Oxytetracycline Blood Serum Levels in Healthy, Pneumonic, and Recovered Cattle

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Summary

Two trials were conducted to study oxytetracycline (OTC) serum levels in clinically healthy, pneumonic, and recovered cattle. Five mg OTC per lb. of body weight was used in the first study and 7.5 mg in the second. Significantly higher serum levels were obtained in diseased cattle than in either the clinically healthy or in the diseased cattle when treated after recovery. Few significant differences were noted when diseased cattle were injected with 7.5 mg OTC per lb. body weight at not more than 5, 10 or 20 cc per injection site.

Trial I. Design:

One hundred and six (106) cattle weighing 210 to 539 pounds each were randomly assigned to one of 9 treatment groups if healthy or to one of four treatment groups if pneumonic (Table 1). A commercially

Table 1

Trial Design - Trial I

Group	Treatment	No. Animals	Avg. Wt. (lb.)
Clinically Healthy			
Group 1	Oral	8	280-384
Group 2	IV	8	220-417
Group 3	IV	2	227-483
Group 4	IM	11	276-400
Group 5	IM-A	9	272-376
Group 6	IM-1	8	295-385
Group 7	SQ	11	278-430
Group 8	SQ-A	8	278-355
Group 9	SQ-1	8	260-435
Pneumonic			
Group 10	IV	8	250-310
Group 11	IM	7	290-400
Group 12	SQ	8	210-355
Group 13	IV/SQ-1	10	227-483
Recovered			
Group 14	IV	8	255-366
Group 15	IM	7	386-539
Group 16	SQ	8	295-450

IV-Intravenous; IM-Intramuscular; IM-A-Intramuscular plus dexamethasone; IM-1-Intramuscular injection, 1 site; SQ-Subcutaneous; SQ-A-Subcutaneous plus dexamethasone; SQ-1-Subcutaneous injection, 1 site.

available injectable preparation containing 50 mg OTC per cc was used in all animals except in group one. Animals in this group received a freshly prepared solution of an oral soluble powder and tap water with a final concentration of 50 mg OTC per cc. Treatment was at the level of 5 mg OTC per lb. body weight in all groups, except group three, which received 2.5 mg per lb. body weight. Blood samples were collected from each animal prior to and at various intervals following treatment.

Trial I was divided into three phases: normal, pneumonic, and recovered animals.

Normal animal study: 73 clinically normal animals weighing from 220 to 483 lbs. were treated as outlined in Table 1. In group one the calculated amount of OTC solution was placed in one-ounce capsules and immediately administered. Cattle assigned to group three were treated intravenously at the rate of 2.5 mg/lb. body weight. Only two animals were treated in this manner, therefore the data was not included in any of the statistical analyses.

Groups four, five, seven and eight were injected with not more than 10 cc in any one injection site. For groups five and eight dexamethasone was added to the injectable OTC at the rate of 2 mg per gm OTC and this combination injected. The purpose was to determine the effect of a low level of an anti-inflammatory compound on OTC absorption. The total dose of OTC was injected in one site in animals in groups six and nine. Blood samples were drawn from each animal just prior to treatment and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 48 hours post treatment.

Pneumonic animal study: 33 calves weighing 210 to 483 pounds and showing signs of pneumonia were utilized in this phase of the study. The calves had been in a commercial feedyard for at least seven days with no history of antibacterial treatment of any kind since arrival. These cattle had been pulled by the cowboy crew for first treatment on the morning the trial started.

Animals in groups 11 and 12 were injected with not more than 10 cc OTC in any one injection site. Group 13 animals received ⅓ of the calculated dose of OTC intravenously and the remaining ⅔ subcutaneously in one injection site. Blood samples were drawn from each animal just prior to the first treatment and at 1, 3, 5, 6, 8, 10, 12, 16 and 24 hours post treatment. Rectal temperatures were taken each time the animals were restrained for sampling.

Recovered animal study: 35 days after their first treatment the 23 animals in groups 10, 11, and 12

were individually weighed and retreated by the same route as originally. Blood samples were collected at the same intervals as in the pneumonic study.

Results

The average value for each time period and treatment group in Trial I is listed in Table 2.

Normal animals: The highest average serum OTC level attained in the orally medicated animals (group 1) was 0.06 mcg at two hours post treatment, which was considerably below a systemic therapeutic level. The highest serum OTC level for any group of animals at any time period was at one hour post treatment in the animals receiving 5 mg OTC IV per lb. body weight (group 2). There was no significant effect on average serum OTC levels at any time period when dexamethasone was mixed with the injectable OTC. The data is combined for groups 4 and 5 and reported in Table 2 as IM multiple site and groups 7 and 8, which are reported as SQ multiple site.

Multiple site injection resulted in statistically higher levels through the fifth hour for those treated IM and through the eighth hour for those treated SQ. OTC disappearance curves for IM and SQ treated normal cattle are depicted in Figures 1 and 2, respectively.

Pair-wise comparisons of treatment groups 2 and 4 through 9 are presented in Table 3.

Pneumonic and recovered animals: The average rectal temperatures for all pneumonic animals at each collection time are listed in Table 4. There were no significant differences at any time period between treatment groups. Serum OTC disappearance curves for all four pneumonic cattle groups (10, 11, 12 and 13) are compared in Figure 3.

Serum levels obtained in the recovered animals were statistically similar to the levels in the normal animals. A statistical comparison of OTC serum levels between the pneumonic and recovered animals is listed in Table 5. Average values were higher in the IV treated pneumonic animals (group 10) than in the same animals after recovery (group 14) at all collection times except one hour post treatment. Levels were statistically higher in the IM treated pneumonic animals (group 11) at all time periods, except one and five hours post treatment, than in the same animals after recovery (group 15). Serum levels of OTC were higher in the SQ treated pneumonic animals (group 12) than the recovered (group 16) only at 24 hours post treatment. Pair-wise comparisons of the pneumonic cattle treatment groups and recovered cattle treatment groups are listed in Table 6.

The animals were weighed just prior to treatment. The pneumonic animals had been hauled approximately five miles from the feedlot to the research facility just prior to weighing. The recovered animals were weighed without a shrink or haul. Taking into account that the pneumonic animals probably had a hauling shrink plus a shrink from being diseased, they most likely received less OTC per pound of metabolic body size than the recovered animals. If this assumption is true, then the spread observed in OTC serum levels between pneumonic and recovered animals actually was less than is the case.

Table 2. Serum Levels (mcg/cc) of Oxytetracycline - Trial I

	Hours after Administration											
Cattle & Treatment	1	2	3	4	5	6	8	10	12	16	24	48
Healthy Cattle												
Oral	0.05 (a)	0.06 (a)	0.05 (a)	0.04 (a)	0.03 (a)	0.04 (a)	0.03 (a)	0.03 (a)	0 (a)	0 (a)	0.03 (a)	0
Intravenous												
5 mcg/lb.	12.9 (d)	8.9 (d)	8.2 (e)	7.1 (e)	4.8 (d)	4.6 (c)	3.4 (bc)	3.3 (b)	2.3 (b)	1.3 (b)	0.5 (b)	0
*2.5 mg/lb.	5.5	3.2	3.0	2.5	2.2	2.2	1.6	–	–	–	0.05	–
Intramuscular												
Multiple sites	3.4 (c)	4.8 (c)	5.2 (d)	5.1 (d)	4.7 (d)	4.6 (c)	3.8 (bc)	3.4 (b)	2.9 (bc)	2.0 (c)	1.2 (c)	0.2
Single site	1.8 (b)	2.6 (b)	2.7 (c)	3.1 (c)	3.3 (c)	3.8 (c)	3.5 (bc)	–	–	–	1.2 (c)	–
Subcutaneous												
Multiple sites	1.6 (b)	2.5 (b)	3.0 (c)	3.5 (c)	4.1 (cd)	4.2 (c)	3.9 (b)	3.6 (b)	3.4 (c)	2.3 (c)	1.4 (c)	0.2
Single site	0 (a)	0.4 (a)	0.8 (b)	1.6 (b)	2.0 (b)	2.4 (b)	3.0 (c)	–	–	–	1.9 (d)	–
Pneumonic Cattle												
Intravenous	12.8 (z)	–	8.9 (z)	–	6.6 (y)	6.3 (y)	5.3 (y)	5.3 (y)	4.0 (x)	–	1.4 (x)	–
Intramuscular	4.4 (y)	–	5.7 (y)	–	5.5 (y)	5.7 (y)	5.0 (y)	5.0 (y)	3.9 (x)	–	2.1 (xy)	–
Subcutaneous	0.8 (x)	–	2.0 (x)	–	3.2 (x)	4.0 (x)	4.3 (xy)	4.6 (xy)	4.1 (x)	–	2.8 (y)	–
Intravenous plus single-site subcutaneous	3.5 (y)	–	2.8 (x)	–	3.8 (x)	4.0 (x)	3.8 (x)	3.7 (x)	3.5 (x)	–	1.5 (x)	–
Recovered Cattle												
Intravenous	13.8 (t)	–	7.3 (t)	–	5.5 (s)	4.8 (r)	3.9 (r)	3.0 (r)	2.2 (r)	–	0.5 (r)	–
Intramuscular	2.6 (s)	–	4.1 (s)	–	4.7 (rs)	4.2 (r)	3.7 (r)	3.6 (rs)	2.9 (rs)	–	1.3 (s)	–
Subcutaneous	0.6 (r)	–	1.9 (r)	–	4.0 (r)	4.3 (r)	4.3 (r)	4.1 (s)	3.6 (s)	–	1.1 (rs)	–

abcdef=Healthy cattle means within the same hour having different superscripts are significantly different at $P < 0.05$.
xyz=Pneumonic cattle means within the same hour having different superscripts significantly different at $P < 0.05$.
rst=Recovered cattle means within the same hour having different superscripts are significantly different at $P < 0.05$.
*Not included in statistical analysis.

Table 3. Healthy Cattle Summary of Pair-Wise 5% Level Significance From Duncan's Test. Trial I

	Hour										
	1	2	3	4	5	6	8	10	12	16	24
IV vs. IM	*	*	*	*						*	*
IV vs. IMA	*	*	*	*						*	*
IV vs. IM-1	*	*	*	*	*			–	–	–	*
IV vs. SQ	*	*	*	*					*	*	*
IV vs. SQ-A	*	*	*	*					*	*	*
IV vs. SQ-1	*	*	*	*	*	*		–	–	–	*
IM vs. IMA											
IM vs. IM-1		*	*	*	*			–	–	–	
IM vs. SQ	*	*	*	*							
IM vs. SQ-A	*	*	*	*							
IM vs. SQ-1	*	*	*	*	*	*		–	–	–	*
IMA vs. IM-1	*	*	*	*	*			–	–	–	
IMA vs. SQ	*	*	*	*							
IMA vs. SQ-A	*	*	*	*							
IMA vs. SQ-1	*	*	*	*	*	*		–	–	–	*
IM-1 vs. SQ					*			–	–	–	
IM-1 vs. SQ-A								–	–	–	
IM-1 vs. SQ-1	*	*	*	*	*	*		–	–	–	*
SQ vs. SQ-A											
SQ vs. SQ-1	*	*	*	*	*	*	*	–	–	–	*
SQ-A vs. SQ-1	*	*	*	*	*	*		–	–	–	

*Denotes significance at the 5% level.
Comparisons left blank were not significant.
–Denotes data from both pairs at the hour indicated were not available, therefore no comparison could be made.

Trial II

Twenty-three mixed breed cattle weighing 152 to 266 pounds and exhibiting clinical signs of pneumonia were treated. The animals had been in a commercial feedyard for a minimum of seven days with a history of no antibacterial treatment since arrival. The animals had been pulled for treatment by the cowboy crew on the morning the study commenced. Following removal from the feeding pens the cattle were transported to the Meloland Research Station.

Upon arrival at the station, the cattle were examined. Those animals exhibiting clinical signs of pneumonia were weighed, ear-tagged, and randomly assigned to one of three groups. Animals in all three groups received 7.5 mg OTC per lb. body weight by deep IM injection. Group 1 was injected at not more than 5 cc OTC per injection site, group 2 at not more than 10 cc, and group 3 at not more than 20 cc (Table 7). Each animal received its appropriate treatment at hour 0, 24, and 48. No other medication was administered during the course of the study.

Table 4
Average Rectal Temperature of Pneumonic Animals. Trial I

Hour Post Treatment	Avg. Temp.
0	105.0°F.
1	104.7°F.
3	104.0°F.
5	104.0°F.
6	103.5°F.
8	103.0°F.
10	102.8°F.
12	102.5°F.
24	102.3°F.

Rectal temperatures were recorded and blood samples taken just prior to the first treatment and at 1, 3, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours thereafter.

Table 5. Comparison of Serum Oxytetracycline Levels (mcg/cc blood serum) in Pneumonic and Recovered Cattle. Trial I

	IV		IM		SQ	
Hr.	Pneum.	Rec.	Pneum.	Rec.	Pneum.	Rec.
1	12.8	13.8	4.4	2.6	0.8	0.6
3	8.9	7.3**	5.7	4.1*	2.0	1.9
5	6.6	5.5*	5.5	4.7	3.2	4.0
6	6.3	4.8**	5.7	4.2**	4.0	4.3
8	5.3	3.9**	5.0	3.7**	4.3	4.3
10	5.3	3.0**	5.0	3.6**	4.6	4.1
12	4.0	2.2**	3.9	2.9*	4.1	3.6
24	1.4	0.5**	2.1	1.3*	2.8	1.1**

*Denotes significance at P <0.05. **Denotes significance at P <0.01.

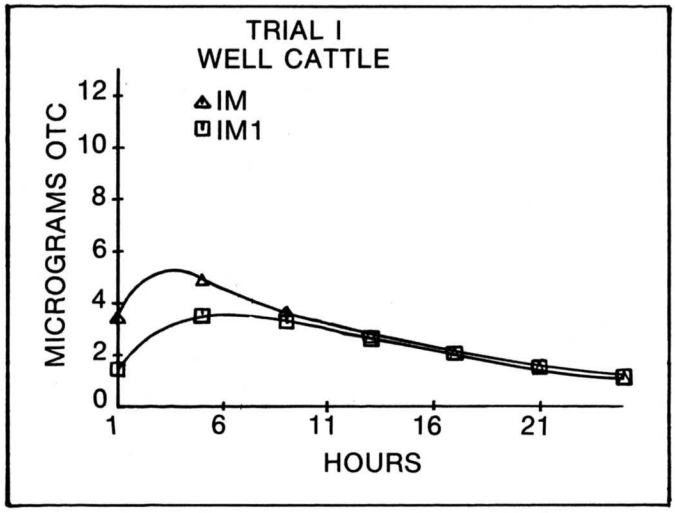

Figure 1. OTC blood serum levels, 5 mg/lb. b.w.

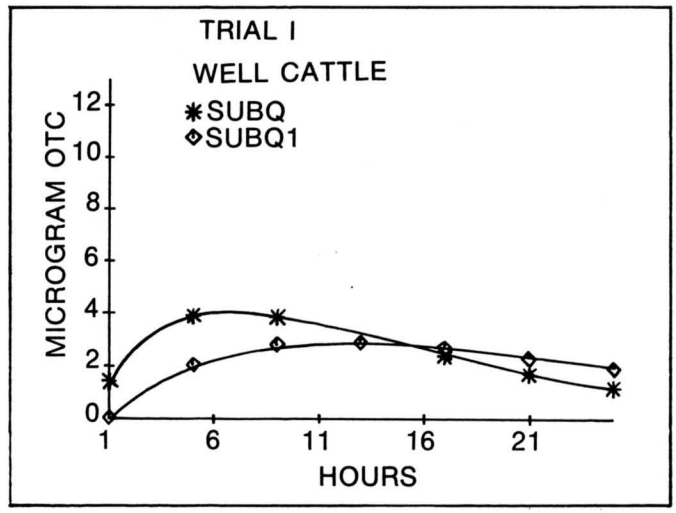

Figure 2. OTC blood serum levels, 5 mg/lb. b.w.

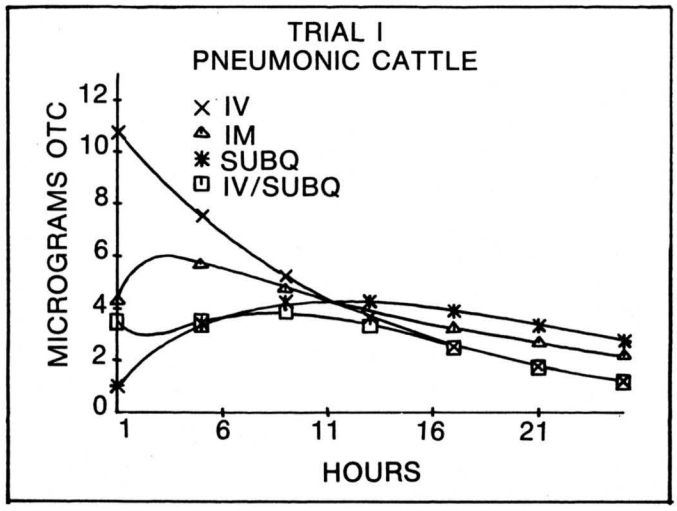

Figure 3. OTC blood serum levels, 5 mg/lb. b.w.

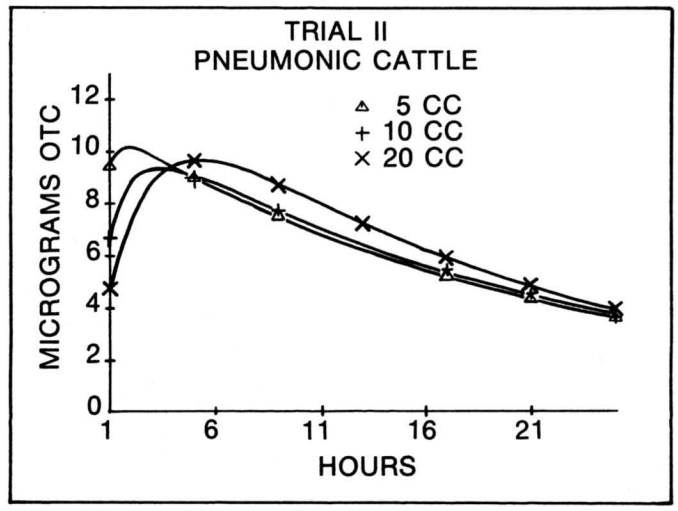

Figure 4. OTC blood serum levels, 7.5 mg/lb. b.w.

Table 6. Summary of Pair-Wise 5% Level Significance from Duncan's Multiple Range Test. Trial I

	Hours							
Pneumonic Cattle	1	3	5	6	8	10	12	24
IV vs. IM	*	*						
IV vs. SQ	*	*	*	*				*
IV vs. IV/SQ-1	*	*	*	*	*	*		
IM vs. SQ	*	*	*	*				
IM vs. IV/SQ-1		*	*	*	*	*		
SQ vs. IV/SQ-1	*							*
Recovered Cattle								
IV vs. IM	*	*						*
IV vs. SQ	*	*	*			*	*	
IM vs. SQ	*	*						

*Denotes significance at the 5% level.

Results

Average serum OTC levels and statistical comparisons for each group at each sampling time are shown in Table 8. The curves developed from this data for the first 24 hours are compared in Figure 4. The only significant differences between groups occurred at hours 1 and 10. At one hour post treatment the serum level in the 5 cc per site animals was significantly higher than for the 20 cc per site animals. The level for the 10 cc per site animals was intermediate, but not significantly different from either the 5 cc or 20 cc animals. At 10 hours post treatment the serum level for the 20 cc per site animals was significantly higher than for either the 5 or 10 cc per site animals. The serum levels at 12 and 24 hours following each of the injections are compared

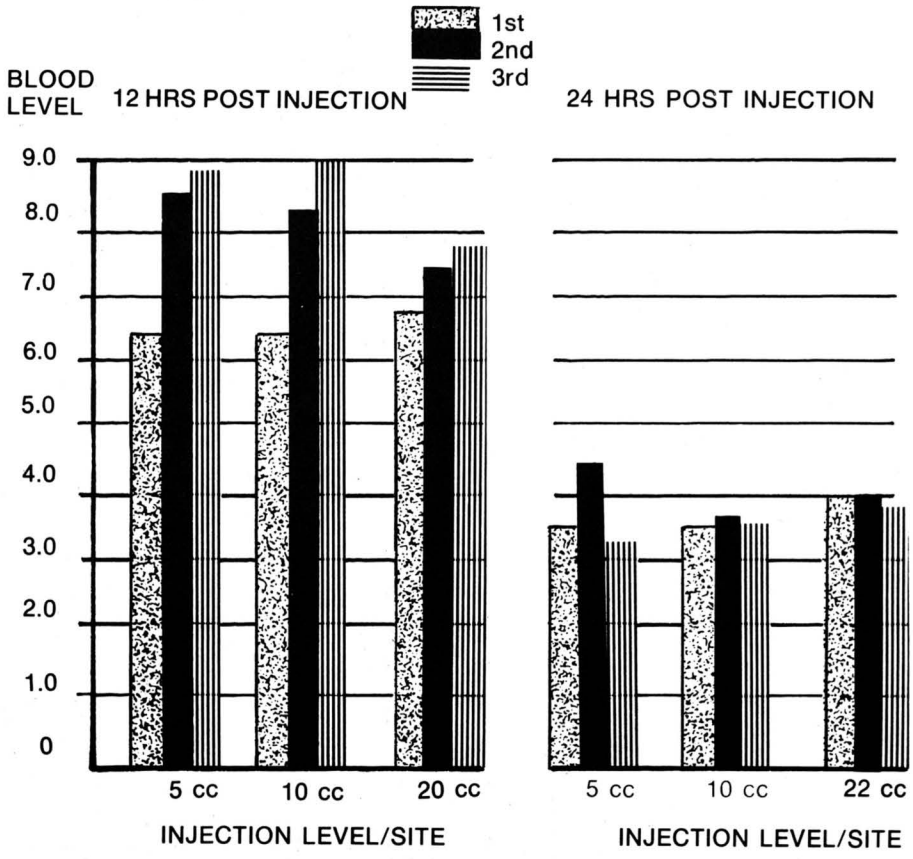

Figure 5.

Figure 6.

Table 7. Trial Design - Trial II. 7.5 mg OTC Per Pound Body Weight

Animal Number	Weight lb.	Total cc OTC Per Treatment	Maximum cc OTC per Site	No. of Sites at Max. cc's	No. cc in 1 Add'l. Site
1	208	31	5	6	1
2	266	40	5	8	0
3	246	37	5	7	2
4	204	31	5	6	1
5	229	34	5	6	4
6	163	24	5	4	4
7	191	29	5	5	4
8	266	40	5	8	0
9	245	37	10	3	7
10	222	33	10	3	3
11	204	31	10	3	1
12	221	33	10	3	3
13	254	38	10	3	8
14	255	38	10	3	8
15	251	38	10	3	8
16	251	38	10	3	8
17	225	34	20	1	14
18	217	33	20	1	13
19	206	31	20	1	11
20	203	30	20	1	10
21	226	34	20	1	14
22	231	35	20	1	15
23	152	23	20	1	3

in Figures 5 and 6, respectively, and in Table 9. In all three treatment groups there was a rise in the 12-hour post-injection levels on successive treatments. However, the rise was statistically significant only in the third treatment over the first treatment in the 5 cc per site group and in the second and third treatments over the first treatment in the 10 cc per site group (Table 9). At 24 hours post treatment there was a rise in the serum OTC levels in all three groups following the second treatment, when compared to the 24-hour post first treatment. The serum OTC levels 24 hours post third treatment in all three groups was lower than 24 hours following the second. The only statistically significant change was in the 5 cc per site group. The 24-hour post second treatment level was significantly higher than after the first or third treatment.

Table 8

Comparison of Three Methods* at Each Sample Time
7.5 mg OTC Per Lb. Body Wt. Trial II

Hour	cc/site 5	10	20
1	9.46# (a)	6.80 (ab)	5.67 (b)
3	9.50	9.13	8.43
5	8.88	8.50	8.64
6	8.50	9.00	9.57
8	8.44	8.00	9.57
10	7.46 (b)	7.69 (b)	9.86 (a)
12	6.38	6.38	6.71
16	5.44	6.02	6.21
24	3.44	3.41	3.94
36	7.65	8.25	7.37
48	4.50	3.74	4.01
60	8.88	9.00	7.71
72	3.24	3.52	3.84

*method=cc/site.
#Duncan's multiple range test. Means with no letter in common are significantly different at the 5% level. Means with a letter in common or with no letter(s) are not significantly different.

The lowest serum OTC level recorded in Trial II was 3.24 mcg at 72 hours in the 5 cc per site group. From a practical standpoint, the proposed minimum of 4 mcg per cc of serum was maintained throughout the study. The lower levels at 24 hours post third treatment may be due to enzyme induction. Additional studies need to be conducted to determine if this is a consistent finding and if so, if the higher treatment levels bring about this effect sooner than lower treatment levels.

Acknowledgements

Appreciation is expressed to the California Cattle Feeders Association for financial support; Chas. Pfizer, Inc., for the oxytetracycline and training of laboratory personnel; Dr. Ron Talbot, for analysis of serum oxytetracycline; El Toro Land & Cattle Company, for the pneumonic animals used in the study.

Table 9

Comparison of 12 Hour (and 24 Hour) Post Treatment Means for Three Treatments (for each method separately)
7.5 mg OTC Per Lb. Body Weight
Trial II

cc/site	Treatment # 1	2	3	
5	6.38 (b#)	7.65 (ab)	8.88 (a)	
10	6.38 (b)	8.25 (a)	9.00 (a)	12 hrs. post
20	6.71	7.37	7.71	treatment
	Treatment # 1	2	3	
5	3.44 (b)	4.50 (a)	3.24 (b)	
10	3.41	3.74	3.52	24 hrs. post
20	3.94	4.01	3.84	treatment

#Duncan's multiple range test. Means with no letter in common are significantly different at the 5% level. Means with a letter in common or with no letters are not significantly different.