Acta vet. scand. 1987, *28*, 343–348.

From the Department of Cattle and Sheep Diseases, Swedish University of Agricultural Sciences, Uppsala.

The Influence of Feeding and Oral Rehydration on the Bioavailability of Oxytetracycline in Calves

By *Jan Luthman* and *Sten-Olof Jacobsson*

Luthman, J. and S.O. Jacobsson: The influence of feeding and oral redydration on the bioavailability of oxytetracycline in calves. Acta vet. scand. 1987, 28, 343–348. – The influence of feeding on the bioavailability of oxytetracycline was studied in preruminant calves. Oxytetracycline was given in water as a drench to fasting calves or was mixed in the milk replacer. Compared to water the bioavailability was significantly reduced (53.5 %) when oxytetracycline was mixed in the milk replacer. A further reduction, 83.3 %, occurred when the calves were treated one hour post milk feeding. Also concentrate was found to reduce the bioavailability. Very high serum levels were recorded when the drug was given in an oral rehydration solution, pH 4.9, containing glycine. The values obtained when an alkaline (pH 8.3) solution without glycine was used did not differ from the levels recorded when oxytetracycline was given in water. It was suggested that the use of oxytetracyclines in feeds may be questioned because of their well-known complex forming ability.

milk; calcium; chelates.

Introduction

Calves are susceptible to infectious diseases and indications for antibacterial therapy occur frequently. Preruminant calves are often treated orally and for practical reasons the drugs are sometimes mixed in the milk or the milk replacer. By this way of administration the bioavailability of certain drugs may be reduced to such a degree that therapeutic concentrations in the body fluids are hardly obtained. Classical tetracyclines are sometimes administered in this way in spite of their well known ability to form chelates with divalent cations, e.g., calcium, which greatly reduces the bioavailability. In humans it has long been recommended that tetracyclines should not be taken orally together with milk or other dairy products. Milk replacers containing tetracyclines intended for prophylactic and therapeutic purposes in calves are however still in use in Sweden.

The influence of milk and milk replacers on the bioavailability of tetracyclines in calves was previously studied by *Luthman & Jacobsson* (1983) and *Palmer et al.* (1983). These studies showed that oxytetracycline (OTC) was bound to the milk replacer and that the binding was not easily reversible. Significantly lower serum levels were obtained in fasting calves when chlortetracycline (CTC) and OTC were given in milk and milk replacers than in water. The reduction in bioavailability was of the order 40–70 %. It was also shown that ions like Ca^{2+} and Fe^{2+} significantly reduced the availability of the studied tetracyclines.

In order to overcome chelation the OTC concentration in the milk replacers which now are on the Swedish market has been increased from 2000 to 6300 mg/kg milk powder. Calves fed these products show maximal serum levels of 0.5–1.1 µg/ml (*Luthman* unpublished).

The aim of the present investigation was to further study the influence of feeding on the bioavailability of OTC in calves. *Palmer et al.* showed that the bioavailability increased when OTC was given in oral rehydration solutions. A study of the effect of the composition of the rehydration solution was therefore included.

Material and methods

Twelve calves of the Swedish Red and White breed were used. At the time of the experiments the animals were 5–6 weeks old and weighed about 50 kg. If not otherwise stated all experiments were performed on calves which had fasted over night. Hay and concentrate were not allowed during the experiments. All animals were kept in individual pens.

The calves were weighed before each experiment and the dose of OTC was 50 mg/kg. The OTC preparation used was Terramycin vet., soluble powder 20 % (Pfizer).

In the first experiment 4 calves were given OTC in 2 l of luke-warm water and blood was sampled at intervals shown in Fig. 1. After 5 days the same calves were given OTC in 2 l of a conventional milk replacer and blood was sampled as previously.

The influence of concentrate feeding on the bioavailability of OTC was studied in 2 calves. The calves were given OTC in water as previously, but when the experiment was repeated the calves had access to mineralized concentrate mixture intended for dairy cows.

Two different oral rehydration formulations were studied, Beecham Calf Scour Formula, (Beecham Pharmaceuticals) and Ewolyt (Ewos AB). The Calf Scour Formula was delivered in 2 sachets, one of which contained only dextrose. The content of the other sachet was according to the labelling: glycine 31.8 %, citric acid 2.5 %, potassium dehydrogen phosphate 21.0 %, sodium chloride 44.1 %. The composition of Ewolyt was according to the labelling: sodium, potassium, bicarbonate, citrate and glucose. No further information was given, but Ewolyte did obviously not contain glycine. The solutions were prepared according to the manufacturers' instruction. The Calf Scour Formula solution showed pH 4.9, while Ewolyte was alkaline, pH 8.3. Six calves were used in this cross-over study. At each time 2 calves were given OTC in water, 2 in Ewolyt and 2 in Calf Scour Formula. The experiment was repeated in a way so that each calf had received OTC in each vehicle at the end of the experiment.

Blood was drawn from a jugular vein and serum was stored frozen until analysed. No samples were stored more than 48 h.

OTC in serum was analysed according to *Wilson et al.* (1976). Area under curve (AUC) was calculated according to the trapezoidal rule (*Baggot* 1977).

The values given in text and figures are mean ± standard error of mean.

Results

The results of the first experiment are shown in Fig. 1. The serum levels of OTC were significantly higher when the drug was given in water than in the milk replacer. The maximum value (Cmax) was 3.95 ± 0.82 µg/ml when OTC was given in water and 1.43 ± 0.12 µg/ml when given in the milk replacer. AUC from zero to 24 h was 35.33 ± 6.15 µg/ml × h in water and 16.42 ± 0.93 µg/ml × h in the milk replacer.

As shown in Fig. 2 the serum levels were lower (Cmax = 0.69 ± 0.21 µg/ml) when OTC was given in water 1 h post feeding

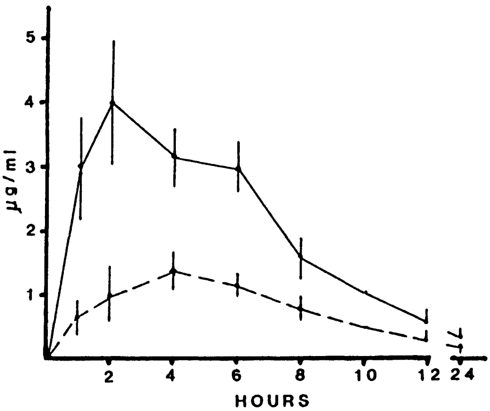

Figure 1. Serum concentrations of oxytetracycline in calves after oral treatment with 50 mg/kg, given in water ——— and mixed in the milk replacer — — —. n = 4, x̄ ± S.E.M.

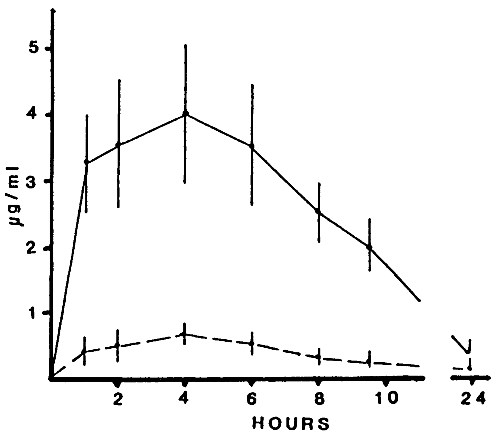

Figure 2. Serum concentrations of oxytetracycline in calves after oral treatment with 50 mg/kg. Fasting animals ———, one hour after milk feeding — — —. n = 6, x̄ ± S.E.M.

than when mixed in the milk replacer. In this experiment AUC was 29.7 ± 6.32 µg/ml × h in the fasting state and 4.98 ± 1.43 µg/ml × h 1 h post feeding.

Concentrate feeding also reduced the bio-

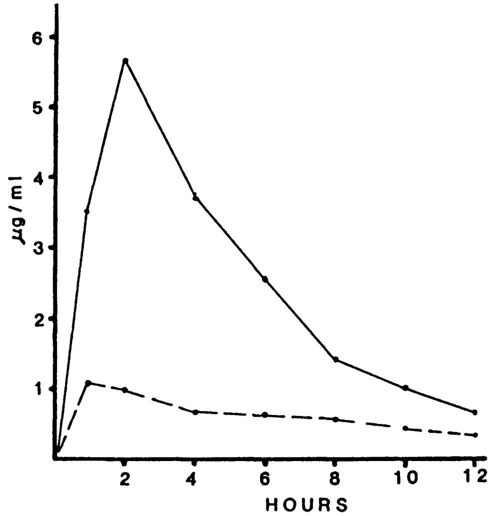

Figure 3. Serum concentrations of oxytetracycline in calves after oral treatment with 50 mg/kg. fasting animals ———, animals with access to concentrate — — —. n = 2, x̄

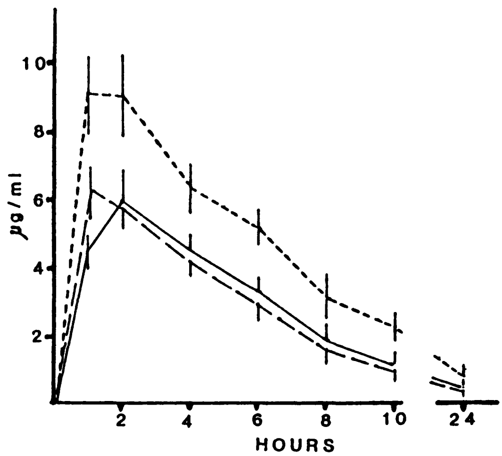

Figure 4. Serum concentrations of oxytetracycline in calves after oral treatment with 50 mg/kg given in water ———, in an alkaline rehydration solution — — — and in an acid glycine containing rehydration solution - - - - - -. n = 6, x̄ ± S.E.M.

availability of OTC (Fig. 3). The 2 calves had access to about 0.6 kg concentrate from the time the drug was given and the whole amount was consumed within 1 h.

The serum levels of OTC after administration in the electrolyte solutions are shown in Fig. 4. The highest levels were reached when OTC was given in the acid glycine-containing solution. These levels differed significantly from those obtained in water and in the alkaline solution. AUC in water was 45.13 ± 7.77, in the alkaline solution 43.75 ± 5.76 and in the acid glycine-containing solution 72.72 ± 4.30 μg/ml × h. The difference between the acid solution and water was statistically significant ($0.05 > p > 0.001$, $t = 4.956$).

Discussion

The serum levels shown in Fig. 1 are of the same order as reported earlier after the same dose of OTC (*Luthman & Jacobsson,* 1978, 1983). The reduction in bioavailability was 53.6 % when OTC was given in the milk replacer which also is in good agreement with earlier results. As shown in Fig. 2 the bioavailability was further reduced, 83.3 %, when the calves were dosed 1 h post feeding. A possible explanation to the very poor bioavailability post feeding may be that the milk replacer was partly coagulated in the abomasum when the calves were treated, which may have delayed the passage of OTC. It is possible that a higher bioavailability had been obtained if the calves had been treated later after feeding. *Gothoni et al.* (1972) studied the influence of iron on tetracycline bioavailability in man. Iron was found to have no effect if given not less than 3 h before and 2 after tetracycline administration.

In the previous calf studies only the influence of milk feeding was reported. Fig. 3 shows that also concentrate reduces the bioavailability of OTC.

The introduction of oral rehydration solutions has revolutionized the treatment of diarrhoea in man and animals. Water absorption is a passive process which entirely follows the absorption of electrolytes. There are rather complicated interactions between the absorption of various solutes. The presence of glucose increases the absorption of sodium and vice versa. Glycine and some other amino acids increase the absorption of both glucose and sodium. A review of these interactions was previously published by *Vandaele* (1983). *Bywater* (1977) also observed that citric acid increased the absorption of water.

As shown in Fig. 4 there were large differences in the serum levels when OTC was given in the two different electrolyte solutions. The highest values were obtained with the acid glycine-containing solution, while there was no significant difference between water and the alkaline solution. The results are probably explained by the different composition of the electrolyte solutions.

The serum levels reported after oral administration in the present and in previous studies (*Luthman & Jacobsson* 1978, 1983) are higher, even when OTC was given in the milk replacer than the levels obtained after intramuscular injection of the highest recommended dose, 10 mg/kg. *Bengtsson et al.* (1986) reported a mean level of 0.9 μg/ml in calves of similar age. The low levels after i.m. injection of 10 mg/kg may be explained by the dose. *Nouws et al.* found that OTC shows age-dependent kinetics. The volume of distribution was found to be larger in calves than in adult cattle. It was calculated that calves require twice the dose recommended in cows to obtain equal serum levels.

The chelate-forming ability of tetracyclines is well known and several efforts have been made to increase their bioavailability when mixed in feeds. Reduction of the calcium content of the diet is a method which have been tried by several investigators (*Eggert et* *al.* 1959, *Coustain & Lloyd* 1962, *Donovan et al.* 1962, *Wahlstrom et al.* 1982).

Citric acid was shown to increase the absorption of tetracyclines (*Eisner et al.* 1953). In later studies *Clary et al.* (1981) found a significant effect of citric acid on the bioavailability of CTC in turkeys. It is believed that citric acid binds to cations in the intestinal tract thereby preventing their complex formation with tetracyclines (*Green et al.* 1968). *Luthman & Jacobsson* (1985) studied the effect of citric acid on the bioavailability of OTC and CTC in calves. A significant positive effect of citric acid was reported. But as the recommended mass ratio citric acid: tetracyclines is 5–8:1, rather large amounts of citric acid were necessary when therapeutic doses of OTC were used. The palatability of the milk replacer was reduced so that some calves did not drink voluntarily.

The results from the present and from earlier studies show that the bioavailability of OTC is significantly reduced when mixed in milk or milk replaces. Remarkably low serum levels were also reported in swine fed a diet containing therapeutic amounts of OTC (*Luthman et al.* 1979). As long as there are very few controlled trials which prove the clinical efficacy, the use of tetracyclines in feed may be questioned.

References

Baggot JD: Principles of drug disposition in domestic animals. W. B. Saunders Co. Philadelphia/London/Toronto 1977.

Bengtsson B, Luthman J, Jacobsson SO: Penetration of oxytetracycline into tissue-cages in calves. J. vet. Pharmacol. Therap. 1986, *9,* 71–80.

Bywater RJ: Evaluation of an oral glucose-glycine-electrolyte formulation for the treatment of diarrhea in calves. Amer. J. vet. Res. 1977, *38,* 1983–1985.

Clary BD, Terry RJ, Creyer CB: The potentiation effects of citric acid on Aureomycin in turkeys. Poultry Sci. 1980, *60,* 1209–1212.

Coustain RA, Lloyd LE: Effect of ration calcium level, oxytetracycline and terephtalic acid upon the performance of growing pigs. J. Anim. Sci. 1962, *21,* 751-753.

Donovan GA, Price KE, Sherman WC, Zoli Z: Antibiotic potentiation. I. Influence of anions and fatty substances in lowering calcium inhibition of intestinal antibiotic absorption by chickens. Poultry Sci. 1962, *41,* 546-555.

Eggert RR, Akers WT, Huhtanen CN: Chlortetracycline and calcium utilization in growing swine as affected by terephtalic acid and calcium source. J. Anim. Sci. (Abstr.) 1959, *18,* 1505.

Eisner HJ, Stirn FE, Dornbush AC: The enhancement of serum levels of Aureomycin in experimental animals. J. Pharmacol. exptl. Ther. 1953, *108,* 442–449.

Gothani GP, Neuvonen J, Mattila M, Hackman R: Iron-tetracycline interactions: Effect of time interval between the drugs. Acta med. scand. 1972, *191,* 409–411.

Green DE, Rinchart KE, Stephenson EL: The influence of EDTA on blood antibiotic levels following oral administration of tetracycline compounds. Poultry Sci. 1968, *47,* 1500–1504.

Luthman J, Jacobsson SO: Serumkoncentrationer av tetracykliner hos nötkreatur efter oral och parenteral tillförsel. (Serum concentrations of tetracyclines in cattle after oral and parenteral administration). Svensk Vet. Tidn. 1978, *30, 87–92.*

Luthman J, Löfstedt M, Martinsson K: Serumkoncentrationer av klortetracyklin hos svin efter utfodring med högdosfoder. (Serum concentrations of chlortetracycline in swine fed a chlortetracycline containing diet). Svensk Vet. Tidn. 1979, *31,* 709–711.

Luthman J, Jacobsson SO: The availability of tetracyclines in calves. Nord. Vet.-Med. 1983, *35,* 292–299.

Luthman J, Jacobsson SO: The effect of citric acid on the availability of tetracyclines in calves. Nord. Vet. Med. 1985, *37,* 22–26.

Nouws JFM, van Ginneken CAM, Ziv G: Age-dependent pharmacokinetics in ruminants. J. vet. Pharmacol. Therap. 1985, *6,* 59–68.

Palmer GH, Bywater RJ, Stanton A: Absorption in calves of amoxicillin, ampicillin, and oxytetracycline given in milk replacer, water or an oral rehydration solution. Amer. J. vet. Res. 1983, *44,* 68–71.

Vandaele W: Fluid therapy in calves. In pharmacological basis of large animal medicine. Ed. Bogan, J. A., P. Lees & A. T. Yoxall. Blackwell Scientific Publications. Oxford, London, Edinburgh, Boston, Melbourne 1983.

Wahlstrom RC, Balios JP, Baker R, Libol GW: Effects of metallic cations on chlortetracycline absorption in swine. Nutr. Reports Int. 1982, *26,* 873–879.

Wilson DM, Lever M, Brosnan EA, Stilwell K: A simplified tetracycline assay. Clin. Chim. Acta 1972, *36,* 260–261.

Sammanfattning

Effekten av utfodring och orala rehydrerings lösningar på tillgängligheten av oxitetracyklin hos kalv.

Effekten av utfodring på tillgängligheten av oxitetracyklin studerades hos kalv. Oxitetracyklin gavs i vatten eller blandades i mjölknäringen till fastade kalvar. Jämfört med vatten reducerades tillgängligheten signifikant (53,5 %) när oxitetracyklin blandades i mjölknäringen. Tillgängligheten reducerades ytterligare, 83,3 %, när kalvarna behandlades en timme efter utfodring. Kraftfoder visades också reducera tillgängligheten påtagligt. Mycket höga serumkoncentrationer uppnåddes när oxitetracyklin gavs i en oral rehydreringslösning, pH 4,9, innehållande glycin. De värden som uppnåddes med en alkalisk rehydreringslösning utan glycin, pH 8,3, var inte signifikant skilda från de värden som erhölls med oxitetracyklin i vatten. På grund av tetracyklinernas komplexbildande förmåga kan inblandning i foder under vissa förhållanden ifrågasättas.

(Received March 16, 1987).

Reprints may be requested from: Jan Luthman, Department of Cattle and Sheep Diseases, Veterinary College, Swedish University of Agricultural Sciences, S-750 07 Uppsala, Sweden.