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Analysis of Oxytetracycline Concentration in some Brands of Oxytetracycline available for Veterinary use in Maiduguri, Northeastern Nigeria

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ABSTRACT

Oxytetracycline is one of the commonly used antibiotics in veterinary practice in Nigeria. Questionnaire survey was conducted to ascertain the brands of oxytetracycline commonly used among veterinary clinicians, veterinary pharmacies, and livestock farmers. Spectrophotometric method was used to determine the actual concentration of some oxytetracycline brands sold over the counter for veterinary use. Five brands of oxytetracycline soluble powder were obtained from veterinary pharmacies in Maiduguri Metropolis. The percentage content of the oxytetracycline brands were 51.72%, 80.82%, 112.30%, 60.34% and 29.50% respectively. Four out of the five brands (80%) contained less than the labelled concentration. There was moderate positive correlation (r = 0.506) between the analyzed brands and their expiring dates. This implies that there is an ongoing administration of sub-standard antibiotics to animals with consequences including but not limited to development of resistance, therapy failure, toxicity, and side effects. Results of survey revealed 97.6% of the respondents use oxytetracycline and 41 different brands were available in Maiduguri. All (100%) the respondents either found oxytetracycline to be very effective or effective, while 80% of the respondents did not notice any side effects following use of the drug. It was concluded that oxytetracycline was widely used and regarded as an effective drug by the respondents but 80% of the brands had oxytetracycline concentration below the labelled concentration. Proper monitoring and quality control assurance should be enforced by regulatory agencies.

Keywords: Concentration; Maiduguri; Oxytetracycline brand; Over the count

INTRODUCTION

Antibiotics have been used extensively in both veterinary and human medicine for therapeutic and prophylactic purposes, as well as for other purposes including as feed additive, growth promoters, and prevention of bacteria-induced crop damage (Boxall *et al.,* 2004). Oxytetracycline is an antibiotic belonging to the class, tetracycline which is used commonly for treating bacterial infections in both humans and animals. High doses of oxytetracycline are generally toxic and produce many adverse effects, some of which can be fatal (Brunton *et al.,* 2005). Oxytetracycline is one of the most used antibiotics in veterinary medicine. Up till the 1950s, approximately 98% of pathogenic and commensal bacterial organisms were sensitive to tetracycline (Levy, 1992). Since then, resistance to tetracycline has been on the rise and it was recently reported that about 85% to 91% of foodborne pathogenic bacteria are resistant to tetracycline (Olatoye and Ehimowo, 2010).

In Nigeria, like in most developing countries of the world, antibiotics like oxytetracycline are widely sold over the counter and are mostly used without prescription by a veterinarian (Dina and Arowolo 1991; Ezenduka *et al.,* 2011). Several brands of oxytetracycline imported into the country and sold in veterinary drug stores and pharmacies, livestock markets and by drug peddlers are commonly used by farmers with neither diagnosis nor prescription by a veterinarian to treat animals (Dina and Arowolo 1991; Idowu *et al.,* 2010). Most of these oxytetracycline formulations are ineffective against tetracycline-resistant bacterial organisms (Ojo *et al.,* 2009). In 2006 World Health Organization (WHO) estimated that around 30% of the pharmaceutical preparations sold in Africa are fake of which antibiotics are popular targets (Okeke *et al.,* 2007). The rise in the number of these fake or sub-standard drugs of which tetracycline is the most common has led to widespread antimicrobial resistance (Shakoor *et al.,* 1997). The high quantity of sub-standard drugs in the market made this study necessary to determine the active pharmaceutical ingredient (API) concentration of some oxytetracycline brands available in Nigeria that are labelled for veterinary use using spectrophotometric analysis. Determination of drug concentration is of utmost importance as a specific dose is required to be administered to each animal patient for the drug to be effective (Safila, 2014). Spectrophotometry has been widely recognized and used in pharmaceutical analysis in place

of high-performance liquid chromatography (HPLC) due to its simplicity, low cost, and short turnaround time (Merey *et al.,* 2017).

MATERIALS AND METHODS

Study Area

This study was carried out in Maiduguri, Borno State. Maiduguri is the capital of Borno State, and it is located between the latitudes of 11°46'18"N and 11°53'21"N, and the longitudes of 13°02'23"E and 13°14'19"E. Maiduguri is situated on the seasonal Ngadda river, which drains into Lake Chad in Northern Borno. Maiduguri, commonly known as "Yerwa" by locals, has a land area of 50,778 km², making it Nigeria's largest metropolis in the north-east region (Abubakar, 2017).

Questionnaire Survey

A questionnaire was designed to determine the oxytetracycline brands labelled for veterinary use among veterinary clinicians, veterinary drug vendors and farmers in Maiduguri and environ. The questionnaire includes the biodata of the respondents as well as availability, brand, preparation, effectiveness, frequency of use and side effects of oxytetracycline. A total of 120 respondents were contacted for the questionnaire survey using convenience sampling technique.

Collection of Oxytetracycline Samples

Five (5) brands of commercially available oxytetracycline soluble powder were obtained from veterinary drug stores in Maiduguri, Borno State and transported to the Veterinary Pharmacology Laboratory, University of Maiduguri. The place of manufacture, batch number, NAFDAC number, production date and expiry date were recorded.

Preparation and Determination of Standard of Oxytetracycline

Analytical grade of laboratory oxytetracycline was from Sigma-Aldrich (St Louis, MO, USA). It was accurately weighed and dissolved in methanol to produce stock concentrations of 5mg/ml. This was later serially diluted to produce working concentrations of 0.3125, 0.625, 1.25 and 2.5mg/ml. The absorbances of these concentrations were measured in triplicates at 450nm wavelength using V1000 Vis-Spectrophotometer (Techmel and Techmel, Nigeria). A calibration curve was prepared by obtaining linear relationship between these known concentrations of the standard and their absorbance (Saba *et al.*, 2012). The experiment was carried out at the Veterinary Pharmacology Laboratory, Faculty of Veterinary Medicine, University of Maiduguri.

Determination of Oxytetracycline Concentration

The commercial preparations of oxytetracycline obtained were accurately weighed and reconstituted to produce a concentration of 5mg/ml for each brand and their absorbance at 450nm were recorded in triplicate using V1000 Vis-Spectrophotometer as in the section above. The mean values and standard deviation were calculated for each sample. The milligram content of each oxytetracycline brand was obtained using the regression equation obtained from the calibration curve plotted from the concentrations of the standard and the absorbance. Percentage content of each oxytetracycline brand was obtained by dividing the sample concentration (mg content) and working concentration and then multiplied by 100 using the formula (Audu *et al.*, 2012):

$$Percentage\ Content = \frac{Milligram\ Content(\frac{mg}{ml})}{5mg/ml} \times 100$$

Data Analysis

All data generated were analyzed using Statistical Package of Social Science (SPSS) Version 20 Software. Variables were analyzed for association using Chi-square and correlation, and significant association was set at $p < 0.05$. Tables, graphs and charts were used for data description.

Ethical Statement

The study did not include use of laboratory animals, hence ethical clearance Not APPLICABLE. Approval of respondents' consent was sought before the administration of questionnaire for this study.

RESULTS

Absorbance and calibration curve of oxytetracycline standard

The absorbances of oxytetracycline standard were recorded at five different concentrations as presented in Table 1. A graph was plotted for the results (Fig. 1). A coefficient of determination (R^2) of 0.9823 and the regression equation was y = 0.2629x + 0.033 were obtained from the graph.

Mean absorbance of commercial brands of oxytetracycline (5mg/ml) with their corresponding concentrations

Five (5) different commercial brands of oxytetracycline labelled A-E were analyzed at 5mg/ml and their absorbance was recorded. Four of the five brands contained less than the labelled oxytetracycline concentration as shown in Table 2. The lowest percentage of 29.5% was found in brand E which was just five months to its expiry date and the highest percentage content of 112.3% was found in brand C which was twenty-five months to its expiry date. There was moderate positive correlation between the percentage content and the expiry (r = 0.506).

Results of questionnaires survey on oxytetracycline in Maiduguri

Questionnaire was shared to 120 respondents of three categories (clinicians, farmers, and veterinary drug vendors) and 84 respondents replied to the questionnaire (70% response). A p-value of 0.002 was obtained indicating significant association between category of respondents and age of respondents as shown in Table 3. The results indicated 54.8% of the respondents were in Maiduguri Metropolitan Council (MMC) while 45.2% were in Jere. Only 36.9% of the respondents have less than 6 years of experience and 97.6% of the respondents use oxytetracycline (Table 4). Then 62.2% of the respondents have 2 or 1 brand of oxytetracycline (Table 5). The p values of 0.036, 0.000 and 0.000 were obtained indicating significant association between category of respondents and frequency of use/request of, preparation available and preferred preparation available/used for oxytetracycline, respectively (Table 5). Also, 40.2% of the available preparation was injectable form (Table 5) while 68.3% of the respondents preferred injectable oxytetracycline over other preparations (Table 6). All (100%) of the respondents said oxytetracycline is either effective or very effective and 80% respondents did not notice any side

effects following oxytetracycline administration. Oxytetracycline is not associated with side effects (Table 6).

Table 1: Absorbance of oxytetracycline standard at various concentrations

Concentration(mg/ml)	Absorbance 1	Absorbance 2	Mean Absorbance
0.3125	0.065	0.071	0.068
0.625	0.186	0.179	0.182
1.25	0.392	0.378	0.385
2.5	0.758	0.793	0.776
5	1.239	1.235	1.237

Table 2: Mean absorbance of oxytetracycline commercial brands (5mg/ml) with their corresponding concentrations

Brand name	Mean Absorbance	Concentration (mg/ml)	Percentage Content (%)	Milligram Content (mg)	Labelled Content (mg/g)	Expiry Date*
A	0.687±0.016	2.586	51.72	25.86	50	02/2023
B	1.055±0.004	4.041	80.82	40.41	50	12/2023
C	1.453±0.001	5.615	112.3	61.77	55	01/2024
D	0.796±0.003	3.017	60.34	10.68	200	04/2022
E	0.406±0.001	1.475	29.5	73.75	250	05/2022

* Correlation coefficient (r) = 0.506 between percentage content and expiry date

Table 3: Distribution based on sex, age and education level of respondents as relate to oxytetracycline prescription, sale and uses in Maiduguri.

Parameters	Frequency	Valid Percent	Cumulative Percent	p value*
Respondent's Category				
Clinician	22	26.2	26.2	
Farmer	33	39.3	65.5	
Veterinary Drug Store	29	34.5	100.0	
Total	84	100.0		
Sex				
Male	67	79.8	98.8	0.019
Female	17	20.2	100.0	
Total	84	100.0		
Age				
20 to 30 years	24	28.6	28.6	0.002
31 to 40 years	40	47.6	76.2	
>40 years	20	23.8	100.0	
Total	84	100.0		
Education Level				
Primary	4	4.8	4.8	0.001
Secondary	12	14.3	19.0	
NCE/ND	25	29.8	48.8	
HND/BSc and above	42	50.0	98.8	
None	1	1.2	100.0	

* p values for association between respective variables compared with the Category of Respondents

Table 4: Distribution for business location, experience, and use of oxytetracycline

Parameters	Frequency	Valid Percent	Cumulative Percent
Business Location			
MMC	46	54.8	54.8
Jere	38	45.2	100.0
Total	84	100.0	
Experience			
1-2years	10	11.9	11.9
3-5years	21	25.0	36.9
6-10years	30	35.7	72.6
>10years	23	27.4	100.0
Total	84	100.0	
Use of oxytetracycline			
Yes	82	97.6	97.6
No	2	2.5	100.0
Total	84	100.0	

MMC, Maiduguri Metropolitan Council

Table 5: Distribution of the respondent's category, frequency of use/request, preparations available and number of brands of oxytetracycline

Parameters	Frequency	Valid Percent	Cumulative Percent	P-value*
Respondent's Category				
Clinician	22	26.2	26.2	
Farmer	33	39.3	65.5	
Veterinary Drug Store	29	34.5	100.0	
Total	84	100.0		
Frequency use/request of oxytetracycline				
Very Frequently	21	25.6	25.6	0.036
Frequently	60	73.2	98.8	
Rarely	1	1.2	100.0	
Sub total	82	100.0		
Missing	2			
Total	84			
Oxytetracycline preparation available				
Injectable	33	40.2	40.2	0.000
Powder	15	18.3	58.5	
More than one	28	34.1	92.7	
All	6	7.3	100.0	
Sub total	82	100.0		
Missing	2			
Total	84			
Total brands of oxytetracycline available				
1	31	37.8	37.8	0.000
2	20	24.4	62.2	
3	17	20.7	82.9	
4	8	9.8	92.7	
5	3	3.7	96.3	
6	2	2.4	98.8	
8	1	1.2	100.0	
Sub total	82	100.0		
Missing	2			
Total	84			

* p values for association between respective variables compared with the Category of Respondents

Table 6: Distribution of the effectiveness, side effects and preferred oxytetracycline preparation used/available.

Parameters	Frequency	Valid Percent	Cumulative Percent
Effectiveness of oxytetracycline			
Very effective	13	65.0	65.0
Effective	7	35.0	100.0
Sub total	20	100.0	
Not applicable	64		
Total	84		
Side effects of oxytetracycline			
None	16	80.0	80.0
Pruritus	3	15.0	95.0
Abscess	1	5.0	100.0
Sub total	20	100	
Not applicable	64		
Total	84		
Preferred oxytetracycline preparation used/available			
Injectable	56	68.3	68.3
Bolus	2	2.4	70.7
Powder	24	29.3	100.0
Sub total	82	100.0	
Missing	2		
Total	84		

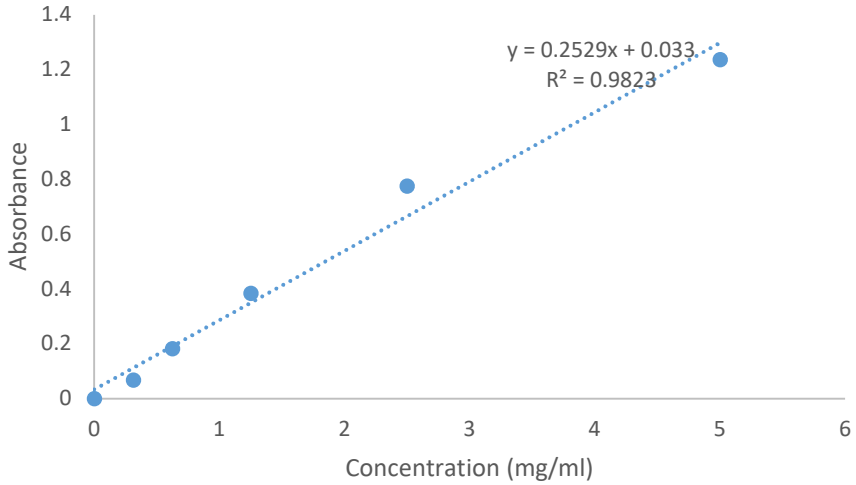

Figure 1: Calibration curve of analytical grade of oxytetracycline

DISCUSSION

This study was carried out to determine the concentrations of active contents in some brands of oxytetracycline sold in Maiduguri as well as the availability and frequency of use. The concentrations obtained from the spectrophotometric analysis of oxytetracycline commercial brands were found to be lower than the labelled concentration for four (80%) out of the five brands analyzed. The finding of this study suggests that the majority of commercially available oxytetracycline products for veterinary use in the study area were sub-standard because they contained active pharmaceutical ingredients that were below those claimed by the manufacturers. This agrees with the findings of Saba *et al.* (2012) who used 12 different brands of injectable oxytetracycline in Ibadan, Southwestern, Nigeria and found out that all 12 contained concentrations lower than what was labelled by the manufacturers. These sub-standard antibiotics, in turn, means that there is an ongoing extensive sub-lethal antibiotic administration to ill animals which can lead to antimicrobial resistance (Zhang *et al.,* 2006). To attain growth promotion and therapeutic effects from these medications, food-producing animals may have been subjected to methods of indiscriminate use, misuse, and overuse of antibiotics (Okonko *et al.,* 2009).

Antimicrobial resistance (AMR) is the inability of a bacterium to be treated with an antimicrobial medicine that was once successful in treating infections caused by that bacterium. It is a serious public health concern that poses a tremendous threat to the global development and reemergence of infectious illnesses that cannot be treated (Levy and Marshall, 2004; Okeke *et al.,* 2005; Erb *et al.,* 2007).

Low concentration of active ingredient in antibiotics may be the result of poor manufacturing or could be the effect of poor transport and storage conditions (Shakoor *et al.,* 1997; Rimoy *et al.,* 2002). Decomposition may also be the cause of low concentration of active ingredient in antibiotics, but it has been shown that many antibiotics, oxytetracycline included, are stable in tropical conditions. Therefore, poor manufacturing is generally believed to be the main contributor of sub-standard antibiotics (Nazerali and Hogerzeil, 1998). Dilution of medications with other substances such as contaminated water (Moken, 2003) and sugar could lead to a decreased concentration of the active ingredient (Reidenberg and Conner, 2001).

Another possible explanation may be the expiry date of the drug samples. While none of them is expired, there was moderate positive correlation (r = 0.506) between expiry date and active pharmaceutical ingredient in the drugs. The chances of this being the reason are small as was confirmed by Cantrell *et al.,* (2012) who tested 14 already expired drugs and found out that 12 (86%) still retained at least 90% of their active pharmaceutical ingredients. Mobile Identification System (MAS), Radio Frequency Identification (RFID), handheld spectrometer (TruScan) are some of the new cutting-edge technologies used by pharmaceutical companies and drug regulatory agencies to stamp out counterfeit and sub-standard drugs (Kovacs *et al.,* 2014).

This study found that oxytetracycline was used by 97.6% of the respondents (clinicians, farmers and veterinary drug stores). Oxytetracycline has been found to be the most used antibiotics in Maiduguri by farmers, veterinarians, and para veterinarians through different research. According to Geidam *et al.* (2012) oxytetracycline (36.5%) was the most used and marketed antibiotic by poultry farmers in Maiduguri. Daniel *et al.* (2021) also reported that oxytetracycline was used by 78.7% of the clinicians in University of Maiduguri, Veterinary Teaching Hospital (UMVTH). Aliyu *et al.* (2018) also reported that oxytetracycline is used by 99.2% of veterinarians and para veterinarians in Niger State. The high percentage of usage of oxytetracycline may not be unconnected to its broad spectrum of activity, low cost and availability (Daniel *et al.,* 2021).

The study revealed that there are 41 different brands of oxytetracycline available for veterinary use in the study area. Three different preparations available include injectable, powder, spray and bolus. Injectable preparation is the most popular with 68.3% of the respondents preferring it to other preparations. This can be explained by the fact that oxytetracycline loses its effect because of the microbial flora of the fore stomach in ruminants and limited absorption in the small intestine of poultry (Kaya, 2007). This is why parenteral route is preferred in relation to other routes and in turn injectable preparations are preferred to other preparations (Özdemir, 2003; Aktas and Yarsan, 2017). A 100% of the respondents either found oxytetracycline to be very effective (65%) or effective

(35%) which agrees with the findings of Keita *et al.* (2007), Shivachandra *et al*. (2011) and Islam *et al.* (2016) who found oxytetracycline to be 100% effective in the treatment of bacterial infections more specifically haemorrhagic septicaemia.

In conclusion, the study has revealed that 4 out of the 5 oxytetracycline commercial brands analyzed representing 80% contained concentrations less than what was labelled by the manufacturers. This study also revealed that oxytetracycline is widely used in the study area and respondents regarded it as an effective antibiotic. Regulatory agencies must properly enforce laws for the assurance and monitoring of quality of drugs.

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Conflict of Interest

The authors have no conflict of interest to declare.

Authors' Contributions

The idea was conceived by SIN, BU and EOA, questionnaire administered by MAA, MMB, UAS and MBB, drug samples collected by MAA, laboratory analysis conducted by AUM, YAZ, MAA, MMB, UAS and MBB under the supervision of SIN, BU and EOA, data analysis and result interpretation by all authors, manuscript prepared by MAA and SIN, manuscript read, corrected, and approved by all authors.

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