



Oxytetracycline Long Acting: A Review

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DOI: 10.31080/ASPS.2024.08.1043

Received: February 19, 2024

Published: March 04, 2024

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Abstract

Oxytetracycline long acting is a broad-spectrum antibiotic used against a variety of pathogens. The term “long-acting” implies that the formulation provides a prolonged circulation of antibacterial concentrations of the active agent (oxytetracycline) and shows a commensurate improvement in clinical efficacy. The long-acting formulation is usually administered once and is expected to maintain a therapeutic plasma concentration for 3 to 4 days before it is repeated to complete the treatment, whereas the short-acting formulation is recommended for daily use for 5 to 7 days to maintain a therapeutic plasma concentration. From a research work carried out using apparently healthy Nigerian indigenous dogs, the action of oxytetracycline long acting when co-administered with diminazene aceturate showed that oxytetracycline long acting could have an adjuvant property and could also be a stabilizer of other drugs, diminazene aceturate, for instance. This review will discuss current knowledge of therapeutic spectrum of oxytetracycline long acting.

Keywords: Oxytetracycline Long Acting; Adjuvant; Stabilizing Properties

Oxytetracycline

Oxytetracycline (OTC), a broad-spectrum antibiotic, is widely used to treat Gram-positive (*Streptococcus* sp., *Staphylococcus* sp.) and Gram-negative (*Escherichia coli*) infections in animals [1]. OTC is a tetracycline derivative produced by *Streptomyces rimosus* [2,3]. Long-acting oxytetracycline (LOTC) formulations are used to treat diseases by maintaining an effective concentration in animals, for 2 or 3 days. It is manufactured easily and used widely in developing countries in veterinary medicine [4]. Long-acting tetracycline injection results in high concentrations of the drug in plasma above minimum inhibitory concentrations for several days, decreasing the number of administration per treatment [5]. Short and long-acting, injectable formulations are commonly used at the dose rates of 10 mg/kg and 20 mg/kg, respectively. The long-acting formulation is usually administered once and is expected to maintain a therapeutic plasma concentration for 3 to 4 days, whereas the short-acting formulation is recommended for daily use for 5 to 7 days to maintain a therapeutic plasma concentration [4].

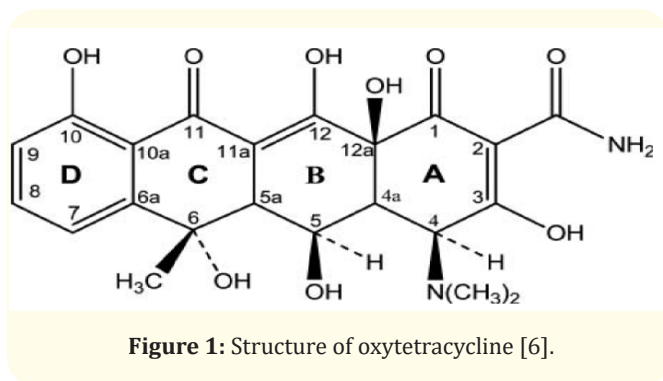
Physical and chemical properties of oxytetracycline

Chemical structure

Oxytetracycline hydrochloride (Figure 1) belongs to chemical class of polycyclic lactones called tetracyclines given the name as 2-Naphthacene Carboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a hexa hydroxy-6-methyl-1,11-dioxo-, monohydrochloride, [4S-(4 α ,4 α ,5 α ,5 α ,6 β ,12 α α)] (USP Dictionary 2002). Its chemical formula is C₂₂H₂₄N₂O₉·HCl [6].

Physical properties

Oxytetracycline hydrochloride USP is a yellow, odorless, crystalline powder. It is hygroscopic, decomposes at a temperature exceeding 180 °C, and exposure to strong sunlight or to temperatures exceeding 90 °C in moist air, causes it to darken. Its potency is diminished in solutions having a pH below 2, and it is rapidly destroyed by alkali hydroxide solutions [7]. Oxytetracycline hydrochloride has a molecular weight of 496.89 [6]. It is soluble in water.



Crystals of the oxytetracycline base could separate as a result of partial hydrolysis of the hydrochloride. It is sparingly soluble in alcohol, less soluble in dehydrated alcohol and insoluble in chloroform and ether [7]. Oxytetracyclines are 30% plasma protein bound [8].

Mechanism of action

Oxytetracycline long acting is a broad-spectrum bacteriostatic agent that inhibits protein synthesis by binding reversibly to receptors of the 30S ribosomal subunit of susceptible microorganisms. The binding of a tetracycline to the subunit, blocks the binding of the aminoacyl tRNA to the acceptor site on the mRNA-ribosomal complex, and prevents the addition of new amino acids to the peptide chain, inhibiting protein synthesis [9], suggesting that oxytetracyclines must enter the target cell to be effective. Uptake appears to depend on passive diffusion and active transport [10]. Susceptible cells concentrate the antibiotic; resistant strains appear to carry an R-factor that inhibits uptake of drug [9].

Toxicity effects of oxytetracycline

Toxicity effects of oxytetracycline are diarrhea, eruption of skin plaques, frothing from the mouth, glassy-eyed appearance, labored breathing, muscle trembling, piloerection, prostration, restlessness, swelling of eyelids, ears, muzzle, anus, vulva and scrotum [11]. High doses cause photosensitization in cattle [12] and nephrotoxicosis [13]. It causes cardiovascular dysfunction, including atrioventricular block, atrial tachycardia, ventricular bradycardia, hypotension, agitation, nervousness, dyspnea, muscle fasciculations, urination, defecation, collapse and death [14]. This is a dose dependent effect with rapid intravenous administration [15]. The propylene glycol vehicle of some oxytetracycline preparations has been shown to have some cardiovascular effects when

administered intravenously [14]. The calcium binding nature of the intravenous tetracyclines has been implicated in cardiovascular dysfunction and sudden collapse in cattle and sheep [15]. Pretreatment with calcium borogluconate has been considered before intravenous administration and hypocalcemia has not been observed [15]. Fever with anorexia, and sometimes diarrhea which usually resolves within 48 h of discontinuing oxytetracycline or tetracycline has been observed in cats [16]. Hemoglobinuria, transient brownish-red urine with parenteral administration of oxytetracycline; hepatitis with fatty degeneration and/or bile stasis were associated with repeated high doses or concurrent debilitating conditions in cattle [14]. Anorexia; diarrhea with doses administered that are two times the recommended dose have been observed in rabbits [17]. It causes yellow, brown, or gray discoloration of teeth in young animals, when administered during late pregnancy or during the period of tooth development [12]. Also, it causes local tissue irritation at site of injection of administered intramuscularly [18]. Overdose of tetracyclines in animals is unusual, because very high doses could be tolerated. However; nephrotoxicosis and possible hepatotoxicity are associated with overdose. Acute toxicity of intravenously-administered tetracyclines in many species is most often seen with rapid administration, and serious toxicity is more likely in animals that are already compromised by disease or dehydration [18].

Pharmacokinetics of oxytetracycline long acting

The absorption of the long-acting formulations of oxytetracycline (with 2-pyrrolidone excipient) administered intramuscularly has a rapid phase of 48 minutes with 14% bioavailability, and a slow phase of 18 hours for 38%, respectively, in cattle administered 20 mg/kg dose [4]. However, a 10 mg/kg dose showed a rapid phase of 16 minutes, and the slow phase was 11 h [10]. The bioavailability of oxytetracycline in various species are 10 mg/kg in Camel (93.7%) [19]; Cattle—51%; 78.5%; 95% for 20 mg/kg dose [4] and Goats—79.4% for 20 mg/kg dose [20]. A single administration of oral oxytetracycline (10-100 mg/kg) resulted in peak blood levels 2 h after dosing giving plasma concentrations, 0.88 to 2.51 µg/ml. These levels dropped to about 60% after 12 h. Slightly higher blood levels were attained after administration of a second dose [21]. In pigs, 20 mg/kg of oxytetracycline led to the detection of 0.1µg/ml for plasma and 0.2 µg/ml for urine, respectively. About 60% of the administered dose was excreted in the urine during the first 24 h and a total of 69% was recovered in the urine within 1 week.

After injection of oxytetracycline long acting (OTC-LA), the initial absorption rate was faster, and the maximum plasma concentration was reached within 1 h after dosing. Although the excretion rate was lower with OTC-LA than with OTC-C, however, the total amounts excreted in urine were comparable. In 3 days, 60-75% of the total dose was excreted in the urine [22]. Oral administration of OTC-LA (50 mg/kg) to Yorkshire swine led to detection of higher quantity of residues in the kidney, followed by liver, lung, adrenal gland, heart, bile, fat, lymph node, spleen, thyroid and urine. The highest residue levels (441 µg/ml) were observed in the urine 3 hours after dosing, and were still detectable at 48 hours. Mean peak plasma concentrations of 4.2-8.7 µg/ml were observed after 3 hours [7]. Weaned piglets were administered a single oral dose of 20 mg/kg OTC-LA and compared with a group administered 400 mg/kg feed for 3 consecutive days. The first group revealed a maximum plasma concentration 6 times higher than that of the second group, respectively. A peak plasma concentration was reached after 3 ± 2 hours in the first group, while the group administered the drug in the feed revealed a steady state concentration of 0.2 µg/ml beyond 30 h post administration of the drug. Within 48 hours after administration, plasma OTC level was below the detection limit of 0.06 µg/ml. The estimated OTC bioavailabilities were 9.0% and 3.7%, respectively [21]. After intravenous administration of OTC 20 mg/kg, the volume of distribution was 1.62 ± 0.83 l/kg. The elimination half-life ranged between 11.6 and 17.2 h, and the mean renal clearance was estimated to be 0.249 l/kg, respectively. Urinary recovery of OTC within 72 h post injection ranged between 42 and 62% of the administered dose [21] (Koc, 2009). Three groups of calves (3, 12, 14) were administered doses of 7.54, 6.88 or 17.00 mg/kg of OTC, respectively, and another two groups of cows, lactating and non-lactating were administered 3.32 and 7.94 mg/kg body weight respectively. The volume of distribution in 3-week old calves was 2.48 l/kg, which was 2 to 3 times higher than in the cows. Half-life was 13.5 ± 3.6 h and 8.8 ± 0.52 h for the 3- and 12-week old calves, respectively. The doses and lactation neither affected the volume of distribution nor the half-life [23]. Dairy cows were injected 5 mg/kg of 10% OTC i.v. and i.m., and volume of distribution (1.00 ± 0.18 l/kg), and did not differ for the two routes. Peak plasma concentration of 2.28 ± 0.15 µg/ml was reached at 7 h after i.m. administration. Plasma half life was 9.02 ± 0.88 h. Most of the OTC was excreted by the kidney (85-86%), and a very small portion (2%) via the bile [23]. Five dairy cows were treated with single i.m. injections of 5 different 20% OTC formulations at a dose rate of 10 mg/kg, concentrations in plasma, renal clearance and

creatinine were determined. The limit of detection using microbiological assay was 0.05 mg/l. Maximum plasma concentrations were achieved between 5 and 10 h, after treatment and varied between 4.6 and 6.8 µg/ml, depending on the formulation involved. Plasma concentrations exceeding 0.5 µg/ml were maintained for 48 to 72 h. Mean renal clearance was 0.062 l/kg/h. The urinary recovery of OTC within 72 h after treatment ranged between 61.7 and 88% of the dose administered [24]. Newborn calves of 1 to 42 days and older calves of 250 days were administered OTC of 10 mg/kg b.w. on day 2 and at 1, 2, 4 and 6 weeks of the study period. The half-life of elimination decreased from 11.2 ± 1.7 h in newborn calves to 6.4 ± 1.3 h in 6 weeks old and 6.3 ± 0.7 h in the 250-day old calves, respectively [25]. Each of five Jersey cows was administered single i.m. dose of 5 mg/kg of OTC, and peak concentrations in plasma (1.67 ± 0.66 µg/ml) and milk (1.38 ± 0.46 µg/ml) were obtained after 6 and 12 h, respectively. The elimination half-life was 7.99 ± 2.20 h [26]. Oxytetracycline (5mg/kg) was administered intravenously to camels, sheep and goats. The calculated kinetic parameters were $t_{1/2\beta}$ (2.8, 3.4, and 3.2 h), C_{max} (10.2, 850, and 780 µg/ml), Vd_{area} (1.41, 13.4, and 12.1 l/kg.), respectively [22] (Al-Nazawi, 2003). In another study, OTC at 5 mg/kg IV resulted in $t_{1/2\beta}$ of 3.89 and 6.30 h for Nubian goats and desert sheep, AUC (12.08 ± 1.50 and 18.37 ± 1.68 µg/ml/h), Vd_{area} (2.53 ± 0.29 and 2.67 ± 0.39 L/kg), CI (436.99 ± 47.94 and 281.31 ± 25.01 ml/kg/h), respectively. Pharmacokinetic differences of OTC for sheep and goat were thought to be caused by protein bindings, and changes in the renal excretions [27]. Oxytetracycline long acting (20 mg/kg) was administered intravenously to goats. The peak plasma concentration t_{max} was 0.77 ± 0.83 h, and C_{max} (8.59 ± 7.47 µg/ml), $T_{1/\beta}$ (14.4 ± 4.92 h), AUC (67.4 ± 21.7 µg/ml/h), Vd_{ss} (4.10 ± 1.65 l/kg), and CI (0.333 ± 0.117 l/kg/h), respectively [36]. Intramuscular oxytetracycline (20 mg/kg) administered to calves and sheep revealed t_{max} (3.5 ± 1.2 h), and C_{peak} (6.1 ± 1.3 µg/ml) in sheep and AUC (168 ± 14.6 µg/ml/h) was found to be significantly lower than that for sheep (209 ± 43 µg/ml/h), respectively. However, Vd_{ss} (3.3 ± 0.49 and 3.08 ± 0.82 l/kg) and CI (1.88 ± 0.12 , 1.65 ± 0.30 ml/min/kg) were reported for calves and sheep, respectively. The difference in pharmacokinetic parameters was related to the differences in species. Kilis goats were found to have shorter t_{max} , higher C_{peak} , and lower AUC values compared to the calf and sheep [28]. Having a long-time effect and long administration intervals, OTC LA preparations are considered convenient [18]. The binding capacities of tetracyclines in various species of animals are as follow: buffalo, 42% [21] and cows, 18 to 22% [19]; horses and cows combined, 50% [29], Pigs, 75.5% [18]

and sheep, 21 to 25%, respectively [19].

However, elimination half-lives are as follow: buffalo, 2.8 to 3.6 h [21], calves, 11.2 h [30], 6-week old calf, 3.5 to 7.2 h [25], 6-week calf infected with *Mannheimia haemolytica* pneumonia, 2.5 h [30]. 8 months old calf, 6.3 h [25], camel, 7.7 h [31], catfish, 80.3 h [20], cow, 10 h [2], dogs, 6 h [31], donkey, 6.5 h [32], foal, 6.7 to 7.3 h [33], goats, 6.5 h [34], horses, 13 h [33] and 15.7 h [29], pig, 11.6 - 17.2 h [35], adult pig, 3.8 to 6.7 h [3], adult pig with pneumonia, 5.1 - 5.2 h [3], ponies, 15 h [29], rabbits, 1.3 h, respectively [36]. A single oral 50 mg/kg dose of oxytetracycline produced >0.5 mcg/mL serum concentrations for at least 8 h [33]. Pigs, when challenged with *Actinobacillus pleuropneumonia* and treated using a single oral 50 mg/kg dose produced >0.5 mcg/mL serum concentrations for at least 24 h [33]. Moreso, pigs, administered 550 mg of oxytetracycline per kg of feed, showed peak plasma concentrations of 0.4 mcg/mL [37].

A single dose of 18 mg/kg to calves maintained serum concentrations > 1 mcg/mL for at least 32 h [37]. Whereas a single dose of 20 mg/kg maintained revealed serum concentration of >0.5 mcg/mL for 52 h [30]. A single dose of 20 mg/kg maintained serum concentrations > 0.5 mcg/mL for 28 to 36 h [17]. Nevertheless, a single dose of 10 mg/kg maintained serum concentrations > 0.5 mcg/mL for 12 to 24h [38] (Sarli., *et al.* 2021), and a single dose of 40 mg/kg administered to ruminating calves maintained serum concentrations > 2 mcg/mL for 48 hours and lung concentrations of 2 mcg/mL at 48 h, respectively [10]. However, a single dose of 10 mg/kg maintained serum concentrations > 0.5 mcg/mL for 72 h in camels [9]. In cows a single dose of 10 mg/kg in the neck muscle maintained >0.5 mcg/mL serum concentration for 48 to 70 h and milk concentration for 33 to 49 h [32], respectively. Whereas a single dose of 20 mg/kg in the hindquarters muscle maintained serum concentrations of > 0.5 mcg/mL for 86 h [34], and a single dose of 20 mg/kg in the gluteal muscles maintains serum concentrations > 4 mcg/mL for 12 h and lung concentrations > 0.5 mcg/mL for 65 h, respectively [17]. A single dose of 20 mg/kg produces serum concentrations > 0.5 mcg/mL for 35 to 48 h in pigs [37]. Long-acting formulation does not produce significantly different plasma oxytetracycline concentrations as compared to other parenteral formulations [37].

Oxytetracycline dihydrate 216 mg contains 200 mg oxytetracycline and 16 mg of excipient. The excipients have sodium formaldehyde sulphonylate, magnesium oxide, dimethylacetamide, so-

dium edetate, ethanolamine and water for injection up to 1 ml [39]. The long acting formulations have a viscous excipient intended to prolong serum concentrations. These products are believed to differ from other oxytetracycline injection products, only in the rate of absorption from intramuscular injection sites. Moreover, some studies using oxytetracycline products with 2-pyrrolidone viscosity excipient, have failed to show that the duration of action was significantly prolonged over that of the conventional formulation after intramuscular injection, when administered at the same dose rate [32]. As such, use of the long-acting formulations, 6 to 11 mg per kg of body weight, may not result in a prolonged duration of action. Also, there was no difference in duration of action between long-acting and other formulations when administered intravenously [9].

Indications

Oxytetracycline long acting is used in treatment of anaplasmosis, cowdriosis, rickettsia disease/infection and theileriosis [40]. It is also useful in the treatment of actinobacillosis, bacterial enteritis, bacterial pneumonia, bovine respiratory disease complex, diphtheria, keratoconjunctivitis, leptospirosis, metritis, acute, pododermatitis, skin and soft tissue infections. However, 6.6 to 11 mg per kg body weight every twenty-four hours for four days was highly beneficial [1]. When it is impractical to give cattle more than a single dose for the treatment of keratoconjunctivitis or pneumonia, a subcutaneous dose of 20 mg per kg of body weight has been recommended [1].

In calves, 40 mg per kg of body weight as a single dose was used in the treatment of bacterial pneumonia unresponsive to 20 mg per kg body weight [39]. This higher dose should not be repeated because of the risk of adverse effects [41]. For thromboembolic meningoencephalitis in cattle, a dose of 11 mg per kg of body weight every twenty-four hours has been recommended [39]. Oxytetracycline is used also in the treatment of bacterial enteritis, bacterial pneumonia and leptospirosis in pigs. Intramuscular, 6.6 to 11 mg per kg of body weight every twenty four hours for four days has been recommended [1]. When it is impractical to give pigs more than a single dose for the treatment of pneumonia, an intramuscular dose of 20 mg per kg of body weight administered as a single dose is recommended [1]. It is used for the treatment of bacterial enteritis in suckling pigs. Intramuscular 6.6 mg per kg of body weight, administered once eight hours before farrowing or imme-

diately after farrowing has been recommended [1].

Oxytetracycline long acting formulations are as follows, Agri-mycin 200; AmTech Maxim -200; Biomycin 200; Duramycin 72-200; Geomycin 200; Liquamycin LA-200; Maxim-200; OT 200; OxyBiotic-200; Oxy cure 200; Oxy-Mycin 200; Oxyshot LA and Pennox200 Injectable. The above products contain the following viscosity excipients: Biomycin 200 contains polyethylene glycol while Duramycin 72-200, Liquamycin LA-200, maxim-200; and Pennox 200 contain 2-pyrrolidone; and Oxyshot LA contains N-methylpyrrolidone [1].

Oxytetracycline analytical methods

The methods used for analysis of oxytetracycline are high performance liquid chromatography (HPLC), thin-layer chromatography (TLC), spectrophotometry, capillary electrophoresis (CE), chemiluminescence (CL), flow injection analysis (FIA), and microbiological assays. Reversed phase version of HPLC, is the most frequently used for the determination of tetracycline antibiotics [42].

Acceptable tissue/milk residues of oxytetracycline

The acceptable daily intake (ADI) for chlortetracycline, oxytetracycline, and tetracycline is 25 micrograms per kilogram of body weight per day. The acceptable residues for tetracyclines including chlortetracycline, oxytetracycline, and tetracycline, in tissues and milk is 2 parts per million (ppm), muscle (2 ppm), liver (6 ppm), fat and kidney (12 ppm) and milk (0.3 ppm), respectively [39].

Adjuvant and Stabilizing properties of oxytetracycline long acting

Adjuvants are substances that enhance the pharmacological effects of a drug, [43] while stabilizers are those substances that protect drugs from being rapidly metabolized and thereby prolonging their therapeutic actions in the system [44]. Onyeachonam, *et al.* [45,46] observed these properties of oxytetracycline long acting in both plasma and assayed tissues in healthy dogs. They reported that the plasma concentration of the group treated with diminazene aceturate combined with oxytetracycline long acting was significantly higher ($p < 0.05$) from 1 hr to 9 hours and at 36th hr post treatment when compared to the group treated with diminazene aceturate alone [45]. This suggests that oxytetracycline long acting stabilizes diminazene aceturate, protects it from being rapidly degraded by metabolic processes in dogs and thereby prolonging its therapeutic actions [44]. Also, the concentrations of diminazene

aceturate in the assayed tissues of animals (brain, skeletal muscle, kidney) treated with oxytetracycline long acting and its combination with diminazene were however, higher than those treated with diminazene alone [45]. Ordinarily, diminazene aceturate (DA) does not or sparingly crosses the blood brain barrier but when DA is combined with oxytetracycline long acting high concentrations of DA were found in the brain. This proposes that oxytetracycline long acting enhanced distribution/accumulation of diminazene aceturate in various tissues of dogs assayed and this effects may enhance therapeutic efficacy of diminazene aceturate. On the contrary, a study done by Jennings [47] on a combination-treatment of 5% oxytetracycline (not long acting) and diminazene aceturate reported no enhanced distribution nor delayed elimination of DA. This suggests that the stabilizing agents used *in vitro* to make oxytetracycline act longer may be stabilizing diminazene aceturate, *in vivo*.

Conclusion

This review suggests that oxytetracycline long acting when combined with other drugs can act as an adjuvant and or a stabilizer perhaps because of its composition.

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