition of antibiotics. Pulm Pharmacol 1995; 8: 65–81.
2. Bergogne-Bérzin E. Predicting the efficacy of antimicrobial agents in respiratory infections – is tissue concentration a valid measure? J Antimicrob Chemother 1995; 35: 363–371.
3. Cazzola M, Blasi F, Terzano C, Matera MG, Marsico SA. Delivering antibacterials to the lungs: considerations for optimizing outcomes. Am J Respir Med 2002; 1: 261–272.
4. Cazzola M, D’Annato G, Matera MG. Intrapulmonary penetration of antimicrobials and implications in the treatment of lower respiratory tract infections. Eur Respir Mon 2004; 28: 13–44.
5. Cazzola M, Matera MG. Interrelationship between pharmacokinetics and pharmacodynamics in the design of dosage regimens for treating acute exacerbations of chronic bronchitis. Respir Med 1998; 92: 895–901.
6. Chiu LM, Amsden GW. Intrapulmonary pharmacokinetics of antibacterial agents: implications for therapeutics. Am J Respir Med 2002; 1: 201–209.
7. Craig WA. The hidden impact of antibacterial resistance in respiratory tract infection. Re-evaluating current antibiotic therapy. Respir Med 2001; 95: Suppl A, S12–S19.
8. Drusano GL, Preston SL, Fowler C, Corrado M, Weisinger B, Kahn J. Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. J Infect Dis 2004; 189: 1590–1597.
9. Highet VS, Forrest A, Ballow CH, Schentag JJ. Antibiotic dosing issues in lower respiratory tract infection: population-derived area under inhibitory curve is predictive of efficacy. J Antimicrob Chemother 1999; 43: Suppl A, 55-63.
10. Honeybourne D. Antibiotic penetration in the respiratory tract and implications for the selection of antimicrobial therapy. Eur Respir Mon 1997; 3: 170–174.
11. Hyatt JM, Mckinnon PS, Zimmer GS, Schentag JJ. The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. Focus on antibacterial agents. Clin Pharmacokin 1995; 28: 143–160.
12. Jacobs MR. Optimisation of antimicrobial therapy using...
pharmacokinetic and pharmacodynamic parameters. Clin Microbiol Infect 2001; 7: 589–596.

13. Nix DE. Intrapulmonary concentrations of antimicrobial agents. Infect Dis Clin North Am 1998; 12: 631–646.

14. Schentag JJ, Gilliland KK, Paladino JA. What have we learned from pharmacokinetic and pharmacodynamic theories? Clin Infect Dis 2001; 32: Suppl. 1, S39–S46.

15. Jacobs M, Johnson C. Macrolide resistance: an increasing concern for treatment failure in children. Pediatr Infect Dis J 2003; 22: Suppl. 8, S131–S138.

16. Klein J. Amoxicillin/clavulanate for infections in infants and children: past, present and future. Pediatr Infect Dis J 2003; 22: Suppl. 8, S139–S148.

17. Grady R. Safety profile of quinolone antibiotics in the pediatric population. Pediatr Infect Dis J 2003; 22: 1128–1132.

18. Jacobs M, Dagan R. Antimicrobial resistance among pediatric respiratory tract infections: clinical challenges. Semin Pediatr Infect Dis 2004; 15: 5–20.

19. Jantausch B, Deville J, Adler S, et al. Linezolid for the treatment of children with bacteremia and nosocomial pneumonia caused by resistant Gram-positive bacteria. Pediatr Infect Dis J 2003; 22: Suppl. 9, S164–S171.

20. Reinner R. Clinical efficacy of ketolides in the treatment of respiratory tract infections. J Antimicrob Chemother 2004; 53: 918–927.

21. Kuhnke A, Lode H. Fluoroquinolones and lower respiratory tract infections. Eur Respir Mon 2004; 28: 94–112.

22. Benavid D, Rahav E, Rubinstein E. Future antibiotics and current practices for treating respiratory tract infections. Eur Respir Mon 2004; 28: 255–267.

Further reading

European Respiratory Monograph, Volume 9, 2004
Antibiotics and the lung
M. Cazzola, F. Blasi, S. Ewig

Answers

For answers and access to the original educational material presented in Glasgow 2004, please go to the Breathe website: www.breathe-cme.org.