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Avermectins, New Family of Potent Anthelmintic Agents: Efficacy of the B_{1a} Component

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When given to sheep as a single oral dose at 0.1 mg/kg, the B_{1a} component of the avermectins caused a reduction of >95% in the numbers of *Haemonchus contortus, Ostertagia circumcincta* (including inhibited L_4 larvae), *Trichostrongylus axei, Trichostrongylus colubriformis, Cooperia oncophora,* and *Oesophagostomum columbianum.* When given to cattle as a single oral dose at 0.1 mg/kg, avermectin B_{1a} was >95% effective in reducing the numbers of *Haemonchus placei, Ostertagia ostertagi* (including inhibited L_4 larvae), *T. axei, T. colubriformis, C. oncophora, Cooperia punctata, Oesophagostomum radiatum,* and *Dictyocaulus viviparus.* Avermectin B_{1a} was similarly effective, with the exception of a detectable loss in activity against adult *C. oncophora,* when administered to cattle as a parenteral injection. Some of these ruminant parasites were fully susceptible to dosages of avermectin B_{1a} at 0.025 mg/kg, e.g., *D. viviparus, O. radiatum, O. ostertagi,* and *H. contortus.* Avermectin B_{1a} removed 83 to 100% of *Ancylostoma caninum* from dogs given a single oral dose of 0.003 to 0.005 mg/kg. The poultry nematodes *Capillaria obsignata* and immature *Ascaridia galli* were effectively removed by avermectin B_{1a} at 0.05 and 0.1 mg/kg, respectively, but 0.1 mg/kg was not effective for *Heterakis gallinarum.* Thus, the avermectins would appear to have unprecedented potency and spectrum of biological activity.

Fermentation-derived natural products which are attributed with anthelmintic activity have been described in the literature. Hygromycin B, which has been used in treating domestic animals in practice, was described in 1958 (8). It was shown to have some effect upon adult swine ascarids when fed to infected pigs (7) but found ineffective against the migrating larvae of *Ascaris suum* (6). The principal utility of hygromycin B appears directed against members of the nematode order Ascaroidea. In this paper we report the anthelmintic activity of a natural product, the B_{1a} component of the avermectins (3, 9), an α-L-oleandrosyl-α-L-oleandroside macrocyclic lactone, against nematode parasites of cattle, sheep, dogs, and chickens.

MATERIALS AND METHODS

Sheep. Sheep raised under "parasite-free" conditions (i.e., management conditions designed to ensure minimal exposure to helminth infection) and weighing between 14 and 25 kg at the time of treatment were experimentally infected with third-stage infective larvae of six nematode species, passaged in the laboratory as pure isolates, according to the following: day 0, 360 *Oesophagostomum columbianum*; day 16, 7,500 *Ostertagia circumcincta* and 7,500 *Trichostrongylus colubriformis*; day 18, 7,500 *Trichostrongylus axei* and 7,500 *Cooperia oncophora*; day 21, 2,000 *Haemonchus contortus.* The isolates of *T. colubriformis* and *H. contortus* used to infect sheep were tolerant to benzimidazole anthelmintic treatment, requiring more than the recommended use level of various benzimidazoles for high-order efficacy. Numbers of larvae were estimated by counting multiple samples of larval suspensions in tap water, and each animal was infected per os with 5 ml of larval suspension containing the desired number.

On day 35, when the infections were patent, 15 infected sheep were randomly allotted to five treatment groups of three sheep each. The groups were randomly allotted to infected control (no treatment, two groups) or treatment with avermectin B_{1a} at 0.1, 0.05, or 0.025 mg/kg. Treatments were administered as solutions of avermectin B_{1a} in sesame oil at the rate of 0.1 ml/kg of body weight as an oral drench. On day 42, 7 days after treatment, the treated and untreated infected control sheep were killed, and their residual worm burdens were recovered at necropsy. The anatomical components of the gastrointestinal tract of each sheep were individually separated and slit open, and the contents were washed into separate containers. The mucosal surface was thoroughly washed under warm tap water, and the washings were added to the appropriate container. Formaldehyde solution was added as a preservative. To recover histotropic

parasitic larvae, the abomasum was placed in 1 liter of 0.85% (wt/vol) sodium chloride containing 600,000 U of procaine penicillin G plus 0.75 g of dihydrostreptomycin sulfate per liter and held at 37°C for 18 to 20 h. The saline was then poured onto a 200-mesh screen (0.074-mm aperture), and the mucosal surface was thoroughly washed under warm running tap water onto the screen. The material caught on the screen was washed onto a container and preserved with formaldehyde solution.

Estimates of the residual worm burdens were made on the basis of microscopic examination of 10% of the individual preserved abomasal content, abomasal soak, and small intestinal content. The 10% samples for each gut portion were obtained by suspending the total preserved material in 2 liters of tap water by mechanical agitation and withdrawing four 50-ml samples. The total content and washings of the large intestine and cecum were examined for worms. All nematodes were identified as to species and stage of development and enumerated as they were encountered.

Cattle. (i) Experiment 1: oral treatment for adult nematodes in cattle. Twelve Jersey calves raised under parasite-free conditions, weighing between 80 and 150 kg at time time of treatment, were experimentally infected with third-stage infective larvae, derived from pure isolates of seven species of nematode parasites of cattle. The calves were allotted to four groups of three calves each by restricted randomization based on body weight at the time of initial infection, and each was exposed to infection, as described for sheep, as follows: day 0, 1,000 *Oesophagostomum radiatum*; day 18, 2,000 *Dictyocaulus viviparus*; day 22, 14,000 *Ostertagia ostertagi*, 15,000 *C. oncophora*, and 4,000 *Haemonchus placei*; day 24, 10,000 *Trichostrongylus axei* and 10,000 *T. colubriformis*. On days 49 to 51, one calf from each of the four groups was randomly selected for treatment with avermectin B_{1a} (three calves per day) or retained as an untreated infected control (one calf per day). Avermectin B_{1a} was administered as a single oral dose as a solution in sesame oil, 0.1 ml/kg of body weight, at dosage levels of 0.1, 0.05, and 0.025 mg/kg, each to one calf for each treatment day. On days 56 to 58, at 7 days after treatment, the calves were killed and examined for residual worm burdens as described for sheep, except that the abomasa were soaked in 2 liters of saline containing penicillin and streptomycin. The lungs were removed from the thoracic cavity, and the left and right portions were dissected by cutting along the bronchial tree to the bronchioles with fine-pointed scissors. Lungworms exposed to view were immediately removed intact and counted before extending the longitudinal cut. The dissected lungs were then placed, cut surface down, in 10 liters of warm tap water and held at 40°C for 2 h. The 10 liters of tap water was then poured onto a 200-mesh screen, and the material retained on the screen was examined under ×10 to 20 magnification for additional lungworms.

(ii) Experiment 2: parenteral treatment for adult nematodes in cattle. Twelve Jersey calves raised parasite-free and weighing between 90 and 160 kg at the time of treatment were allotted to four groups of three calves each as for experiment 1. The calves were exposed to infection as described for sheep as follows: day 0, 1,000 *O. radiatum*; day 11, 2,000 *D. viviparus*; day 16, 5,000 *H. placei*, 15,000 *O. ostertagi*, and 15,000 *C. oncophora*; day 18, 10,000 *T. axei* and 10,000 *T. colubriformis*. On days 42 to 44, calves were treated with avermectin B_{1a} at dosages of 0.1, 0.05, or 0.025 mg/kg administered as subcutaneous or intramuscular injections of solutions in isopropyl myristate at the rate of 0.025 ml/kg. Injection sites were in the neck midway between the jaw and shoulder and slightly above the cervical vertebrae. The treated and untreated infected control calves were killed 7 days after treatment (days 49 to 51) and examined for residual burdens of gastrointestinal nematodes and lungworm as described above.

(iii) Experiment 3: oral activity against immature nematodes of cattle. Sixteen Jersey calves raised parasite-free and weighing between 75 and 125 kg were allotted to five groups of three calves each (the extra median calf was allotted at random to one group designated as untreated infected control) by restricted randomization based on body weight. On day 0, each calf was exposed to infection by oral administration of 5 ml of tap water containing 7,500 *H. placei*, 15,000 *O. ostertagi*, 10,000 *T. axei*, 10,000 *T. colubriformis*, 10,000 *C. oncophora*, 10,000 *Cooperia punctata*, 1,000 *O. radiatum*, and 2,000 *D. viviparus* infective third-stage larvae. At 8 days postinfection, two randomly selected groups of three calves each were treated with avermectin B_{1a} as a single oral dose of a solution in sesame oil at 0.022 or 0.011 mg/kg at a volume of 0.1 ml of solution per kg. At 15 days postinfection, the remaining two groups of three calves each were treated similarly. At 35 days postinfection, the calves were killed and examined for residual worm burdens as previously described.

Dogs. Purebred beagle dogs, weighing 4 to 8 kg, were inoculated subcutaneously with an estimated 413 *Ancylostoma caninum* larvae each. Treatment was administered at 2 months after inoculation, the maturation of the hookworms having first been demonstrated in all dogs by the finding of hookworm eggs in the feces. Treatment was given as a single oral dose and consisted of avermectin B_{1a} dissolved in a mixture of two parts of dimethylsulfoxide and one part of polyethylene glycol in a volume of 0.1 ml/kg of body weight. Each control dog received a corresponding volume of vehicle alone. The dogs were killed at 14 days after treatment. The entire small intestine was opened and examined for worms.

Poultry. Preliminary experiments indicated that all four major natural avermectins were active against mature *Ascaridia galli* infections in experimentally infected chickens (D. A. Ostlind and S. Cifelli, unpublished data). Subsequently, from a flock of chickens with natural helminth infections, 12 chickens were selected and assigned to four groups of three each, on the basis of balanced *Capillaria obsignata* infection (determined by fecal egg output) but with consideration also given to the presence of other nematodes. One group served as untreated controls, while the other chickens each received a single oral dose of avermectin B_{1a} at 0.1, 0.05, or 0.025 mg/kg dissolved

in sesame oil administered at 1.0 ml/kg. At 7 days after treatment, the treated and control chickens were killed, and the intestines and ceca were examined for worms.

Statistical methodology. Frequency distributions of parasite counts in ruminants are positively skewed (nonnormal), thus requiring normalization by transformation in order to apply parametric tests of significance, etc., or the use of distribution-free nonparametric methods (5). Parasite counts in poultry are similarly skewed. Since estimates of the dosage of avermectin B_{1a} required to produce a given level of efficacy were desired, parametric methods were used to analyze the experimental worm count data from ruminants and poultry after logarithmic transformation. Transformed worm counts were subjected to analysis of variance within species or stage of development (10). The magnitude of the differences in efficacy between various treatments or between treatments and untreated infected controls, where significant differences ($P \leq 0.05$) were found on analysis of variance, were further examined by the use of the Duncan multiple-range t-test (4). In those ruminant experiments for which data were available on three dosage levels, the dose-response curve for species or stage of development was examined by linear regression of log worm count on log dosage level (2). When applicable, the dosage of avermectin B_{1a} which would produce a 95% reduction in worm burden was then calculated. For purposes of summary and analysis, when a count of zero worms was found for a nematode in which the total gut content was examined, one unit was added to each observed count (1). When no worm was found for a given species or stage of development on examination of 10% of the total material, a number less than 10 but larger than 0 was substituted for that specific count, the number dependent upon the total number of animals within that treatment group for which no worm of that species or developmental stage was found and the size of the sample examined (N. R. Bohidar, D. G. Gruber, and J. W. Tukey, Exp. Parasitol., in press).

RESULTS

Sheep. The anthelmintic efficacy of avermectin B_{1a} as a single oral dose against six common gastrointestinal nematodes of sheep is summarized in Table 1. In addition to adult nematodes, untreated infected control sheep were infected with inhibited fourth-stage larvae (EL_4) of *H. contortus, O. circumcincta,* and *C. oncophora.* A broad spectrum of anthelmintic activity resulted from treatment with avermectin B_{1a} with a dosage as low as 0.05 mg/kg, and efficacy against the less sensitive worms decreased noticeably when the dosage was only 0.025 mg/kg. As shown in Table 2, the least sensitive or dose-limiting parasite, *C. oncophora* adults, required less than 0.1 mg of avermectin B_{1a} per kg for high-order efficacy. Graphic inspection of the dose response obtained for adult *C. oncophora* was utilized to approximate the 95% effective dose (ED_{95}) of about 0.09 mg/kg since a nonsignificant ($P > 0.05$) regression resulted from the observed data. Inspection of the worm counts for this species from untreated infected control sheep revealed that inhibition of development to the adult stage was highly variable, ranging from 2 to 39% of the worm burden (median, 7.5%), in six individual sheep, thus introducing an uncontrollable variable which confounds the interpretation of the dose-response curve. A similar situation occurred with *O. circumcincta,* the next least responsive parasite when in the inhibited (EL_4) stage of development. Inhibition of *O. circumcincta* in infected controls ranged from 35 to 74% (median, 64.5%) in six sheep. Graphic estimation was again used to approximate the ED_{95} at about 0.08 mg/kg. A dosage of $\leq$0.060 mg of avermectin B_{1a} per kg was found to produce $\geq$95% reduction in worm burden for the remainder of the parasites present.

Cattle. (i) Experiment 1. The anthelmintic efficacy of avermectin B_{1a} against adult nematodes of cattle is summarized in Table 3. A dosage of <0.1 mg/kg per os was highly efficacious against all species or stages of development present. As indicated in Table 4, the dose-limit-

TABLE 1. *Anthelmintic efficacy of avermectin B_{1a} by oral administration against patent infections in experimentally infected sheep*

Dosage (mg/kg)	No. of sheep	Efficacy (%)								
		H. contortus[a]		*O. circumcincta*		*T. axei*	*T. colubriformis*[a]	*C. oncophora*		*O. columbianum*
		EL_4	Adult	EL_4	Adult			EL_4	Adult	
None	6	(70)[b]	(442)	(1,421)	(1,137)	(2,852)	(4,110)	(193)	(1,761)	(61)
0.1	3	>96[c]	98[d]	95[e]	98[c]	>99[c]	>99[c]	97[c]	94	100[d]
0.05	3	>96[c]	>99[c]	94[e]	>99[c]	>99[c]	>99[c]	>98[c]	93	100[d]
0.025	3	>96[c]	96[e]	38	74	49	86[e]	11	40	97[e]

[a] Benzimidazole-tolerant isolates.
[b] Numbers within parentheses indicate the geometric mean number of worms per control sheep.
[c] Reduction from control value due to treatment: $P < 0.001$.
[d] Reduction from control value due to treatment: $P < 0.01$.
[e] Reduction from control value due to treatment: $P < 0.05$.

TABLE 2. *Regression equations and estimated ED_{95} values for avermectin B_{1a} per os against patent infections in experimentally infected sheep*

Parasite	Regression equation[a]	Significance of regression (P)	Estimated[b] ED_{95}, (mg/kg)
H. contortus, EL_4	None, maximal efficacy		<0.025
H. contortus	None, maximal efficacy		<0.025
O. circumcincta, EL_4	None, variable inhibition ratio		≃0.08
O. circumcincta	Log $\hat{Y} = -2.0019 \log X - 1.2041$	0.088	0.033
T. axei	Log $\hat{Y} = -3.7024 \log X - 3.1281$	0.005	0.037
T. colubriformis	Log $\hat{Y} = -3.3288 \log X - 2.8282$	0.0007	0.029
C. oncophora, EL_4	Log $\hat{Y} = -2.4610 \log X - 2.0477$	0.013	0.059
C. oncophora	None, variable inhibition ratio		≃0.09
O. columbianum	None, maximal efficacy		<0.025

[a] Where $\hat{Y}$ is the predicted number of worms at dosage X (milligrams per kilogram).
[b] Estimates with ≃ or < preceding them are graphical approximations from the data of Table 1; all others are calculated point estimates from the respective regression equations.

TABLE 3. *Anthelmintic efficacy of avermectin B_{1a} by oral administration against patent infections in experimentally infected cattle*

Dosage (mg/kg)	No. of calves	Efficacy (%)								
		H. placei	*O. ostertagi*		*T. axei*	*T. colubriformis*	*C. oncophora*		*O. radiatum*	*D. viviparus*
			EL_4	Adult			EL_4	Adult		
None	3	(338)[a]	(193)	(709)	(2,187)	(1,156)	(55)	(5,753)	(24)	(5)
0.1	3	>99[b]	97[c]	>99[b]	>99[c]	>99[c]	>94[c]	97[b]	100[b]	100[d]
0.05	3	98[b]	77[d]	>99[b]	>99[c]	96[c]	>94[c]	69	100[b]	100[d]
0.025	3	97[b]	83[d]	>99[b]	>99[c]	49	>94[c]	0	100[b]	100[d]

[a] Numbers within parentheses indicate the geometric mean number of worms per control calf.
[b] Reduction from control value due to treatment: $P < 0.01$.
[c] Reduction from control value due to treatment: $P < 0.001$.
[d] Reduction from control value due to treatment: $P < 0.05$.

TABLE 4. *Regression equations and estimated ED_{95} values against patent infections by oral administration of avermectin B_{1a} in experimentally infected cattle*

Parasite	Regression equation[a]	Significance of regression (P)	Estimated[b] ED_{95} (mg/kg)
H. placei	None, maximal efficacy		<0.025
O. ostergagi, EL_4	Log $\hat{Y} = -1.3968 \log X - 0.5532$	0.045	0.077
O. ostertagi	None, maximal efficacy		<0.025
T. axei	None, maximal efficacy		<0.025
T. colubriformis	Log $\hat{Y} = -3.5177 \log X - 2.8788$	0.00003	0.048
C. oncophora, EL_4	None, maximal efficacy		<0.025
C. oncophora	Log $\hat{Y} = -2.5418 \log X - 0.2150$	0.017	0.089
O. radiatum	None, maximal efficacy		<0.025
D. viviparus	None, maximal efficacy		<0.025

[a] Where $\hat{Y}$ is the predicted number of worms at dosage X (milligrams per kilogram).
[b] Estimates with ≃ or < preceding them are graphical approximations from the data of Table 3; all others are calculated point estimates from the respective regression equations.

ing parasite was adult *C. oncophora* for which an ED_{95} of 0.089 mg/kg was calculated by linear-regression methods.

(ii) Experiment 2. The anthelmintic activity of avermectin B_{1a} by parenteral injection against patent infections in cattle is summarized in Table 5. The results for all but *C. oncophora* are similar to those of experiment 1. *C. oncophora*, both inhibited fourth-stage larvae and adults, were considerably less responsive to parenteral treatment than to oral treatment. (The apparent requirement of an increased dosage of the com-

pound for comparable efficacy against this species on subcutaneous or intramuscular injection over that required by oral administration has been confirmed in experiments not reported here.) As shown in Table 6, all other parasites or stages of development were effectively removed with dosages of ≤0.06 mg/kg.

(iii) Experiment 3. Table 7 contains a summary of the efficacy of avermectin B_{1a} as a single oral dose against immature nematodes of cattle. The compound was highly effective against all eight nematode species when treatment was administered at a dosage as low as 0.022 mg/kg at 8 days after infection, including EL_4 *O. ostertagi* which had entered the hypobiotic state at the time of treatment as indicated by their contin-

TABLE 5. *Anthelmintic efficacy of avermectin B_{1a} by parenteral administration against patent infections in experimentally infected cattle*

Dosage (mg/kg)	No. of calves	Efficacy (%)								
		H. placei	*O. ostertagi*		*T. axei*	*T. colubriformis*	*C. oncophora*		*O. radiatum*	*D. viviparus*
			EL_4	Adult			EL_4	Adult		
None	3	(278)[a]	(336)	(6,117)	(4,610)	(1,897)	(54)	(6,195)	(31)	(207)
0.10	3	>98[b]	>99[b]	>99[b]	>99[b]	98[c]	89[c]	75	100[b]	100[b]
0.05	3	>98[b]	>99[b]	>99[b]	>99[b]	96	91[c]	47	100[b]	100[b]
0.025	3	>98[b]	89[d]	>99[b]	>99[b]	28	63	3	100[b]	>99[b]

[a] Numbers within parentheses indicate the geometric mean number of worms per control calf.
[b] Reduction from control value due to treatment: $P < 0.001$.
[c] Reduction from control value due to treatment: $P < 0.05$.
[d] Reduction from control value due to treatment: $P < 0.01$.

TABLE 6. *Regression equations and estimated ED_{95} values for parenteral administration of avermectin B_{1a} against patent infections in cattle.*

Parasite	Regression equation[a]	Significance of regression (P)	Estimated[b] ED_{95} (mg/kg)
H. placei	None, maximal efficacy		<0.025
O. ostertagi, EL_4	Log $\hat{Y} = -1.7838 \log X - 1.4856$	0.0013	0.030
O. ostertagi	None, maximal efficacy		<0.025
T. axei	None, maximal efficacy		<0.025
T. colubriformis	Log $\hat{Y} = -2.8509 \log X - 1.6860$	0.085	0.056
C. oncophora, EL_4	None		≃0.17
C. oncophora	Log $\hat{Y} = -0.9748 \log X + 2.2290$	0.0033	0.538
O. radiatum	None, maximal efficacy		<0.025
D. viviparus	None, maximal efficacy		<0.025

[a] Where $\hat{Y}$ is the predicted number of worms at dosage X (milligrams per kilogram).
[b] Estimates with ≃ or < preceding them are graphical approximations from the data of Table 5; all others are calculated point estimates from the respective regression equations.

TABLE 7. *Anthelmintic activity of avermectin B_{1a} as a single oral dose against immature nematode infections in experimentally infected cattle*

Dosage (mg/kg)	No. of calves	Efficacy (%)								
		H. placei	*O. ostertagi*		*T. axei*	*T. colubriformis*	*C. oncophora*	*C. punctata*	*O. radiatum*	*D. viviparus*
			EL_4	Adult						
None	4	(2214)[a]	(577)	(4949)	(2712)	(5680)	(5220)	(6662)	(240)	(350)
8-Day infection										
0.022	3	>99[b]	98[b]	97[c]	>99[b]	>99[b]	99[b]	99[d]	>99[b]	100[b]
0.011	3	>99[b]	59	94[d]	98[b]	95[c]	92[d]	81	>99[b]	100[b]
15-Day infection										
0.022	3	>99[b]	78	99[b]	>99[b]	99[b]	71	99[c]	100[b]	100[b]
0.011	3	>99[b]	0	95[c]	99[b]	86[d]	18	72	100[b]	100[b]

[a] Numbers within parentheses indicate the geometric mean number of worms per control calf.
[b] Reduction from control level due to treatment: $P < 0.001$.
[c] Reduction from control level due to treatment: $P < 0.01$.
[d] Reduction from control level due to treatment: $P < 0.05$.

ued presence in the untreated infected controls at 35 days postinfection. Numerically, the compound would appear to be somewhat less efficacious against at least some 15-day-old worms, but only with *C. oncophora* could this be substantiated statistically. For both dosage levels, 8-day-old *C. oncophora* were significantly ($P < 0.05$) more responsive to treatment than were 15-day-old *C. oncophora*. No regression-derived estimates of the ED_{95} values could be obtained from this experiment, but those derived previously from oral treatment of adult infections (experiment 1) would adequately cover the dosage requirements for the treatment of immature infections.

Dogs. Three control dogs given vehicle only had 61, 149, and 197 *A. caninum* at necropsy. Two dogs given avermectin B_{1a} at 0.005 mg/kg were found to harbor 7 and 25 worms at necropsy. Two dogs were given avermectin B_{1a} at 0.015 mg/kg, and two were given a dosage of 0.025 mg/kg; at necropsy, no hookworms were found in any of these four dogs.

Poultry. The untreated control chickens harbored a geometric mean of 64 *C. obsignata*, 38 *A. galli*, and 63 *Heterakis gallinarum*. The worms were adult, except in the case of *A. galli*, which were immature. Since these were natural infections, the age of the infections is not known.

The *C. obsignata* infections in the treated birds were not significantly reduced by avermectin B_{1a} at 0.025 mg/kg per os. However, dosages of 0.05 and 0.1 mg/kg gave reductions of 98 to 100% with respect to the untreated control values. These differences were significant ($P < 0.01$). The immature *A. galli* infections were significantly reduced only at the highest dosage tested (0.1 mg/kg), at which dosage there was an 87% reduction with respect to the control values ($P < 0.05$). The *H. gallinarum* infections were not significantly reduced at any of the three dosages tested.

DISCUSSION

For nematodes found experimentally to be susceptible to therapy with avermectin B_{1a}, excellent efficacy has been demonstrated at dosages considerably below 1 mg/kg, both orally and parenterally. Treatment of domestic animals by either route is facilitated when the amount of active ingredient and excipients is minimized. In our sheep, cattle, and dog experiments, we used dosage volumes of 0.1 ml/kg by oral administration and for cattle 0.025 ml/kg parenterally for convenience, but lower dosage volumes having higher concentrations of avermectin B_{1a} have also been used successfully.

Oral administration of avermectin B_{1a} to both sheep and cattle at dosages of 0.1 mg/kg produced excellent broad-spectrum anthelmintic activity against common gastrointestinal nematodes and lungworms. Comparable results, except for some loss of activity against *C. oncophora*, were demonstrated when avermectin B_{1a} was administered parenterally to cattle.

The results of the small experiment conducted in dogs indicate that avermectin B_{1a} is extremely potent against adult *A. caninum*. Additional small-scale trials (L. S. Blair and W. C. Campbell, in press) add further support to the conclusion that moderate to high efficacy against hookworms is achieved with a dosage of 0.005 mg/kg.

In naturally infected chickens, avermectin B_{1a} was effective against adult *C. obsignata* and immature *A. galli* at dosages of 0.05 and 0.1 mg/kg, respectively. It was not effective against *H. gallinarum* at 0.1 mg/kg, but higher dosages have not been tested.

The results presented here show that the avermectins have potent activity against a wide range of nematodes in domestic animals. They are effective against both mature and immature worms, both hypobiotic and normal fourth-stage larvae, both benzimidazole-susceptible and benzimidazole-resistant nematode strains, and both intestinal and extra-intestinal forms. No grossly observable toxic reactions were noted in any animal treated with the efficacious levels of avermectin B_{1a} in these experiments.

Our results, together with data showing efficacy against *Trichinella spiralis, Syphacia obvelata,* and *Aspiculuris tetraptera* (W. C. Campbell and L. S. Blair, in press), indicate that the anthelmintic activity of avermectins extends to at least eight families of nematodes: Filariidae, Oxyuridae, Trichinellidae, Trichuridae, Heterakidae, Metastrongylidae, Trichostrongylidae, and Strongylidae. Thus, the avermectins would appear to be natural products with an unprecedented potency and spectrum of anthelmintic activity.

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