Amoxicillin

Bactericidal aminopenicillin with same spectrum as ampicillin (ineffective against bacteria that produce beta-lactamase)

Most likely adverse effects are GI-related, but hypersensitivity and other adverse effects rarely occur

Available in oral and parenteral dosage forms

Pharmacology/Uses/Indications

Although there may be some slight differences in activity against certain organisms, amoxicillin generally shares the same spectrum of activity and uses as ampicillin. Because it is better absorbed orally (in non-ruminants), higher serum levels may be attained than with ampicillin.

Penicillins are usually bactericidal against susceptible bacteria and act by inhibiting mucopeptide synthesis in the cell wall resulting in a defective barrier and an osmotically unstable spheroplast. The exact mechanism for this effect has not been definitively determined, but beta-lactam antibiotics have been shown to bind to several enzymes (carboxypeptidases, transpeptidases, endopeptidases) within the bacterial cytoplasmic membrane that are involved with cell wall synthesis. The different affinities that various beta-lactam antibiotics have for these enzymes (also known as penicillin-binding proteins; PBPs) help explain the differences in spectrums of activity the drugs have that are not explained by the influence of beta-lactamases. Like other beta-lactam antibiotics, penicillins are generally considered more effective against actively growing bacteria.

The aminopenicillins, also called the "broad-spectrum" or ampicillin penicillins, have increased activity against many strains of gram-negative aerobes not covered by either the natural penicillins or penicillinase-resistant penicillins, including some strains of *E. coli, Klebsiella,* and *Haemophilus*. Like the natural penicillins, they are susceptible to inactivation by beta-lactamase-producing bacteria (e.g. *Staph aureus*). Although not as active as the natural penicillins, they do have activity against many anaerobic bacteria, including *Clostridial* organisms. Organisms that are generally not susceptible include *Pseudomonas aeruginosa*, *Serratia*, Indole-positive *Proteus* (*Proteus mirabilis* is susceptible), *Enterobacter*, *Citrobacter*, and *Acinetobacter*. The aminopenicillins also are inactive against *Rickettsia*, mycobacteria, fungi, *Mycoplasma*, and viruses.

In order to reduce the inactivation of penicillins by beta-lactamases, potassium clavulanate and sulbactam have been developed to inactivate these enzymes and thus extend the spectrum of those penicillins. When used with a penicillin, these combinations are often effective against many beta-lactamase-producing strains of otherwise resistant *E. coli, Pasturella* spp, *Staphylococcus* spp, *Klebsiella*, and *Proteus*. Type I beta-lactamases that are often associated with *E. coli, Enterobacter,* and *Pseudomonas* are not generally inhibited by clavulanic acid.

Uses/Indications

The aminopenicillins have been used for a wide range of infections in various species. FDA-approved indications/species, as well as non-approved uses, are listed in the Dosages section below.

Pharmacokinetics (General)

The oral absorption characteristics of the penicillins are dependent upon its class. Penicillin G is the only available oral penicillin that is substantially affected by gastric pH and can be completely inactivated at pH's of less than 2. The other orally available penicillins are resistant to acid degradation but bioavailability can be decreased by the presence of food (not amoxicillin). Of the orally administered penicillins, penicillin V and amoxicillin tend to have the greatest bioavailability in their respective classes.

Penicillins are generally distributed widely throughout the body. Most drugs attain therapeutic levels in the kidneys, liver, heart, skin, lungs, intestines, bile, bone, prostate, and peritoneal, pleural and synovial fluids. Penetration into the CSF and eye only occur with inflammation and may not reach therapeutic levels. Penicillins are bound in varying degrees to plasma proteins and they cross the placenta.

Most penicillins are rapidly excreted largely unchanged by the kidneys into the urine via glomerular filtration and tubular secretion. Probenecid can prolong half-lives and increase serum levels by blocking the tubular secretion of penicillins. Except for nafcillin and oxacillin, hepatic inactivation and biliary secretion is a minor route of excretion.

Pharmacokinetics (Specific)

Amoxicillin trihydrate is relatively stable in the presence of gastric acid. After oral administration, it is about 74-92% absorbed in humans and animals (monogastric). Food will decrease the rate, but not the extent of oral absorption and many clinicians suggest giving the drug with food, particularly if there is concomitant associated GI distress. Amoxicillin serum levels will generally be 1.5-3 times greater than those of ampicillin after equivalent oral doses.

After absorption, the volume of distribution for amoxicillin is approximately 0.3 L/kg in humans and 0.2 L/kg in dogs. The drug is widely distributed to many tissues, including liver, lungs, prostate (human), muscle, bile, and ascitic, pleural and synovial fluids. Amoxicillin will cross into the CSF when meninges are inflamed in concentrations that may range from 10-60% of those found in serum. Very low levels of the drug are found in the aqueous humor, and low levels found in tears, sweat and saliva. Amoxicillin crosses the placenta, but it is thought to be relatively safe to use during pregnancy. It is approximately 17-20% bound to human plasma proteins, primarily albumin. Protein binding in dogs is approximately 13%. Milk levels of amoxicillin are considered low.

Amoxicillin is eliminated primarily through renal mechanisms, principally by tubular secretion, but some of the drug is metabolized by hydrolysis to penicilloic acids (inactive) and then excreted in the urine. Elimination half-lives of amoxicillin have has been reported as 45-90 minutes in dogs and cats, and 90 minutes in cattle. Clearance is reportedly 1.9 ml/kg/min in dogs.

Contraindications/Precautions

Penicillins are contraindicated in patients who have a history of hypersensitivity to them. Because there may be cross-reactivity, use penicillins cautiously in patients who are documented hypersensitive to other beta-lactam antibiotics (e.g., cephalosporins, cefamycins, carbapenems).

Do not administer systemic antibiotics orally in patients with septicemia, shock, or other grave illnesses as absorption of the medication from the GI tract may be significantly delayed or diminished. Parenteral (preferably IV) routes should be used for these cases.

Reproductive/Nursing Safety

Penicillins have been shown to cross the placenta and safe use of them during pregnancy has not been firmly established, but neither have there been any documented teratogenic problems associated with these drugs. However, use only when the potential benefits outweigh the risks. In humans, the FDA categorizes this drug as category **B** for use during pregnancy (**Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.)** In a separate system evaluating the safety of drugs in canine and feline pregnancy, this drug is categorized as in class: **A (Probably safe. Although specific studies may not have proved the safety of all drugs in dogs and cats, there are no reports of adverse effects in laboratory animals or women.)**

Adverse Effects/Warnings

Adverse effects with the penicillins are usually not serious and have a relatively low frequency of occurrence.

Hypersensitivity reactions unrelated to dose can occur with these agents and can be manifested as rashes, fever, eosinophilia, neutropenia, agranulocytosis, thrombocytopenia, leukopenia, anemias, lymphadenopathy, or full-blown anaphylaxis. In humans, it is estimated that up to 15% of patients hypersensitive to cephalosporins will also be hypersensitive to penicillins. The incidence of cross-reactivity in veterinary patients is unknown.

When given orally, penicillins may cause GI effects (anorexia, vomiting, diarrhea). Because the penicillins may also alter gut flora, antibiotic-associated diarrhea can occur, as well as selecting out resistant bacteria maintaining residence in the colon of the animal (superinfections).

High doses or very prolonged use has been associated with neurotoxicity (e.g.,ataxia in dogs). Although the penicillins are not considered hepatotoxic, elevated liver enzymes have been reported. Other effects reported in dogs include tachypnea, dyspnea, edema and tachycardia.

Overdosage/Acute Toxicity

Acute oral penicillin overdoses are unlikely to cause significant problems other than GI distress, but other effects are possible (see Adverse Effects). In humans, very high dosages of parenteral penicillins, especially in patients with renal disease, have induced CNS effects.

Drug Interactions

In vitro studies have demonstrated that penicillins can have synergistic or additive activity against certain bacteria when used with **aminoglycosides** or **cephalosporins**.

Use of **bacteriostatic antibiotics** (e.g.,**chloramphenicol, erythromycin, tetracyclines**) with penicillins is generally not recommended, particularly in acute infections where the organism is proliferating rapidly as penicillins tend to perform better on actively growing bacteria. In low concentrations, certain penicillins (e.g.,ampicillin, oxacillin or nafcillin) may have additive or synergistic effects against certain bacteria when used with **rifampin**, but there is apparent antagonism when the penicillin is present in high concentrations.

Probenecid competitively blocks the tubular secretion of most penicillins, thereby increasing serum levels and serum half-lives.

Doses

Dogs

For susceptible infections:

1. For Gram + infections: 10 mg/kg PO, IM, SC twice daily for at least 2 days after symptoms subside. For Gram-infections: 20 mg/kg PO three times daily or IM, SC twice daily; for at least 2 days after symptoms subside

2. For susceptible UTI's: 10-20 mg/kg PO q12h for 5-7 days. For susceptible systemic infections: 22-50 mg/kg PO q8h for 7 days. For susceptible orthopedic infections: 22-30 mg/kg IV, IM, SC, or PO q6-8h for 7-10 days. NOTE: Duration of treatment are general guidelines, generally treat for at least 2 days after all signs of infection are gone.

3. For Lyme disease: 22 mg/kg PO q12h for 21-28 days

Cats

For susceptible infections:

1. For Gram + infections: 10 mg/kg PO, IM, SC twice daily for at least 2 days after symptoms subside. For Gram-infections: 20 mg/kg PO three times daily or IM, SC twice daily; for at least 2 days after symptoms subside

2. For susceptible UTI's and soft tissue infections 50 mg (total dose per cat) or 11-22 mg/kg PO once daily for 5-7 days. For sepsis:: 10-20 mg/kg IV, SC, or PO q12h for as long as necessary. NOTE: Duration of treatment are general guidelines, generally treat for at least 2 days after all signs of infection are gone.

3. *C. perfringens*, bacterial overgrowth (GI): 22 mg/kg PO once daily for 5 days

4. *C. perfringens* enterotoxicosis: 11-22 mg/kg PO *bid-tid* for 7 days

5. For treating *H. pylori* infections using triple therapy: amoxicillin 20 mg/kg PO twice daily for 14 days; metronidazole 10-15 mg/kg PO twice daily; clarithromycin 7.5 mg/kg PO twice daily

Ferrets

1. For eliminating *Helicobacter* gastritis infections: Using triple therapy: Metronidazole 22 mg/kg, amoxicillin 22 mg/kg and bismuth subsalicylate (original *Pepto-Bismol*®) 17.6 mg/kg PO. Give each 3 times daily for 3-4 weeks.

2. For susceptible infections: 10-35 mg/kg PO or SC twice daily

Rabbits/Rodents/Pocket Pets

1. Hedgehogs: 15 mg/kg IM or PO q12h

Cattle

For susceptible infections:

1. 6-10 mg/kg SC or IM q24h (Withdrawal time = 30 days)

2. For respiratory infections: 11 mg/kg IM or SC q12h

3. **Calves**: Amoxicillin trihydrate: 7 mg/kg PO q8-12h

4. 13.2-15.4 mg/kg IM or SC once daily

Horses

For susceptible infections:

1. For respiratory infections: 20-30 mg/kg PO q6h

2. Amoxicillin trihydrate: 20 mg/kg q12h IM

3. **Foals**: Amoxicillin Sodium: 15-30 mg/kg IV or IM q6-8h; amoxicillin trihydrate suspension: 25-40 mg/kg PO q8h; amoxicillin/clavulanate 15-25 mg/kg IV q6-8h

Birds

For susceptible infections:

1. For most species: 150-175 mg/kg PO once to twice daily (using 50 mg/ml suspension)

2. 100 mg/kg q8h PO

3. 100 mg/kg q8h, IM, SC, PO

4. **Ratites**: 15-22 mg/kg PO twice daily; in drinking water: 250 mg/gallon for 3-5 days

Reptiles

For susceptible infections:

1. For all species: 22 mg/kg PO q12-24h; not very useful unless used in combination with aminoglycosides

Client Information

The oral suspension should preferably be refrigerated, but refrigeration is not absolutely necessary; any unused oral suspension should be discarded after 14 days. Amoxicillin may be administered orally without regard to feeding status. If the animal develops gastrointestinal symptoms (e.g.,vomiting, anorexia), giving with food may be of benefit.

Chemistry

An aminopenicillin, amoxicillin is commercially available as the trihydrate. It occurs as a practically odorless, white, crystalline powder that is sparingly soluble in water. Amoxicillin differs structurally from ampicillin only by having an additional hydroxyl group on the phenyl ring.

Storage/Stability/Compatibility

Amoxicillin capsules, tablets, and powder for oral suspension should be stored at room temperature (15-30°C) in tight containers. After reconstitution, the oral suspension should preferably be refrigerated (refrigeration not

absolutely necessary) and any unused product discarded after 14 days. After reconstitution, the injectable veterinary suspension is stable for 3 months at room temperature and 12 months when refrigerated.

Dosage Forms/Approval Status/Withholding Times

Amoxicillin Oral Tablets: 50 mg, 100 mg, 150 mg, 200 mg, 400 mg; *Amoxi-Tabs*® (Pfizer); (Rx). Approved for use in dogs and cats. *Biomox*® (Virbac), *Robamox-V*® (Fort Dodge); (Rx). Approved for use in dogs only.

Amoxicillin Powder for Oral Suspension 50 mg/ml (after reconstitution) in 15 ml or 30 ml bottles; *Amoxi-Drop*® (Pfizer); (Rx); Approved for use in dogs and cats. *Biomox*® (Virbac), *Robamox-V*® (Fort Dodge); (Rx). Approved for use in dogs.

Amoxicillin Oral Bolus 400 mg; *Amoxi-Bol*® (Pfizer); (Rx). Approved for use in non-ruminating calves, including veal calves. Slaughter withdrawal (when administered as labeled)= 20 days.

Amoxicillin Powder for Suspension (Injection): 3 gram vial (Dogs, Cats) and 25 g vial (non-lactating cattle); *Amoxi-Inject*® (Pfizer); (Rx). Approved for use in dogs and cats (3 g vial), Slaughter withdrawal for cattle (when administered as labeled) = 25 days. Milk withdrawal (when administered as labeled) = 96 hours.

Amoxicillin Intramammary Infusion 62.5 mg/syringe in 10 ml syringes; *Amoxi-Mast*® (Pfizer); (Rx). Approved for use in lactating dairy cattle. Slaughter withdrawal (when administered as labeled) = 12 days; Milk withdrawal (when administered as labeled) = 60 hours.