CURRENT APPROACHES TO INTERNAL PARASITE CONTROL IN SMALL ANIMALS

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Introduction

Treatment of young dogs for parasites routinely has been done following weaning, i.e. when the pup is 7 to 8 weeks of age. The typical pattern is for a litter of pups to be disbursed to new owners after weaning and the pup is taken to a veterinary clinic for the first time at 7 to 8 weeks of age for its vaccinations and deworming. Flotation of feces at this time almost invariably reveals eggs of the common ascarid, Toxocara canis, and usually shows eggs of the common hookworm, Ancylostoma caninum.

How have pups acquired these infections? Environmental contamination? Prenatally via the uterus of the mother? Lactationally via the milk of the mother? Earlier studies concerning prenatal and lactational transmission of hookworms and ascarids to pups have been reviewed by Burke and Roberson.[3] In spite of the investigative attention to bitch-to-pup transmission of these parasites, the relative importance of each of these two routes remained in question. We were able to quantitate the importance of prenatal and lactational transmission of these parasites to pups in a recent study[3] in which we found that ascarids (T. canis) were transmitted to pups both prenatally (98.5%) and lactationally (1.5%) and that hookworms (A. caninum) were transmitted to pups only through the bitch's milk.

Subsequent studies[2] in which we have placed a new parasite-free litter of pups each week on lactating infected bitches indicate that hookworm transmission via the milk occurs throughout the lactation period. Heaviest hookworm transmission occurs, however, during the first week of lactation. Even the small number of ascarid larvae which pass to pups via the milk did so throughout the 4 to 5 week lactation period covered by our studies.

What does this mean concerning the necessity for treatment of young pups? It means they need to be treated early while still nursing. Ascarid larvae (L_2 stage) which have prenatally invaded the fetus will be located in the liver of the pup at birth.[11] From the liver, they will pass via the circulatory system to the lungs, break into the respiratory passage and ascend the respiratory tree from which they get into the pharynx and are swallowed. They can grow in the digestive tract to egg-laying adults by the time the pup is 4 weeks of age. A pup with a heavy ascarid burden at this age will show the typical pot-bellied appearance. The earlier lung phase of migration may be fatal to heavily infected pups when they are but 2 days of age.[5] Hookworms acquired as 3rd stage larvae in the first milk a pup takes from its infected mother will develop to patency by the time the pup is 2 weeks of age. Heavy hookworm infections may be fatal to pups before they reach 3 weeks of age.

Treatment of Nursing Pups

A treatment regimen for nursing pups should routinely start when pups are 2 weeks of age and continue at 2 week intervals until 2 weeks after weaning, i.e. until pups are approximately 8 weeks of age. Such a regimen has several advantages. (1) Hookworms which are continuously acquired through the milk

are eliminated before they are large enough to take significant amounts of blood. (2) Prenatally acquired ascarids are eliminated on the first treatment thereby preventing their growth to adult size which is more liable to compromise the health of the pup. (3) Both parasites are eliminated before patency, thus preventing contamination of the environment with potentially infective stages. This is important, not only to the future well-being of canines, but to the human population as well since both of these canine parasites are associated with clinical entities in humans.[10] Infective larvae of hookworms cause "cutaneous larval migrans" and those of ascarids cause "visceral" or "ocular larval migrans."

What drugs are available which can be used safely in nursing pups? Two can be recommended which are effective for both immature and adult stages of both ascarids and hookworms. They are pyrantel pamoate[a] and fenbendazole.[b] Both are available in suspension formulation for oral administration to nursing pups. Pyrantel pamoate is given in a single administration at a dosage of 5 mg/kg of body weight. Fenbendazole is given for 3 consecutive days at a dosage of 50 mg/kg each day. The 3 day contact is needed to expel parasites with fenbendazole. One or two day regimens give only partial efficacy.

Treatment of the Pregnant Bitch

What about the bitch? Will a routine deworming during pregnancy help prevent parasite infection of her pups after whelping? A routine deworming is worthwhile in that it will eliminate adult parasites (hookworms, whipworms) from the bitch's digestive tract and thereby will cut down on environmental contamination. A routine deworming, however, does apparently nothing to reduce the number of somatically located larvae of either *T. canis* or *A. caninum*. One drug which has given favorable reduction of larval ascarid and hookworm burdens in the bitch is fenbendazole[b] but this requires a rigorous treatment regimen of 37 consecutive days starting on the 40th day of pregnancy and continuing until the 14th day after whelping, using 50 mg fenbendazole/kg body weight once each day. Pups from experimentally infected bitches that were so treated had 89% fewer ascarids and 99% fewer hookworms than pups born to similarly infected unmedicated controls.[1] While the logistics and cost (approximately $1.00/day for a Beagle-size dog) prevent widespread use of this regimen in pregnant dogs, there are particularly valuable animals and special situations where the regimen is useful.

Routine Treatment of Older Dogs

The parasites which commonly infect older dogs are hookworms, whipworms and tapeworms, especially *Dipylidium caninum*. Hookworms occur as frequently in older dogs as they do in pups among either pound dogs (82% infected) or owned dogs (37%).[9] In Georgia, we have found whipworms in 62% of older stray dogs and 23% of owned dogs. Of interest is the fact that for several years now at the Georgia clinic we have been seeing occult infections of whipworms associated with lower bowel diarrhea. No eggs are found in feces but examination of the bowel using a fiberoptic endoscope has revealed the

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a Nemex-2, Pfizer, Inc., New York, NY 10017.

b Panacur, American Hoechst Corporation, Animal Health Division, Somerville, NJ 08876.

presence of adult whipworms in the cecum. Such occult infections may represent as much as 10% of clinical whipworm cases seen at the Georgia clinic.[4]

Current anthelmintics for treatment of parasite infections of older dogs are listed in Table 1. The first four drugs, especially butamisole HCl and fenbendazole, are widely used to treat whipworm and hookworm infections. Of the drugs useful for the treatment of tapeworm infections, the benzimidazoles are effective for Taenia but not Dipylidium caninum. Both older drugs, niclosamide and bunamidine HCl, have varied activity for Dipylidium. These drugs often result in destrobilization of Dipylidium but the retained scolex will regenerate a body in approximately 3 weeks. The greatest efficacy (100%) for tapeworm infections in dogs or cats is obtained with praziquantel using either the oral or injectible formulation.

Table 1.

ANTHELMINTICS USED IN ADULT DOGS

Generic Name	Trade Name	%Efficacy		%Dogs Cleared	
		Whip-worms	Hook-worms	Taenia	Dipylidium
Dichlorvos	Task	90-100	95		
Butamisole HCl	Styquin	99	92		
Mebendazole	Telmintic	95	95	85	0
Fenbendazole	Panacur	100	98	88-100	0
Niclosamide	Yomesan			80	18-56
Bunamidine HCl	Scoloban			100	56-90
Praziquantel	Droncit			100	100

Modes of Action of Anthelmintics

How do anthelmintics affect the parasite, i.e., what are the modes of action? In general, helminth parasites are most vulnerable to interferences either with biochemical mechanisms essential for the parasite's motor activity or with reactions that provide generation of metabolic energy.[8]

Neuromuscular System. Pyrantel and several other anthelmintics affect the parasite's neuromuscular system by acting as cholinergic agonists (cholinomimetics); i.e. they have functional groups similar to acetylcholine (ACh), bind to ACh binding sites and cause a continual ACh stimulatory effect, but are not inactivated by acetylcholinesterase. Drugs that produce this effect include the pyrimidines (pyrantel, morantel), pyridines (methyridine), imidazole (levamisole), and quaternary ammonium salts (bephenium, thenium).

Organophosphorus drugs, such as dichlorvos, also affect the neuromuscular system of nematodes. Instead of acting, however, as a cholinomimetic, this class of anthelmintics covalently binds with the parasite's acetylcholinesterase preventing the normal action of this enzyme, i.e. destruction of acetylcholine. In the absence of acetylcholinesterase, the excess neurotransmitter (acetylcholine) overstimulates the muscular system. Parasites, no

longer able to maintain their position in the ingesta or attachment to the mucosa, are swept along with ingesta and pass in the feces.

The action of the newest anthelmintic, ivermectin, relates to inhibition of the parasite's nervous system. The drug blocks signal transmissions at the presynaptic junction of nematodes or the neuromuscular junction of arthropods by opening the gamma-aminobutyrate (GABA) mediated Cl-channels on the parasite's nerve or muscle membranes.[6] The result is that the membrane surface remains negatively charged so that no signals (excitatory or inhibitory) are perceived and the parasite becomes immobile.

Energy Metabolism. Biochemical reactions involved in the parasite's energy metabolism are the most frequent sites of drug action. Rew[7] categorized classes of commonly used anthelmintics under the following energy-generating biochemical events that the drug interrupts.

1. Inhibitors of glucose transport--cyanine dyes (dithiazinine, pyridinium, styrylpyridinium); benzimidazole (mebendazole); praziquantel. In parasites treated with these drugs, the diminished uptake of glucose generally results in reduced quantities of adenosine triphosphate (ATP) and glycogen levels and ultimately leads to death of the parasite.

2. Inhibitors of glycolysis--arsenicals (thiacetarsamide); antimonials (potassium antimony tartrate, stibophen). These drugs are organic trivalent heavy metals. They tend to bind sulfhydryl (-SH) groups, thereby altering the tertiary structure of proteins and the active site of enzymes in both parasite and host.

3. Inhibition of mitochondrial reactions--benzimidazoles (albendazole, cambendazole, fenbendazole, oxfendazole, oxibendazole, parbendazole, thiabendazole, and probably thiophanate). Evidently, in a number of anaerobic helminths (e.g. Ascaris) metabolic formation of high-energy bonds (ATP) for muscular contraction is associated with reduction of fumarate to succinate in the mitochondria. The reaction serves to reoxidize nicotinamide adenine dinucleotide phosphate formed during glycolysis and to generate ATP. The enzyme fumarate reductase, necessary for reduction of fumarate to succinate, appears to be the primary site of action of all the benzimidazoles except mebendazole. Basically, these drugs inhibit fumarate reductase enzyme activity, thus blocking generation of energy bonds and resulting in muscular paralysis and eventual death of the parasite.

4. Uncouplers of electron transport-associated phosphorylation--salicylanilides (clioxanide, niclosamide, oxyclozanide, and rafoxanide); substituted phenols (bithionol, dinitrophenol, hexachlorophene, niclofolan, nitroxylnil). Several anthelmintics of the phenolic type interfere with the phosphorylation process (i.e. generation of ATP) in parasites by interrupting electron transport-associated events. The fumarate to succinate conversion takes place but no chemical energy is produced. Drugs that cause this effect are active primarily against flukes and cestodes. Although the nematode mitochondrial phosphorylation system is similar to that of cestodes, these drugs are not effective against nematodes, perhaps because of inability of the drugs to penetrate the tissues of the intact nematode.

References

1. Burke, T.M. and Roberson, E.L.: Fenbendazole treatment of pregnant bitches to reduce prenatal and lactogenic infections of Toxocara canis and Ancylostoma caninum in pups. J.A.V.M.A. 183: pp. 987-990, 1983.

2. Burke, T.M. and Roberson, E.L.: Studies on prenatal and lactogenic transmission of Toxocara canis and Ancylostoma caninum IIa. Experimental infection of the bitch at mid-pregnancy and at parturition b. Longevity of lactogenic transmission. Proceedings 28th Annual Meeting Am. Assoc. Vet. Parasitol, New York City, July 17-19, 1983.

3. Burke, T.M. and Roberson E.L.: Prenatal and lactational transmission of Toxocara canis and Ancylostoma caninum: Experimental infection of the bitch before pregnancy. Intl. J. Parasitol (accepted for publication), 1984.

4. Cornelius, L.M.: College of Veterinary Medicine, University of Georgia, Athens, Georgia 30602 (personal communication).

5. Petrov, A.M.: Importance de l'invasion intrautérine dans l'epizootologie de la toxocarose des renards noirs-argentés. Vestn Selkhoz Nauk Vet 3: 84-92, 1941.

6. Pong, S.S. and Wang, C.C.: Effect of avermectin B_{1a} on the release of γ-aminobutyrate from brain nerve endings in vitro. Fed. Proc. 38 (Part 1): 2425, 1979.

7. Rew, R.S.: Mode of action of common anthelmintics. J. Vet. Pharmacol. Ther. 1: 183-198, 1978.

8. Roberson, E.L.: Chemotherapy of Parasitic Diseases. In Veterinary Pharmacology and Therapeutics. 5th ed., N.H. Booth, L.E. McDonald, editors, Ames, Iowa State Univ. Press, p. 799-801, 1983.

9. Roberson, E.L. and Cornelius, L.M.: Gastrointestinal parasitism. In Current Veterinary Therapy VIII Small Animal Practice. R.W. Kirk, editor, Philadelphia, W.B. Saunders Co., p. 798, 1983.

10. Schantz, P.M. and Glickman, L.T.: Canine and human toxocariasis: The public health problem and the veterinarian's role in prevention. J.A.V.M.A. 175: 1270-1273, 1979.

11. Scothorn, M.W., Koutz, F.R. and Groves, H.F.: Prenatal Toxocara canis infection in pups. J.A.V.M.A. 146: 45-48, 1965.

Points raised during discussion

Question: Concerning the use of ivermectin in small animals?

Dr. Roberson: Merck has spent a lot of money investigating the use of ivermectin in small animals. They ran into problems with the polysorbate 80 which is the vehicle causing or perhaps exacerbating the reaction in Collie dogs. Some Collie dogs have been lost using it because veterinary practitioners have taken it upon themselves to use the Eqvalan product, available for horses, in dogs in an effort to clear them of microfilaria. The problems exists because of the difficulty in some cases of getting Diazon, the product that is normally used as microfilaricide, the alternative to which is an FDA unapproved levamisole. Practitioners are constantly searching for something to use as a microfilaricide and thus have used Eqvalan. Merck's position is now that they really have a lot of work to redo with different formulations of the product to finally make it available for use in dogs. I am amazed at the number of practitioners who call me wanting to know about using ivermectin in dogs. I discourage it because Merck does not yet have the background on any new formulations and the quantity that could be used as a microfilaricide which would be effective even as a preventative for heartworm if given on a monthly basis. Theoretically ivermectin should be effective against gastrointestinal parasites, hookworms, ascarids and whipworms, if one increases the dosage a little bit. At this point Merck says they have a lot to do with new formulations before it will be made available.

Question: What about hormonal influences affecting transuterine migration of larvae?

Dr. Roberson: We have considered this but have not gotten to the point of manipulating the hormones to look at this type of thing. There are perhaps so many factors involved that it is going to be difficult to piece them all together. I do not know that anyone is studying this yet, the idea is certainly meritorious. I do not know much about hormonal influences but for those larvae to begin almost at the 42nd day or immediately after the 42nd day it must be a very exact kind of triggering mechanism that is allowing those Toxocara canis larvae to then begin to move to the pups.

Dr. Paul: It has been suggested that prolactin may be involved in the process but that is only a guess and I am not even sure an educated guess. I do not know how that works out on timing.

Question: Concerning the use of benzimidazoles in dogs?

Dr. Roberson: Because of the effect of thiabendazole against Strongyloides of cattle or sheep, it was recognized that probably it would do the job in dogs and it does a reasonable job. Nevertheless, total clearance of a colony of animals infected does not seem to come about. A few veterinary practitioners have mentioned to me subsequently that using mebendazole may be equal or perhaps a little better than using thiabendazole. Actually I have had a number of practitioners say they did not quite get rid of the problem with mebendazole and have tried the fenbendazole product. Rather than just for a 3 day regimen they gave it for 5 consecutive days at the dosage I was talking about treating those pregnant bitches, namely 50 mg/kg/day. These people have had better success with that than they had using either of the previous two products. That is subjective though. It is easy to use mebendazole or fenbendazole which has just been made available for use in dogs and has been packaged for that purpose with a little dispenser.