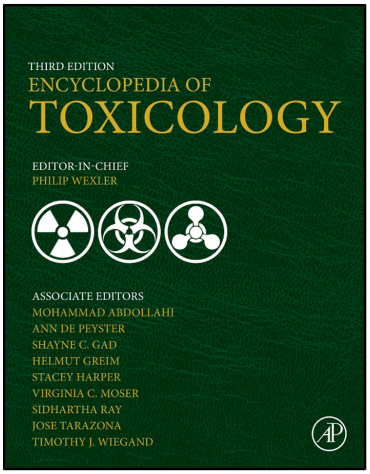

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Penicillins

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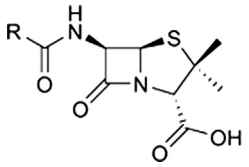
- Name: Penicillin
- Synonyms: Natural penicillins: Penicillin G, Procaine penicillin, Penicillin V, Benzathine penicillin; Penicillinase-resistant penicillins: Methicillin, Oxacillin, Dicloxacillin, Nafcillin, Cloxacillin; Aminopenicillins: Ampicillin, Amoxicillin, Bacampicillin; Antipseudomonal penicillins: Carbenicillin, Ticarcillin, Piperacillin, Azlocillin, Mezlocillin; Beta-lactam antibiotics
- Chemical/Pharmaceutical/Other Class: Antibiotic
- Molecular Mass: 334–539 g mol^{-1}
- General Chemical Structure:



Background

Since its accidental discovery in 1928, penicillin is the oldest known and still one of the most widely used antibiotic agents. It is derived from the mold or fungi *Penicillium chrysogenum*. The penicillin group is characterized by the presence of the 4-membered β-lactam ring fused to a 5-membered thiazolidine ring and an acyl side chain to the β-lactam ring. The penicillins are also called beta-lactam antibiotics. The presence of the lactam ring is essential for biological activity and is usually the site of cleavage by bacterial penicillinase or by an acid. The nature of the *R* (variable) group determines the drug's stability to enzymatic and acidic hydrolysis and its activity against different bacteria. Alteration of the *R* group, such as the addition of bulky side chains or functional groups, gives different variants of penicillins that are known to enhance activity, show resistance to penicillinase, and are more resistant to acid. Although penicillins have structural differences that dictate their antimicrobial activity, stability against penicillinase and acids, and behavior within the body, they uniformly have low toxicity. Unless used in high dosage, the absence of direct toxicity is one of the most remarkable properties of penicillin as antibiotics.

Penicillin acts as a bactericidal agent since the mode of action is the inhibition of the bacterial cell wall synthesis. They act on the peptidoglycan layer of gram-positive and gram-negative bacteria. Since penicillins are dipeptide analogs of D-ala-D-ala, it does prevent the assembly of the peptidoglycan by binding to and competitively inhibiting the transpeptidase enzyme used by bacteria to cross-link the peptide (*D-alanyl-alanine*). This destroys the ability of the peptidoglycan to bear the stress of osmotic pressure that acts on a bacterium. The resultant weakening of the peptidoglycan fabric of the growing bacterial cell results in osmotic lysis. In gram-positive organisms, the antibacterial effect of β-lactam antibiotics depends on the affinity of the antibiotic for the essential penicillin binding proteins (PBPs) of the organism because the cell wall peptidoglycan offers no resistance to the diffusion of small molecules. In gram-negative bacteria, antibiotic efficacy depends on the ability of the antibiotic to diffuse through the pores in the outer membrane of the bacteria and reach the target PBPs.

Occurrence and Classifications

Penicillin antibiotics, based on the way they are synthesized, can be classified into two groups, the naturally occurring and the semisynthetic penicillins. Naturally occurring penicillins are derived from the fermentation process of *Penicillium*, and include the pioneer group of antibiotic used clinically. Further, they are derived from the original penicillin-G structure, and the derivatives included are penicillin G (benzyl penicillin), penicillin V (phenoxymethylpenicillin), penicillin VK (phenoxymethylpenicillin potassium), and procaine penicillin. The large-scale production of these penicillins is done by feeding the culture medium with precursors such as phenylacetic acid for penicillin G or phenoxyacetic acid for penicillin V. Penicillin G is only used intravenously since it is destroyed by the acid in gastric juices, but penicillin V is the chemically improved form that combines acid stability with immediate solubility and rapid absorption. The natural penicillins are effective against non β-lactamase–producing gram-positive cocci (*Pneumococci*, *Staphylococci*, and *Streptococci*), few gram-negative cocci (*Meningococci* and *Monococci*), gram-positive bacilli (*Bacillus anthracis*, *Bacillus perfringens*, and *Bacillus diphtheriae*), anaerobes (*Clostridium perfringens* and *Clostridium perfringens tetani*), and spirochetes (*Treponema pallidum*, *Treponema pertenue*, and *Leptospira*). They are very susceptible to inactivation by β-lactamases and penicillase.

All other penicillins not produced naturally can be classified as semisynthetic penicillins, and are prepared from (+)-6-aminopenicillanic acid (6-APA), known as the core or nucleus of penicillins. Semisynthetic penicillins are obtained from the fermentation brew of the *Penicillium* mold, which is then broken down chemically or enzymatically to form 6-APA. The semisynthetic penicillins can be divided into several classes based on their ability and effectiveness in killing various types of bacteria, or the types of functional groups or

Encyclopedia of Toxicology, Third Edition, 2014, 768–772

side chains present in them. Semisynthetic penicillins constitute the penicillinase-resistant penicillins, extended-spectrum penicillins (aminopenicillins), and the broad-spectrum penicillins (antipseudomonal penicillins).

The penicillinase-resistant penicillins have a narrower spectrum of activity in comparison to the natural penicillins due to their bulky side chain, which prevents them from penetrating the bacterial cell membrane. Also known as the antistaphylococcal penicillins, the bulky side chains prevent the inactivation of the lactam ring by the staphylococcal β-lactamases. These penicillins are useful in treating infections caused by *Staphylococcus aureus* and *Staphylococcus epidermidis*. Among these groups are the methicillin (first member of the group and first penicillin developed through rational drug modification), oxacillin, dicloxacillin, and nafcillin. They are the only penicillins that by themselves are resistant to penicillinases.

Aminopenicillins, on the other hand, contain an amine group in their structure and comprise ampicillin and amoxicillin, the most prescribed and commonly used antibiotics. The aminopenicillins have wider range of activity than natural or antistaphylococcal penicillins. However, they lack the bulky side groups and are susceptible to inactivation by β-lactamases. The presence of additional hydrophilic groups allows the drug to penetrate into gram-negative bacteria via the porins. Since aminopenicillins are acid resistant, they are administered orally. They are also the first penicillins to be discovered to be active against gram-negative bacteria like *Escherichia coli*. Further, aminopenicillins are more effective against *Enterococci* and *Listeria monocytogenes* compared to penicillin G. They are also effective against gram-negative spectrum, including *Haemophilus influenzae*, *Salmonella*, *Shigella*, *E. coli*, *Proteus mirabilis*, *Neisseria gonorrhea*, and *Neisseria meningitidis*.

The antipseudomonal penicillins are similar to aminopenicillins in terms of susceptibility to β-lactamases and in structure, but have either a carboxyl group or urea group instead of the amine. It has also the same spectrum as the aminopenicillins, although it has additional activity against several gram-negative organisms (*Pseudomonas* and *Proteus*) due to their enhanced penetration through the cell wall of these bacteria. They include the carboxypenicillins (carbenicillin and ticarcillin) and ureidopenicillins (piperacillin, azlocillin, and mezlocillin).

Uses

Penicillin has been used to treat many different types of infections caused by bacteria, such as ear infections, bladder infections, pneumonia, gonorrhea, and *E. coli* or *Salmonella* infection. It has also been used for treatment of upper respiratory tract infections, pneumonia, skin and soft tissue infections, susceptible respiratory tract infections, genitourinary tract infections, septicemia, meningitis, endocarditis, and gastrointestinal tract infections. The choice of penicillin to be used depends on the causative bacteria.

Toxicokinetics (Pharmacokinetics)

The penicillins are usually administered orally, intravenously, and intramuscularly. When administered intramuscularly or subcutaneously, aqueous penicillin G is rapidly absorbed by the body. Following parenteral administration, initial blood levels are high but transient. Following intravenous infusion of penicillin G, peak plasma levels (C_{max}) are reached 15–30 min after, and concentrations fall by half within 1 h. Oral absorption is only about 15–30% as it is very susceptible to acid-catalyzed hydrolysis. Penicillin V, on the other hand, is acid stable unlike penicillin G and about 25% of a dose is absorbed and 50–60% is biologically available. It reaches C_{max} of 3 μg ml^{-1} after a 500 mg dose. The average blood levels are 2–5 times higher with penicillin V than levels following the same dose of oral penicillin G and show less individual variation. In terms of binding with serum proteins, mainly albumins, there is 45–68% binding of penicillin G and 80% of penicillin V.

Both penicillin G (16–30% intramuscular dose) and penicillin V (35–70% oral dose) are metabolized to form an inactive metabolite, penicilloic acid, and small amounts of 6-APA have been recovered in the patients' urine. In addition, both penicillins have one or more active metabolites formed by hydroxylation and excreted via urine. Penicillins are primarily and rapidly eliminated from the kidney by renal tubular secretion. About 60–90% of intramuscular aqueous penicillin G dose is eliminated in the urine, primarily within 1 h after injection, while penicillin V is eliminated as rapidly as it is absorbed in patients with normal renal and hepatic functions. Elimination of penicillins is delayed considerably in patients with impaired renal function.

Absorption of penicillase-resistant penicillins (dicloxacillin, oxacillin, and nafcillin) is rapid but incomplete after oral administration. It is delayed when the drugs are administered after meals. Only 33% of an oral dose of oxacillin is absorbed systemically in patients with normal renal and hepatic functions. The average plasma protein binding are high, ranging from 92 to 95% for oxacillin, from 93 to 98% for dicloxacillin, and from 88 to 91% for nafcillin in patients with normal renal and hepatic functions. The average plasma protein binding decreases in patients with renal dysfunction and with liver cirrhosis. Both oxacillin and dicloxacillin are rapidly excreted as unchanged drug in the urine by glomerular filtration and active tubular secretion. Urinary excretion of unchanged drug accounts for approximately 50% of oxacillin elimination and 61–77% of total dicloxacillin elimination. Oxacillin also undergoes hydroxylation in the liver and is excreted in bile. On the other hand, nafcillin is primarily metabolized by the liver. Urinary excretion of any unchanged penicillin drug accounts for 25–30% of drug elimination. Hepatic metabolism accounts for less than 30% of the biotransformation of most penicillins.

For the aminopenicillins, ampicillin is administered orally, intravenously, and parenterally while amoxicillin is only available by oral administration. Amoxicillin is well absorbed in comparison to ampicillin, with bioavailability ranging from 32 to 76% for ampicillin and from 73 to 97% for amoxicillin. Administration with food significantly decreases rate of absorption but not the extent of the extended-release tablet absorption in amoxicillin. Optimal absorption of amoxicillin occurs with lower dosages and when doses are taken with 250 ml of water. The plasma protein binding averages 20–29% for ampicillin and 18–20% in patients with normal renal and hepatic functions. Although ampicillin is partially metabolized by hydrolysis of the β-lactam ring, it is excreted largely

unchanged (73–92%) in the urine while the remainder is eliminated via biliary excretion or through metabolic pathways. On the other hand, amoxicillin is primarily eliminated through the kidneys via glomerular filtration and tubular secretion. Urinary excretion of unchanged drug is between 57 and 86%, and another 20% is excreted as the inactive penicilloic acid metabolite.

Carbenicillin is administered orally while ticarcillin and piperacillin are both administered parenterally. Carbenicillin is incompletely absorbed from the gastrointestinal tract, with bioavailability averaging from 30 to 40%. The plasma protein binding for carbenicillin averages 50% while it is 45–65% for ticarcillin and 16% for piperacillin in patients with normal renal and hepatic functions. Elimination of the three penicillins is primarily by the kidneys' glomerular filtration and tubular secretion, with 30% of an oral dose of carbenicillin excreted into the urine unchanged within 12 h, 77–92% ticarcillin excreted unchanged in the urine, and 60–80% of a dose of piperacillin excreted unchanged in the urine within 24 h.

In animals, penicillins are used as therapeutic agents applied orally and parenterally. Available data in birds suggest that the hepatic excretion pathway may predominate rather than the renal excretion pathway. Penicillin G intravenously administered to turkeys and chickens showed the same half-lives as that reported to humans and other mammals. The elimination of broad-spectrum penicillins in birds seems to be more dependent on biotransformation than in mammals. High dosages are needed to reach the same C_{max} in birds as in mammals after extravascular administration. Ampicillin and amoxicillin were found to have a low availability in the body after oral administration in birds in comparison to intramuscular injections.

Mechanism of Toxicity

As one of the safest antibiotics, penicillin has remarkably low toxicity against humans and animals. Toxicity only comes when there is an overdose of the drug and when renal excretion is not functioning well due to factors such as age, kidney disease, and allergic reaction. Although nontoxic, penicillin is highly immunogenic and it is the most common drug to cause allergy, which affects 1–10% of the population. The allergic reaction is a result of the formation of a hapten (penicillin)–protein complex, which stimulates an immune response. Those who have allergic response to penicillins have an immunoglobulin E (IgE)-antibody response and with other immunologic and non-immunologic factors may render then sensitive to subsequent exposure.

Acute and Short-Term Toxicity or Exposure

Human

Various routes of exposure for penicillin include inhalation, dermal, intravenous, and intramuscular routes, although oral administration is considered to be the most common form. Workers producing penicillin end products are likely to be exposed to penicillin in different physical forms via the inhalation and dermal routes. Exposure would be expected to occur during fermentation, chemical synthesis of derivatives, and formulation of end products. Adverse reactions have been reported upon exposure to penicillin agents, which include mild eye irritation, skin irritation, and respiratory tract irritation. Hypersensitivity reactions may occur with any dosage but is usually more severe following parenteral administration, although all degrees of hypersensitivity including anaphylaxis follows even after oral administration of the drug. The most common manifestations of hypersensitivity include skin eruptions (from mild rash to exfoliative dermatitis) with an overall incidence of approximately 2%, urticaria, chills, fever, edema, eosinophilia, and anaphylaxis (overall incidence about 0.05%). A serum sickness-like reaction has been reported, characterized by fever, malaise, urticaria, arthralgia, myalgia, lymphadenopathy, and splenomegaly. Hepatotoxicity may also be associated with hypersensitivity. Hematologic reactions, which are more common with larger parenteral doses of penicillin, are also observed and include hemolytic anemia, transient neutropenia, and leukopenia. Other adverse reactions of oral and parenteral exposure to penicillins include gastrointestinal effects such as nausea, vomiting, and diarrhea.

High doses of parenterally administered penicillin sodium or potassium may result in electrolyte disturbances, especially in patients with poor renal function. The central nervous system is also affected with large parenteral dosages, especially in patients with impaired renal function, manifested as hallucinations, confusion, lethargy, dysphasia, twitching, hyperreflexia, asterixis, localized or generalized seizures, coma, or fatal encephalopathy. Oral ingestion of excessive amounts may cause nausea, vomiting, diarrhea, and abdominal pain. Parenteral administration of high doses may lead to cardiovascular or electrolyte abnormalities or neurological effects such as drowsiness, seizures, or coma.

Although the toxic level has never been established, the tolerances of penicillins to humans were reported in one study. Humans were found to tolerate the following dose of penicillin applied parenterally per day at 1000 mg kg^{-1} for penicillin G, 400 mg kg^{-1} for methicillin, 100 mg kg^{-1} for ampicillin, and 80 mg kg^{-1} for cloxacillin.

Animal

Although penicillins are used in veterinary medicine orally and parenterally, allergic reactions in animals were not reported. Neurological adverse reactions, including convulsions, may occur with the attainment of high cerebrospinal fluid levels of β-lactams. Side effects in dogs and cats administered orally with aminopenicillins include diarrhea, excessive drool, and loss of appetite. Toxic amounts of penicillin in animals are not established except for rats. The oral LD_{50} in rat is 8900 mg kg^{-1} for penicillin G, 1040 mg kg^{-1} for penicillin V, 3597 mg kg^{-1} for dicloxacillin, and 5000 mg kg^{-1} for cloxacillin.

The tolerance dose level to penicillins of most animals is lower than in humans except for rat and mice. The tolerance dose level to penicillin G is 3000 mg kg^{-1} for mouse, 3500 mg kg^{-1} for rat, 5 mg kg^{-1} for guinea pig, 500 mg kg^{-1} for rabbit, and 500 mg kg^{-1} for dog. For methicillin, this level is 3000 mg kg^{-1} for mouse, 4000 mg kg^{-1} for rat, 10 mg kg^{-1} for

guinea pig, 500 mg kg^{-1} for rabbit, and 250 mg kg^{-1} for dog, while for cloxacillin a tolerance dose level is 2000 mg kg^{-1} for mouse, 500 mg kg^{-1} for rat, 5 mg kg^{-1} for guinea pig, 500 mg kg^{-1} for rabbit, and 500 mg kg^{-1} for dog. For ampicillin, the tolerance level is 5000 mg kg^{-1} for both rat and mice.

Chronic Toxicity or Exposure

Human

There are no specific studies that looked for adverse effects of long-term use of penicillins. In addition, no unusual safety issues were reported in studies with extended use of penicillin and amoxicillin for a variety of infections and prophylactic indications. However, neutropenia can occur if high doses are administered consistently for over 2 weeks.

Animal

The toxic effect of ampicillin trihydrate and penicillin VK was determined in one study where both drugs were administered by oral gavage in corn oil. Ampicillin trihydrate was administered for 2 years to rats at doses of 0.750 or 150 mg kg^{-1} and to mice at doses of 0, 1500, or 3000 mg kg^{-1} for ampicillin trihydrate while penicillin VK was administered to rats and mice at doses of 0, 500, or 1000 mg kg^{-1}. Results showed toxic lesions of the stomach in rats and mice after ampicillin trihydrate administration and in mice after penicillin VK administration. In male rats that received ampicillin trihydrate, there was a marginal increase in incidence of mononuclear cell leukemia and pheochromocytomas of the adrenal gland medulla.

Environmental Fate and Behavior

The penicillins are metabolized in the body and some of their metabolites are released to the environment. Among the metabolites are penicilloyl, penicilloic acid, and penilloic acid, in addition to the parent compound itself. The known metabolites for amoxicillin are amoxicilloic acid and amoxicillin diketopiperazine-2′,5′-dione, while for ampicillin the metabolite is ampicilloic acid. These metabolites are released in urine that ultimately goes to wastewater treatment plants and then is introduced into the environment. However, these metabolites are nontoxic, unlike other antibiotic residues, whose metabolites are more toxic than their parent compound. In addition, ecotoxicity studies using wastewater samples containing amoxicillin showed no toxicity to *Pseudokirchneriella subcapitata*. On the other hand, ampicillin did not inhibit growth ($EC_{50} > 1000$ mg l^{-1}) of green algae, *Selenastrum capricornutum* and *Chlorella vulgaris*. However, high dose of ampicillin caused toxic effects on *Folsomia candida* Willem (Isotomidae: Collembola), an edaphic parthenogenetic species commonly used in ecotoxicity studies.

The presence of the drug residues is also reported in food products. Meat and milk from animals administered with penicillins were found to contain small amount of penicillins and its residues/metabolites. These trace residues also caused hypersensitivity for those with allergy problems.

Reproductive and Developmental Toxicity

The teratogenic potential of penicillin agents was monitored in various studies. Results of the studies varied, with some showing no effect while others exhibited minor malformations. No teratogenic risk to the fetuses was observed for oral penicillin V and oral oxacillin even if the treatment was done on the second and third months of gestation. However, in another study, 14 embryos exposed to β-lactams (amoxicillin and ampicillin) *in utero*, malformations were detected, although these malformations are minor and often pass undetected. A higher prevalence of cleft palate was found after ampicillin treatment during the second and third months of gestation.

The teratogenic potential of piperacillin mixed with tazobactam (a compound that inhibits the action of bacterial β-lactamases) was studied in rats given daily intravenous doses (625, 1250, 2500, or 3750 mg kg^{-1} day^{-1}) from day 7 to day 17 of pregnancy. Results showed no teratogenic potential for the piperacillin-tazobactam mixture as there were no fetal malformations or variations observed in the treated animals. Postnatal growth and development, behavior, and reproductive performance of the first filial generation were also not affected.

Genotoxicity/Mutagenicity

Several studies were conducted to look on the genotoxicity and mutagenicity of penicillins. One study that looked on the genotoxic effects of ampicillin and carbenicillin in human lymphocytes *in vitro* showed neither drug affected the frequency of chromosome aberrations, satellite associations, mitotic index, and cell turnover rate at plasma level concentrations. However, all these parameters were affected at higher concentrations. Both ampicillin and carbenicillin were genetically nontoxic for the end points measured and non-clastogenic *in vitro* at therapeutic doses.

Amoxicillin did not induce sister chromatid exchanges or chromosomal aberrations in human peripheral blood lymphocytes both in the presence and in the absence of the metabolic activator. Amoxicillin did not decrease the proliferation index and mitotic index in the presence of the metabolic activator. Furthermore, it neither induced the formation of micronucleus nor decreased the nuclear division index in human peripheral blood lymphocytes both in the presence and in the absence of the metabolic activator. This shows that amoxicillin does not pose a genotoxic risk for patients who are under therapy against bacterial infections.

The mutagenic potential of amoxicillin and clavulanic acid (a mechanism-based β–lactamase inhibitor) in combination was studied *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test, and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All results were negative with the exception of the *in vitro* mouse lymphoma assay, in which weak activity was found at very high, cytotoxic concentrations.

Microbial mutagenicity studies with piperacillin and tazobactam combinations at concentrations of up to 14.84 and 1.86 μg, respectively, per plate were negative. Negative results were also found in the unscheduled DNA synthesis (UDS) test

at concentrations of up to 5689 and 711 μg ml^{-1}, respectively, in the mammalian point mutation (Chinese hamster ovary cell HPRT) assay at concentrations of up to 8000 and 1000 μg ml^{-1}, respectively, and in the mammalian cell (BALB/c-3T3) transformation assay at concentrations of up to 8 and 1 μg ml^{-1}, respectively. *In vivo*, piperacillin and tazobactam combinations did not induce chromosomal aberrations in rats administered intravenous doses of 1500 and 187.5 mg kg^{-1} of body weight, respectively; this dose is similar to the maximum recommended human daily dose based on mg per square meter of body surface area (milligram per square meter). Studies for ticarcillin and clavulanic acid combinations performed *in vitro* and *in vivo* did not indicate a potential for mutagenicity.

Carcinogenicity

Long-term carcinogenicity studies in animals are limited for penicillins. In one study, no evidence for carcinogenic activity in female rats or male and female mice was observed after ampicillin trihydrate administration or in rats and mice after penicillin VK administration. Both administrations of penicillins were done for 2 years.

Clinical Management

Penicillin allergy is the main problem for penicillins. Diagnostic skin test reagents have been used to develop safe and useful skin testing to predict immediate IgE-mediated reactions. In cases of anaphylaxis, the primary treatment is injection of epinephrine, with other measures such as hemodialysis being complementary. In cases of very large overdose, discontinue penicillin, treat symptomatically, and institute supportive measures as required. If necessary, hemodialysis may be used to reduce blood levels of penicillin. Most penicillins are removed by hemodialysis such as amoxicillin (41–59 ml min^{-1} and 44% of a dose), ampicillin (51 ml min^{-1} and 35% of a dose after 4 h), and ticarcillin (33 ml min^{-1} and 23–61% of a dose). However, cloxacillin and oxacillin are not removed by hemodialysis. Another alternative for removing penicillin is by peritoneal dialysis.

Exposure Standards and Guidelines

There are no established exposure standards and guidelines for penicillins since it is used as antibiotics. However, the European Union set maximum residue levels for penicillin amoxicillin and ampicillin at 50 μg l^{-1} and for cloxacillin at 300 μg l^{-1} for all meat products (chicken, cattle, sheep, turkey and hogs) and 4 μg l^{-1} for milk (50 μg l^{-1} for cloxacillin).

See also: Drug Regulations, Europe; *Salmonella*; Sister Chromatid Exchanges; Hypersensitivity, Delayed Type; Skin.

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