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## MICROBIOLOGY FOR ANAESTHETISTS PART 1 - THE PHARMACOLOGY OF ANTIBACTERIAL AND ANTIVIRAL DRUGS

### ANAESTHESIA TUTORIAL OF THE WEEK 190

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#### QUESTIONS:

Before continuing try to answer the following questions. The answers can be found at the end of the article.

1. The following antibacterial agents interfere with protein synthesis
  - a) Amoxicillin
  - b) Erythromycin
  - c) Tetracycline
  - d) Trimethoprim
  - e) Penicillin
  
2. Cefuroxime is
  - a) Bacteriostatic
  - b) Active against gram positive organisms only
  - c) Contains a beta lactam ring
  - d) Active against Methicillin Resistant Staph Aureous (MRSA)
  - e) Is resistant to stomach acid
  
3. The Aminoglycoside antibiotics
  - a) Are well absorbed from the GI tract
  - b) Are toxic to the liver
  - c) Shorten the duration of neuromuscular blocking drugs
  - d) May cause deafness
  - e) Affect bacterial wall formation

## INTRODUCTION

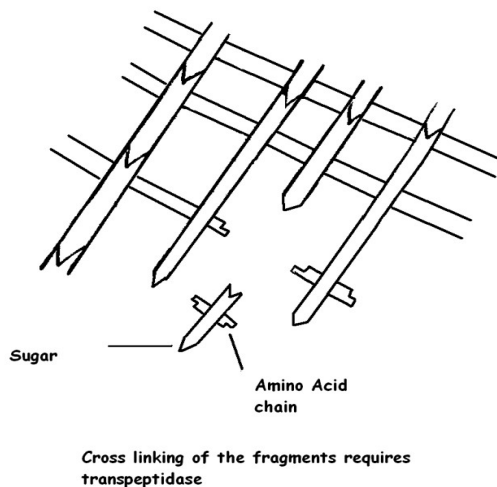
Antibacterial and antiviral drugs includes the antibiotics, which are drugs produced by micro-organisms and chemotherapeutic agents that are chemically synthesised. Antibacterial drugs may be used to treat infection, or may be given prophylactically to prevent the development of infection. This latter use is common in some forms of surgery and anaesthetists are often responsible for giving these drugs. Therefore it is important to understand their pharmacology and the nature of any interactions with other drugs used in anaesthesia.

Antibacterial drugs bring about their action by one of two mechanisms. They can limit bacterial growth, a **bacteriostatic** effect, slowing growth and allowing the immune system to remove the bacteria from the body. Alternatively they cause bacterial death, a **bacteriocidal** effect. At the same time, the host cells are undamaged by the drug. With antiviral drugs the virus replicates with in the host cells, so drugs are required to selectively inhibit the metabolic processes specific to viral replication. This can only be achieved to a limited extent.

## ANTIBACTERIAL DRUGS MECHANISMS OF ACTION

### Inhibitors of cell wall synthesis.

These drugs act on bacteria that have a cell wall consisting of a lattice work of murein. They prevent the cross linkage of the molecules that make up the lattice. Mammalian cells do not have these rigid cell walls so are unaffected.



**Figure 1:** Bacterial cell wall structure

Drugs in this group include:

#### *Penicillins*

This is the oldest group of drugs and obtained from a mould, penicillium notatum. They inhibit the enzyme transpeptidase that forms the lattice cross links. Their action is bacteriocidal, because the defects in the murein wall allow the bacteria to swell and burst. The penicillin molecule contains a beta-lactam ring, which confers its anti-transpeptidase activity. In this original form it has a narrow antibacterial spectrum, confined to gram-positive bacteria, gram negative cocci and spirochetes. Many gram negative bacteria are unaffected by penicillin. Some bacteria produce a penicillinase (beta-lactamase) which cleaves the beta-lactam ring and confers penicillin resistance on the organism.

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Penicillins are well tolerated, but at high doses are neurotoxic and convulsions may be seen with sudden high concentrations in the brain. This is due to GABA antagonism and can occur after intrathecal or high dose intravenous administration.

Chemical manipulation of the penicillin molecule has been performed to give better bioavailability, penicillinase resistance and a wider spectrum of activity:

- Flucloxacillin is penicillinase resistant and orally absorbed.
- The aminopenicillin amoxicillin has a wider spectrum being active against many gram negative organisms. It is often combined with clavulanic acid, a beta-lactamase inhibitor that prevents the action of penicillinase.
- Carboxypenicillins such as carbicillin, ticarcillin and acylaminopenicillins such as mezlocillin and azlocillin have a very broad spectrum but are not acid stable, or penicillinase resistant. They are active against pseudomonas species. Piperacillin is often combined with a beta-lactamase inhibitor, tazobactam.

### *Cephalosporins*

These drugs also come from fungi and contain the beta-lactam group in their molecules. These are classified in generations.

- The earliest first generation cephalosporin was cephalexin, which is a broad-spectrum oral cephalosporin with activity largely against gram positive bacteria. It is bacteriosidal. Subsequent developments have produced a wider spectrum of activity.
- The second generation includes cefuroxime which has a broader spectrum including many gram negative species. Resistance to second generation cephalosporins is increasing.
- Third generation includes cefotaxime and ceftazidime, these have increased activity against gram negative species. They penetrate the CNS and are useful to treat meningitis caused by meningococci, pneumococci and H. influenzae.
- The fourth generation consists of one drug cefepime, which is active against pseudomonas aeruginosa.
- The fifth generation, soon to be launched, is called ceftobiprol is active against methicillin resistant staphylococcus aureus. (MRSA)

### *Vancomycin*

This drug is a glycopeptide and structurally unlike any other antibacterial drug. It inhibits cell wall production but also affect cell synthesis. It is highly polar and not absorbed from the gut. As a result it has been used to treat pseudomembranous enterocolitis caused by clostridium difficile. Resistance to this drug appears to be stable.

## **Inhibitors of tetrahydrofolate synthesis**

### *Trimethoprin and co-trimoxazole*

These two drugs inhibit the conversion of dihydrofolate to tetrahydrofolic acid by blocking dihydrofolate reductase. Tetrahydrofolic acid is a co-enzyme in the synthesis of purine bases and thymidine. These are required for the synthesis of DNA and RNA. The effect is to limit cell growth. They are therefore bacteriostatic.

Trimethoprin has selectivity for bacterial dihydrofolate reductase, but can affect human folate metabolism, occasionally causing bone marrow depression. It is usually combined with a sulphonamide sulfamethoxazole, which also affects folate metabolism but at a different step in the pathway. The combined preparation is more effective than either alone, and example of pharmacological synergy. Resistance to these drugs is rare.

Dapsone, acts by the same mechanism and is used prophylactically and as chemotherapeutic agent in leprosy, toxoplasmosis and acinomyosis.

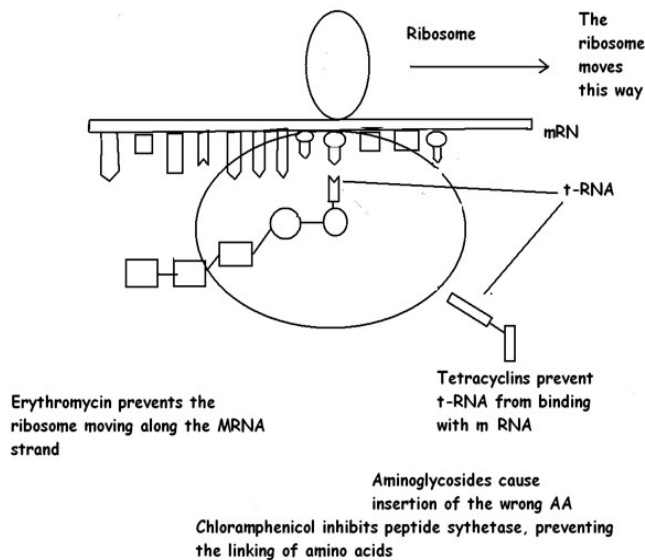
## Inhibitors of DNA function

### *Metronidazole and rifampicin*

Metronidazole damages DNA by complex formation with the DNA molecule and strand breakage. In anaerobic organisms it is converted to a reactive metabolite which attacks the DNA. It is bacteriocidal and also anti-protozoal and anti-amoebic. The drug is potentially mutagenic, teratogenic and should be avoided in pregnancy and lactation.

Rifampin prevents RNA transcription and is bacteriocidal against mycobacteria species as well as gram positive and gram negative organisms. Resistance develops and it is reserved for the treatment of TB and leprosy.

## Inhibitors of Protein Synthesis



**Figure 2:** Mechanisms of action of the Protein synthesis inhibitors

### *Tetracyclines, aminoglycosides, chloramphenicol and erythromycin.*

Tetracyclines and aminoglycoside drugs both alter transcription of RNA and creation of proteins. They bind to ribosomes and prevent the initiation of protein synthesis. Tetracyclines are broad spectrum and bacteriostatic. The aminoglycosides induce the production of 'false proteins' and are bacteriocidal. They are active against gram negative organisms. Gentamicin is not active against anaerobes because oxygen is needed for its uptake into the bacterial cell. It is synergistic with the beta-lactam containing antibiotics. The aminoglycosides are taken up in the tubular cells of the kidney and can cause renal tubular damage. They are also concentrated in the endolymph of the inner ear and can cause damage to the 8<sup>th</sup> cranial nerve. The toxic effects are associated with high peaks of serum concentration. Gentamicin levels may need to be monitored in renal impairment. If bolus doses are given they should be injected slowly over 5 minutes to prevent the peak concentration rising into the toxic range.

Chloramphenicol inhibits peptide synthetase, it has a bacteriostatic effect. It is toxic to bone marrow, particularly in babies. It is used in bacterial meningitis.

Erythromycin inhibits transfer RNA preventing the assembly of proteins. It is active against gram positives but most gram negative organisms are resistant to it. Clarithromycin is a derivative with better acid resistance and bioavailability. Clindomycin is a semisynthetic analogue that is well absorbed orally. These drugs are bacteriostatic.

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## Interactions between antibiotic drugs and anaesthetic agents.

Interactions can be pharmacokinetic or pharmacodynamic. Many antibacterial agents are highly protein bound and will displace other drugs, thereby affecting their toxicity and metabolism. Drugs which suppress synthesis of protein can affect the metabolism of other drugs. Classically gentamicin and the other aminoglycoside antibiotics prolong the duration of action of muscle relaxant drugs. They may also worsen symptoms in myasthenia gravis.

## ANTIVIRAL DRUGS MECHANISMS OF ACTION

In the last ten years the number of available antiviral drugs has increased from 5 to nearly 40. The mechanism of action of these drugs is aimed at various targets in the viral replication process. To replicate the virus needs to:

- 1) Enter the cell and separate from its protein coat
- 2) Interact with the cell DNA and produce viral RNA
- 3) Transcribe the viral RNA into viral proteins and new DNA.
- 4) Assemble the viral DNA and proteins into new viral particles

RNA viruses are simpler entities and need only replicate their own RNA and proteins for the outer coat.

The major target of these drugs is an enzyme called reverse transcriptase, which is involved in the synthesis of new viral molecules. The assembly of the viral particles requires a protease to cut larger protein molecules into the smaller molecules that make up the coat.

The three main classes of drugs used in the management of Human Immunodeficiency Virus (HIV) infection are:

- The Nucleoside Reverse Transcriptase Inhibitors (NRTI)
- The Nucleotide Reverse Transcriptase Inhibitors (NtRTI)
- The Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

They are usually used in combination therapy to reduce the incidence of viral resistance .

**Table 1.** Classification of antiviral drugs

Class of Antiviral Drug	Examples of this class
NRTI	Zidovudine, abacavir and emtricitabine;
NtRTI	tenofovir disoproxil fumarate
NNSRI	nevirapine, delavirdine and efavirenz;
Protease inhibitors	saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir (combined with ritonavir at a 4/1 ratio) and atazanavir;
Viral entry inhibitor	enfuvirtide.
Anti herpes virus drugs	Acyclovir, penciclovir, idoxuridine
Anti Influenza drugs;	
Prevents virus de-coating	Amantidine
Prevents release of viral particles from cells	Oseltamivir (tamiflu)
Anti Hepatitis C	
Used combined with Interferon Alpha	Ribavirin

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All these drugs are toxic, with particular risks of liver and renal toxicity. In any patient presenting for anaesthesia on these drugs, liver and renal impairment should be considered.

There is evidence that Zivodudine does not interact with paracetamol or non-steroidal anti-inflammatory drugs, and is also safe with codeine. There have been no other formal drug interaction studies with these drugs. The majority of the antiviral drugs require an acidic medium in the stomach for effective absorption. Patients give antacids or proton pump inhibitors as acid aspiration prophylaxis should not take antivirals after they have received this therapy, but wait until after anaesthesia has been safely performed.

## MEASUREMENT OF ANTIBIOTIC ACTIVITY AND EFFECTIVE DOSING

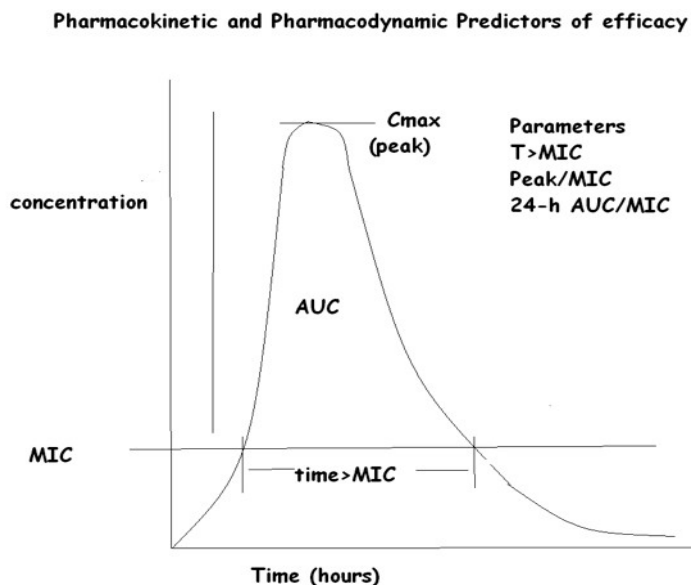
The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC). This is defined as the lowest concentration of an antibiotic that completely inhibits the growth of the micro-organism in vitro. Inhibition of growth is used because it is easier to look at the size of the colony on a plate than to look at actual cell death which requires counting of cells, a very labour intensive exercise. This is obviously an in vitro measure and does not tell us anything about the time course of activity in the body.

Pharmacokinetic parameters that are important in the action of antibiotic drugs are the peak serum level ( $C_{max}$ ), the trough level ( $C_{min}$ ) and the Area Under the serum concentration Curve (AUC). These are useful for knowing how much antibiotic is in the body, but don't tell us much about the killing activity of the drug. To integrate the 2 sets of measurements to get some idea of actually antibiotic activity, 3 combined parameters are used

These are

1. The ratio of the Peak/MIC
2. The time at a greater concentration than MIC;  $T > MIC$
3. The 24-hour AUC/MIC ratio.

These are all displayed on the graph below.



**Figure 3:** Pharmacokinetic & pharmacodynamic predictors of efficiency

Antibiotic effectiveness is either dependent on Time or Concentration at the site of infection. There is also a persistent or post-antibiotic effect where there is persistent suppression of bacterial growth following antibiotic exposure.

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**Table 2.** Type of antibiotic activity and goal of therapy.

Pattern of Activity	Antibiotics	Goal of Therapy	Parameter of importance
Type I Concentration dependent killing and prolonged persistent effect	Aminoglycosides Daptomycin Fluroquinolones Ketolides	Maximize concentration	24 AUC/MIC ratio and Peak/MIC ratio
Type II Time dependent killing and minimal persistent effects	Carbopenems Cephalosporins Erythromycin Penecillins	Maximise duration of exposure	T>MIC
Type III Time dependent killing and moderate to prolonged persistent effects	Azithromycin Clindamycin Oxazolidinones Tetracycline Vancomycin	Maximise amount of drug	24 AUC/MIC

With Type I drugs, the dosing regime should maximize concentration and for aminoglycosides the Peak/MIC ration should exceed 8 to prevent resistance developing. For fluoroquinolones, when used against gram negative bacteria, an optimal Peak to MIC ratio is 125. Against gram positive bacteria, 40 seems adequate but there is wide variation in the literature.

With Type II drugs the dosing regime is designed to maximise the duration of exposure. For beta-lactams and erythromycin the maximum killing is seen when the time above the MIC is at least 70% of the dosing interval

Type III Antibiotics have mixed properties. The amount of drug at the site is important and the 24-hour AUC/MIC ratio is the most important parameter. For vancomycin this ratio should be at least 125, or for more problem organisms as high as 400.

These combined pharmacokinetic and pharmacodynamic criteria give the most useful information for prescribing antibiotics.

## ANSWERS TO QUESTIONS

1. FTFTF
2. FFTFF
3. FFFTF

## WEBLINKS, REFERENCES and FURTHER READING

- [www.merk.com](http://www.merk.com). The Merk Manuals On Line Library covers a n enormous range of pharmacology and is always worth a look!
- Pharmacology for Anaesthesia and Intensive Care. Peck, Hill, Williams, Cambridge University Press.
- Antiviral Drugs in current clinical use. De Clercq E, Journal of Clinical Virology 30;2; 115-113 June 2004.