

Advantages of semisynthetic penicillins biology essay



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Introduction

Amoxicillin is a semisynthetic β -lactam antibiotic derived from a common chemical nucleus of naturally occurring Penicillin G, 6-aminopenicillanic acid. Vital to Amoxicillin's biological effects is the β -lactam ring contained within this nucleus. Amoxicillin is bacteriolytic and bacteriocidal to susceptible gram positive and gram negative microbacteria. Today, amoxicillin is the 9th most prescribed drug in the world.

Penicillin discovery

Up until the early 1900's, the only treatment for bacterial infection was antiseptic which was only useful for surface wounds. In 1928, Alexander Fleming made a momentous albeit accidental discovery in St Mary's Hospital in London. He noticed that a Staphylococci plate being grown in culture had been contaminated with mould of the species *Penicillium notatum* and that this had resulted in the inhibition of bacterial growth in the vicinity of the mould. Fleming subsequently isolated the mould and formulated an antibacterial mould broth. In 1938 at Oxford, Howard Florey and his biochemist Ernst Chain extracted penicillin from the mould and established that it was nontoxic and had chemotherapeutic effects. In 1941 an injectable form of penicillin became available for therapeutic use

Advantageous of Semisynthetic Penicillins

Penicillin G (naturally occurring) is poorly stable in gastric acid and broken down rapidly as it passes through the stomach. Therefore, Penicillin G must be given intramuscularly which limits its usefulness. Semisynthetic penicillins such as Amoxicillin with increased oral bioavailability were a major

advancement in therapeutic antibiotics. Furthermore, while aminopenicillins and natural penicillins have similar efficacy against gram positive bacteria, semisynthetic aminopenicillins (such as Amoxicillin) are more active against certain strains of gram negative rods.

Amoxicillin Discovery

In Beecham Laboratories in 1957, 6-aminopenicillanic acid (6-APA) was isolate from penicillin. Through chemical modification of the β -lactam thiazolidine ring side chains semisynthetic penicillins were developed. In 1961, Ampicillin was created which was quickly followed in 1964 by the introduction of a *p*-hydroxyl group in Ampicillin's side chain creating amoxicillin. Amoxicillin was found to have improved absorption following oral administration and 2-2.5 times greater plasma concentrations compared to an equivalent dose of Ampicillin.

In 1967 Beecham laboratories discovered that the susceptibility of Amoxicillin to β -lactamase could be overcome with co-administration of clavulanic acid (a β -lactamase inhibitor isolated from *Streptomyces olivaceus*).

Chemistry

Amoxicillin is a white crystalline powder that is somewhat soluble in alcohol and water. Amoxicillin's chemical name is (2S, 5R, 6R)-6-[(R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. It has a molecular weight of 419.4.

Figure 1: Chemical Structure of Amoxicillin

Pharmacodynamics

Amoxicillin functions by inhibiting the biosynthesis of cell wall mucopeptides of susceptible gram positive and negative microorganism's actively synthesizing peptidoglycan and undergoing multiplication. The molecular target of Amoxicillin and other β -lactam antibiotics are the Penicillin Binding Proteins. Upon drug-target interaction transpeptidation is blocked and thus inhibiting the synthesis of peptidoglycan, a vital cell wall component. Subsequently, the inhibitor of autolytic enzymes in the cell wall, is removed resulting in active autolytic enzymes and bacteriolysis.

Pharmacokinetics

Amoxicillin complies with the two compartment model with elimination occurring from the central compartment. Figure 2 demonstrates Amoxicillin's biexponential decline of serum concentration with time. Table 1 and 2 document the pharmacokinetic parameters of Amoxicillin.

Figure 2: Average serum concentration versus time after 500mg IV dose of Amoxicillin.

Table 1: Pharmacokinetic parameter and absolute bioavailability of a 500mg oral dose of Amoxicillin.

Table 2: Pharmacokinetic parameter of a 500mg IV dose of Amoxicillin.

Administration

Amoxicillin is usually administered orally. The relationship between dose and extent of absorption is not linear with a plateau at higher oral

concentrations. Dose adjustments need to be made in patients with renal dysfunction.

Bioavailability

Drug bioavailability is the proportion of drug that passes into systemic circulation after oral administration. It is dependent upon absorption across the gastrointestinal tract and first pass clearance by the liver. After oral administration of a dose of 250mg and 500mg of Amoxicillin the average peak serum concentrations (observed between 1-2 hours after administration) were 5.0mg/mL and 6.0 - 10.8 mg/mL respectively. The variation of plasma concentration with time is demonstrated in Figure 3. The oral bioavailability of Amoxicillin is 77.4% Amoxicillin is stable in gastric acid and is rapidly absorbed after oral administration regardless of absence or presence of food products and thus a high proportion of administered dose reaches the systemic circulation..

Figure 3: Mean serum levels following oral administration of 125mg and 250mg of Amoxicillin to 11 normal volunteers. (95% confidence).

Volume of Distribution

Volume of distribution is defined as the volume of fluid in which the amount of drug in the body would need to be uniformly distributed to produce observed plasma concentrations. Amoxicillin distributes widely and rapidly into most body tissues and fluid. Despite this, Amoxicillin remains extracellular due to lipid insolubility and thus does not cross the blood brain barrier unless the meninges are inflamed. Volume of distribution of Amoxicillin is 20.2L (0.3 L/kg).

Clearance

Clearance is defined as the volume of blood cleared of drug per unit time. It is dependent on renal excretion hepatic elimination. The clearance of Amoxicillin is 221mL/min.

Renal Excretion

Amoxicillin is excreted predominantly via the urine in biologically active form or as penicilloic acid. 75% of a 1 gram dose is excreted in the urine within 6 hrs (60% biologically active form, 15% is in the form of penicilloic acid).

Biological Half life

Elimination half life is defined by the time taken for the plasma concentration of drug to reach half the steady state concentration. The biological half life is 61. 3 minutes with normal renal function. Half life increases with renal dysfunction.

Clinical Uses

Amoxicillin is a broad spectrum β -lactam antibiotic with effectiveness against many pathogenic microorganisms. It is commonly used to treat bacterial infections such as otitis media, tonsillitis, throat infections, laryngitis, bronchitis, pneumonia, urinary tract infections, gonorrhoea and skin infections.

Indications for use

Location of infection

Microorganism

Skin and skin structure

E coli, Staphylococcus, nonpenicillinase producing streptococcus

Respiratory (Acute and chronic)

nonpenicillinase producing E coli, Streptococcus, Strep. Pneumonia, H. influenzae, staphylococcus

Genitourinary tract (Complicate and uncomplicated, acute and chronic)

E. Coli, P. mirabilis and Strep. Faecalis

Gonorrhoea

N. Gonorrhoea (nonpenicillinase producing)

Prophylaxis of endocarditis

Used in people at particular risk (e. g. individuals who have previously had endocarditis or with a prosthetic heart valve)

Table 3: Indications for use of Amoxycillin

Precautions

Drug interactions

Amoxicillin is rarely associated with adverse drug interactions however the following reactions have been demonstrated in some cases.

Drug

Interaction

Oral anticoagulants (e. g. Warfarin and Acenocoumarol)

Results in abnormal prolongation of prothrombin time (or international normalised ratio.)

Allopurinol

Results in increased rate of rash reactions. It is unknown whether this is due to Amoxicillin reacting with the allopurinol itself or the hyperuricaemia that it is treating.

Combined Oral Contraceptives

Like all penicillin, Amoxicillin can affect the commensal gut flora which results in decreased oestrogen absorption. This has been associated with decreased efficacy of combined oral contraceptives.

Tetracyclines or other bacteriostatic drugs

Bacteriostatic drugs have been known to interfere with the bactericidal effects of Amoxicillin

Clavulanic acid

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Amoxicillin therapeutic effects are inactivated by penicillinase (β -lactam) producing organisms. It is possible to co-administer Amoxicillin with clavulanic acid (β -lactamase inhibitor) to broaden the spectrum of susceptible bacteria (e. g.. co-amoxiclav).

Probenecid

Renal excretion can be delayed by administration of Probenecid as demonstrated by Figure 4. When used in conjunction there is an increased plasma concentration of Amoxicillin reached and longer duration of effect. This is a beneficial interaction.

Table 4: Some common drug interactions when co-administered with Amoxicillin

Figure 4: Mean serum levels following oral administration of 1 gram of Amoxicillin with and without probenecid.

Pregnancy and Lactation

While penicillin can cross the placenta, no teratogenic effects have been uncovered through animal studies. Similarly, Amoxicillin can be excreted in breast milk resulting in potential side effects for the nursing infant including diarrhoea or allergic response. However, Amoxicillin is generally considered safe for use in pregnant women and nursing mothers.

Adverse reactions

Side effects are uncommon however potentially include insomnia, diarrhoea, dizziness, confusion, heartburn, easy bruising, itching, nausea, vomiting, abdominal pain, bleeding, rash and allergic reactions.

The most common adverse reaction is hypersensitivity reactions in patients with allergies to β lactam antibiotics, penicillin or cephalosporins.

Anaphylaxis can be fatal and occurs more frequently following parenteral administration.

All penicillins have been associated with seizures when administered in excessive doses or administered intrathecally.

Conclusion

The discovery of penicillin by Alexander Flemming lead to the subsequent generation of the semisynthetic aminopenicillin, Amoxicillin. This β -lactam antibiotic has a broad spectrum of therapeutic use, high oral bioavailability and lack of toxic effects.