Prevention of Equine Protozoal Myeloencephalitis*

By J. Lane Easter, DVM, DACVS, and Tad B. Coles, DVM

Veterinarians who routinely handle competition horses that are being trained for performance events may observe a higher-than-average incidence of equine protozoal myeloencephalitis (EPM), presumably because of the stress of training and the demands associated with having these horses work at higher levels of muscular challenge. Although the treatment of horses with EPM has improved over the years, controlling this disease will require better methods of prevention. This update describes an extralabel prophylactic regimen to consider.

EPM is a neurologic syndrome of horses usually caused by the parasite *Sarcocystis neurona*.[1] This syndrome, first recognized in the early 1960s, is one of the most important neurologic diseases in horses.[2] The definitive host of *S. neurona* is the opossum, and horses become infected by ingesting food or water contaminated with opossum feces. Therefore, the incidence of EPM should reflect the habitat range of the opossum.

The prevention of EPM can be frustrating because *Sarcocystis* sporocysts in opossum feces contaminate the environment, can survive for up to 1 year, are resistant to common disinfectants, and can be disseminated by birds that feed on insects or plant material in opossum feces. Although it makes sense to trap and remove opossums and to keep feed stored in opossum-proof containers, it is important to remember that the opossum is ubiquitous in many areas, even though it may not commonly be seen because of its nocturnal nature, and there is no practical way to prevent pastured horses from being exposed to opossum feces.

Based on studies conducted in the United States, 33% to 53% of horses tested seropositive for *S. neurona*, thereby indicating that exposure is high.[3] However, only a small percentage of horses develop clinical neurologic disease. For example, based on a survey conducted by the Department of Agriculture (USDA), only 14 cases of EPM were diagnosed per 10,000 horses (0.14%) in 1998.[4] Presumably, the development of clinical signs of EPM in horses exposed to *S. neurona* is related to the strain of parasite, infective dose, and immune status of each horse.[3]

During a 5-year period, veterinarians at Performance Equine Associates in Whitesboro, Texas, noticed a higher-than-expected incidence of clinical EPM in 2- to 3-year-old horses during competition training in cutting, reining, western pleasure, and other western performance events. For example, the incidence of EPM from 2001 to 2004 on one farm ranged from 10% to as high as 16%, or about 100 times the national average. Because of the high incidence of disease and the economic value of the individual horses, it became obvious that economic losses attributed to EPM in young training horses in this geographic area could be substantial. Therefore, an alternative approach to controlling the disease, based on the use of prophylactic drug therapy protocols used to prevent and control other parasitic diseases, was considered rather than using the available EPM vaccine, which contains killed organisms and can result in seroconversion that is indistinguishable from that occurring in horses exposed to the parasite.

The characteristics of an ideal pharmaceutical for prophylaxis of an infectious disease of this sort should include:

- Efficacy in preventing infection by the target biologic agent
- Safety measures for the patient
- Assurance that it is unlikely to induce resistance
- Ease of administration
- Low cost

Before 2001, a human-labeled antimalarial and antiprotozoal drug, pyrimethamine, was used with a sulfonamide drug for extralabel treatment of

*Funding for this study was provided by IDEXX Pharmaceuticals, Greensboro, N.C.

EPM, after which time ponazuril was approved for equine use. Both the pyrimethamine–sulfonamide combination and ponazuril are static rather than cidal in activity, however.[2,5] In addition, it takes several days of ponazuril treatment to achieve adequate levels of the drug in blood and spinal fluid.[6]

Nitazoxanide (NTZ) is the only approved antiprotozoal agent with cidal activity against *S. neurona*,[7] making it a logical choice for prophylactic use. When NTZ contacts protozoa, it kills the organisms rather than simply inhibiting replication. NTZ, a thiazolide antiparasitic agent with good in vitro activity against a variety of protozoa, is available as a 32% oral paste (Navigator, IDEXX Pharmaceuticals) labeled for the treatment of EPM caused by *S. neurona*. The approved dose regimen entails a 28-day course of treatment (25 mg/kg q24h PO for 5 days, then 50 mg/kg q24h PO for 23 days). NTZ also is approved in the United States for the treatment of adults and children with diarrhea induced by *Giardia* or *Cryptosporidium* organisms.[8,9]

NTZ treatment of equine protozoal myeloencephalitis appeared to be safe, efficacious, and cost-effective.

In plasma, NTZ is rapidly metabolized to tizoxanide, which appears to be the active metabolite in vivo. Its precise mechanism of action is unknown but is believed to be related to the inhibition of the pyruvate–ferredoxin oxidoreductase enzyme-dependent electron transfer reactions essential to anaerobic energy metabolism.

Because NTZ seemed to be the most promising drug to evaluate for prophylactic efficacy, a clinical study was conducted using the drug. The purpose of the study was to evaluate the efficacy of NTZ when used to prevent clinical EPM in a prophylactic protocol for young horses in training.

Clinical case study

All horses in this study were located on a farm where the incidence of clinical EPM in 2- to 3-year-old training horses had been monitored since 2000. Clinical EPM classification for the purpose of the study was reserved for horses with cerebrospinal fluid (CSF) antibodies to *S. neurona* and clinical neurologic disease that had responded to treatment with antiprotozoal drugs.

All horses in this report trained heavily for 10 months from approximately February 1 to the first week of December. None of the horses received an EPM vaccine before or during the study. Horses in the treatment group — monitored from 2005 to 2006 — were male or female, 3-year-old, 400- to 500-kg American quarter horses that had been serologically tested for equine infectious anemia (EIA; Texas Coggins Lab) every 6 months since they were approximately 1 year of age, and tested by Western blot analysis (Equine Biodiagnostics, IDEXX Laboratories) immediately before the start of the trial for evidence of previous exposure to *S. neurona*. During training, horses in the treatment group received NTZ at 25 mg/kg PO sid on the 2 days each week that they were not trained (i.e., Saturday and Sunday). Horses in the untreated group — monitored from 2000 to 2004 — had not been tested for *S. neurona* unless they had developed clinical signs of EPM.

Except for the NTZ prophylactic dose given to the treatment group and the drugs used to treat horses that developed clinical signs of EPM, no other antiprotozoal drugs were used in the study. All horses were subjected to a strenuous exercise program and were monitored closely for abnormalities, such as laminitis, lethargy, reduced appetite, and changes in fecal consistency. There were no obvious differences between the treated and untreated groups regarding opossum control measures or feed-handling methods.

The incidence of EPM in the 2005–2006 treatment group and the untreated 2000–2004 group were compared using the Fisher exact test.

Findings

The annual breakdown of EPM cases is summarized in Table 1 and collated in Table 2. The incidence of EPM cases in the treatment group was significantly different ($P < 0.05$) from the incidence of EPM cases in the untreated group.

All of the horses in the study were serologically negative for EIA as tested by agar-gel immunodiffusion (Coggins AGID, Texas Coggins Lab). Of the 43 horses in the treatment group, 31 had previous exposure to *S. neurona*, as evidenced by Western blot detection of IgG antibodies. None of the horses in the

table 1

Annual Breakdown of EPM Cases

Year	Training Horses	EPM Cases	Percentage of EPM Cases (%)
2000	30	3	10%
2001	30	3	10%
2002	30	3	10%
2003	26	4	15%
2004	31	5	16%
2005[a]	30	0	0%
2006[a]	13	0	0%

[a]Received prophylactic NTZ treatment.

table 2

EPM Incidence by Group

Group	Training Horses	EPM Cases	Percentage of EPM Cases (%)
Untreated	147	18	12%
Treated	43[a]	0[a]	0%

[a]EPM incidence between treated and untreated groups was significantly different at $P < 0.05$.

treatment group had clinical signs indicative of adverse drug experience during the treatment period.

Discussion

In this clinical study, twice-weekly prophylactic administration of NTZ in 2005 and 2006 may provide significant protection against the development of clinical EPM compared with the incidence of EPM on the same farm during the previous 5 years. The economic implications of the results are encouraging when considering the costs incurred in a training facility and the effects on horses with the disease versus the moderate costs of using NTZ in a prophylactic protocol (approximately $16/dose).

Implementing any treatment or prophylactic regimen requires evaluation of multiple risks and benefits. Many factors influence the risk for EPM. For example, young horses are at high risk for EPM, as are horses used in races and shows. In one study of EPM risk factors,[10] horses used for breeding had about one-fifth the risk of developing EPM than did horses used for racing. In addition, a strong relationship was identified between the development of EPM and various other stressful events, such as injury, parturition, and surgery.

Increased serum concentrations of cortisol, a commonly used marker of stress in the body, have been linked with the suppression of immune system function, especially cell-mediated immunity. Alterations in cell-mediated immunity may play a major role in the susceptibility of individuals to protozoal infections, as horses with EPM have depressed cell-mediated immunity. It is still unclear whether immune compromise plays a role in contraction of the disease, is a manifestation of the disease, or both.[3] Immunosuppression induced by dexamethasone can reduce the time from *S. neurona* sporocyst challenge to the appearance of CSF antibodies, suggesting that immunosuppression may facilitate central nervous system (CNS) invasion.[1] Horses with severe combined immune deficiency (SCID), an autosomal recessive genetic mutation, lack B and T cells, cannot synthesize immunoglobulin, and have severe thymic hypoplasia.[11] Prolonged parasitemia and persistent visceral infection can occur when horses with SCID are infected with *S. neurona* experimentally.[12]

Studies in the incidence of equine gastric ulcer syndrome indicated that stresses associated with training can have a profound effect on immune responses. Similarly, high-intensity exhaustive exercise has been shown to suppress the immune system of both horses and humans.[13,14] Thus, it is possible that high-intensity exercise required during training can adversely affect immune function, thereby increasing the susceptibility of young horses training in geographic areas with high exposure to *S. neurona* and to the development of clinical EPM. Data from the study presented here indicate that prophylactic administration of NTZ could help resolve the problem, although the drug is not completely innocuous.

The most common adverse events noted in NTZ studies conducted to receive US Food and Drug Administration (FDA) approval were fever, anorexia, and lethargy.[15] Although the clinical study presented here was not designed to evaluate potential side effects and adverse events, all of the horses in the treatment group remained in training for 10 months on the described NTZ dose regimen without any side effects being observed. These observations, combined with the results of studies conducted for FDA approval of NTZ as an EPM treatment, suggest that NTZ should be safe if routinely used as a prophylactic.

History has proven that parasitic resistance is an

inevitable consequence of treatment with antiparasitic drugs, but the rate of resistance development is affected by many factors. Logic infers that the development of drug resistance is more likely if drug-exposed organisms survive and are able to pass genetic material onto the next generation. It is commonly believed that the horse is an aberrant, dead-end host of *S. neurona*.[2] Thus, the development of resistance of *S. neurona* to NTZ, a cidal drug, is unlikely to result from its prophylactic use in horses.

Another drug purported to have potential as an EPM prophylactic agent is pyrantel tartrate (Strongid C, Pfizer Animal Health),[16] which was recently tested by sequentially increasing daily exposure to *S. neurona* sporocysts until seroconversion occurred.[17] In this study, seroconversion began after horses were administered the highest daily dose of 1,000 sporocysts for 21 days. Although prophylactic treatment with pyrantel tartrate did not alter the rate of seroconversion, the model used in the study holds some promise for evaluating potential EPM prophylactic agents.

In summary, prophylactic administration of 32% NTZ oral paste for 2 years in the clinical study presented here appeared to be safe, efficacious, and cost-effective in preventing clinical EPM in young horses during western performance training. However, many variables need to be addressed because no control group (i.e., untreated horses) was included in the study presented here and because the incidence of clinical EPM in the 2005–2006 treatment group was compared with that of the previous 5 years. Further evaluation needs to be conducted in a double-blinded, placebo-controlled study using either a *S. neurona* seroconversion-inducing model or an EPM disease-inducing challenge model. **vF**

Acknowledgment

The authors extend their appreciation to Randy C. Lynn, DVM, MS, DACVP, and Douglas I. Hepler, PhD, of IDEXX Pharmaceuticals for technical assistance with this study, John Brejda, PhD, of Alpha Statistical Consulting for statistical analysis of the data, and James N. Moore, DVM, PhD, department of large animal medicine at The University of Georgia College of Veterinary Medicine, Athens, for his editorial guidance in preparing this manuscript.

References

1. MacKay RJ, Granstrom DE, Saville WJ, Reed SM: Equine protozoal myeloencephalitis. *Vet Clin North Am Equine Pract* 2000; 16(3):405–425.
2. Grandstrom DE: *Understanding EPM—Equine Protozoal Myeloencephalitis.* Lexington, The Blood Horse, 1997.
3. Spencer JA, Ellison SE, Guarino AJ, Blagburn BL: Cell-mediated immune responses in horses with equine protozoal myeloencephalitis. *J Parasitol* 2004;90(2):428–430.
4. National Animal Health Monitoring System, 2001, Equine protozoal myeloencephalitis (EPM) in the US: USDA:APHIS:VS, CEAH, NAHMS. Available at: www.aphis.usda.gov/vs/ceah/ncahs/nahms/equine. Accessed Feb. 9, 2007.
5. Food and Drug Administration, 2001, Freedom of Information Summary for NADA 141-188 Marquis (15% w/w ponazuril) antiprotozoal oral paste. Available at: www.fda.gov/cvm/FOI/141-188.pdf. Accessed Feb. 9, 2007.
6. Schott H, 2002, Treatments for EPM: what's new for 2002? EPM Newsletter, March 2002, vol 4. East Lansing: EPM research group, department of large animal clinical sciences, Michigan State University College of Veterinary Medicine. Available at: www.cvm.msu.edu/news/press/EPM4-0302.pdf. Accessed Feb. 9, 2007.
7. Gargala G, Delaunay A, Pitel PH, et al: In vitro efficacy of nitazoxanide and its metabolites tizoxanide and tizoxanide glucuronide against *Sarcocystis neurona. Am Assoc Vet Parasitol:* 2001.
8. Fox LM, Saravolatz LD: Nitazoxanide: a new thiazolide antiparasitic agent. *Clin Infect Dis* 2005;40(8):1173–1180.
9. Romark Laboratories LC, 2005, Prescribing information alinia. Available at: www.romark.com/index.php/media_center/press_releases/35.html. Accessed July 25, 2006.
10. Saville WJ, Reed SM, Morley PS, et al: Analysis of risk factors for the development of equine protozoal myeloencephalitis in horses. *JAVMA* 2000;217(8):1174–1180.
11. Wiler R, Leber R, Moore BB, et al: Equine severe combined immunodeficiency: a defect in V(D)J recombination and DNA-dependent protein kinase activity. *Proc Natl Acad Sci* 1995;92 (25):11485–11489.
12. Sellon DC, Knowles DP, Greiner EC, et al: Infection of immunodeficient horses with *Sarcocystis neurona* does not result in neurologic disease. *Clin Diag Lab Immunol* 2004;11(6): 1134–1139.
13. Hines MT, Schott 2nd HC, Bayly WM, Leroux AJ: Exercise and immunity: a review with emphasis on the horse. *J Vet Intern Med* 1996;10(5):280–289.
14. Nieman DC: Exercise immunology: practical applications. *Intl J Sports Med* 1997;18(Suppl)1:S91–S100.
15. Food and Drug Administration, 2003, Freedom of Information Summary NADA 141-178 NAVIGATOR (32% nitazoxanide) antiprotozoal oral paste. Available at: www.fda.gov/cvm/FOI/foiabst2.html. Accessed Feb. 10, 2007.
16. Mansfield LS, 2002, Prevention of EPM. EPM Newsletter, March 2002 vol. 4: EPM research group, department of large animal clinical sciences, Michigan State University College of Veterinary Medicine. Available at: www.cvm.msu.edu/news/press/EPM4-0302.pdf. Accessed Feb. 9, 2007.
17. Rossano MG, Schott 3rd HC, Kaneene JB, et al: Effect of daily administration of pyrantel tartrate in preventing infection in horses experimentally challenged with *Sarcocystis neurona. Am J Vet Res* 2005;66(5):846–852.

Dr. Easter is co-owner of Performance Equine Associates, a full-service equine practice in Whitesboro, Texas, with six associate veterinarians. He specializes in lameness and orthopedic surgery of western performance horses. **Dr. Coles** is a medical writer and veterinary consultant headquartered in Overland Park, Kansas.