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The bioavailability of ampicillins in some animals

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ABSTRACT

Ampicillin, a partially synthetic derivative of penicillin, has been widely used in both human and veterinary medicine for a long time. As a result of its limited ability to be absorbed into the bloodstream when taken orally by humans, precursor chemicals such bakampicillin, pivampicillin, and talampicillin have been created. Although ampicillin is widely used in veterinary treatment practice, the applications of ampicillin esters in animals have not gone beyond scientific trials and have not found widespread use. Since there are not many antibiotic options authorized for use in poultry, in our review, the pharmacokinetic properties of ampicillins, especially oral bioavailability, in some animal species will be mentioned and the need for studies that will examine the bioavailability of pre-ampicillins will be emphasized.

Keywords: ampicillins, poultry, bioavailability, horse

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Introduction

In contemporary poultry farming, various medications, primarily antibiotics, are used for the treatment and control of infectious diseases in winged animals. Antibacterial drug classes commonly preferred in poultry diseases include penicillins, aminoglycosides, macrolides, lincosamides, phenicols, tetracyclines, sulfonamides, and fluoroquinolones (Sumano and Gutierrez Olivera, 2010).

Use of ampicillin in horses and poultry

Ampicillin, being a member of the aminopenicillin group, functions by interacting with penicillin-binding proteins (PBPs) localized in the bacterial cell wall membrane. This interaction prevents the synthesis of peptidoglycan, which is crucial for the bacterium's resilience in the external environment. Inactivation of PBPs hinders the cross-linking of peptidoglycan chains necessary for the formation of the bacterial cell wall, thereby impeding cell wall synthesis in susceptible bacteria. Consequently, the bactericidal effect of ampicillin leads to the demise of the bacteria (Bolme et al., 1976; Goren et al., 1981; Demain and Solomon, 1983; Sumano Lopez and Gutierrez Olivera 2010; Landoni and Albarellos, 2015). Due to its broad antibacterial spectrum, ampicillin is utilized in poultry for the treatment of secondary infections in chronic respiratory diseases caused by Escherichia coli, Pasteurella multocida, and Salmonella spp. Additionally, it is employed for the treatment and control of necrotic enteritis caused by Clostridium perfringens (Ensley and Janssen, 1981; Sumano Lopez and Gutierrez Olivera, 2010; Landoni and Albarellos, 2015). Ampicillin is susceptible to hydrolysis by beta-lactamases secreted by certain bacteria (Demain and Solomon, 1983). In animals, a small portion of ampicillin is converted to the main inactive metabolite, penicilloic acid, in the organism (Tsuji, 1983). It is

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generally indicated that ampicillin binds to serum proteins in animals to a low extent (Villa et al., 1994). In horses, ampicillin is not significantly metabolized, but it is rapidly eliminated through glomerular filtration and renal tubular secretion. A small fraction of ampicillin (<4%) in horses can enter the enterohepatic cycle and be eliminated via bile after intravenous administration (Horspool et al., 1992). The binding of ampicillin to serum proteins in horses is reported to be less than 10% (Dürr, 1976). In poultry, oral absorption generally occurs rapidly. Ampicillin exhibits a wide distribution in body fluids and tissues. The primary elimination route is through the urinary tract, with minimal amounts being excreted in bile (Sumano Lopez and Gutierrez Olivera, 2010).

Ampicillin, being a member of the beta-lactam group, exhibits time-dependent antibacterial activity. In other words, initiating treatment with high concentrations in the target site does not contribute to the rate of bacterial death. In recent years, the approach of correlating pharmacokinetic and pharmacodynamic parameters used in predicting the success of antibacterial therapy (PK/PD) emphasizes the importance of maintaining effective concentrations in the infection site for a certain duration (T>MIC) for beta-lactam antibiotics (Yıldırım, 2008).

Pharmacokinetic properties of ampicillin in some animal species

The oral bioavailability of ampicillin in humans can vary between 39-54%, as reported by Bolme et al. (1976). However, data in avian species show significant differences. In a study focused on broilers, it was indicated that the oral bioavailability of ampicillin is around 30% (Sumano Lopez and Gutierrez Olivera, 2010). Another study revealed that in healthy 6-day-old chicks, the oral bioavailability of ampicillin was approximately 55%, whereas in those with coccidiosis, it was considerably lower at 14% (Kandeel, 2014).

For laying hens and broilers, the direct administration of ampicillin trihydrate at a dose of 7 mg/kg in the crop resulted in undetectable drug levels in the plasma. After administration of a 70 mg/kg dose, very low plasma concentrations (an average of 1 µg/ml) were observed within the first 2 hours. Furthermore, at doses of 20, 30, 40, and 50 mg/kg, the plasma Cmax values were found to be 1.6, 3.4, 4.7, and 9.4 µg/ml, respectively. The study emphasized the rapid absorption and elimination of ampicillin (Goren et al., 1981).

The pharmacokinetic profile of ampicillin was examined in different parrot species. In the first stage, oral ampicillin trihydrate equivalent to 175 mg/kg was given to four of six Amazon parrots and 150 mg/kg to the remaining two. After a one-month waiting period, IM ampicillin sodium 100 mg/kg was administered to all parrots. In the second phase of the study, five blue Naped parrots were first administered oral ampicillin trihydrate at 150 mg/kg, and one month later, a single dose of 100 mg/kg IM ampicillin sodium was administered (Ensley and Janssen, 1981). The study showed that the drug level in plasma reached peak levels within two hours following oral ampicillin administration, and in a short time in those administered IM ampicillin; It has been emphasized that it reaches peak levels in plasma within thirty minutes (Ensley and Janssen, 1981). In a study investigating the pharmacokinetic parameters of ampicillin and another aminopenicillin, amoxicillin, using a similar design in pigeons, ten pigeons were initially administered a single intravenous (IV) dose equivalent to 100 mg/kg ampicillin sodium. After a 3-week waiting period, a single oral dose of 100 mg/kg ampicillin trihydrate was given. Six weeks later, a single intramuscular (IM) dose of ampicillin sodium equivalent to 100 mg/kg was administered. The authors of the study reported that the oral bioavailability of ampicillin in pigeons was 26%, and the Cmax value in parrot species administered IM at a dose of 100 mg/kg of Ampicillin sodium was 3-4 times higher than in pigeons administered 100 mg/kg IM ampicillin sodium (Dorrestein et al. al., 1987).

In a study conducted on ducks, pharmacokinetic parameters were investigated after a single dose of intravenous (IV), intramuscular (IM), subcutaneous (SC), and oral administration of ampicillin. A total of 120 ducks were divided into four equal groups. After administering ampicillin orally at an equivalent dose of 20 mg/kg through IM, IV, SC, and oral routes, blood samples were collected at 0.15, 0.30, 1, 2, 3, 4, 5, 6, 8, 12, 16, and 24 hours, and plasma was obtained. Subsequently, ampicillin concentrations were determined from the plasma samples. The study revealed that compared to IV administration, the intramuscular bioavailability was 91.11%, oral bioavailability was 17.78%, and subcutaneous bioavailability was 62.22% (Poapolathep et al., 2001).

In a study involving chickens (6-9 months old) and turkeys (6-8 weeks old), a single intramuscular dose of 25 mg/kg ampicillin sodium was administered to 31 chickens. After application, serum concentration peaked at 4.6 µg/ml at 30 minutes, dropped to 0.75 µg/ml two hours later, and was undetectable in serum at 6 hours. In the same study, the second group of 17 chickens received a direct esophageal administration of ampicillin trihydrate at a dose of 25 mg/kg. The highest concentration was reported as 0.6 µg/ml, and

antibiotic serum levels were very low at 8 hours. In the third group, consisting of 10 chickens, a single dose of 50 mg/kg ampicillin trihydrate was directly administered to the esophagus. After four hours, the animals were slaughtered, and ampicillin concentrations in their internal organs were determined. The concentrations were found to be 0.36 µg/ml in the liver, 1.48 µg/ml in the kidneys, 0.18 µg/ml in the spleen, 0.32 µg/ml in the lungs, and 0.20 µg/ml in the muscle tissue, respectively. The authors of the study emphasized the low oral absorption of ampicillin in poultry (Ziv et al., 1979).

The data concerning the oral bioavailability of ampicillin with specified studies in avians indicate variable outcomes. Due to the generally low and inconsistent oral bioavailability of ampicillin in both humans and animals, prodrug forms of ampicillin have been developed for human use. Ampicillin prodrugs, also referred to as esters of ampicillin, are typically administered orally and are rapidly hydrolyzed to ampicillin by nonspecific esterases in the digestive system, following absorption. The conversion to ampicillin can occur during absorption from the gastric and intestinal mucosa, depending on the specific ampicillin prodrug. It is emphasized that these prodrugs lack intrinsic antimicrobial activities (Demain and Solomon, 1983).

Among the prodrugs designed for use in human medicine, such as pivampicillin, bakampicillin, hetacillin, and talampicillin, there is a lack of relevant data on their oral bioavailability in avian species.

Ampicillin esters

The chemical structure of ampicillin has been modified to develop numerous prodrug forms. These drugs, released into the market by enhancing characteristics such as bioavailability, water solubility, and chemical stability, have been utilized in the practice of human medicine for years (Demain and Solomon, 1983).

Hetacillin

Hetacillin is obtained by condensation with acetone of ampicillin. Its oral bioavailability in humans is approximately 38%. Apart from the increased chemical stability, there is no pharmacokinetic superiority of ampicillin over amoxicillin (Demain and Solomon, 1983). In a study, oral absorption levels of hetacillin were examined in rats, rabbits and dogs and it was determined that hetacillin showed a similar absorption compared to the same dose of ampicillin (Gubert et al., 1987)

Pivampicillin

Pivampicillin is the pivaloyloxymethyl ester of ampicillin. Due to its high solubility in water, it is predominantly utilized in the form of its hydrochloride salt. Following oral administration in humans, it undergoes hydrolysis in the gastrointestinal tract via nonspecific esterases to yield formaldehyde and ampicillin. The oral bioavailability in humans is significantly higher than that of ampicillin, ranging from 82% to 92% (Demain and Solomon, 1983). In horses, the oral bioavailability of pivampicillin has been determined as 30.9% under fasting conditions and 35.9% under fed conditions (Ensink et al., 1992). The effectiveness of ampicillin in the treatment of equine infectious diseases is directly associated with the concentration reached at the site of infection and the duration of exposure. These two factors are dependent on the physicochemical properties of the antibiotic, the route of administration, and the applied dosage (Prescott and Baggot, 1988). In another study, different doses of ampicillin and pivampicillin were administered to horses, and the concentrations of ampicillin in plasma and pulmonary epithelial lining fluid (PELF) were determined. The results were correlated with the minimum inhibitory concentration (MIC) of common respiratory pathogens in horses. Following a single intravenous dose of 15 mg/kg ampicillin and a single intragastric dose of 19.9 mg/kg pivampicillin, the drug concentrations in the pulmonary epithelial lining fluid (PELF) and plasma of horses were investigated. Following intravenous administration, the elimination of ampicillin is reported to be rapid, with the drug being undetectable in the plasma 12 hours after administration in three out of six horses. Pivampicillin, when administered to fed horses, has been found to have an oral bioavailability of 36%. The degree of penetration of ampicillin into the pulmonary epithelial lining fluid (PELF) was determined by the ratio of the area under the concentration-time curve for PELF to that for plasma in the 0-12 hours post-intravenous administration period, resulting in a ratio of 0.40. This ratio was found to be 1.00 when oral pivampicillin was administered. In a study conducted in horses, orally administered pivampicillin was emphasized to provide clinically significant drug concentrations in the PELF for at least 12 hours (Winther et al., 2012).

Bacampicillin

Bacampicillin is the acid-stable ethoxycarbonyloxymethyl ester of ampicillin. Esterification of the carboxyl group on the thiazolidine ring of ampicillin reduces polarity and increases lipid solubility at physiological pH, leading to only minimal decrease in water solubility. This results in increased oral absorption. The ester is completely hydrolyzed by esterases in enterocytes and plasma. It exhibits a similar oral bioavailability to pivampicillin in humans.

Following oral administration, bacampicillin in humans is absorbed almost entirely by passive diffusion (Demain and Solomon, 1983). In a study conducted in horses, the absolute bioavailability was found to be 39% (Ensink et al., 1996).

Talampicillin

Talampicillin is the phthalidyl ester of ampicillin. Its absorption rate is higher compared to ampicillin, and when administered orally to humans, serum concentrations 2.5 to 3 times higher than the equivalent amount of ampicillin are achieved (Demain and Solomon, 1983). In a study conducted in horses, oral bioavailability was found to be 23% (Ensink et al., 1996).

Conclusion

However, the time-consuming nature of these studies, the economic burden they pose, and the lack of guaranteed success have directed researchers towards prolonging the lifespan and efficacy of existing drugs rather than developing new ones (Çolak, 2009). Therefore, we believe that investigating the pharmacokinetic properties of ampicillin esters, which exhibit high bioavailability in humans compared to ampicillin, after a single oral dose in various animal species will contribute to the literature and scientific knowledge.

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