Experimental Oxytetracycline Toxicity in Feedlot Heifers

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Introduction

Tetracyclines have been used extensively in veterinary medicine for almost thirty years. Reported side effects include gastro-intestinal disorders, occasional anaphylactoid reactions, photosensitivity, dental discoloration, bone growth retardation, inhibition of protein synthesis, negative nitrogen balance, hepatic fatty degeneration, azotemia, clotting disorders, aplastic anemias and central nervous system disorders. (12, 14, 18, 24, 25)

Several syndromes associated with tetracycline nephrotoxicity in man have also been recognized. The use of degraded tetracyclines has led to a Fanconi-like syndrome characterized by glycosuria, amino aciduria, acidosis and decreased phosphate clearance. In patients with pre-existing azotemia, therapy with tetracyclines has been incriminated in the death of humans suffering from a variety of diseases and the pathological changes found in these people have been reproduced experimentally in animals. (4, 5, 15, 16, 19, 20, 22)

Many of the pathological changes which occur in patients suffering from tetracycline toxicity are reversible. The present study was undertaken to determine if metabolic alterations would occur in a therapeutic regimen frequently used in feedlot cattle. (2, 4, 13, 18)

Methods and Materials

The experiment was conducted on 15 feedlot heifers, acquired at public auction. These heifers were introduced into the feedlot and allowed two months acclimatization. All animals were kept in an open dirt lot approximately 50 meters square with a three sided shed open to the south available for shelter. The handling equipment was typical of small midwestern feedlots. They were fed a typical feedlot non-medicated ration of corn silage, and corn adequately supplemented with natural protein. Pregnant heifers were treated with prostoglandin F2 as an abortifacient 30 days prior to the experiment. Four days prior to the beginning of the experiment animals were identified, randomly assigned to treatment groups, and weighed.

Treatment Regimen

Animals assigned to the "High" dose group (n=7) received 33 mg/kg oxytetracycline[a] and the "Low" dose group (n=8) received 11 mg/kg oxytetracycline intravenously once daily for three days.

Clinical Pathology

Blood was collected by jugular venipuncture. Voided urine was collected mid-stream following perivulvar stimulation. Samples were collected day four pretreatment, prior to each treatment and days one and two posttreatment.

Urinalysis[b], blood urea nitrogen (BUN), hematology,[c] and fibrinogen[d] assays were conducted on all samples from each animal. A platelet count[e] and sorbitol dehydrogenase (SDH)[f] assay were performed on day four pretreatment, day one of treatment and day one posttreatment samples.

Animals which had abnormal clinical pathology values on the initial sampling were resampled 24 hours prior to the first oxytetracycline treatment to reassess their physiologic state.

a. Liquamycin; Pfizer Inc., 235 E. 42nd St., New York, NY
b. included measurements were Multistix, Ames, Co., Elkart, Indiana 46514 (pH, protein, glucose, ketones, occult blood urobilogen, bilirubin), specific gravity, RBC's/high power field (hpf), WBC's/hpf, bacteria count/hpf, casts/low power field, cast identification and crystal identification
c. included measurements of total protein, PCV, Hb, RBC's, and differential WBC count.
d. the difference in protein between plasma and heat treated (56°C for three minutes) plasma
e. Unipet #5806
f. spectrophotometric assay

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All pretreatment samples were evaluated to establish normalcy of each animal.

Statistical Analysis

Numerical values were assigned to each clinical pathologic parameter based on the predictive value of each parameter as a measure of altered renal function reported with tetracycline nephrotoxicity. Further, the points assigned to each clinical pathology parameter increased on a basis proportionate to the severity of alteration. The distribution of the maximum of 50 points among the various parameters was; urinalysis 31 points, blood urea nitrogen 10, hemogram 5, sorbitol dehydrogenase 3 and fibrinogen 1. The 31 points assigned urinalysis were derived from urinary casts 16, occult blood to RBC ratio 8, protein 4, glucose 2 and calcium oxalate crystals 1.

The mean number of points accumulated for each altered clinical pathology parameter within each treatment group was calculated for each sampling. The mean number of points for all altered clinical pathology parameters was also calculated. The data was then analyzed via difference in means. (17)

Results

Statistical analysis of the data indicated no significant change in hematologic parameters. Fibrinogen increased significantly ($p < 0.1$) in the "High" group from 350 to 570 mg/dl in 24 hours and to 870 mg/dl in 48 hours. The increase in fibrinogen of 450 to 730 mg/dl between the second and third treatment was significant ($p < 0.1$) in the "Low" dose group.

Decreases in the SDH values from a mean of 410 to 320 SU in the "High" group and from 430 to 250 SU in the "Low" group were not statistically significant.

The platelet count, packed cell volume (PCV), hemoglobin (Hb), red blood cell count (RBC) and total plasma protein remained essentially unchanged throughout the experiment. The urine occult blood, urine red blood cells/high power field and their ratio to each other did not change significantly between or within groups.

Analysis of the results of the urinalysis and BUN indicated that the only significant changes occurred in BUN values and the number of urinary casts observed. The point values for urine protein in the pretreatment samples of 0.3 for "High" and 0.5 for "Low" groups were not significantly different. The increases in urine protein in both groups during the experiment were not statistically significant. The mean urine glucose in the "Low" group of 0.2 in pretreatment samples was negative in all samples collected subsequent to the second treatment.

No casts were found in any of the pretreatment urine samples. Rare, fine granular cast formation was found in one urine sample from the "High" dose group following the first treatment. Cast formation continued to increase in the "High" dose group through the third treatment. All urine samples collected following the third treatment and through the posttreatment period of the "High" dose group contained casts ranging in numbers from rare to 0.5 casts per low power field (lpf). In the "Low" group rare fine granular cast formation was found in one urine sample following the first and one following the third treatment. These two urine samples with positive cast formation were not collected from the same animal. The difference in urinary cast formation between "High" and "Low" dose groups and during treatments in the "High" dose group was statistically significant ($p < 0.1$). (Fig. 1)

The urine specific gravity did not vary significantly between treatment groups. The mean specific gravity of both groups throughout the experiment tended to be lower than normal.

Blood urea nitrogen increased in the "High" group from a mean of 14.6 mg/dl in the pretreatment samples to a mean of 25.0 mg/dl in the samples following the third treatment. The mean BUN then decreased to 22.1 mg/dl at 48 hours posttreatment. Statistical analysis of the data indicated a significant ($p < 0.1$) increase in the BUN of the "High" dose group. Changes in the mean BUN in the "Low" group were not significant. (Fig. 2)

Discussion

The feedlot industry suffers a devastating loss of livestock each year from bacterial penumonia. Tetracyclines are the most frequently used antibiotic in the treatment of this respiratory disease. The merits of high serum concentrations of tetracyclines have been reported. (10) Evidence is presented in this experiment which demonstrates that iatrogenic disease can be produced by treatment with levels of oxytetracycline, 33 mg/kg, that are similar to treatment regimens used in many feedlots for respiratory disease.

The use of tetracyclines and subsequent renal tabular necrosis has been reported numerous times in clinical situations. (4, 7, 9) Experimental renal tubular necrosis has been produced with doses of 25 mg/kg to 250 mg/kg of tetracycline in laboratory animals. (26) Although finding the sporadic granular cast in a urine sample may not indicate significant renal disease, consistent granular cast formation is recognized as evidence of tubular damage. Urinary granular casts were found in every animal treated in the "High" group indicating tetracycline, dose related, tubular damage. (Figure 1)

Several mechanisms for tetracycline induced tubular damage have been proposed. The damage to renal tubules produced by tetracyclines may be due to the direct toxic effect of the drug on the oxidative enzyme systems of the tubular cells. (15) Members of the tetracycline group have been shown to inhibit a c-AMP-dependent protein kinase in the renal medulla. Tetracyclines are capable of impairing urinary concentrating ability. The common tetracyclines differ structurally in their side chain substitution. This difference alters their major physiologic properties: penetration of the drug into the cell through lipid soluble membranes, calcium chelation and its effect on epithelial

water permeability, and membrane phosphoproteins as effectors of ADH action. (20) The urine specific gravity, while not significantly varying between treatment groups, tended to be lower than normal in both groups throughout the experiment.

The diuretic effect of tetracyclines may tend to produce dehydration which in many feedlot animals is a problem concurrent to their entry into a new environment. However, no clinical pathologic evidence was found to support dehydration in this experiment. It should be noted these animals were well adjusted to the feedlot before the experiment began thus were not suffering from shipping stress or other diseases. Dehydration can contribute to urinary cast formation. (6) Histologic renal lesions have not been reported in experimental tetracycline toxicity studies although an increase in BUN has been observed. (20)

Renal lesions have been described in suspected cases of tetracycline toxicity which include varying degrees of swelling of the tubular epithelial cells and tubules which contain eosinophilic protein casts. (3) The proposed pathogenesis included dehydration, and subsequent azotemia with elevation of BUN. (4) Another proposed mechanism for azotemia and accompanying metabolic changes is associated with tetracycline inhibition of protein systhesis and its antianabolic effects. (2) In this experiment a significant ($p<0.1$) increase in BUN in the "High" group was observed. (Figure 2)

A number of reports associate tetracycline therapy with hemolytic syndromes. (12, 14, 24) Experimentally imposing tetracyclines on existing hemoglobinuria has produced renal tubular lesions. (15, 22) Procedures for quantitative evaluation of intravascular hemolytic disorders and subsequent hemoglobinuria provided no evidence of an intravascular hemolytic problem that could have contributed to the urinary cast formation in the "High" treatment group.

Urine protein was measured as a screening parameter for glomerular function, Fanconi Syndrome, and as an additional parameter for presence of hemoglobin which would be associated with hemolytic disorders. It is not unusual to find a small amount of protein in the urine of cattle. (6) In this study the values observed for urine protein in both groups were in the normal range throughout the experiment providing additional evidence that the urine casts did not originate from a hemolytic process.

Although glucose is reabsorbed in the proximal tubules, an increase in urine glucose is not an accurate measure of the tubular function without a concurrent determination of blood glucose. Urine glucose was measured for three reasons: first, as a parameter along with the differential

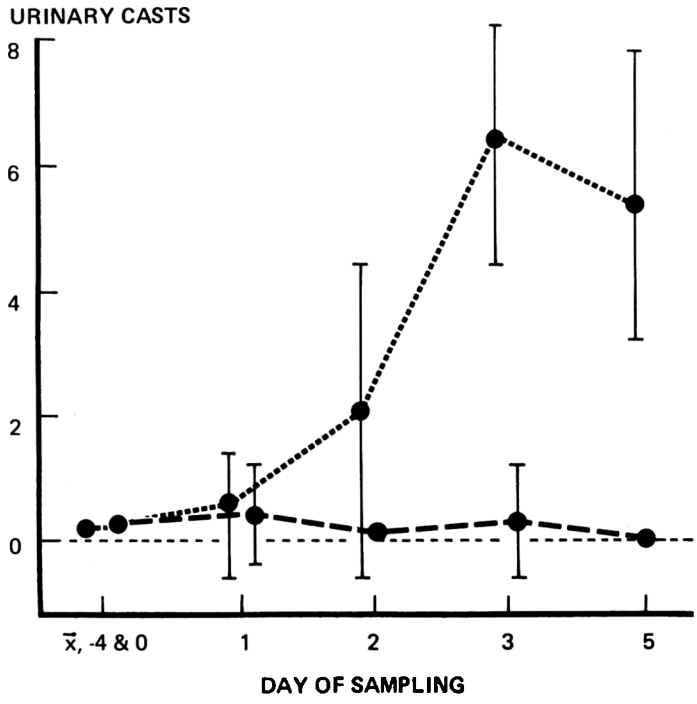

Figure 1
Mean and standard deviation of urinary cast per lower field.
..... "High" dose group (33 mg/kg oxytetracycline)
– – – – "Low" dose group (11 mg/kg oxytetracycline)

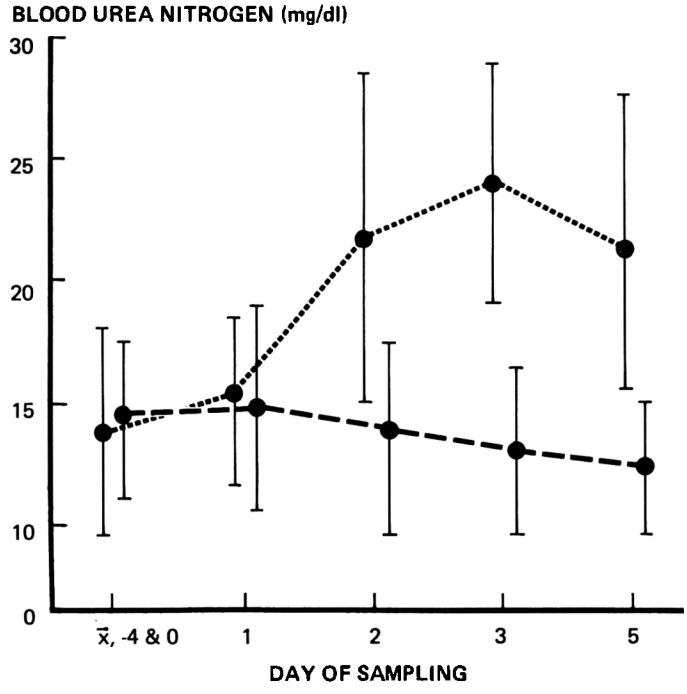

Figure 2
Mean and standard deviation of blood urea nitrogen (mg/dl).
..... "High" dose group (33 mg/kg oxytetracycline)
– – – – "Low" dose group (11 mg/kg oxytetracycline)

white blood cell counts, to establish the stress effect of handling; secondly, to determine if the conversion of the propylene glycol vehicle to glucose in the liver would cause hyper-glycemia and thirdly, as a monitor for Fanconi's Syndrome. One pretreatment urine sample in the "Low" group contained two (+) urine glucose, possibly due to stress, medication, or both. Glucose was not found in any urine samples collected throughout the remainder of the experiment, which may indicate an adaptation to the handling stress or the metabolism of the propylene glycol. This tends to substantiate previous reports of tetracycline toxicity in which glomerular damage was not observed and also provides evidence that Fanconi's Syndrome was not involved in this study. (2, 4, 23)

Hepatic toxicity from tetracyclines has been well documented, particularly in pregnant women treated intravenously with tetracycline. (7) However, hepatic toxicity has also been reported in non-pregnant women, men and children. (7, 11) The principal liver lesion documented in tetracycline toxicosis has been fatty degeneration. (7, 11) It has not only been observed in human cases but has also been produced experimentally in animals. (11, 23)

Extensive investigation of hepatic fatty degeneration experimentally induced by 100 to 300 mg/kg of tetracyclines in rats and mice has left the pathogenesis in doubt. Two hypotheses have been proposed. The first suggests that tetracycline, which uncouples oxidative phosphorylation, may depress hepatic adenosinetriphosphate (ATP) synthesis, interfering with energy-dependent fat oxidation. Secondly, an agent whose action depends on impairment of amino-acyl-s RNA attachment to ribosomes may also interfere with the synthesis of the very low density lipoproteins in the liver decreasing hepatic output of triglycerides. (8, 11)

SDH is an hepatocellular enzyme assay most commonly used in evaluating acute hepatic disease in the bovine species. Hepatocyte damage or death due to reduced oxygen supply to the liver, damage from inflammatory byproducts or the direct effects of chemicals results in increased serum SDH values. (6) All three of these mechanisms (decreased oxygen, increase in inflammation and direct chemical effect) have been reported in tetracycline hepatotoxicity. Significant changes in serum SDH level were not observed in either treatment group, indicating that the dosages used did not result in insult severe enough to cause hepatocyte damage or death. The absence of positive clinical pathologic evidence of acute hepatic disease may be due to dosage of oxytetracycline, duration of treatment, animals which were not under the stress of pregnancy, or lack of correlation between the SDH assay and fatty degeneration of the liver. The inability to detect fatty degeneration by a single assay is substantiated by numerous reports both clinical and experimental, of failure to demonstrate fatty degenerative changes prior to necropsy by alterations in hepatic function values (1, 4, 20)

Nephrotoxicity and hepatotoxicity to parenterally administered oxytetracycline have been reported in numerous human clinical cases as well as controlled experiments in laboratory animals. The pathogenesis of either toxicity is not well defined but dependent on dose, duration of treatment and the status of the patient. Oxytetracycline has been considered safe and efficacious in feedlot cattle for the treatment of bovine respiratory disease. The increased prevalance of strains of *Pasteurella sp.* resistant to oxytetracycline has resulted in recommendations for increasing the dose from 11 mg/kg to 33 mg/kg or as much as 55 mg/kg. The 33 mg/kg dose produced a lethal nephrotoxicity in feedlot heifers with acute BRD (See page). The 33 mg/kg dose administered IV for three successive days produced signs of nephrotoxicity in clinically normal feedlot heifers but not deaths. The stressed animal appears to have a much greater sensitivity to the nephrotoxic potential of oxytetracycline than the normal animal.

Summary

Oxytetracycline has been widely used at 11 mg/kg for the treatment of resipiratory disease in feedlot cattle. The increased prevalence of resistant strains of *Pasteurella sp.* has resulted in recommendations for increasing the dose to 33 mg/kg or as much as 55 mg/kg. The 33 mg/kg dose administered to normal feedlot heifers I.V. for three successive days produced signs of nephrotoxicity but no deaths.

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Effect Of Birth Weight On Efficiency Of Beef Production

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Birth weight (BW) is related to calving difficulties (CD), calf mortality (CM) and infertility carry-over effects. Calving difficulty is a most serious problem facing efficient beef production, and though many factors are involved in CD, the dystocia level increased linearly with BW (Smith et al, 1976). Few producers are aware of the relative magnitude of the monetary losses resulting from calf wastage (Martin et al, 1976). Presently, losses are being exacerbated by the unskilled use of the large continental breeds for more lean and less fat in beef. Rejection of fatty meat at home and abroad is decisive, and incompatabilities between dam and lean beef progeny must be alleviated. So, the purpose of the research was to determine how to lower BW for ease of calving yet maintain, or enhance if possible, livability of the calf and postnatal growth for desirable end product.

Tauras, indicus taurus, "lean beef" taurus, lean beef indicus and indicus genotypes at the AMRC (U.Q.10) 128 cow unit facility at the Queensland Agricultural College (QAC), generated the data for this report (Dowling, 1974). The procedure is to artificially inseminate the cows and to calve in yards so calf is weighed forthwith. Records are computerised.

Selection was made for factors eg. for low birth weight (22 kg) of indicus Sahiwal with the extant taurus Shorthorn (BW 31 kg) to develop hybrids (BW 25 kg). At the other extreme, the Chianina was selected for livability and carcass factors. The progeny (BW 29 kg) produced high yielding carcass (360 kg; 19% fat at 20 months).

The indicus taurus hybrid dam is fitter and bigger than the beef taurus but has a calf with a lower BW. The BW of ¾ "Lean Beef" progeny out of the indicus hybrids is significantly lower for a superior carcass, than those from the lean beef on taurus dams (39 kg). Conversely the backcross to indicus (¾) resulting in a highly significantly ($P < 0.01$) lighter (26 kg) calf out of the large lean beef hybrid dams, with postnatal growth lower but not significantly different from the ¾ "lean beef" crosses.

Thus carcass characters can be combined with optimal BW and resistance for efficiency. Importantly, the use of a "lean beef" factor from the large European breeds permitted high indicus content (¾ indicus, ¼ lean beef) to breed "no dip" resistant cattle which were efficient for beef. There may be no better low-cost solution.

Hence, it could be tragic for the industry in Australia if misuse of "lean beef" breeds, precipitating high BW and CD, delayed their use advantageously.

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