KINETIC FATE OF ANTHELMINTICS AND THERAPEUTIC IMPLICATIONS

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Introduction

Until recent years, the pharmacology of anthelmintics had not been extensively studied. With the introduction of modern drugs, notably the benzimidazoles, levamisole and ivermectin, a new interest to investigate the pharmacokinetics and pharmacodynamics of anthelmintics has arisen. Regulatory requirements for approval of anthelmintics for use in food-producing animals have dictated the necessity of more elaborate pharmacological studies. For this reason, and in an effort to gain more scientific knowledge about the use of new drugs, the pharmaceutical industry, in cooperation with academia, has been instrumental in the development of pharmacological data with anthelmintics.

Previously, anthelmintics had been evaluated mainly for efficacy in removing adult parasites from the gastrointestinal tract and for safety to the host; pharmacokinetics and pharmacodynamics did not seem to be important. Now, with the application of pharmacological data, it is possible to predict how to remove adult parasites such as lungworms and kidneyworms from other sites in the body. In addition, various immature forms of parasites in histotropic stages can now be controlled. Obviously, the parasites, regardless of their location or stage of development, must be susceptible to the action of the drug.

It must be pointed out that there are certain limitations with pharmacokinetic studies with many of the currently available anthelmintics because of the difficulty in administering these drugs intravenously; benzimidazoles due to low solubility, levamisole and ivermectin due to toxicological consideration. The information presented in this paper is limited to data collected following oral administration of drugs.

Benzimidazoles

Since the introduction of thiabendazole[a] in the early 1960's, several other new benzimidazoles have been developed and are now available in the United States. Cambendazole[b], oxfendazole[c] and oxibendazole[d] are approved for use in horses only; mebendazole[e] is approved for use in horses and dogs. Albendazole[f] is available under special and restricted Investigational New

[a]Omnizole®, Equizole®, TBZ®: MSD AGVET, Division of Merck & Co., Inc, Rahway, NJ 07065.
[b]Camvet®: MSD AGVET, Division of Merck & Co., Inc., Rahway, NJ 07065.
[c]Benzelmin®: Diamond Laboratories, Inc., Des Moines, IA 50317.
[d]Anthelcide EQ®: Norden Laboratories, Lincoln, NB 68501.
[e]Telmin®, Telmintic®: Pitman-Moore, Inc., Washington Crossing, NJ 08560.
[f]Valbazen®: Norden Laboratories, Lincoln, NB 68501.

Animal Drug provisions for treatment of liver flukes in cattle. Febantel[a] is chemically classified as a phenylguanide and is approved for horses only. A portion of febantel is metabolized to fenbendazole sulfone in vivo[1] and, therefore, is referred to as a pro-benzimidazole; as such, febantel is mentioned with the benzimidazoles. Fenbendazole[b] was introduced to the U.S. animal health market in 1977 and is now approved for use in horses, cattle, swine and dogs. Because of the pharmacokinetic data for fenbendazole available to the author, this drug will be used as an example in this presentation about the kinetic fate and therapeutic implications of anthelmintics.

Benzimidazoles all share the same structural nucleus. The various sidechains and substitutions impart some important differences in potency, efficacy and safety (Figure 1). The predominant mode of action of benzimidazoles is interference with energy metabolism via enzyme inhibition in susceptible parasites.

Fenbendazole Use in Horses

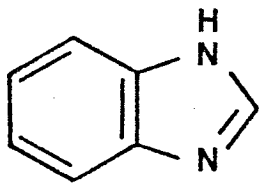
Blood levels of fenbendazole following oral doses, ranging from 6.5 to 11.0 mg/kg body weight, were determined in horses. Two treatments at least 3 weeks apart were administered to each of 5 horses. Peak blood levels occurred at 7 hours post-treatment and markedly declined to approximately 0.1 µg/ml at 24 hours. Blood levels of fenbendazole were virtually 0 at 72 hours post-treatment[2] (see Figure 2). Fenbendazole blood levels were also determined in another study in which each of 5 horses was given one oral dose of 7.5 mg fenbendazole/kg body weight. As in the previous study, blood levels peaked at 6 to 8 hours but the peak was approximately only one-half as high. Blood levels were virtually 0 at 30 hours.[3]

Based on the information obtained in the above blood level studies in horses, it was concluded that fenbendazole should be dosed at 24 hour intervals in order to maintain measurable blood levels. Studies were then undertaken to evaluate the efficacy of fenbendazole against fourth stage larvae of Strongylus vulgaris during their arterial migration.

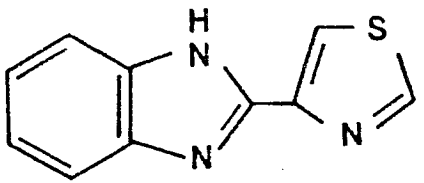
In the first study, ponies were inoculated with infective larvae of Strongylus vulgaris. The ponies were assigned to 4 groups of 4 ponies each. Seven days after inoculation, the ponies were given fenbendazole at the rate of 50 mg/kg for either 1, 2 or 3 consecutive days while a control group was given tap water only. The ponies were necropsied 28 days after inoculation or at death (3 of 4 control ponies died between post-inoculation days 13-17 due to acute verminous arteritis). S. vulgaris larvae were recovered from the cranial mesenteric artery and its branches and pathology in the arteries was assessed. The results (see Table 1) showed that the effectiveness of fenbendazole was dose related against early 4th stage larvae of S. vulgaris.[4]

[a]Rintal®: Haver-Lockhart Laboratories, Shawnee, KS 66201.
[b]Panacur®: American Hoechst Corporation, Animal Health Division, Somerville, NJ 08876.

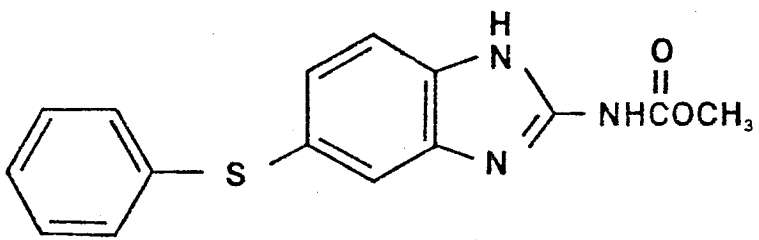
FIGURE 1. Benzimidazole Structural Relationships



Benzimidazole Nucleus



Thiabendazole: Effective equine dose - 44-88 mg/kg



Fenbendazole: Effective equine dose - 5-10 mg/kg

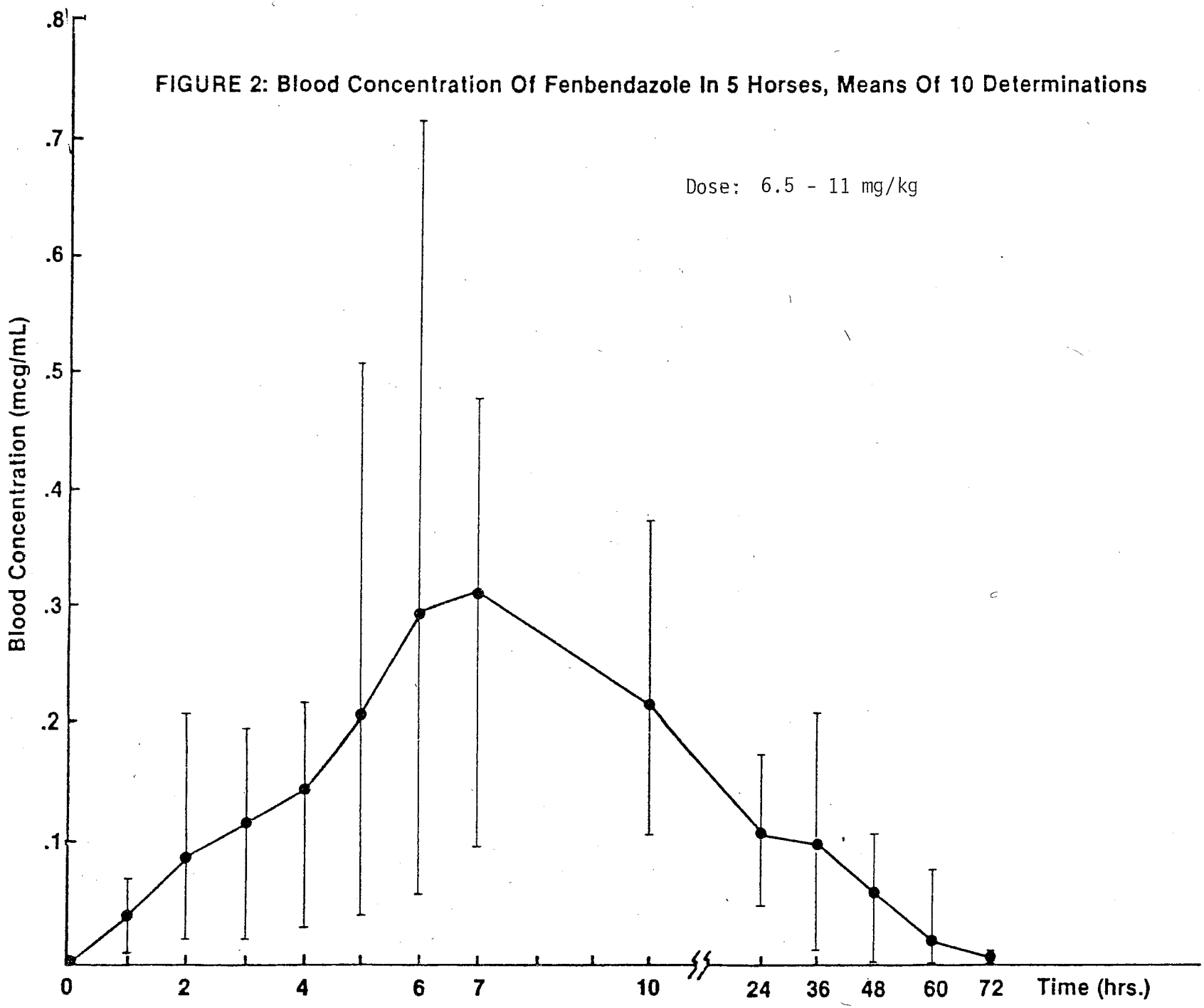


FIGURE 2: Blood Concentration Of Fenbendazole In 5 Horses, Means Of 10 Determinations
Dose: 6.5 - 11 mg/kg
Blood Concentration (mcg/mL)
.8
.7
.6
.5
.4
.3
.2
.1
0
2
4
6
7
10
24
36
48
60
72
Time (hrs.)

Table 1. NUMBER OF EARLY 4th STAGE S. VULGARIS LARVAE RECOVERED AND ARTERIAL LESIONS IN PONIES TREATED WITH FENBENDAZOLE

Dose Group	Mean No. of Live Larvae Recovered (Range)	Arterial Lesions
0	84.5 (2 - 141)	Severe
50 mg/kg x 1	56.5 (28 - 106)	Moderate to Severe
50 mg/kg x 2	23.0 (1 - 60)	Minimal to Moderate
50 mg/kg x 3	1.0 (1 - 3)	None to Minimal

From: Slocombe & McCraw, 1982.

In the second study, ponies were also inoculated with infective larvae of S. vulgaris. The ponies were assigned to three groups of four ponies each. On Day 56 postinoculation, ponies were given fenbendazole at the rate of 50 mg/kg for 3 consecutive days or 10 mg/kg for 5 consecutive days while controls were given tap water only. All ponies were necropsied 35 days after treatment. Viable S. vulgaris were recovered from the cranial mesenteric artery and its branches and arterial pathology was assessed. The results (see Table 2) showed that both dosage regimes were highly effective against later 4th stage S. vulgaris larvae. By taking advantage of longer sustained blood levels in the 5-day treatment with 10mg/kg/day (total dose of 50mg), comparable effectiveness was achieved compared to the shorter treatment of 3 days with 50 mg/kg/day (total dose of 150 mg).[5] Also, 50 mg fenbendazole/kg divided over a 5-day treatment was much more effective than a single dose of 50 mg/kg.

Table 2. NUMBER OF LATER 4th STAGE S. VULGARIS LARVAE RECOVERED AND ARTERIAL LESIONS IN PONIES TREATED WITH FENBENDAZOLE

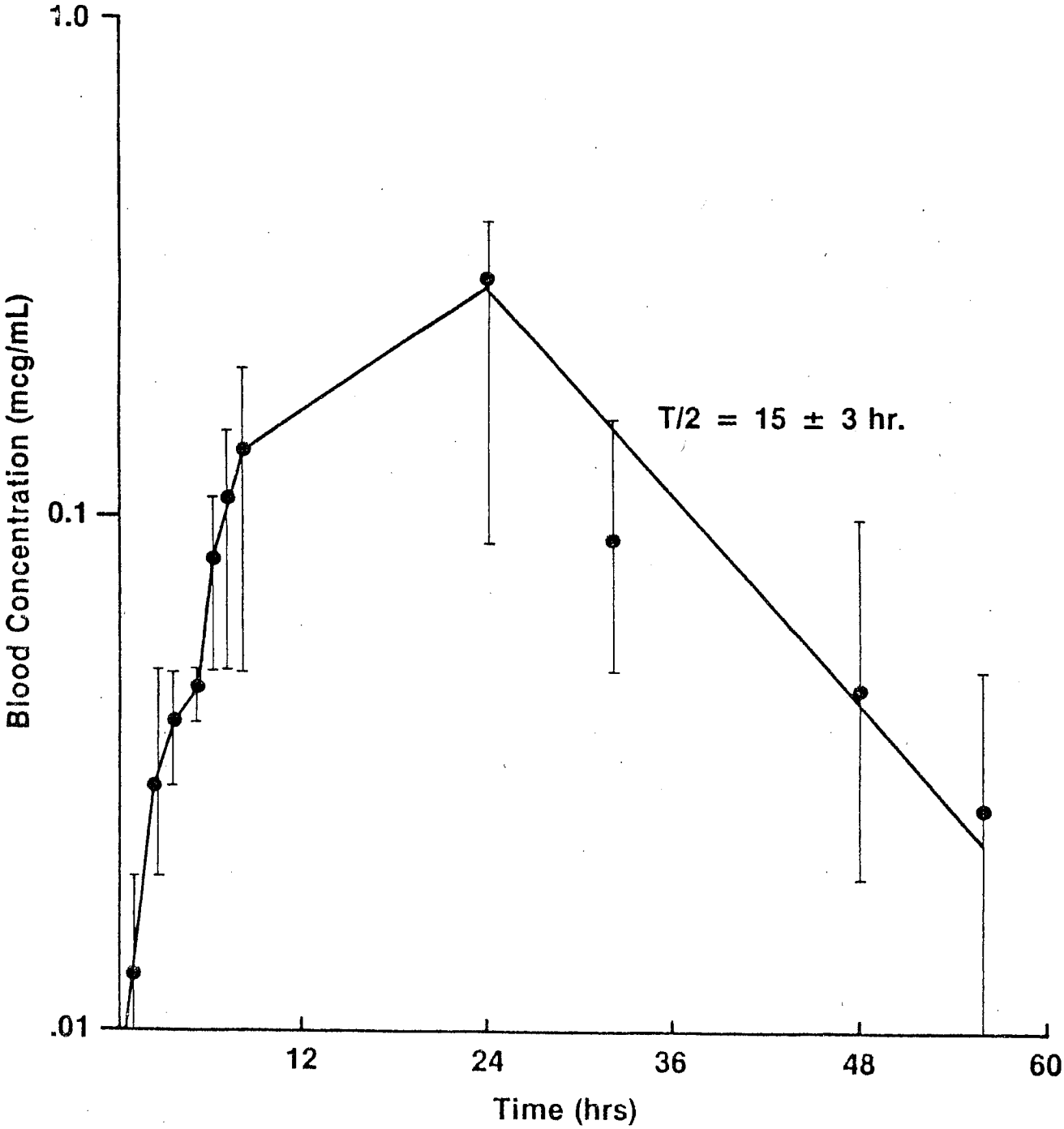
Dose Group	Mean No. of Live Larvae Recovered (Range)	Arterial Lesions
0	69.7 (23 - 159)	Moderate to Severe
50 mg/kg x 3	1.0 (0 - 4)	None to Minimal
10 mg/kg x 5	0.25 (0 - 1)	None to Minimal

From Slocombe, et al, 1983.

Fenbendazole Use in Dogs

Fenbendazole-^{14}C was prepared for pharmacokinetic studies in several animals species including dogs. The result of these studies showed that fenbendazole (10mg/kg) was absorbed faster but to a lesser extent in dogs when compared to animals with a more complex gastrointestinal tract, e.g. sheep. The half-life of elimination in the dog was approximately 15± 3 hours (see Figure 3) and radioactivity was found mainly in the feces with only about 5± 2% recovered in the urine. The amount excreted in the urine after oral administration is no indication of the quantity actually absorbed considering

FIGURE 3: Blood Levels Of Fenbendazole -^{14}C
After Oral Administration To Dogs (n = 3), 10 mg/kg



the possibility of biliary excretion[6]. The short intestinal length of the dog may help to explain the lesser absorption of fenbendazole in dogs and the higher doses required for dogs -- 50 mg/kg daily for 3 days, as compared to ruminants and horses (5 mg/kg as a single dose). Of course the ratio of body surface area to body weight in the dog would also predict a higher dose of a given drug as compared to larger species. The ratio of the gastrointestinal volume to body mass may also be important in dosing anthelmintics.

Hypobiotic larvae of Toxocara canis become encysted in body tissues of adult dogs. In the pregnant bitch, some of these larvae become activated and migrate to the uterus giving rise to prenatal infection in the puppies. The activation and mobilization of these larvae does not occur prior the 42nd day of gestation.[7] A study was conducted to evaluate the ability of fenbendazole to eliminate or reduce the T. canis burden in puppies whelped by treated bitches. This study was also designed to evaluate the ability of fenbendazole to control the transmammary transmission of Ancylostoma caninum larvae to the nursing puppies.

A total of twenty-three bitches in two experiments were artificially infected with embryonated eggs of T. canis and infective larvae of A. caninum on 3 occasions (5th-14th days, 35th day, and 60th day) during pregnancy. The bitches were assigned to 3 different groups. Two groups were treated with fenbendazole, 50 mg/kg daily from the 40th day of pregnancy until either whelping or until Day 14 post-whelping. The other group served as untreated controls. Pups were allowed to nurse until necropsied at 5 weeks of age. The results (see Table 3) show that treatment with fenbendazole markedly reduced T. canis and A. caninum burdens, especially in in the case of the longer treatment. Clinical illness was prevented with the longer treatment and was reduced with the shorter treatment as compared with controls.[8]

Fenbendazole Use in Swine

A pharmacokinetic study was conducted in swine using ^{14}C-labeled fenbendazole. Following oral administration of 5mg fenbendazole/kg body weight, peak blood concentrations were by far the highest in the pigs as compared to rats, goats, rabbits, and sheep, which were also utilized in this study (see Figure 4). The peak concentrations had appeared in the blood by 5 hours and persisted until 24 hours post-treatment. The calculated elimination half-life was 9.4±1 hour (see Figure 4). More fenbendazole-^{14}C was excreted in the urine of pigs, 33 ± 2.5% as compared to 5-19% for the other species studied.[6]

Results from a previous efficacy study had established that repeated low doses of fenbendazole were as effective as large single doses. In the case of Trichuris suis, 3 daily doses of 3 mg/kg and single doses of 10 mg/kg or 25 mg/kg were 99.8%, 93.8%, and 97.4% effective, respectively. With Ascaris suum, the same doses of fenbendazole were 98.9%, 96.8%, and 98.4% effective[9] (see Table 4).

Table 3. MEAN WORM BURDENS AND PERCENT REDUCTIONS IN PUPPIES FROM BITCHES TREATED WITH FENBENDAZOLE FROM DAY 40 OF PREGNANCY

Treatment Group	T. canis		A. caninum	
	Mean Worm Burden	Percent Reduction	Mean Worm Burden	Percent Reduction
Experiment 1:				
Untreated Controls (n=11)	399	--	51	--
Fenbendazole, 50 mg/kg/day to whelping (n=8)	145	63.7	6	88
Fenbendazole, 50 mg/kg/day to whelping + 14 days (n=13)	42	88.2	1	98
Experiment 2:				
Untreated Controls (n=22)	29	--	59	--
Fenbendazole, 50 mg/kg/day to whelping + 14 days (n=21)	<1	97	<1	99.7

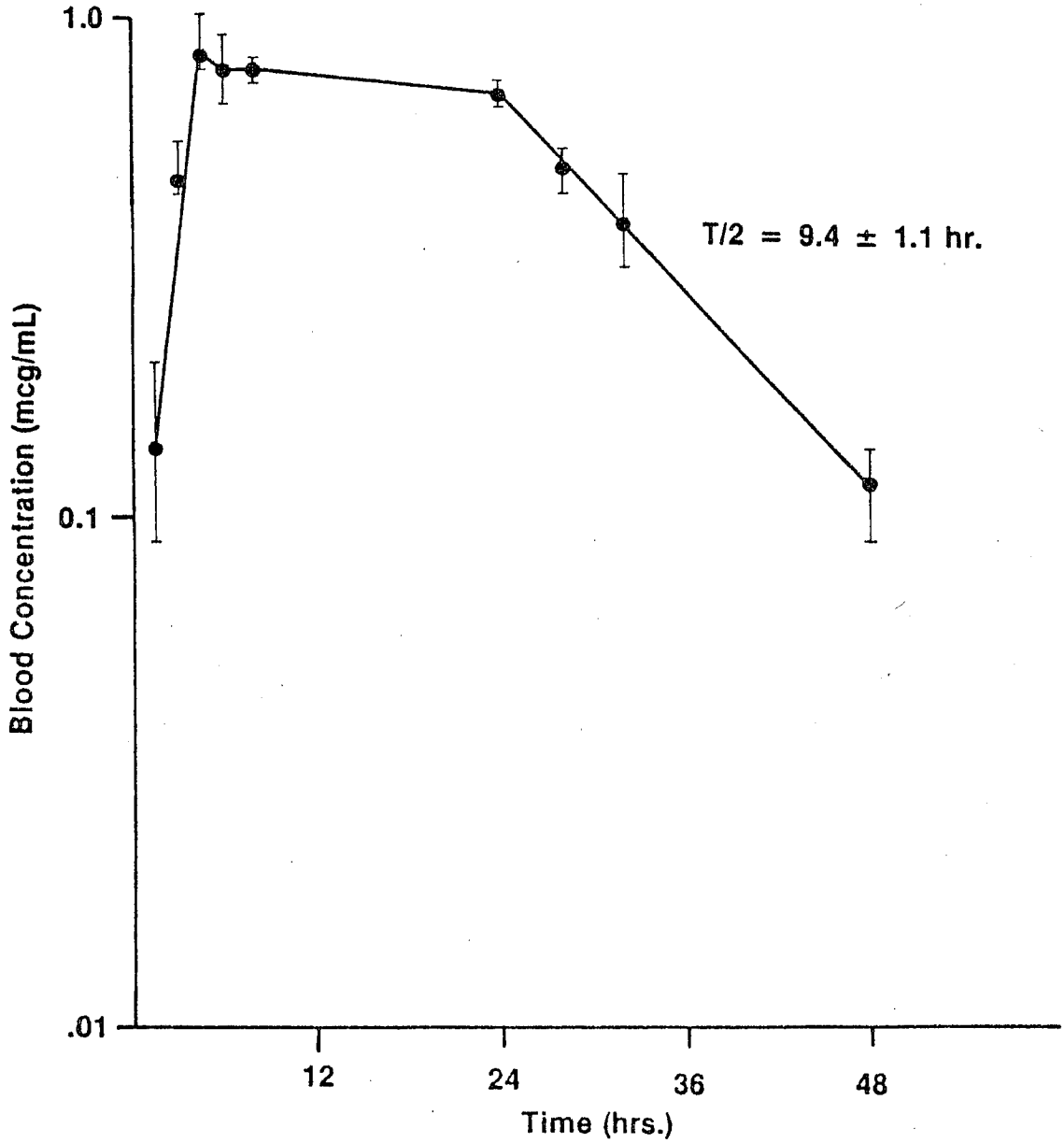
From: Burke & Roberson, 1983.

Table 4. EFFECT OF VARIOUS DOSES OF FENBENDAZOLE ON REMOVAL OF T. SUIS AND A. SUUM IN SWINE

Dose	% Removal	
	T. suis	A. suum
3 x 3 mg/kg	99.8	98.9
1 x 10 mg/kg	93.8	96.8
1 x 25 mg/kg	97.4	98.4

From: Batte, 1978.

FIGURE 4: Blood Levels Of Fenbendazole -^{14}C
After Oral Administration To Pigs (n = 3), 5 mg/kg



While fenbendazole is apparently well absorbed in the pig, it is also rapidly excreted, which explains why repeated low doses are more effective than large single doses. Adult kidneyworms reside in the renal pelvis, perirenal fat and walls of the ureters. The migrating larvae cause severe damage to the liver and loin muscles. Hence, where this parasite occurs, it is of economic importance to swine producers. To be effective against this tissue dwelling parasite, a drug must be sufficiently absorbed to achieve tissue levels.

An efficacy study with fenbendazole against the kidneyworm, Stephanurus dentatus, in pigs was performed. Fenbendazole premix was added to ground feed and administered at the rate of 3 mg/kg daily for 3 days to 15 sows infected with S. dentatus. An additional 15 infected sows served as untreated controls. Urine samples from treated sows became negative for kidneyworm eggs by the 5th to 12th days post-treatment, except one sow passed a few eggs on the 12th day and another sow passed a few eggs on the 19th and 33rd post-treatment days. Hatchability of eggs from treated sows was greatly reduced during the first 5 post-treatment days, and subsequently the number of eggs passed was not sufficient to determine hatchability. Control sows continued to excrete eggs at the same level as during the pretreatment period.

All sows were necropsied on post-treatment Day 61. No kidneyworms, either adult or larvae, were recovered from the kidneys, ureters, livers or carcasses of treated sows compared to an average of 56 worms recovered from all tissues per control sow. Fenbendazole was highly effective against both adult and larval forms of S. dentatus (see Table 5).[10]

Table 5. MEAN NUMBERS OF KIDNEYWORM EGGS (EPML) IN URINE AND KIDNEYWORMS RECOVERED AT NECROPSY OF SOWS TREATED WITH FENBENDAZOLE, 3 MG/KG FOR 3 DAYS, VS UNTREATED CONTROLS

			Mean No. of Worms Recovered:		
Group	Mean EPML 5 days Prior	Mean EPML 1-8 Weeks Post	Kidney, Ureters	Liver, Carcass	Total
Treated	106 - 537	0.1	0	0	0
Control	38 - 334	2.7 - 265	28	28	56

From Stewart, et al, 1981.

Fenbendazole Use in Cattle

The results of another pharmacokinetic study with fenbendazole-^{14}C in cows showed relatively slow absorption. The peak blood level of approximately 1.6 µg/ml was not reached until 24 to 32 hours after drug administration. Fenbendazole levels of 0.01 µg/ml could be detected in the blood up to 25 days after treatment. The detection limit of 0.003 µg/ml could be measured in one cow up to 65 days. The biological half-life of elimination from the blood was biphasic with T 1/2 values of 16.8± 2.4 hours and 15.9± 1.9 days (see

Figure 5). Approximately 77% of the fenbendazole was recovered in the feces and 14% was recovered in the urine.[11]

The slow absorption and prolonged blood levels of fenbendazole in cattle (and other ruminants) is, in part, due to the drug remaining in the rumen which serves as a drug reservoir. It has been shown that thiabendazole (100mg/kg) was absorbed from the rumen to a greater extent - approximately 70%. The ruminal half-life was one hour for thiabendazole compared to 4 hours for fenbendazole. There was also evidence of considerable hepatic recycling of both drugs and their metabolites into the small intestine. For example, approximately 27% of the fenbendazole dose left the abomasum in digesta and about 52% appeared at the terminal ileum. Maximal concentrations of thiabendazole occurred in the blood in 4 hours compared with about 24 hours for fenbendazole. Excretion of fenbendazole was slower than thiabendazole; half-lives in the blood were 31 and 8 hours, respectively.[12]

The preceding information helps explain why fenbendazole has greater biological potency as compared to thiabendazole. With the knowledge that fenbendazole achieves high blood levels and persists in the blood of ruminants for prolonged periods, studies were undertaken to evaluate the efficacy of fenbendazole against a tissue dwelling stage of an important parasite in cattle.

Type II ostertagiasis is a disease of cattle which can be devastating and even fatal. The disease is caused by Ostertagia ostertagi, specifically the inhibited early 4th stage larvae which are located in the abomasal wall. The inhibition of the larvae occurs during adverse climatic conditions which are not conducive to survival of the parasite in the environment. Thus, residency of the larvae in the host in an inhibited or hypobiotic state enables the parasite to survive. When climatic conditions improve, the inhibited larvae resume development and cause severe damage to the mucosa as they return to the lumen of the abomasum as adults.[13] Knowledge of the epidemiology of this disease is important in treatment. An anthelminitic which is capable of achieving prolonged serum levels may also be an important consideration for successful treatment.

Naturally infected yearling cattle in Louisiana were treated with fenbendazole in April 1978. Ten cattle each were given fenbendazole at doses of 10 mg/kg or 15 mg/kg while 11 other cattle served as untreated controls. All animals were necropsied 7 to 9 days post-treatment. Parasites remaining in the gastrointestinal tract were identified and counted. Efficacy was established by comparing the numbers of parasites in the treated and control groups. The results (see Table 6) indicated a high degree of efficacy against the early 4th stage larvae of O. ostertagi as well as adults. The higher dose appeared to be more effective against developing stages.[14]

Summary

The development of pharmacokinetic data with the anthelmintic, fenbendazole, in horses, dogs, swine and cattle has been discussed and important species differences have been shown. With the application of pharmacokinetics, along with an understanding of certain parasitological concepts, it has been possible to develop new and important therapeutic regimens with an anthelmintic.

FIGURE 5: Blood Levels Of Fenbendazole - ^{14}C
After Oral Administration To Cows (n = 4), 10 mg/kg

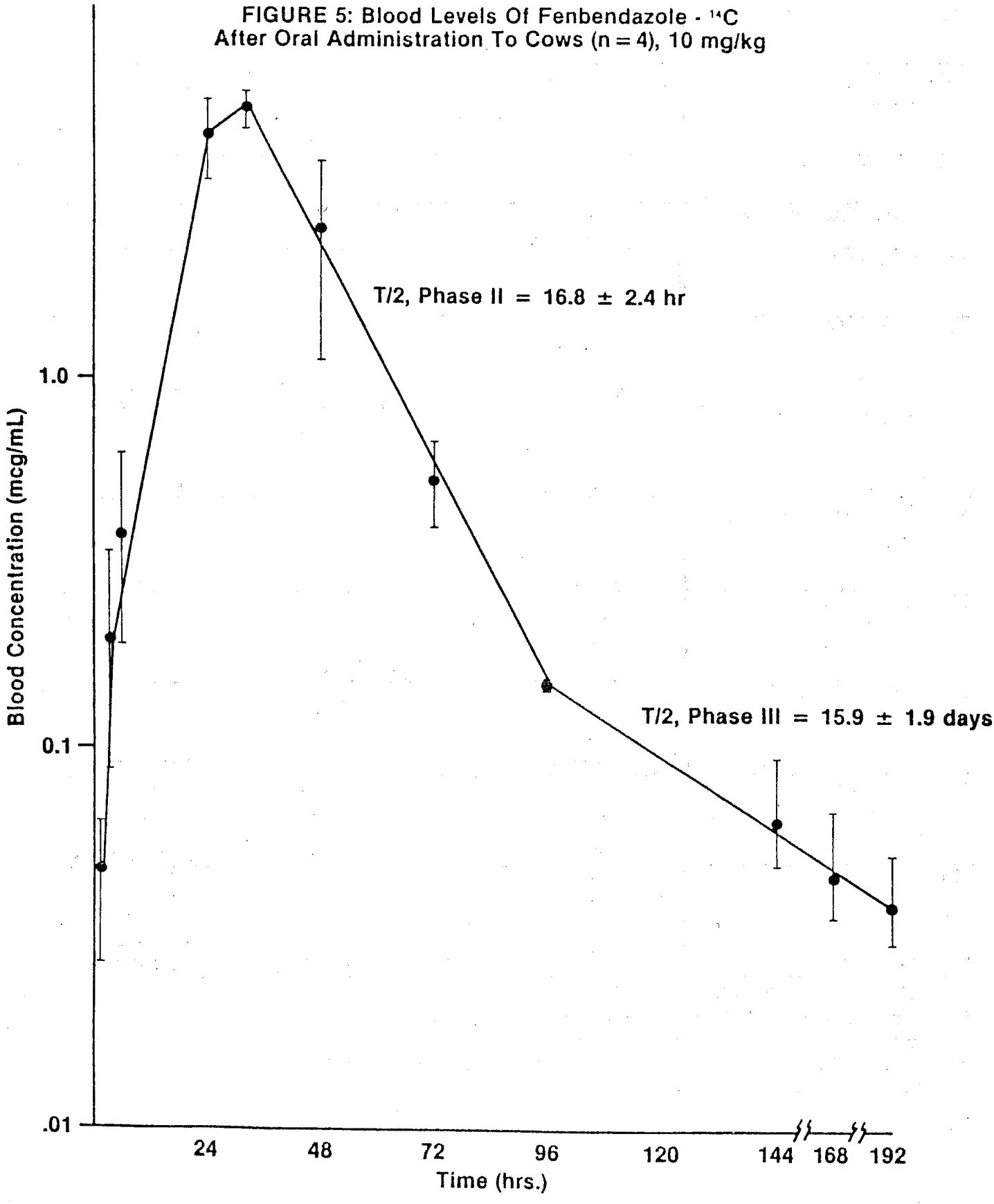


Table 6. RECOVERY OF O. OSTERTAGI FROM CONTROL AND FENBENDAZOLE TREATED CATTLE

	O. ostertagi					
	Adult		Developing Stage		Inhibited Early 4th Stage	
	Mean No. Recovered	Percent Reduction	Mean No. Recovered	Percent Reduction	Mean No. Recovered	Percent Reduction
Control	2620	--	1102	--	107166	--
10mg/kg	0	100	221	80	3547	97
15mg/kg	0	100	23	98	1181	99

From: Williams, et al, 1979.

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Point raised during discussion

Question: Although MICs can be done for anthelmintics, the problem is really one of time of exposure to the drug and the host's reaction. The fact that subMIC levels over prolonged periods of time can be efficacious is most interesting. Could you comment further?

Dr. Paul: Time of exposure of the drug to the larvae that are somewhere in the animal seems to be important. In our work we showed similar efficacy between 10 mg/kg for 5 days and 50 mg/kg (the same total drug level). Perhaps 10 mg/kg/day is really sublethal and the effect depends on the exposure time.