Treatment and Control

Review: Current Status of Control and Treatment With Drugs

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Anaplasmosis, an infectious disease of cattle, is recognized in both the acute and chronic form. The acute disease is most easily recognized, having a characteristic clinical syndrome which may lead to death in affected animals. For years treatment of anaplasmosis implied the use of drugs and supportive care of this phase of infection (35). In recent years, however, greater attention has been given the chronic or carrier phase of infection. The disease in this phase does not usually pose a threat to the animal’s well-being and is usually asymptomatic, but it does represent a reservoir of infection capable of transmission to non-infected animals. The elimination of carrier infection has assumed importance in those herds where preventive measures and disease eradication are feasible (38).

This review will consider the treatment of anaplasmosis in the context of the acute infection and the chronic or carrier infection, the first being primarily concerned with the interruption of the clinical syndrome by reversal of characteristic signs of infection, the second being the elimination of the causative organism, *Anaplasma marginale*, in the carrier animal. In recent years greater emphasis has been placed on the latter.

Treatment of Acute Anaplasmosis

A common pitfall in the evaluation of therapeutic agents used for anaplasmosis is the fairly large number of spontaneous recoveries which might mislead the observer to believe that a specific drug or therapeutic procedure was effective, when in reality recovery would have occurred without treatment. A second problem is that often the animal with anaplasmosis may go unrecognized until the terminal phases of infection, at which time even specific therapy is unsuccessful. Early treatment is recognized as being important to ensure success (9,10).

Prior to the introduction of the tetracyclines and other chemotherapeutic compounds, treatment of acute anaplasmosis was limited largely to supportive therapy including a variety of hematinics, blood transfusions, good nursing, and care (35). These procedures were aimed largely toward the elimination of stress and alleviation of the anemia until such time as the immune mechanism and hemopoietic system could adequately respond. It would appear that blood transfusions could and should play an important role in the treatment of acute anaplasmosis (12,19,26) but there are conflicting reports (18) and some suggestion of caution in this procedure (3,9). There is always a danger in treating weakened animals, particularly range cattle when the excitement and exertion associated with handling and restraining may do more harm than the treatment will do good (9). Extensive treatment of the semi-wild range animal may be contraindicated; whereas, treatment of a docile dairy animal may be useful and successful.

Until the last few years, the only specific chemotherapeutic compounds have been the tetra-
cycelines, principally oxytetracycline\textsuperscript{a}, chlortetracycline\textsuperscript{b}, and tetracycline hydrochloride\textsuperscript{c}. These compounds all appear similar in suppressing the reproduction of the \textit{Anaplasma} organism. Foote (13) described this action in 1951, but noted that chlortetracycline was not effective when given late in the course of infection. The desirability of using the tetracyclines early in the course of infection was noted by others (10,27,28). Carriçaburu (9) indicated considerable success in treating naturally occurring field cases of anaplasmosis with 3 mg/lbs. oxytetracycline given intramuscularly (I/M). Brock, et al. (5), described the use of tetracycline hydrochloride. In their opinion, when used at the rate of 3 mg/lbs. I/M it was essentially equal in effect to either oxytetracycline or chlortetracycline.

The chemoprophylactic effect of feeding low levels of the tetracycline drugs has been described (7,11,34). It was found that as little as 0.5 mg/lbs. fed daily would prevent acute anaplasmosis, even though exposure to \textit{A. marginale} did occur.

Two new compounds, 356C61\textsuperscript{d} and 4A65\textsuperscript{e}, have recently been described as having a specific chemotherapeutic effect on \textit{Anaplasma} (2,20,21,22,23,25,30,31,32,33). In premunization experiments, Kuttler and Todorovic (24) showed 356C61 (5 mg/kg) and 4A65 (4 mg/kg) superior to oxytetracycline (12 mg/kg) in moderating the course of infection in adult cattle intentionally exposed to virulent \textit{A. marginale}. Roby (30) has reported that the development of acute anaplasmosis in splenectomized calves has been inhibited with a single injection of 2.5 mg/kg 4A65. These drugs, 356C61 and 4A65, are not available commercially and, hence, have not been used extensively in cases of acute anaplasmosis but on limited experimental work show promise.

\textbf{Treatment of Carrier Infections to Eliminate \textit{Anaplasma}}

Soon after the tetracyclines were observed to inhibit growth of \textit{Anaplasma}, experiments were conducted to evaluate these drugs in relation to the removal of carrier infections (4,6,14,16,29,31,36). These experiments indicated that such therapy would eliminate carrier infections, but only after the prolonged administration of fairly large amounts of these agents. Nevertheless, this significant breakthrough stimulated a great deal of research on this subject with the evolvement of numerous successful treatment regimes which will effectively eliminate carrier infections. A list of these procedures is given in Tables 1 and 2, which under varying conditions have proven successful.

Carrier status has been eliminated by the I/V or I/M injection of 5 mg/lbs. tetracycline 10 times at daily intervals (29). The injection of oxytetracycline and chlortetracycline is also effective at 12 to 16 daily injections (36). These drugs are relatively non-toxic; however, they do produce considerable irritation at the site of I/M injections, and if given too rapidly I/V can produce a transient mild to moderate respiratory distress.

The smallest amount of chlortetracycline that has proven effective in eliminating infection was 0.5 mg/lbs. orally for a 120-day period (15). This treatment was administered during the winter season when re-exposure was not occurring. The negative status of treated animals was established by serologic means. A similar experiment, using 0.5 mg/lbs. orally for 90 days, conducted during the vector season failed to eliminate the \textit{Anaplasma}; however, containment and reduced infectivity level was detected (11,34).

It is probable that oral treatment with low levels while effective may be influenced by factors such as continued exposure, lack of consumption by some animal, or differences in individual animals to the extent that 100% results may not always occur. For these reasons chlortetracycline levels higher than 0.5 mg/lbs. are generally used. A treatment consisting of 5 mg/lbs. daily for 30 to 60 days has generally been successful (17,31,37). This treatment regime gives room for animal variation and has provided more consistent removal of carrier infections.

The prolonged periods of treatment are frequently in conflict with various management practices. This, plus the expense of the drug and labor to supervise such a program, has led many workers to search for a better system. In 1965, Barrett et al. (2) described an \textit{alpha} dithiosemicarbazone (356C61) which had specific activity against \textit{Anaplasma}. This dithiosemicarbazone is an insoluble powder which is prepared as an aqueous suspension. If injected I/V, it may produce a respiratory distress. When diluted in PSS this can be minimized. Several workers have reported the apparent value of this drug (8,20,21,22,23,25,32). Comparisons between 5 mg/kg 356C61 and 11 mg/kg oxytetracycline when given I/V to splenectomized calves showed 356C61 to be superior based on a significantly faster return of packed cell.

\textsuperscript{a}Oxytetracycline: Terramycin – Chas. Pfizer & Co., Inc.
\textsuperscript{b}Chlortetracycline; Aureomycin – Lederle Laboratories, American Cyanamid Co.
\textsuperscript{c}Tetracycline Hydrochloride: Kyocotic – Lederle Laboratories, American Cyanamid Co.
\textsuperscript{d}356C61: Gloxazon – Alpha-Ethoxyethylglyoxal Dithiosemicarbazone; Burroughs Wellcome Co.
\textsuperscript{e}4A65: Imidocarb – 3,3'-Bis-(2-imidazolin-2-yl)-carbanilide dihydrochloride (or dipropionate); Burroughs Wellcome Co.
Table 1
Successful Treatment Procedures for the Elimination of *Anaplasma* Infection Using the Tetracycline Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate of Admin.</th>
<th>Route</th>
<th>No. of Treatments</th>
<th>Interval</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>5 mg/lbs</td>
<td>I/V or I/M</td>
<td>10</td>
<td>Daily</td>
<td>Pearson (29)</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>5 mg/lbs</td>
<td>I/V or I/M</td>
<td>12-14</td>
<td>Daily</td>
<td>Splitter (36)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>1.5 mg/lbs</td>
<td>I/V</td>
<td>16</td>
<td>Daily</td>
<td>Splitter (36)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>1.0 mg/lbs</td>
<td>Orally</td>
<td>41</td>
<td>Daily</td>
<td>Franklin (16)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>2.5 mg/lbs</td>
<td>Orally</td>
<td>45</td>
<td>Daily</td>
<td>Franklin (16)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>0.5 mg/lbs</td>
<td>Orally</td>
<td>120</td>
<td>Daily</td>
<td>Franklin (15)*</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>5 mg/lbs</td>
<td>Orally</td>
<td>30-60</td>
<td>Daily</td>
<td>Franklin (17)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>5 mg/lbs</td>
<td>Orally</td>
<td>60</td>
<td>Daily</td>
<td>Brock (6)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>2.5 mg/lbs</td>
<td>Orally</td>
<td>60</td>
<td>Daily</td>
<td>Brock (6)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>1.5 mg/lbs</td>
<td>Orally</td>
<td>60</td>
<td>Daily</td>
<td>Brock (6)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>5 mg/lbs</td>
<td>Orally</td>
<td>45-60</td>
<td>Daily</td>
<td>Roby (31)</td>
</tr>
<tr>
<td>Chlorotetracycline</td>
<td>5 mg/lbs</td>
<td>Orally</td>
<td>30</td>
<td>Daily</td>
<td>Twiehaus (37)</td>
</tr>
</tbody>
</table>

*Negative Status Determined by Serologic Procedures.

Table 2
Use of 4A65, Oxytetracycline, and 356C61 to Eliminate *Anaplasma* Infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate of Admin.</th>
<th>Route</th>
<th>No. of Treatments</th>
<th>Interval</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytetracycline*</td>
<td>11 mg/kg</td>
<td>I/V</td>
<td>3</td>
<td>24 or 48</td>
<td>Kuttler (20,21,22)</td>
</tr>
<tr>
<td>356C61</td>
<td>5 mg/kg</td>
<td>I/V</td>
<td>3</td>
<td>Daily</td>
<td>Kuttler (21)</td>
</tr>
<tr>
<td>4A65*</td>
<td>5 mg/kg</td>
<td>I/M or S/C</td>
<td>3</td>
<td>Daily</td>
<td>Kuttler (21)</td>
</tr>
<tr>
<td>4A65*</td>
<td>2 mg/kg</td>
<td>I/M or S/C</td>
<td>3</td>
<td>Daily</td>
<td>Kuttler (21)</td>
</tr>
<tr>
<td>356C61</td>
<td>5 mg/kg</td>
<td>I/M or S/C</td>
<td>2</td>
<td>14 Days</td>
<td>Roby (33)</td>
</tr>
</tbody>
</table>

*Spentecotomized calves used
(1) Adult cattle used

volumes to normal following treatment (23). The injection of 356C61 10 times at the level of 5 mg/kg produced a fatal toxicosis in six of seven animals (1). Deaths occurred as early as one day and as late as 41 days after the last of 10 injections. Clinically, the animals showed chronic tympanites, rumen atony, and depression prior to dying. Animals were treated symptomatically with ruminatorics and laxatives but failed to respond. Relief of bloat by trocharization or the passage of a stomach tube was only transitory.

Other attempts to eliminate the *Anaplasma* infection in carriers were made using 356C61. The injection of 5 mg/kg five times at 24-hour intervals was unsuccessful (23). The injection of 356C61 at the rate of 5 mg/kg three times at two-day intervals, four times over a two-week period at three- and four-day intervals, three times at weekly intervals, and three times at two-week intervals were all unsuccessful.

The addition of oxytetracycline to 356C61, giving both drugs simultaneously, was consistently successful in *Anaplasma* infected splenectomized calves not previously treated (20,21,22). Oxytetracycline (11 mg/kg) was combined with 356C61 (5 mg/kg), both drugs being diluted in 150 ml sterile saline and then injected I/V. Three treatments at either 24- or 48-hour intervals were successful. At 72-hour intervals, only two of three responded favorably.

Imidocarb (4A65), a white, readily soluble powder, originally recognized for its babesiacidal activities, has also shown promise for use in anaplasmosis (21,30,33). Imidocarb given at the rate of 4, 5, and 6 mg/kg on three successive days has successfully eliminated the *Anaplasma* carrier status in splenectomized calves (21). The addition of 356C61 to 4A65 appears compatible and was effective in eliminating *Anaplasma* with reduced dose rates of 4A65 (21). The use of 2 mg/kg 4A65 when given together with 5 mg/kg 356C61 three times at 24-hour intervals was effective. In this instance, 4A65 was administered I/M and the 356C61 I/V. The reverse dosage consisting of 5 mg/kg 4A65 and 2 mg/kg 356C61 was also effective when administered as described. Unpublished evidence is available that the carrier status of splenectomized calves may be terminated with as little as 2 mg/kg of each 4A65 and 356C61 given three times at 24-hour intervals.

A total of 15 mg/kg 4A65 when given over a three-day period was effective, but 15 mg/kg 4A65 when given over a three-day period was effective, but...
given in one injection was ineffective in eliminating the carrier state (21). A single injection of 4 and 6 mg/kg 4A65 combined with 15 mg/kg 356C61 was also ineffective.

The apparent synergistic or at least additive effect of oxytetracycline and 356C61 prompted the author to try combining oxytetracycline and 4A65. Every such trial was unsuccessful.

More recently Roby and Mazzola have described the use of 4A65 at the level of 5 mg/kg in adult carrier cattle (33). A single injection was ineffective in eliminating the carrier status, but two injections of the same amount at two-week intervals was successful in eliminating infection in all five cattle so treated. They used both the dihydrochloride and the dipropionate salts successfully. Both salts had identical effects on the parasites; however, the dipropionate was less parasitic. Both salts had identical effects on the parasites; however, the dipropionate was less active. Work is in progress to further explore other treatment programs.

There are several large-scale field trials using 4A65 presently underway. Analysis of these results will undoubtedly contribute to our better understanding of the potential of drug therapy in an eradication program.

References


