Investigation of Oxytetracycline and Enrofloxacin Residue in Beef Collected from Hatay Province

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Abstract
Aim to study: This study purposed to investigate the residues of oxytetracycline and enrofloxacin in beef samples collected from different districts of Hatay province.
Material and methods: Fifty beef samples, each weighing 100 grams, were randomly acquired from butchers and markets. High-performance liquid chromatography was utilized for sample analysis.
Results: The maximum residue limits for red meat in the European Union and the Turkish Food Codex is 100 µg/kg for enrofloxacin, ciprofloxacin and oxytetracycline, while according to the Food and Agriculture Organization it is 200 µg/kg. Residues of oxytetracycline, enrofloxacin, and its metabolite ciprofloxacin were found below the maximum residue limits determined by the Turkish Food Codex and Food and Agriculture Organization in 5 (10%) out of 50 beef samples. In 90% of the samples, no residues of enrofloxacin, oxytetracycline, and ciprofloxacin were detected. However, enrofloxacin residues were found in 2 muscle samples (4%) at concentration of 47 and 57 µg/kg, and ciprofloxacin residues of 60 µg/kg. Additionally, oxytetracycline residues were detected in 2 samples (4%) at concentrations of 88 and 95 µg/kg.
Conclusion: It was observed that oxytetracycline and enrofloxacin are used in fattening in Hatay province and pre-slaughter waiting periods are adhered to.
Keywords: Beef, ciprofloxacin, enrofloxacin, HPLC-UV, oxytetracycline.

Hatay İlinden Toplanan Sığır Etlerinde Oksitetrasiklin ve Enrofloksasin Kalıntısının Araştırılması

Öz
Çalışmanın amacı: Bu çalışma, Hatay ilinin farklı ilçelerinden toplanan sığır eti örneklerinde oksitetrasiklin ve enrofloksasin kalıntısının araştırılması amacıyla yapılmıştır.
Materyal ve yöntemler: Çalışma materyali, kasap ve marketlerden rastgele 50 adet sığır eti, her biri 100 gr olacak şekilde toplanmıştır. Numuneleri analiz etmek için yüksek performanslı bir sıvı kromatografi yöntemi kullanılmıştır.
Bulgular: Avrupa Birliği ve Türk Gıda Kodeksi'nde kırmızı et için maksimum rezidüel limit enrofloksasin, siprofloksasin ve oksitetrasiklin için 100 µg/kg iken Gıda ve Tarım Örgütü göre 200 µg/kg'dir. Oksitetrasiklin, enrofloksasin ve metaboliti olan siprofloksasin kalıntıları, 50 sığır örneğinin 5'inde (%10) Türk Gıda Kodeksi ile Gıda ve Tarım Örgütü tarafından belirlenen maksimum kalıntı limiti altında bulundu. Örneklerin %90'ında herhangi bir konsantrasyonda enrofloksasin, oksitetrasiklin ve siprofloksasin kalıntılarına rastlanmamıştır. Kas numunelerinin ikisinde (%4) 47 ve 57 µg/kg konsantrasyonlarda enrofloksasin kalıntısı, birinde (%2) 60 µg/kg konsantrasyonda siprofloksasin kalıntısına rastlanmıştır. Ayrıca iki numunede (%4) 88 ve 95 µg/kg konsantrasyonlarında oksitetrasiklin kalıntısı tespit edildi.
Sonuç: Hatay ilinde sığır yetiştiriciliğinde oksitetrasiklin ve enrofloksasin kullanıldığı ve kesim öncesi bekleme sürelerine uyulduğu belirlendi.
Anahtar kelimeler: Sığır eti, siprofloksasin, enrofloksasin, HPLC-UV, oksitetrasiklin.

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Introduction

Access to healthy food is crucial for consumers. Medications administered to farm animals can enter the human body through the food chain, potentially causing adverse effects for consumers (Jayalakshmi, 2017). Antibiotics represent one of the most extensively used drug groups in both human and animal context. According to the World Health Organization (WHO), approximately half of the antibiotics produced in the world are used for non-human applications (WHO, 2022). In veterinary medicine, antibiotics serve therapeutic purposes for treating sick animals, prophylactic purposes to prevent infections, and are utilized as feed additives at sub-therapeutic levels to enhance growth (Tadesse & Tadesse, 2017).

Antibiotics can be administered to food-producing animals in various forms including oral, parenteral, muscular, and topical applications. The elimination time of different antibiotics from the animal body varies, influenced by factors such as dosage form, antibiotic type, and method of administration (Bou-Mitri et al., 2019). While some antibiotics become harmless and ineffective by decomposing to inactive metabolites, some accumulate in the animal body and transfer into the milk, meat, or egg. For this reason, some health problems may occur in humans who consume foodstuff of animal origin, which is exposed to improperly used antibiotics (Ortelli et al., 2018). Many studies show that antibiotics accumulate in the liver, kidney, muscle, and bone tissues of livestock animals, which exceeds acceptable limits determined by authorities (Sarker et al., 2018; Amagon et al., 2017). The most commonly used antimicrobials in food-producing animals are tetracyclines and fluoroquinolone (Lee et al., 2001).

Tetracyclines are broad-spectrum antibiotics that are widely used in humans and animals against both Gram-positive and Gram-negative bacteria, as well as bacteria such as *Mycoplasma*, *Rickettsia*, and *Chlamydia* (Cinquina et al., 2003). Tetracyclines can be administered to animals orally with food or drinking water, parenterally, or by intramammary infusion. Due to enterohepatic circulation, tetracycline antibiotic residues may remain in the body long after administration (Botsoglou, 2001). Enrofloxacin is a third-generation fluoroquinolone antibiotic with a very broad spectrum used in the treatment of respiratory tract infections, digestive, urinary, joint, genital, mammary, and dermal infections in all animals (Cinquina et al., 2003; CVMP, 2007). Enrofloxacin is known to be partially metabolized to ciprofloxacin in cattle, with the concentration of ciprofloxacin in blood being 25 to 35% of the parent drug (Pyun et al., 2008). Ciprofloxacin is effective against microorganisms resistant to other antimicrobial agents such as aminoglycosides, tetracyclines, macrolides, and β-lactams (Sultan, 2014).

While some antibiotics, such as penicillins, are easily degraded, antibiotics such as fluoroquinolones and tetracyclines are more persistent, remain in the environment longer, spread more, and reach higher concentrations, so their residues can be found in the environment (Li et al., 2008; Sim et al., 2011). Antibiotic residues present in animal foods pose a significant risk to human health, manifesting in various ways such as gastrointestinal disorders (Sarmah et al., 2006), allergic reactions, toxic effects (Fabrega et al., 2008), and the transmission of antibiotic-resistant bacteria to humans (Nisha, 2008). Additionally, tetracyclines may cause staining of young children's teeth and poor fetal development (Botsoglou et al., 2001). Some countries and national organizations set limits for residue levels of veterinary drugs using risk-based assessments (EEC, 1990; Tollefson & Miller, 2000) to ensure that consumers are not exposed to high levels of residues in foods of animal origin. In the

European Union (EU) and our country, the Ministry of Agriculture and Rural Affairs has determined maximum residue limits (MRLs) for antibiotics in foods and the use of antibiotics as feed additives for growth promotion purposes is prohibited (EEC, 1996; Resmi Gazete, 2017). In the EU and Turkish Food Codex (TFC), the MRL for red meat is 100 µg/kg for enrofloxacin and its metabolite ciprofloxacin and 100 µg/kg for tetracycline.

High levels of tetracycline and quinolone occurrence in red meat have been reported (Kimera et al., 2015; Omotoso & Omojola, 2015). There are a few studies about the residues of enrofloxacin and oxytetracycline in beef samples in Türkiye (Erdoğdu et al., 2009; Er et al., 2013). To the best of our knowledge, there is no existing study in the literature that has investigated enrofloxacin and oxytetracycline residues specifically in beef sold in Hatay province so far. This study aims to investigate oxytetracycline and enrofloxacin residues in beef samples collected from Hatay province by using the high performance liquid chromatography (HPLC) method to determine the residue level of enrofloxacin and oxytetracycline, which are antibiotics used in livestock, and to increase food safety.

Material and Methods

This study was conducted on 50 edible beef muscle tissues obtained from local butchers and markets randomly in Hatay province Antakya, Samandağ, İskenderun, Arsuz, Belen, Defne, Yayladağı, Reyhanlı, Altınözü, Kırıkhan, Kumlu districts in February 2021. Beef muscle sample was collected at 100 g each and brought to the laboratory. Samples were frozen at -20°C till the day of analysis.

High performance liquid chromatography analysis

HPLC system (Shimadzu, Tokyo, Japan) CBM-20A system-controlled pump (LC-20AT), degasser (DGU-20A), autosampler (SIL-20A) column oven (CTO-10A) and ultraviolet detector (SPD-20A UV-VIS) was built. For ciprofloxacin, oxytetracycline, and enrofloxacin, the wavelength was adjusted to 280 nm. For chromatographic separation, a Gemini TM C18 column (250 × 4.6 mm; internal diameter, 5 µm; Phenomenex, Torrance, CA) was utilized. Temperatures for the column and autosampler were 40°C and 24°C, respectively. With the aid of a pump equipped with a low-pressure gradient system, the mobile phase, which consisted of aqueous solution 88% (0.4% orthophosphoric acid, and 0.4% triethylamine, and 12% acetonitrile) was supplied to HPLC at a flow rate of 1 mL/min. Data analysis was done using LC solution software that was managed by an Asus PC.

Preparation and analysis of beef samples

Analysis of enrofloxacin and its active metabolite ciprofloxacin and oxytetracycline from muscle samples were performed using HPLC-UV using previous methods (Corum et al., 2019; Tekeli et al., 2020; Uney et al., 2021; Corum et al., 2023). Beef muscle tissues were thawed at room temperature and then weighed as 1 gram and homogenized at 10000 rpm for 45 seconds (Heidolph Silent Crusher M, Germany). The homogenized muscle tissue was added to the microcentrifuge tubes as 100 µg. Then, 200 µL of acetonitrile for enrofloxacin and ciprofloxacin analysis and 200 µL of methanol (0.1% trifluoroacetic acid) for oxytetracycline analysis were added to the muscle tissue. The mixture was vortexed for 45 seconds and then centrifuged at 10000 x g for 10 minutes. For analysis of enrofloxacin and ciprofloxacin, 100 µL of water was added to 100 µL of supernatant and vortexed

for 5 seconds. All samples were transported in autosampler vials and 25 µL of them were injected into the HPLC system.

Method validation

The chromatographic procedure was established following the European Medicines Agency (EMA, 2011) recommendations. Oxytetracycline stock solution was prepared in distilled water, while enrofloxacin and ciprofloxacin stock solutions were prepared in 0.01 M NaOH to be concentration of 1mg/ml and all solutions stored at -80°C in the freezer. Enrofloxacin, ciprofloxacin, and oxytetracycline standard solutions were added to blank samples of beef muscle to provide quality control samples and calibration standards (0, 0.04, 0.1, 0.2, 0.4, 1, 2, 4 and 10 µg/g). To detect the recovery, precision, and accuracy, the quality control samples of enrofloxacin, ciprofloxacin, and oxytetracycline at low, medium, and high concentrations (0.1, 1 and 10 µg/g) were used. The peak areas of matter, measured on plasma samples and analyzed in the same manner as any other sample, were compared to the peak areas of the standards to calculate recovery. Recovery was >90.46% for enrofloxacin and ciprofloxacin and >87.24% for oxytetracycline. To ascertain the limit of detection (LOD) and limit of quantitation (LOQ), blank plasma samples were loaded with the lowest standard solutions of enrofloxacin, ciprofloxacin, and oxytetracycline (0.01-0.1 g/mL). A concentration with an signal to noise ratio of 3 was designated LOD and a concentration with an S/G ratio of 6 was designated LOQ on the chromatogram. For enrofloxacin, ciprofloxacin, and oxytetracycline, the LOD value was 0.02 µg/ mL and the LOQ value was 0.04 µg/mL. Precision was determined using the repeatability of the intra-assays and inter-assays. Six iterations of analyses were carried out on six separate days for each level of quality control samples at low, moderate, and high concentrations (0.4, 4 and 40 g/mL) to determine intra-assay and inter-assay variations. The concentration was measured for each sample and the concentration in the enriched plasma samples was used to calculate the percentage of coefficients of variation. The intra-assay and inter-assay coefficients of variation were determined as ≤4.72% and ≤5.80% for enrofloxacin and ciprofloxacin, and ≤5.64% and ≤7.24% for oxytetracycline, respectively.

Results

As a result of HPLC analysis of beef collected from butchers and markets in the districts of Hatay, 5 (10%) of 50 beef samples were detected as positive for oxytetracycline, enrofloxacin, and ciprofloxacin residues. All 5 of the samples were under the determined by the TFC and FAO. Oxytetracycline, enrofloxacin, and its metabolite ciprofloxacin residues were not found in 90% of the samples. Enrofloxacin residues were detected at 47 and 57 µg/kg concentrations in 4% of the 50 samples. Ciprofloxacin residue was found at 60 µg/kg concentration in only 2% of the samples. Also, oxytetracycline residues were detected in 88 and 95 µg/kg concentrations in 4% of the samples.

Discussion

Antibiotics have been used for decades to treat and prevent bacterial infections and stimulate growth in animals. However, non-compliance with the withdrawal periods after antibiotic use causes residues in products obtained from animals and may threaten human health as a result (Olatoye & Ehinmowo, 2010; Turk & Oguz, 2016). FAO and WHO recommend MRLs for veterinary drugs in edible tissues of animal origin to prevent the residue concern. The maximum oxytetracycline residue limits in beef muscle tissues have been determined as 200 µg/kg by FAO (2015) and 100 µg/kg by EMA (2002), the TFC (2017). The maximum enrofloxacin and

ciprofloxacin residue limits were determined as 100 µg/kg for beef muscle tissues by EMA (2002) and the TFC (2017). In this study, 10% of samples were found positive for the oxytetracycline, enrofloxacin, and ciprofloxacin residues under the TFC, FAO and EMA maximum residue limit standards.

Kimera et al. (2015) determined a total of 60 cattle muscle samples in Tanzania and found the mean of oxytetracycline residue in muscle samples was 2604.1±703.7 µg/kg. Also, 71.1% of the samples included oxytetracycline residue, and 68.3% of the samples were above acceptable limits. When this study was compared with the current study, the number and concentration of residue samples in Tanzania were higher than the results in the study. Abbasi et al. (2012) investigated the level of oxytetracycline residues in 22 cattle muscles in Iran. The mean oxytetracycline level of muscle tissues was found between 154.2±79.2 µg/kg. It was determined that 16.6% of the muscle samples exceeded the 100 µg/kg limit recommended by the EMA.

Muriuki et al. (2001) detected oxytetracycline residues in 110 (44%) and chlortetracycline residues in 4 (1.6%) out of 250 samples, which included muscle, liver, and kidney tissues from beef carcasses in a study conducted in Kenya. Beef muscle tissue accounted 7.6% of these residues, with mean oxytetracycline residues in muscles ranging from 524 to 1060 µg/kg. These results were determined to be higher than 100 µg/kg, which is the MRL in edible muscle tissues determined by EMA (Muriuki et al., 2001). In Hatay province, oxytetracycline reside levels in two samples were lower than those found in Kenya, with a detection rate of 4% in muscle tissues, compared to 7.6% in Kenya. Olatoye & Ehinmowo (2010) investigated oxytetracycline residues in 60 cattle muscles in their study in Nigeria. The mean residual level of muscle tissues was determined as 51.80±90.53 µg/kg, and the lowest and highest value range was determined as 0-220 µg/kg. oxytetracycline residue was found above the acceptable limits in 11.62% of the samples in the study in Nierya. In the study in Hatay, it was found below the acceptable limits in 4% (Olatoye & Ehinmowo, 2010).

Baghani et al. (2019) investigated tetracycline and ciprofloxacin residues in 41 cattle muscles in a study conducted in Iran. In cattle samples, tetracycline residue was found positive in 31 samples, in the range of 0-1.78 µg/kg. It was observed that none of the samples exceeded the MRL of 100 µg/kg. Besides, ciprofloxacin residue was present in all 41 samples, residue amounts were in the range of 0.1-43.2 µg/kg and were below the residue limit set by EMA, 100 µg/kg. The results of this study show similarity to our study, while the levels of residues found are significantly lower than those found in the samples from Hatay. In Tehran, it can be said that the cattle are sent to slaughter after complying with the legal withdrawal periods of antibiotics.

Ramatla et al. (2017) determined the levels of tetracycline in 20 beef and ciprofloxacin in 15 beef in Mafikeng in the Northwest province of South Africa. The mean concentration in bovine muscle tissues was 110.3±9.4 µg/kg for ciprofloxacin and 48.6±30.2 µg/kg for tetracycline. Five of the beef muscle tissues exceeded the ciprofloxacin MRL, while no muscle tissue exceeded the maximum tetracycline residue level. When this study was compared with the study conducted in Hatay, tetracycline residue levels were similar and ciprofloxacin residues were higher.

Aliu & Sulaj (2014) reported quinolone residue in 14 (15.7%) of the 89 beef samples at the 28.22±1.11 µg/kg mean concentration, in Kosova. Enrofloxacin and ciprofloxacin residue was detected in 6.7% and 3.35% of the samples respectively. This study was compared with the

study conducted in Hatay, tetracycline residue levels were similar. In their study in Iran, Mashak et al. (2017) found quinolone residues in 79 of 162 beef obtained from local meat markets. The mean residue level was 5.51±1.17 µg/kg. It has been observed that beef meat does not exceed 100-120 µg/kg, which is the national residue limit standard set by the state of Iran. Considering the province of Hatay in terms of quinolones, residue levels exceeding MRL (100 µg/kg) were not found in both studies.

Türksever & Öner (2021) analyzed meat samples taken from 20 different places in Van province with the CHARM II test for tetracycline group antibiotics. As a result of the analysis of the samples, they determined that there was no detectable level of tetracycline group antibiotics.

Erdoğdu et al. (2009) examined 250 cattle and 25 sheep meat samples in Izmir for the residue of tetracycline-derived antibiotics. Oxytetracycline residue was found in 11 (4.4%) of the samples. The mean of oxytetracycline residue in cattle samples was 906.6 µg/kg in the range of 275-2540 µg/kg which is above the acceptable limits Oxytetracycline residue levels found in this study were higher than the current study. Er et al. (2013) analyzed fluoroquinolone residue in 104 beef muscle meat samples collected randomly from markets in Ankara. As a result of the analysis, 57.7% of the beef samples were positive and the mean residue concentration was 6.64±0.14 µg/kg. When compared with our current study, both were found below the maximum residue limits. However, while it was positive in 4% of the samples in the current study, it was positive in 57% of the samples in this study.

Conclusion

Public health is severely threatened by residue in foods. Antimicrobial agents, commonly used in livestock animals can cause important health issues such as antibiotic resistance and toxic reactions in humans through residues. For this reason, the withdrawal period of the products of animal origin should be followed, and care should be taken not to exceed the MRL in foods such as meat, milk, and eggs. In this study, it was observed that 10% of the beef offered for sale in Hatay under the maximum concentration limit of pharmacological active substance residues allowed in animal foods determined by the TFC and FAO. To eliminate the residue problem in foods of animal origin, the awareness of the animal producers and sellers about residues should be increased by organizing training.

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Ethical Statement

This study was approved by the Hatay Mustafa Kemal University Animal Experiments Local Ethics Committee (2021/01-10).

Author Contributions

Ö.Ç.D. and E.T. contributed to the study design and study material collection. D.D.Ç. contributed to the data analysis. All authors participated in writing the manuscript, and collectively reviewed and approved the final version.

Conflict of Interest

The authors declared that there is no conflict of interest.

Data Availabilty Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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