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Antibiotic treatments in zootechnology and effects induced on the food chain of domestic species and, comparatively, the human specie

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Abstract

Introduction: **Antibiotics are largely employed in zootechnical feed to preserve human and animal species from zoonosis due pathogenic infective agents.**

Aim: **Due to the increasing number of pathologies related to diet (e.g. food intolerances), we investigated the toxic effects induced by antibiotics residues, oxytetracyclines, present within the industrial food on both human and domestic animals' health. Zootechnical products obtained from animal bones industrial transformation, and their related toxic effects have been pointed out.**

Methods: **Comparative analysis of published papers has been conducted from 1910 up to 2014.**

Results: **The comparative analysis revealed the presence of oxytetracycline residues and other antibiotics in food intended for human and animal consumption, which resulted in multisystemic toxic effects.**

Discussion: **Either metabolism and possible measures to prevent exposure to oxytetracycline have also been examined, however a more detailed understanding of biochemical effects of such class of antibiotics is required.**

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Key words: *Oxytetracycline. Antibiotics. Toxicology. Human. Immunity.*

TRATAMIENTOS ANTIBIÓTICOS EN ZOOTECNOLOGÍA Y LOS EFECTOS INDUCIDOS SOBRE LA CADENA ALIMENTICIA DE LAS ESPECIES DOMÉSTICAS Y COMPARATIVAMENTE SOBRE LA ESPECIE HUMANA

Resumen

Introducción: los antibióticos se emplean ampliamente en la alimentación zootécnica para proteger a las especies humana y animal de las zoonosis por agentes infecciosos patogénicos. Objetivo: dado el creciente número de enfermedades relacionadas con la dieta (p. ej., intolerancias alimentarias), investigamos los efectos tóxicos inducidos por los residuos antibióticos, oxitetraciclinas, presentes en los alimentos industriales tanto sobre la salud humana como animal. Se destacan los productos zootécnicos obtenidos de la transformación industrial de los huesos animales y sus efectos tóxicos relacionados. Métodos: análisis comparativo de las publicaciones realizadas desde 1910 hasta 2014. Resultados: el análisis comparativo reveló la presencia de residuos de oxitetraciclina y otros antibióticos en alimentos pensados para el consumo humano y animal, lo que produjo efectos tóxicos multisistémicos. Discusión: el metabolismo y las posibles medidas para evitar la exposición a la oxitetraciclina también se han examinado, sin embargo, se precisa de un conocimiento más detallado de los efectos bioquímicos de tal clase de antibióticos.

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Palabras clave: *Oxitetraciclina. Antibióticos. Toxicología. Humano. Inmunidad.*

Abbreviations

ROS: Reactive Oxygen Species.
PMNL: Polymorphonuclear Leukocyte.
UV: Ultraviolet.
EU: European Union.
SLE: Systemic Lupus Erythematosus.
FEDESA: European Federation of Animal Health.
MRL: maximum residue limit.
SDR: residues syndrome.
BCS: Body Condition Score.

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Introduction

The use of antibiotics has undoubtedly helped preserving the human and animal species from zoonosis due pathogenic infective agents, but few research studies have been run to reduce its toxic and ecological effects and their consequences on health. This issue becomes particularly important especially in the zootechnical use of antibiotics in industrial breeding of animals for slaughter and edibility, with particular reference to its accumulation in animal feed and food and the eventual chronic consequences deriving from its ingestion to the species fed with these foods.

Aim of the project

Our study model refers to the domestic animals, provided of great species affinity with the owner's. The analogy of any possible pathological findings related to the human race seems to be of great help in the a possible pathophysiological perspective interpretation and, consequently, prevention of similar or identical diseases.

Methods

We searched Pubmed/Medline using the terms "antibiotics", "industrial", "food", "oxytetracycline", "human", "pets", "toxicity", "immunological" and "reactions".

Selected papers from 1910 to 2014 were chosen on the basis of their content (evidence-based quality and reliability). Clinical and experimental articles on the environmental effects of antimicrobials were also included.

Results

Oxytetracycline is one of the most widely used compounds for pharmacoeconomic reasons but on which the attention of the veterinary medicine is directed to due to certain observed findings in animal pathology. The oxytetracycline, chemically (4S,4aR,5S,5aR, 6S,12aS)-4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide, on a pharmacokinetic profile, is absorbed in the duodenum almost completely after 2-3 hours, it forms complexes with metallic ions, unstable at acid pH and for this reason the introduction of this molecule in parallel with the introduction of foods reduces its serum concentrations by 20%. It is accumulated in lower amounts in bone tissue, skin, fat, tendons and muscles, and in greater amounts in the liver and in the gastrointestinal tract. Finally, it is excreted through the kidneys and the bile ducts and discharged with urine (35-60%) and stools[1].

As to the pharmacological range, oxytetracycline belongs to the tetracyclines class and is mainly active towards *Mycoplasma pneumoniae, Borrelia spp, Hemophylis ducreyi, Yersinia pestis, Vibrio cholerae, Neisseria spp, Treponema spp, Clostridium spp, Bacillus anthracis, Chlamydia spp* and secondarily (when intolerances toward penicillin are present) is used to treat infections by *Streptococcus spp, Escherechia coli, Enterobacter aerogens, Shigella spp and Klebsiella spp*[2].

Several studies have investigated, in humans, the toxic effects of these antibiotics, ingested in therapeutic doses, with the specific purpose of the eradication of pathogenic bacterial species, correlated with long-term exposure. The use of oxytetracycline showed teratogenic effects[3]. Gentamicin is responsible for the production of Reactive Oxygen Species (ROS) in the mitochondria of the epithelial cells of the renal tubules, where it activates the inflammatory mechanism by promoting apoptosis of these cells and macrophage infiltration in the renal tubular interstice[4]. Also streptomycin and vancomycin are responsible for renal damage[5,6]. Kanamycin and neomycin, on the other hand, by bonding copper ions in physiological pH, become potential oxidizing agents and therefore affect the production of ROS and hydrogen peroxide, correlated with the mechanisms of oxidative stress, ototoxicity and nephrotoxicity, hepatotoxicity, neurotoxicity and hematotoxicity[7]. Finally, chloramphenicol is considered a carcinogenic agent because it inhibits protein synthesis in the mitochondria by ribosomal binding in blood cells, exhibiting aplastic anemia and leukemia[8]. A positive association between long-term treatment with cyclosporine (post kidney transplant) and basal cell carcinoma and sebaceous gland hyperplasia was identified by Yayli S et al. (2010)[9].

Several studies have highlighted the effects of the oxytetracycline on the immune system, the pro-inflammatory effects and the activation of reactive species. Glette J et al. (1984) demonstrated, in vitro, that concentrations > 10 g/ml of oxytetracycline induced an increase of oxygen consumption by the human Polymorphonuclear Leukocyte (PMNL) when stimulated with Ultraviolet (UV) light and a transformation of the molecular oxygen in toxic species (superoxide anion, singlet oxygen, hydrogen peroxide), causing cellular damage and their chemotaxis toward the skin where skin damage is present[10]. Potts RC et al. (1983) have tested the effects of the antibiotic on mononuclear cells, observing how therapeutic doses (about 100 mg/day) determine a inhibition of protein synthesis by interfering with the aminoacyl-s-RNA in ribosomal complex and a 50% reduction in DNA synthesis and proliferation in the cells themselves, assuming a potential immunosuppressive effect in vivo in a long-term treatment with the antibiotic[11]. Similar results were obtained by Van de Bogert C and Kroon AM (1982) in rats, which showed an inhibition of the proliferation of lymphocytic cells, but not ertyhrocytic cells, after continuous intravenous administration of 0.15 ml/h of oxytetracycline[12]. Greater susceptibility to the antibiotic on cell proliferation in swine monocytes compared to PMNL (10-1500 g/ml of antibiotic) has been demonstrated by Myers MJ et al. (1995) by observing an imbalance in the respiratory functionality, in the peroxidase activity and the antibacterial activity[13]. Chi et al. (2010) studied the effects of the oxytetracycline (1.00×10^{-3} mol/L) on inhibition of bovine hepatic catalase activity, demonstrating that the antibiotic interacts with the catalase through Van der Waals forces and hydrogen bonds, destabilizing the secondary structure of the enzyme and its activities[14]. Peters TL et al. (2002), on the other hand, have demonstrated the role of oxytetracycline (200 μg/ml) in the destruction of the cartilage tissue in chickens, thereby preventing the deposition of bone tissue due to the tetracyclines, bone tissue uptake , interfering with its mineralization and remodeling[15]. An accumulation of oxytetracycline has been detected in swine hair (85.1-1742.8 ng/g) and in muscle tissue (1010.2-1361.0 ng/g) after administration of 220 mg/day for 28 days of antibiotic through feed; while in cattle, a single intramuscular dose (8 mg) of oxytetracycline has determined an accumulation of 116.3-187.7 ng/g in the hair and 1660.1-1080.0 ng/g in the muscle[16]. Recently, Barros-Becker F et al. (2012) have observed that, by exposing a population of zebrafish to concentrations of oxytetracycline of 50-100 μg/kg/day from 3 to 21 days, the activation of their immune system was unbalanced, with the production of reactive species and pro-inflammatory molecules (cytokines, myeloperoxidase, transcription of the cytochrome P-450) that persist even after the interruption of the inflammatory process, extending the validation of the model to aquatic species which are in contact with the antibiotic in question for a prolonged period of time[17]. A similar result was also obtained byYonar ME (2012) in a population of rainbow trout. He have observed an increase in the levels of malondialdehyde (indicator of lipid peroxidation), a reduction of levels of superoxide dismutase, catalase and glutathione peroxidase in the blood, liver, kidney and spleen, as well as a suppression of hematocrit values, the number of lymphocytes, of the total amount of proteins in the plasma, the immunoglobulins and phagocytic activity[18]. Lastly, Nonga HE et al. (2012) report the activation of the immune system in susceptible subjects, after the consumption of poultry meat and eggs; These effects are related to concentrations of oxytetracycline within the industrial foods suggesting it's involvement in food allergic responses[19]. The analysis of 60 poultry meats from the Turkish market and distributed in the markets or supermarkets, finding residues of oxytetracycline that, although under the limits established by the European Union (EU) (100 μg/kg for meat; 300 μg/kg for the liver; 600 μg/kg for the kidney), are to keep under close monitoring due to the effects on the inception of allergic reactions and the dissemination of the phenomenon of the antibiotic-resistance against various bacterial species[20,21]. Sternberg TH et al. (1963) focused their attention on a series of clinical disorders caused by food additives, among these, systemic lupus erythematosus (SLE), very similar to the idiopathic type and often not distinguishable (fever, myalgia, arthritis, polyneuritis, subcutaneous nodules, splenomegaly and lymphadenopathy and skin rashes), triggered by residues of penicillin, sulfonamides and tetracyclines in alimentary products. The mechanism of the onset of this syndrome is not entirely clear, but it is thought that there is a mechanism of hypersensitization to drugs, which, binding endogenous proteins, might cause haptens delivery that would trigger immune reactions, in subjects genetically predisposed[22].

A recent study (2013-unpublished data) showed the toxicity of milled bone from chickens treated with administration of oxytetracycline at 20% through the mechanism of watering carried out for 4 days of treatment and 2 weeks of suspension, compared to bone specimen from untreated animals. The first specimen displayed cytotoxicity up to a 1:4 dilution, from the analysis of the intact and not diluted specimen, while the bone specimen coming from non-treated animals did not show any cytotoxic effect; a second phase of the study, carried out later on another group of chickens, confirmed the same results.

In 1996, approximately 10200 tons of antibiotics have been used in the EU, half of which were intended for veterinary medicine as growth promoters. According to data provided by FEDESA (European Federation of Animal Health) in 1999, the consumption of antibiotics has increased by about 3000 tons, but only 6% of the total was intended for the promotion of growth in animals. This reduction was due to many antibiotics discharge for the industrial veterinary practice. In any case, it has been estimated that approximately 150000 tons of antibiotics are released into the environment each year with different consequences, not only ecological but also clinical[23].

The EU has set as the MRL (maximum residue limit) value for residues of tetracyclines in foods of animal origin to 100 μg/kg. This legislation became official in 1999. To test for these residues, both immunological and bacterial methods can be used. The immunological methods are very quick and simple to perform, but relatively more expensive; while the bacterial methods are fast enough (3-4 hours) and simple, but have a low sensitivity to antibiotic residues. Virolainen et al. (2013) have devised a bioluminescent bacterial test using cells of *Escherichia coli* K 12 (pTetKux1) as biosensors to detect the presence of residues of tetracyclines in poultry meat. This method also allows to detect the presence of the epimers for doxycycline, tetracycline, chlortetracycline and oxytetracycline, which are stereoisomers of the original compounds, with antibacterial activity similar with respect to the original compound. These cells enclose a plasmid coding for the Photorhabdus luminescens luciferase (enzyme capable of producing luminous energy), which is controlled by Tn10 transposon in tetracyclines that becomes active without the need for an additional substrate. Being able to quantify the concentrations of the epimers in the compounds of animal origin, therefore, is important in order to understand the effects of these metabolites, keeping in mind the possibility of a reversion to their compound of origin[24].

Antibiotics are used in the commercial farms (table I and table II) to prevent infections in animals and

Table I
Antibiotics employed in industrial meat food and their related effects on human health

Antibiotic	*Target*	*Effect*
Bacitracin	Human	No risk.
Bambermycin	Human	Positive: prevents antibiotic resistance because it is capable of improving the bacterial flora, which is able to counteract the Salmonella pathogen.
Chlortetracycline	Human	Development of pathogenicity of the Coli intestinal commensals.
Erythromycin, ampicillin, tetracycline, chloramphenicol, streptomycin, gentamicin	Human, dog and cat	Development of resistance to these antibiotics.
Erythromycin	Human	Development of resistance by fecal enterococci and transfer of resistance to other antibiotics (vancomycin and ampicillin) by plasmid transfer.
Erythromycin, vancomycin	Human	Development of resistance of fecal enterococci.
Lasalocid	Human	No development of antibiotic resistance
Salinomycin	Human	Apoptosis of tumor cells.
Streptomycin, oxytetracycline, ampicillin, kanamycin, chloramphenicol, sulfametazol/trimethoprim,	Human	Development of resistance to these antibiotics.
Streptomycin, kanamycin, monomycin	Human	Resistance by strains of Proteus toward those antibiotics.
Tylosin, tetracycline, sulfamethazine, chloramphenicol	Human	Increase of resistance to these antibiotics.
Tylosin, virginiamycin, avoparcin	Human	Increase of the resistance toward macrolides, lincosamides, vancomycin, teicoplanin antibiotics by gene transfer.
Tylosin	Human	No development of resistance. No effect.
Gentamicin	Human	Colonization of the human intestine of enterococcus faecalis resistant to the antibiotic and responsible for intra-abdominal and pelvic abscesses, endocarditis and occasionally meningitis or pneumonia. This colonization can persist in the intestines for at least 10 days.
		Transfer of resistance by plasmids to other intestinal bacteria.
Nourseothricin	Human	Discovery of bacteria in the commensal intestinal flora and in Shigella pathogen resistant to the antibiotic in human population outside the hospital environment. Transfer of resistance from animal to human bacteria.
Vancomycin, erythromycin	Human	Antibiotic-resistant bacteria (enterococci) in the population in contact with animal meat treated with these antibiotics.
Avoparcin	Human	Responsible for vancomycin resistance in human enterococci.
Avoparcin	Human	Responsible for the resistance to vancomycin, quinupristin-dalfopristin and everninomicin in enterococci. Responsible for resistance to fluoroquinolones in campylobacter and responsible for multiple antibiotic resistances in E. coli and in thypimurium DT 104 salmonella.
Avoparcin	Human	Responsible for the resistance to oxacillin in staphylococcus haemolyticus.

increase their fitness and wellness. Several studies have highlighted the effects of these drugs on humans and on domestic animals (dogs and cats), which are in contact with the antibiotics through their daily diet. The main clinical adverse effects caused by these antibiotics are extension of antibiotic-resistance in humans and domestic animals both against the antibiotic itself and toward other classes of antibiotic by plasmid transfer between bacteria and the development of pathogenicity in generally harmless bacteria, such as

Table II
Antibiotics employed in industrial meat food and their related effects on peats health

Antibiotic	*Target*	*Effect*
Erythromycin, ampicillin, tetracycline, chloramphenicol, streptomycin, gentamicin	Human, dog and cat	Development of resistance to these antibiotics.
Ampicillin, enrolfloxacin, gentamicin	Dog and cat	Development of resistance on the part of E. faecium and E. faecalis to these antibiotics
Carbadox	Dog	No toxic effect.
Vancomycin	Dogs	No resistant bacteria in dogs that have consumed raw meat.

the Coli of intestinal microflora. This effect would have a significant impact at the clinical level because it would lead to an increase in the number of pathology cases, an increase of the duration of the pathology and symptomatology, an increase in the number of cases of bacteremia with hospitalization and deceases[25]

Discussion

Analysis on the assessment of antibiotic residues in meat, milk and eggs intended for human consumption within the African states, conducted by Darwish FS et al. (2013), has reported that 41.7% of the total of such residues concern tetracyclines, 17.60% B-lactam antibiotics, 5.88% chloramphenicol, nitrofurans, quinolones, macrolides. Specifically, it was found that 66 specimens of fresh poultry meat from the retail trade of the city of Cairo contained residues in excess of tetracyclines (+8% in the chest, +7% in thighs and +13% in the liver) with respect to the maximum limits allowed; while the analysis of 600 specimens of bovine meat has revealed that 2% was positive to residues over the allowable limit of oxytetracycline (+1.3%), evidencing the problem of non-compliance to production procedures, contamination of foods with fecal material and use of disallowed antibiotics, constituting a high risk, as a result of continuous exposure, for immunopathogenicity, carcinogenicity, mutagenicity, nephrotoxicity, hepatotoxicity, reproduction disorders, and allergic reactions[26]. Specifically, allergic reactions due to hypersensitivity concern, between 7% and 10% of the cases, penicillin and, 50% of these cases are chronic urticaria and asthma. Sulfonamides produce hypersensitivity in 3% of the patients and Netromycin in 10-30%. Streptomycin and spiromycin are responsible for contact dermatitis. Dayan AD (1993) supposes that these allergic reactions to antibiotic residues in foods due to the presence of specific antibodies would take place following a prolonged exposure in genetically prone subjects[27]. Previously Levy SB et al., in 1976, had emphasized the role of antibiotic contamination in humans through the consumption of poultry meat and eggs in animals fed with feed treated with tetracyclines, revealing the presence in the intestinal bacterial flora of the chickens of microorganisms resistant to these antibiotics, and in a family of farmers living with these animals who had eaten chicken meat and eggs daily for two months. Complex is instead the case of the concentration of antibiotics in honey, used for the control of the reproduction of bees and the increase in their growth and therefore the production of food, for which there is no legislation to determine the maximum dosages allowed. The consumption of tetracyclines in beekeeping also contributes to the spread of the phenomenon of antibiotic resistance by the bacteria of the intestinal flora of these insects, as well as in humans and other animals, as demonstrated by Levy SB and Marshall BM (2013) reporting the presence of 8 similar genes responsible for this phenomenon in both bees and humans, speculating an alimentary and environmental spread[28]. Another potential risk to human health potentially linked to the antibiotic residues is represented by aquafarming; in fish farms, in fact, antibiotics are used, which, in addition to accumulating in the water basins, marine sediments and in bred fish species on which they have a potential toxic effect, come into contact with humans through food consumption. Particularly we suppose that people following high-protein diets, such as athletes and overweight patients have a major risk to develop oxytetracycline related side effects, in addition to kidney damage[29].

Oxytetracycline, one of the antimicrobials most widely administered to cattle, was recently the object of specific studies in domestic animals, particularly dogs, since, accumulating in bone tissue that acts as a substrate for feed, triggers a chain of intestinal, integumental, energy and behavioral functional IM balances that have aroused considerable attention in the field of veterinary medicine, especially in domestic animals. As evidence of the etiopathogenetic role of this family of molecules, diets, selectively deprived of this pollutant, restore normal fitness and physical integrity to the same animals as demonstrated by a study (1995) on 1312 dogs followed between 1980 and 1995 that showed different clinical pictures (defined as residues syndrome-SDR) acknowledged responsibility to the presence of residues of oxytetracycline in regularly consumed foods (not published study). Replacing the daily diet with food free of antibiotic residues, based on rice, vegetable oil, vegetables and sea fish (cod and hake) for 15 days a total remission of symptoms in 850 dogs (49% of symptoms) was observed. To support the hypothesis that these contaminants were responsible for SDR, the eliminated foods were gradually reintroduced (each food every 15 days), observing the symptoms reappear with a latency period varying from a few minutes to 12 hours, suggesting the sensitization of the subjects to these substances. Furthermore, recently, Pasquini et al. (2013) investigated the effects of diet on body weight and the oxidative and inflammatory status in a group of 12 adult dogs, showing a significant change, in terms of improvement, of parameters such as Body Condition Score (BCS), hematocrit, number of platelets, derivatives of oxygen reactive species and retinol, stressing the importance of antioxidants in the diet of the domestic animals.

The presence of a global market and the high index of mobility of the inhabitants of the planet, potentially, enhances the spread of this noxa, in the presence of well assessed iatrogenic pathology in domestic animals. A troubling, explosive escalation of food intolerances in humans is currently reported, without any apparent explanation, if not invoking the presence of impurities and contaminants, including no doubt the antibiotics that can act as haptens to unleash the immunoglobulinical reaction to many different types of food: ergo, in clinical analysis laboratories, food intolerance should be more appropriately investigated, performing tests that can detect antibiotics used in zootechnology and also from the study of the relationship between omega 3 and omega 6 in foods, as a possible contributory cause of phlogogenic imbalance of the alimentary metabolism. Sometimes currently drugs are not effective in the treatment of diseases, and patients have to resort to supplements[30]. In table III, the protective mechanisms, carried out by a correct Omega 6-Omega 3 fatty acid balance, are summarized. Moreover, physiological aging is related to immune system deregulation, called as immunosenescence, such as decreased activity of lymphocyte cells and increased levels of pro-inflammatory cytokines. Dietary fatty acids have been considered as regulators of inflammatory processes age-related[31].

In conclusion, our discussion on the iatrogenic damage of compounds with antibacterial action chronically absorbed by animal species and humans that are nourished by zootechnically contaminated foods, expresses a warning of attention, not only for the domestic animals symptoms, but also for polymorphous human inflammatory and degenerative unexplained diseases. Also the development of food quality control promotion should be necessary to perform, in order to sensitize people about this problem[32]. Realistically, also in humans the antibiotic catabolites, contained as a fraction of impurities in consumed food and perhaps even in subliminal doses at the law. Limits could be, in chronic use, responsible or share responsibility for these phenomena, particularly where the action of the hapten or haptens triggering an immunological disorder is amplified by imbalances potentially related either to fatty acids in the diet or to excess of alimentary free radicals with a reduction in the amount of highly antioxidant foods: the synergy of these copathogenetic moments has to be highlighted and should be carefully investigated for each individual risk factor within the background of the individual genetic reactivity.

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Table III
Anti-inflammatory and anti-oxidant mechanism of Omega 6 and Omega 3 fatty acids

Therapeutic application	*Mechanism of action*
Inflammation	Inhibition of the NLRP3 inflammasome in macrophages and the release of pro-inflammatory cytokines (IL-1, IL-8, IL-33).
Cancer	Consolidation of the muscle structural proteins; inhibition of pro-inflammatory cytokines (TNF, IL-6); weight gain; best response to antitumoral therapies.
Angiogenesis	Inhibition of VEGF receptor (FLK-1) on the vessels endothelial cells (stopping the proliferation, cellular migration and the formation of vessels); reduction of the mRNA of PDGF-A and PDGF-B expression.
Neurodegenerative diseases	Antioxidant activity
Metabolic diseases (dyslipidemias and type II diabetes)	Antioxidant activity
Atherosclerosis and ischemia	Antioxidant activity
Multiple sclerosis	Immunomodulatory

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