

Can Encephalitozoon cuniculi, a protozoal parasite of the nervous system, be treated with pyrimethamine ?

Esther van Praag, Ph.D.

THE INFO PRESENTED HERE IS FOR EDUCATIONAL PURPOSES ONLY—NOT TO SUBSTITUTE FOR A VETERINARY CONSULTATION. PLEASE, SEEK ADVICE FROM A PROFESSIONAL PRACTITIONER BEFORE ADMINISTERING THE DRUGS LISTED IN THIS PAPER.

Various studies suggest that up to 80% of the healthy rabbit population carries the protozoa *Encephalitozoon cuniculi* in its body, without ever showing clinical symptoms of the disease and without development of the disease. Not much is known about the biology and the life cycle of *E. cuniculi* and its mode of transmission is not yet fully determined. The main path of transmission seems to be vertical: from mother to her litter, rather than horizontal: via infected droppings and urine. Possibly a rabbit may also be contaminated later in life from an infected companion or from contaminated dirt, although there are numerous examples where an *E. cuniculi* positive rabbit lived together with a *E. cuniculi* negative rabbit.

The parasite attacks the nervous system and major organs, causing a variety of symptoms including torticollis (commonly called head tilt or wry neck), liver failure, kidney failure, incontinence, phacoclastic uveitis, cataracts, fore- or hindquarter paresis (one, or both sides), nystagmus (eye twitching), and/or other neurological symptoms. Invariably the rabbit will die of meningo-encephalitis.

The presence of the Microsporidae parasites in mammals leads to a micronutrient/vitamin deficiency, which can result in anemia. Not specific information is available for *E. cuniculi*.

Regular treatment: Benzimidazoles

E. cuniculi is now routinely treated with benzimidazoles. While these drugs have been used successfully on many rabbits, they may cause mild to moderate elevation of liver enzymes.



The action of benzimidazoles is slow, and depends rather on their presence in the gastro-intestinal tract and the blood than on the concentration present. Benzimidazoles will bind to the tubulin of the parasite and block it. The assemblage of this dimeric tubulin protein form microtubules, that plays important functional and structural roles in the parasites (transport of nutritive molecules, cell division). Benzimidazoles will furthermore block a certain metabolism of parasites, such as the transport and uptake of glucose, without affecting the host (rabbit, cat, dog). The properties of the various benzimidazoles used in the treatment of *E. cuniculi* varies:

- Albendazole is known to be broken down in the liver into more hydrophilic products, which decreases its capacity to pass through the brain-blood barrier; the efficacy of the breakdown products against *E. cuniculi* is, however, not known. The use of albendazole, a drug not licensed for use in rabbits, has led to the acute death of healthy rabbits or the appearance of bone marrow failure, although this has not been clinically tested.

It was generally found that albendazole was less efficacious than oxibendazole

- Oxibendazole is a rather lipophilic molecule that is not degraded in the body. The advantages of oxibendazole are its passage through the blood-brain barrier into the brain or CNS (Central Nervous System), its lack of teratogen properties in rabbits, and its non-degradation in the liver, prior to passing in the body, unlike albendazole. It is, however, not yet known to what extent oxibendazole is efficacious against *E. cuniculi*, and what are the long-term side effects of this compound.
- Fenbendazole was studied for its preventive and curing properties in rabbits affected by *E. cuniculi* and the results have been reported in a scientific journal (Veterinary Record, 2001, pp.478-480). This was a major breakthrough, both because there was scientific data to support the findings and because this was the first treatment that was believed to cure (rather than simply control) the condition. It was furthermore shown that fenbendazole alone crosses the blood-brain barrier in mice. In rare cases, long-term intake of fenbendazole has been associated with the onset of bone marrow failure, digestive problems and anorexia, though this was not clinically investigated.

Lab rabbits have shown a high titer one year after being treated with fenbendazole and remaining clinically asymptomatic during that year. Those rabbits, that were euthanized a year after the fenbendazole treatment, still



presented the parasite in their brain. They were nevertheless totally asymptomatic.

REMARK:

Fenbendazole remains currently the drug of choice for the treatment of *E. cuniculi*.

Lately however, more and more rabbits treated with one or with several benzimidazoles compounds showed relapse during the treatment period or after the treatment was stopped. Recently, several caretakers who have been treating rabbits long-term with oxibendazole have reported that the treatment gradually stops working, as if the parasite is developing a resistance to it. Or could two different parasites infect the rabbit, like *E. cuniculi* and toxoplasmosis ?

Use of pyrimethamine ?

Based on scientific literature or a veterinary's experience, some alternative drugs are tried in "desperate cases", rabbits that faced euthanasia. The tried compounds include lufenuron, pyrimethamine (used to treat toxoplasmosis in rabbits) or ponazuril and have shown more or less successful.



H. McMurray

Sweetie, a 10 year old rabbit with high *E. cuniculi* titer, and first rabbit trying the pyrethamine protocol successfully.

A treatment protocol for *E. cuniculi* was developed based on treatment against *Sarcocystis* sp. or *Toxoplasma* spp. in horses and cats, respectively, using the anti-protozoal drug pyrimethamine (Daraprim), associated with trimethoprim-sulfa coupled with non-steroidal anti-inflammatory. The treatment is given during one month in horses and two weeks in cats. Side effects appear to be rare.

Although a previous study showed that pyrimethamine was ineffective against *E. cuniculi* at the studied



concentrations of 5 and 20 mg/ml, the 50 mg/ml showed a 35% growth inhibition. Recent preliminary in-vivo tests have, however, shown that the growth of *E. cuniculi* spores were stopped in presence of therapeutic concentration of pyrimethamine.

In rabbits, pyrimethamine has been used to treat toxoplasmosis, *Pneumocystis carinii*, hepatic coccidial infection, etc. It has been shown that use of pyrimethamine is safe in rabbits when used at the right dosage. The anti-protozoal drug will directly attack the parasite, where it will both block the metabolism of folic acid in the parasite and increase the activity of trimethoprim-sulfa against the parasite.

This treatment is based on a protocol used in cats, in order to treat toxoplasmosis:

- Folic acid: 3 to 5 mg given twice a week to daily,
- Pyrimethamine: 0.5 mg/kg twice a day,
- Sulfadiazine (long acting sulfa drug): 30 mg/kg twice a day.

REMARK:

The dosage of folic acid seems high, but is the one that corresponds that the treatment of toxoplasmosis in cats.

Folic acid could be replaced by thiamine. Folinic acid is best, but more expensive. The use of trimethoprim is contraindicated. Indeed, this sulfa antibiotic is thought to add to the toxicity of pyrimethamine.

Treatment is a minimum of a month. Since the combination pyrimethamine-sulfadiazine affects the function of the bone marrow, anemia and leucopenia (decrease of white blood cells) is observed. The effects are rarely severe; it is nevertheless advisable to closely monitor the rabbit and have a CBC done on a regular basis. The administration of folinic (folic) acid decreases the appearance of those side effects.

The rabbit must remain on both sulfa drug and pyrimethamine on a daily basis. Indeed, appearance of resistance *Sarcocystis* spp. to pyrimethamine has been observed, in the absence of the sulfa antibiotic.

The rabbits currently treated with those drugs are under the supervision of Mark Lennox, DVM and Joanne Hach, DVM.

Sweetie rabbit is around 10 years old, with a high *E. cuniculi* titer, and total paresis of its sole hind limb. He was lying in one place, most of the time, and depressed. After a few days, he suddenly attempted to move more, to stand up, though his sole limb has stiffened. He is certainly no more



depressed, showing much interest in his companion rabbit and life. The rabbit treated with those drugs has shown tremendous improvement in its quality of life and mobility.

The same positive effects were observed with Sidney, a 4.5 year old rabbit, with a high *E. cuniculi* titer, suffering from paralysis of the hind limbs. After 18 days of treatment, he is able to move around and attempted to jump in his litter-box via the high backside.



Sharon McGovern



Left: Sidney, suffering from a high positive *E. cuniculi* titer and paralysis of the lower limbs, is the second rabbit to start this protocol.

Right: After 18 days of the pyrimethamine treatment, Sidney attempts to jump over the backside of his litter-box.

Acknowledgement

Thanks are due to Heather McMurray (USA), and Sharon McGovern (USA) for sending pictures of their rabbits currently following this treatment, and their regular feedback, and to Sue Chang for trying this new treatment on their rabbits.

Many thanks also to P. Deplazes, (DVM, Switzerland) for taking the time to share his knowledge on *E. cuniculi*.

Thanks also to Sweetie, Sidney and his partner for being patient during the picture sessions.

Further information

1. Biderre C, Mathis A, Deplazes P, Weber R, Metenier G, Vivares CP. Molecular karyotype diversity in the microsporidian *Encephalitozoon cuniculi*. Parasitology. 1999; 118 (Pt 5):439-45.
2. Deplazes P, Mathis A, Baumgartner R, Tanner I, Weber R. Immunologic and molecular characteristics of Encephalitozoon-like microsporidia isolated from humans and rabbits indicate that *Encephalitozoon cuniculi* is a zoonotic parasite. Clin Infect Dis. 1996; 22(3):557-9.



3. Gomez-Bautista M, Rojo-Vazquez FA. Chemotherapy and chemoprophylaxis of hepatic coccidiosis with sulphadimethoxine and pyrimethamine. Res Vet Sci. 1986; 41(1):28-32.
4. Gray LC, Magdesian KG, Sturges BK, Madigan JE. Suspected protozoal myeloencephalitis in a two-month-old colt. Vet Rec. 2001; 149(9):269-73.
5. Lindsay DS, Dubey JP. Determination of the activity of pyrimethamine, trimethoprim, sulfonamides, and combinations of pyrimethamine and sulfonamides against *Sarcocystis neurona* in cell cultures. Vet Parasitol. 1999; 82(3):205-10.
6. Mrema JE, Rieckmann KH. A rabbit--in vitro system to evaluate drug action against *Plasmodium falciparum*. Trans R Soc Trop Med Hyg. 1983; 77(1):130-5.
7. Mathis A, Akerstedt J, Tharaldsen J, Odegaard O, Deplazes P. Isolates of *Encephalitozoon cuniculi* from farmed blue foxes (*Alopex lagopus*) from Norway differ from isolates from Swiss domestic rabbits (*Oryctolagus cuniculus*). Parasitol Res. 1996; 82(8):727-30.
8. Mathis A, Michel M, Kuster H, Muller C, Weber R, Deplazes P. Two *Encephalitozoon cuniculi* strains of human origin are infectious to rabbits. Parasitology. 1997; 114 (Pt 1):29-35.
9. Moore LA, Johnson PJ, Messer NT, Kline KL, Crump LM, Knibb JR. Management of headshaking in three horses by treatment for protozoal myeloencephalitis. Vet Rec. 1997; 141(11):264-7.
10. Peeters JE, Geeroms R, Halen P. Evolution of coccidial infection in commercial and domestic rabbits between 1982 and 1986. Vet Parasitol. 1988; 29(4):327-31.
11. Peeters JE, Geeroms R, Froyman R, Halen P. Coccidiosis in rabbits: a field study. Res Vet Sci. 1981; 30(3):328-34.
12. Suter C, Muller-Doblies UU, Hatt JM, Deplazes P. Prevention and treatment of *Encephalitozoon cuniculi* infection in rabbits with fenbendazole. Vet Rec. 2001; 148(15):478-80.
13. Sobottka I, Albrecht H, Visvesvara GS, Pieniazek NJ, Deplazes P, Schwartz DA, Laufs R, Elsner HA. Inter- and intra-species karyotype variations among microsporidia of the genus *Encephalitozoon* as determined by pulsed-field gel electrophoresis. Scand J Infect Dis. 1999; 31(6):555-8.
14. Thomas C, Finn M, Twigg L, Deplazes P, Thompson RC. Microsporidia (*Encephalitozoon cuniculi*) in wild rabbits in Australia. Aust Vet J. 1997; 75(11):808-10.
15. Tassignon MJ, Brihaye M, De Meuter F, Vercruyssen A, Van Hoof F, De Wilde F. Efficacy of treatments in experimental toxoplasmosis Bull Soc Belge Ophtalmol. 1989; 230:59-72. French.

The information on these pages may not be reproduced, or republished on another webpage, website, or elsewhere.

NOVEMBER 2003
Updated: Mai 2005

