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Review

Toxicology of baytril (enrofloxacin)

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The prophylactic use of drugs, chemicals and biological substances is necessary to meet the sanitation standards used to maintain high levels of health status. The aim of this article was to present the basic data of the active substance, enrofloxacin, the pharmacokinetics, pharmacodynamics and also the pharmacological safety of this drug. Enrofloxacin as a molecule belonging to the quinolone antimicrobial family is a wide spectrum antibiotic that inhibits DNA gyrase activity in bacterial cells with bactericidal effect. It is at the center of growing attention because of its potential efficacy for the treatment of diseases. This drug is a fluorinated quinolone carboxylic acid derivative, traded as baytril, which has been widely used in veterinary medicine because of its broad spectrum activity. Enrofloxacin has extensively been tested for its safety and it was proven that this medication is rarely toxic in both intravenous and oral routes. Significant side effects occurred only in laboratory animals having a 10 times higher than the recommended dose. The active substance is not teratogenic or mutagenic and in most scientific findings, there is no evidence of a potential risk to applicators and consumers. As a conclusion it can be used in different administration routes in farm animals against a wide range of microorganism but it is important to say that enrofloxacin has not been shown to be safe for use in poultry as *Campylobacter* infections resistant to fluoroquinolones has increased significantly since the use of enrofloxacin in poultry was approved.

Key words: Enrofloxacin, spectrum, safety, teratogenic, mutagenic.

INTRODUCTION

There are a numbers of very active drugs developed under the trade name of baytril, with oral and parenteral employment combating bacterial diseases in cattle, pigs, poultry, dogs and cats. These drugs contain enrofloxacin as the active substance. This review aim to present the basic data on the chemistry and toxicology of the active substance (enrofloxacin) together with the waste assessment after administration of the drug which is useful for the husbandry of farm animals. Enrofloxacin is
a synthetic chemotherapeutic agent of the fluoroquinolone carboxylic acid derivatives. It has antibacterial activity against a wide spectrum of gram-negative and gram-positive bacteria. Though the mechanism of action of this drug is not thoroughly understood, it is believed that this formulation inhibits bacterial DNA gyrase (a type-II topoisomerase), DNA supercoiling and DNA synthesis (Booths, 1994).

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It is effective against *Pseudomonas aeruginosa*, *Klebsiella, Escherichia coli*, *Enterobacter, Shigella, Salmonella, Aeromonas, Haemophillus, Proteus, Yersinia, Serrations, Vibrio, Brucella, Chlamydia, Staphylocci* (including some methicillin resistant strains), *Mycoplasma and Mycobacterium*. It is not effective against anaerobic bacteria with variable efficacy against *Streptococcus* infections. enrofloxacin has a similar spectrum of activity as ciprofloxacin but it has been shown that enrofloxacin has a better bioavailability. With the exception of cerebral-spinal fluid, enrofloxacin attains therapeutic levels in most body tissues so that it has been formulated as the antibiotic of choice for the treatment of difficult infections, particularly those need long-term antibiotics like osteomyelitis, sinus infections, otitis, difficult soft-tissue infections, peritonitis, and pleuritis or pneumonia. Animals with impaired kidney or liver function may need extra monitoring and dose adjustments to prevent excess drug accumulation because enrofloxacin is eliminated by both renal and hepatic metabolism (Gardiner, 2009).

CHEMICAL DATA

Enrofloxacin presents 1,4–dihydro -1– cyclopropyl–7- (4–ethyl–1-piperazinyl)–6–fluoro–4–oxo–3-quinoli;3-quinoline carboxylicacid (Wolfson et al.,1985). A further synthesis allowed reaching active substances of cyclopropyl, as an antibacterial action to get a further extension. A crystalline active substance with faint yellow color that was obtained to develop in high purity (Grobe and Heitzer, 1987) is hardly soluble in water at pH 7, but as the molecule contains acidic and basic groups, it is easily dissolved at both alkaline and acid pH. Hence, the liquid formulations of baytril, which can be administered both orally and parenterally contain readily soluble salts of enrofloxacin in aqueous solution. It has given a high hydrolytic stability of the active substance therefore, such solutions are very stable. The solid formulations, tablets and catkins are containing the active substance as early betaine (Scheer, 1987).

BAYTRIL SAFETY

The question about the safety of baytril for animal's farm and households, the normal treated and excessive doses as well as the local and the general tolerance are answered by some clinical trials. It is presented in some paper as the toxicological studies in which they judged its safety to the consumer and also assessed the situation of the waste as was prescribed in standard communities. These studies are part of the safety pharmacology, acute and sub chronic toxicity, embryo toxicity, teratogenicity and mutagenicity effects (Bauditz, 1987a; Bachoual, 2001).

PHARMACOLOGICAL SAFETY

The studies carried out on its pharmacological safety in laboratory animals such as rats, mice and guinea pigs using doses ten times greater than the therapeutic ones, did not recognize a significant effect on blood composition, glucosemia and serum triglycerides, or on blood coagulation. They could not find any abnormalities in urine output except the increased in potassium level after 100 mg / kg. The alteration after the elimination of an electrolyte using the maximum dose is not relevant with its application in practice (Albrecht, 1977). Oral doses of enrofloxacin up to 100 mg/kg (20 times the recommended dosage) showed no significant adverse effects on blood composition, blood coagulation or dieresis. Applying the brunch activity test, no evidence of any effect on the smooth muscles of the respiratory system was found (Bauditz, 1987c; NOAH, 2010) .It was also shown that baytril did not elicit any ant allergic or pseudo allergic reactions. Applying the rabbit local irritation test and guinea pig skin sensitization test, enrofloxacin as the active substance did not produce a skin irritation but only draw slight irritation in eyes. A baytril 0.5% eye drop formulation, however, did not produce any irritation after application to the rabbit eyes (Altreuther, 1987). Studies on the effects of drug on the central nervous system showed only a weak stimulation of spontaneous motility after 100 mg / kg, but at a lower dose, there was no evidence of an influence exerted on the central nervous system (Takayama et al., 1995).

In addition, no adverse effects are observed on the CNS of mice, rats, dogs and cats. The recommendation not to treat dogs with CNS disorders, e.g., epilepsy, is a matter of precaution, which applies to all fluoroquinolones (Altreuther, 1992). There were no allergic or pseudo-allergic effects observed conducting some in vitro test using the peritoneal mast cells. Also, the smooth muscle of the airways in guinea pigs was not affected (Albrecht, 1977). Some trials on dogs revealed that vomiting was induced only in doses far exceeding the therapeutic recommendations (>1000 mg/kg b.w. PO) (Altreuther, 1987). As baytril has only minimal effects on anaerobic organisms, which represent a considerable part of the normal bowel flora, the incidence of intestinal side effects may be less frequent compared to anti-infective of other families (Hooper et al., 1993). Also, there was no evidence of an impact on the cardiovascular system. These evidences demonstrated that enrofloxacin at therapeutic or even excessive doses does not exert significant effects on vital parameters. In the clinic, there is no expected side effect of acute nature (Boothe, 1994).

ACUTE TOXICITY

Enrofloxacin has undergone considerable toxicological and safety testing in laboratory species such as mice, rats and guinea pigs, as well as in the target species dog and cat (Takayama et al., 1995). In general, some side effects of quinolones on different organ systems (e.g. CNS, gastrointestinal tract or locomotory system) are reported. Enrofloxacin has been proven to be safe and well tolerated as no adverse effects on blood composition or kidney function were observed as well as any teratogenic or mutagenic effects (Brown, 1996; Flammer, 1991). It is unlikely that an overdose of both compounds would result in acute symptoms more serious than anorexia or vomiting as only the latter ones could occur. Dogs receiving doses ten times the standard rate of enrofloxacin for at least 14 days developed only some vomiting and anorexia. However, death did occur in some dogs when fed 25 times the labeled rate for 11 days, (Wolfson et al., 1985). The LD_{50} values were determined in different species. All acute effects only appeared at doses far exceeding the therapeutic range (Altreuther, 1992). Dogs vomit after oral application of doses above 1000 mg/kg b.w, which is 200 times the recommended dosage, so that an LD_{50} could not be determined

Table 1. Acute toxicity after oral and parenteral administration.

Animal Species	Sex	Administration	Approximately LD_{50} (mg/kg b.w)
Rat	Male, Female	oral	≥ 5.000
Mouse	Male, Female	I.V	≥5.000
Mouse	Male, Female	oral	=200
Rabbit	Male, Female	oral	500 - 800

(Altreuther, 1987; Bauditz, 1987a; NOAH, 2010). The approximate LD_{50} values were listed in Table 1.

SUB-CHRONIC TOXICITY TESTING

It was shown that enrofloxacin had impact on the joint of a few rats medicated with highest dose (Altreuther, 1987). It has been demonstrated to cause cartilage erosion in the joints of growing dogs (Bauditz, 1987b). Histologically, vesicles are formed in the articular cartilage, which can progressively rupture and produce cartilaginous erosion. Experimental and clinical findings suggest that bearing of weight by joints may be important in the pathogenesis of these lesions (Brown, 1996). In contrast to dogs, cartilage lesions could not be demonstrated in growing cats, from 2 to 10 months of age, when treated for 30 days with baytril doses of up to 25 mg/kg b.w. It can be concluded that cartilage tolerance towards enrofloxacin is higher in cats than in dogs (Altreuther, 1992). In sub-chronic feeding studies of enrofloxacin as an active substance, the no-effect level (NOEL), which is the dose that can be administered with food over prolonged periods without adverse effects, was determined (Altreuther, 1992). For rats, mice and adult dogs, general NOELs of 165, 550, and 52 mg/kg b.w., respectively, were detected (Takayama et al., 1995; Altreuther, 1992). Without recognizable injury, both rats and dogs tolerated up to 2000 mg of active ingredient / kg feed (Boothe, 1994). Permanent blindness and vision loss have been reported more than 0.5 % eye drop formulation dose with fluoroquinolones, including enrofloxacin (Brown, 1996; Altreuther, 1992). On the other hand, enrofloxacin was banned for poultry use in 2005 as data showed that the use of this drug in poultry can cause resistance to *Campylobacter*. That bacterium causes foodborne illness and is normally harbored in the digestive tracts of chickens and turkeys (Washington Post, 2005).

EMBRYOTOXICITY AND TERATOGENICITY

The daily treatment of 6 to 15 pregnant rats did not provide any clue about the teratogenic effects of enrofloxacin in the maximum dose of 875 mg/kg (Altreuther**,** 1987). However some toxic effects in females after 210 and 875 mg/kg were slightly determined such as the decrease of the fetal weights and reduction of litter in the group having the highest dose. Using the active substance at the dose of 50 mg/kg was tolerated without any adverse effect on females or on their progenies (Plumb et al., 2008). Trials in daily treated rats with enrofloxacin (0, 50, 210, and 875 mg/kg b.w.) from the 6th to the 15th day of gestation showed no evidence of teratogenic effects from enrofloxacin, even with the highest dosage group. On the contrary, maternal toxic effects after 210 and 875 mg/kg, resulted in slightly reduced fetal weights and delayed ossification (Altreuther, 1987). In the highest dosage group receiving 175 times the recommended dose for dogs and cats, smaller litter sizes were observed (Altreuther, 1987). A dose of 50 mg/kg enrofloxacin was tolerated without any adverse effect to mothers and their offspring (Boothe, 1994; Altreuther, 1987).

MUTAGENICITY

Enrofloxacin was checked using salmonella microsomal test (Ames test) (Altreuther, 1987), Chinese Hamster Ovary Cells Test (Cho test - HGPRT) (Altreuther,1987) as well as unscheduled DNA synthesis test (Altreuther, 1987) for the presence of any point mutagenic affects. There was no evidence of anymutagenic effect or any damaged DNA detected in these test systems (Plumb et al., 2008)

CONCLUSION

The relative safety of enrofloxacin has been proven during many trials - testing this medication on different farm animals, even at doses many times greater than the standard one, where the route of administration was oral, intravenous and intramuscular and because of its low minimum inhibitory concentrations (MIC), usually 0.1 to 2.0 ug/mL, its broad spectrum activity which is useful at farms, and its property of leaving little or no residue in edible tissues have encouraged its use in veterinary medicine (Vancutsem et al., 1990; Greene, 1993). As a conclusion, it can be used in different administration routes in farm animals against a wide range of microorganism but it is important to say that enrofloxacin

has not been shown to be safe- for use in poultry as *campylobacter* infections resistant to fluoroquinolones has increased significantly since the use of enrofloxacin in poultry was approved.

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