A Sustained-release Oxytetracycline Bolus for Ruminants

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Abstract

A matrix containing a hydrophobic binder, high-density non-toxic metal derivative, a polymer and the active ingredient, oxytetracycline constituted the components of the bolus. When 15, 17 or 20% oxytetracycline boluses were administered to fistulated Hereford and Angus heifers weighing ca 364 kg and maintained on a dry-lot maintenance ration, a mean release of 92-172 mg oxytetracycline/bolus/day over a 60-70 day period was recorded.

The use of controlled-release devices in ruminants was reported some time ago but until recently had not provided sufficient dosages or longevity necessary to release biologically active compounds at effective rates for extended periods of time. Early efforts employing this technique and crude technology provided cobalt at 1 mg/day for 100 days to grazing sheep on cobalt deficient pastures in Australia (Dewey *et al.*, 1958). Pellets providing small amounts of trace elements have also been retained within the rumen in excess of 1 year (Marston *et al.*, 1962). More recently, Miller *et al.* (1977) reported on the use of a bolus to supply methoprene to cattle for 10-12 weeks for control of the horn fly *(Haematobia irritans),* and Teel *et al.* (1978) reported the feasibility of incorporating pesticides for ectoparasite control in a sustained-release system and demonstrated that a 50% famphur® systemic acaracide bolus offered effective control against two 3-host tick species for up to 60 days. Likewise, Hair *et al.* (1979) demonstrated the effectiveness of the same system against *Boophilus* ticks.

As a result of several successful attempts to develop sustained-release systems in our laboratory we proposed that oxytetracycline might be administered to bovine animals continuously via a rumen bolus for disease control. Of particular interest to us was the control of vector-borne anaplasmosis [*Anaplasma marginale* (Theiler)] and other haematozoans. Anaplasmosis is an infectious, non-contagious disease of cattle and deer which causes annual economic losses of several $ millions in the United States (Schilf 1971). Although younger animals are susceptible and develop the subclinical disease, the organism normally invades and destroys the mature bovine erythrocytes. Mortality rates in infected, older, untreated cattle may reach 10-15%. The broad spectrum antibiotic, oxytetracycline, has been shown to be successful in combating *A. marginale* (Brock 1959) and other haematazoan diseases of bovine.

By the use of the complement-fixation test for detection of the disease, Franklin *et al.* (1965) found that intravenous injections at 1.5 mg and oral feedings of tetracyclines at 5.0 mg/kg/day would provide effective control against anaplasmosis, and Pearson *et al.* (1957), reported that intramuscular injections of 5 mg/lb of body weight for 10 consecutive days would eliminate anaplasmosis-carrier infections. More recently, Roby *et al.* (1978) found that a long-acting formulation of oxytetracycline (L-200) given I.M. at 200 mg/kg once every 7 days for 28 days was sufficient to eliminate *A. margainale* from recently infected yearling cattle.

With an increasing incidence of anaplasmosis in most of the Plains and West Coast states, an effective and economically feasible method of control is needed. Current methods of using parenteral dosages and feed additives have limitations, especially under rangeland conditions where periodic treatment proves laborious, time consuming and expensive. Also, when agents are introduced via rations, intake is generally variable and inadequately monitored.

The phenomenon of a controlled-release oxytetracycline bolus offers an approach to anaplasmosis control that may potentially solve many of the problems associated with current protection methods. The principle on which this device works is based on retention of the boluses in the rumeno-reticular sac of the ruminant. The active agent is

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released through erosion facilitated by normal rumination. The purpose of the present study was to design and evaluate the feasibility of a sustained-release bolus treatment program for use in ruminants.

Methods and Materials:

Eight Hereford and Angus heifers having an average weight of 364 kg were fistulated for rumenal cannulas (Bar Diamond Inc., Parma, ID.). The aperture allowed for entry to the rumen on a bi-weekly basis for bolus retrieval and evaluation. After 10 days post-operative antibiotic treatment, the heifers were maintained on a cotton seed-hull based ration (Williams *et al.* 1977) under dry-lot conditions to minimize gain during the test period. Boluses in each animal were coded in order to monitor the degradation of individual boluses. Bolus erosion, and thus oxytetracycline delivery, was monitored by removing the boluses from the rumen, drying them with a paper towel, weighing them on an electronic balance and calculating release rates estimated from bolus weight loss. The boluses were then reinserted in respective host.

Oxytetracycline boluses were prepared using a matrix containing a highly-hydrophobic carnauba wax, barium sulfate, a high-density non-toxic metal derivative, and a polymer, polyethyleneglycol, to facilitate bolus degradation. The matrix was screened through a U.S. Standard mesh sieve to obtain a uniform particle size and then blended with the active ingredient, oxytetracycline. Appropriately forty-five gram aliquots of the final formulation were hydraulically compressed in a steel mold using a model CT-710 hydraulic press (Soil Test Inc., Dallas, Texas) to form a conventional veterinary bolus 7.6 x 2.2 cm with an average density of 1.89 g/cm^3. Since testing conducted by Siegrist and Katz (1970) reported that the rate of release of the therapeutic agent is inversely proportional, within limits, to the compression rates, bolus formulations were compressed at a pressure conducive for proper cohesion and binding of particles.

Results from earlier pilot studies indicated that in order to achieve a bolus with a high-specific gravity that would effectively deliver desired therapeutic dose over a 45-60 day period, the proper bolus components, rates of each and sufficient compression were needed to accomplish such an objective. Considerations in matrix formulation were therefore based on a number of factors which included bolus size and density, utilization of non-toxic matrix ingredients, desired release rates and bolus longevity. In an initial trial, four 20% oxytetracycline boluses were prepared using candidate matrix A and administered to 4 fistulated heifers.

Based on the results of this first trial, we believed that the bolus release rate could be improved to provide a less variable and more consistent release of oxytetracycline. Therefore, in a second trial we utilized matrix B, which was a slight modification of matrix A. In this trial a lesser amount of polymer was used. It was thought that the amount of polymer present would affect the binding of the particles. The lesser the amount, the stronger the binding effect and consequently, a more controlled release of oxytetracycline. Four 20% boluses were prepared and administered to the remaining 4 fistulated heifers.

In summarizing results of the above mentioned trials, data illustrated that oxytetracycline could be formulated in a sustained-release system and that therapeutic dosages could be maintained. In order to develop a sustained-release formulation that could be used in treatment regimens, we felt it necessary to illustrate that bolus degradation was proportional to the amount of active ingredient and to determine the level of oxytetracycline most compatible with the developed matrix formulation. Therefore, we set up a trial in which we varied the % of oxytetracycline content blended with matrix so that different oxytetracycline release rates could be obtained. Five boluses of each of 3 concentrations (15, 17 and 20%) were prepared from matrix B and administered to 8 fistulated heifers.

Results and Discussion:

Results obtained during the 3 trials indicated that the sustained-release of oxytetracycline from an inert matrix within the bovine rumen was achieved. Figure 1 gives estimated daily release rates of oxytetracycline from 20% boluses tested in trials 1 and 2. Boluses of matrix A (trial 1) were consistent in eroding at a rate of 162 mg/bolus/day for the first 34 days. After this period, release rates became irregular due to an incidence of bolus breakage within the rumen. The breakage problem was thought to be due to a level of polymer that was not conducive for proper binding and delivery of oxytetracycline.

The 20% oxytetracycline boluses formulated from matrix B (trial 2) followed the same general erosion pattern as those of matrix A. These boluses maintained a mean ($\bar{X}$) release rate of over 150 mg/bolus/day between the 15th and 55th

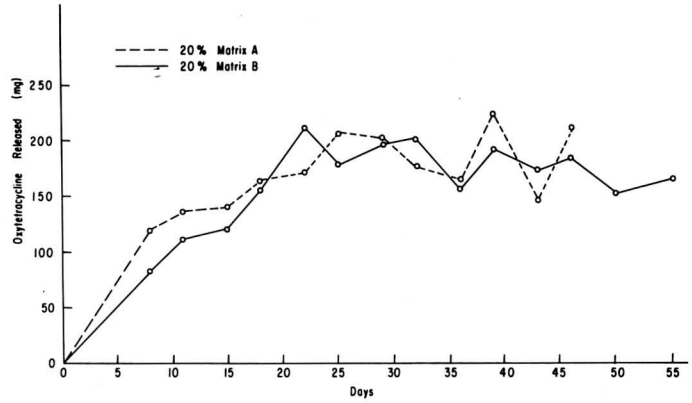

Figure 1
Mean ($\bar{x}$) Daily Release Rates of Oxytetracycline Through In-Vivo Degradation of Two 20% Oxytetracycline Bolus Formulations.

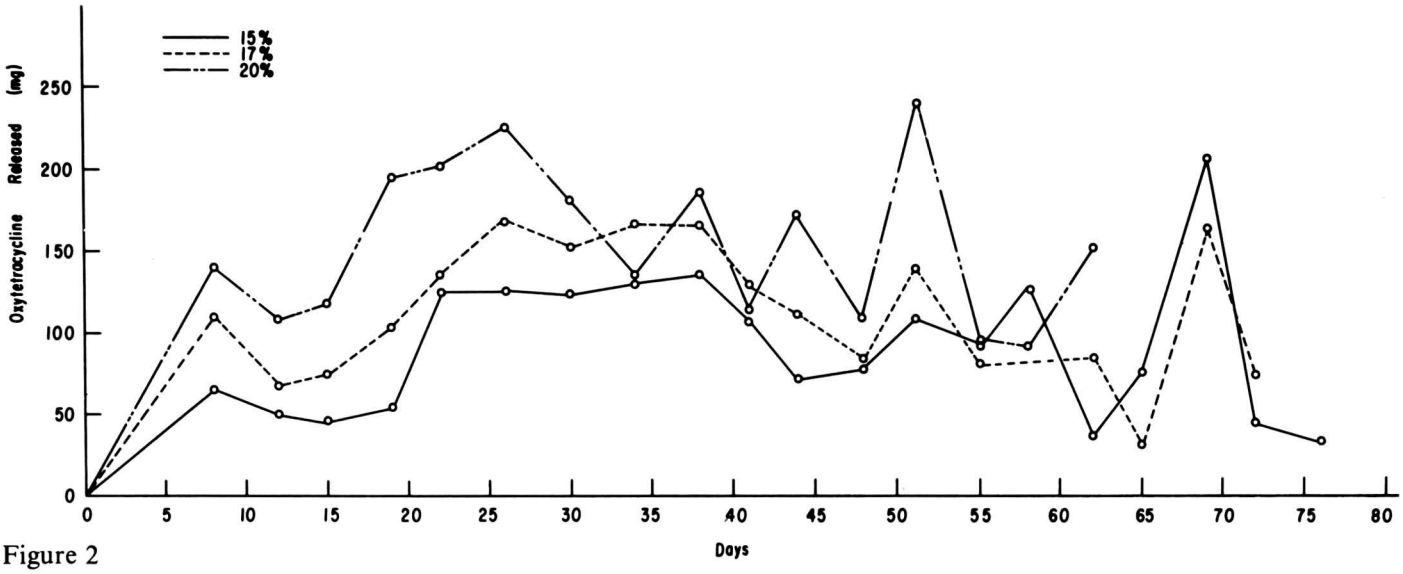

Figure 2

Mean ($\bar{x}$) Daily Release Rates of Oxytetracycline from 45g Boluses Containing Different Percentages of Active Ingredient.

day. We found that as the amount of polymer increased or decreased, the release rate responded accordingly. This alteration in the amount of polymer gave us the uniformity for a consistent release of drug that was missing in trial 1. The mean ($\bar{X}$) release rate until the termination of the study on day 55 was 162 mg/bolus/day. Resulting properties due to the matrix modification were a more uniform and consistent release rate, an increase in bolus longevity of 10 days, and the arrest of bolus breakage within the rumen.

The release rates given in Figure 2 illustrate the significant differences between the 15, 17, and 20% oxytetracycline boluses assayed for longevity and oxytetracycline release. As the amount of active ingredient increased, the bolus release rate also increased and as suspected this was followed by a shortening in bolus longevity. The 15% boluses had a mean ($\bar{x}$) release rate of 54 mg/bolus/day for the first 19 days. During days 19-58, the mean ($\bar{x}$) release rate increased to 110 mg/bolus/day. At the reduced bolus weight of ca 5 g, the boluses began to chip and break in half. It is believed that the tensile strength was greatly reduced as the boluses became smaller in both size and weight. After such occurrences, broken boluses appeared to affect the release rates beyond normal variability.

When compared to 20% boluses, the 17% boluses released lesser amounts of oxytetracycline/day as was noted by the mean ($\bar{x}$) release of 123 mg/bolus/day for the first 51 days. Again, as the boluses eroded to the smaller size and weight, the release rates were exceeding normal viriability. This was probably due to the increase in surface area of the boluses as they broke in half. This trial was terminated after 72 days at which time a mean ($\bar{x}$) release of 100 mg/bolus/day had been recorded.

The highest release rates were recorded from the 20% boluses. A mean ($\bar{x}$) release of 163 mg oxytetracycline bolus/day for the first 34 days was recorded. This increase in release rate supported the assumption that an increased amount of oxytetracycline would result in higher degradation and daily release rates since less binder was present in the formulation to hold the active ingredient. The study continued for 62 days with a mean ($\bar{x}$) release of 152 mg/bolus/day, or a difference of 42 mg oxytetracycline/day from the 15 and 17% boluses.

The success of these trials indicated that there was evidence for commercially producing a sustained-release formulation for use in disease therapy in ruminants. Data (unpublished) shows that oxytetracycline can be formulated in the above manner to give prolonged blood values after administration. It is recognized that antibiotic levels normally used are so high that daily treatments of diseased animals are often economically impractical. However, it is probable that a sustained-release oxytetracycline bolus could offer, with a single therapeutic dose, effective treatment and control of disease for a period of 60 days. Based on a therapeutic dosage of 1.0 mg/kg of bw./day for anaplasmosis (Richey *et al.* 1976), a treatment of 1-2½ boluses, depending on oxytetracycline content, would be sufficient to effectively treat a 364 kg animal.

Our findings showed that bolus release rates for oxytetracycline were proportional to the amount of oxytetracycline blended with inert matrix. The level of drug in the animal is, of course, an important factor in the successful treatment of anaplasmosis. Data from these trials illustrated that therapeutic levels of drug could be maintained for disease treatment for an extended period of

time using a practical and potentially economical treatment route.

We believe that following further in-vivo testing for efficiency in prophylaxis and control of anaplasmosis, that such a system will eliminate the costly and frequent treatment of anaplasmosis infected animals and protect noninfected treated cattle in areas adjacent to herds with carrier animals.

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ATTENTION STUDENTS

The AABP Executive Board, meeting in Washington, D.C., on July 21, 1980 approved a recommendation from the Forward Planning Committee to encourage veterinary medicine students to write case reports for *The Bovine Practitioner*. Prizes will be offered in the amounts of $200, $100 and $50 for the best case reports submitted. The case reports should be forwarded to the Editor, 1226 N. Lincoln, Stillwater, OK 74074 before April 30, 1981. The prize winners will be selected by the Editorial Board.