Acyclovir as Treatment for EHV-1 Myeloencephalopathy  

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Abstract

Acyclovir is a rational, affordable, and potentially useful directed therapy for equine herpesvirus type-1 (EHV-1) myeloencephalopathy.

1. Introduction

Several recent outbreaks of equine herpesvirus type-1 myeloencephalopathy (EHM) have raised awareness of the disease within the equine veterinary community and with the public at large. In the 1970s, equine viral rhinopneumonitis type 1 virus was isolated from spinal cord and brain of paretic horses with disseminated necrotizing myeloencephalitis. Necrotic arteriolitis, non suppurative necrotizing myeloencephalitis, and Gasserian ganglion neuritis were present [1-3]. EHM was initially thought to be an immune-mediated vasculitis, and some early descriptions of the disease suggested that it was mediated by antigen-antibody complex deposition and initiation of an Arthus Type III reaction, based on observation and identification of circulating immune complexes in horses with experimental EHM and initial reports of failure to identify equine herpesvirus type 1 (EHV-1) antigen in affected tissues using fluorescent antibody techniques [4-6]. It is now clear that the virus has a tropism for vascular endothelium and spreads to the endothelium of the central nervous system through circulating mononuclear cells. Viral antigen has been clearly demonstrated within the nucleus and cytoplasm of vascular endothelium and associated myocytes, and sometimes pericytes, of horses with EHM using indirect immunohistochemistry techniques [7,8]. Virus-induced endothelial cell death is followed by thrombosis [5,7-11]. Activation of endothelial and leukocyte adhesion molecules is a key step in transferring virus from infected leukocytes; it determines the restricted tissue tropism [12,13]. Latency occurs after EHV-1 infection in horses, and reactivation of the virus from CD5/CD8 cells has been observed with interleukin (IL)-2 and/or chorionic gonadotropin [14]. EHM clearly differs from herpesvirus-associated neurologic disorders in other species in that there is no clear evidence of direct neuronal invasion or damage caused by the virus itself in EHM. 

The treatment of EHM has been historically supportive [4,15]. Anti-inflammatory drugs, most notably corticosteroids (dexamethasone and prednisolone), have been advocated in the treatment of EHM, purportedly for treatment of immune-mediated vasculitis [11,16-19]. Because exogenous steroid administration has been shown to reactivate presumed latent infection in horses, use may be associated with some risk [20]. Additionally, corticosteroid use in horses has been associated with an increased risk of laminitis. However, judicious anti-inflammatory administration would seem to be reasonable in management of horses with EHV-1 myeloencephalitis. Two reports describing the use of acyclovir, an antiviral drug, in the management of EHM exist; however, no clear-cut benefit was established in those reports, and debate remains as to the efficacy of this therapy in the management of EHM [7,15,21].

We recently had the opportunity to determine blood concentrations of acyclovir in five horses receiving acyclovir associated with a large outbreak of EHM at a university owned riding and boarding facility. We hypothesized that acyclovir was present in the blood of these horses in measurable concentrations.

2. Material and Methods

Blood samples were obtained from five horses being treated with acyclovir for concurrent EHM. Horses had been treated for
3 - 4 days before blood sampling at a dose of 10 mg/kg orally five times daily. Blood was obtained at 30, 60, and 300 min post-acyclovir administration for acyclovir assay by high pressure liquid chromatography (HPLC) [a].

3. Results
Acyclovir was detected in all five treated horses. Median blood concentration at 30, 60, and 300 min post-administration was 0.287 µg/ml (range, 0.226 - 0.869 µg/ml), 0.204 µg/ml (range, 0.110 - 0.380 µg/ml), and 0.222 µg/ml (range, 0.070 - 0.386 µg/ml), respectively. All five horses were confirmed to have EHM, and all five horses survived.

4. Discussion
Acyclovir [9-(2-hydroxyethoxymethyl)guanine] is an acyclic nucleoside analog that has a high activity and selectivity for herpes viruses, particularly herpes simplex viruses types 1 and 2 and varicella zoster virus, described in 1982 [22]. Acyclovir's selectivity is because of the initial activation of the drug by phosphorylation by a herpesvirus-specified thymidine kinase. Acyclovir monophosphate is converted to a triphosphate that is a more potent inhibitor of herpesvirus DNA polymerases than of cellular DNA polymerases. The relationship between the amount of acyclovir triphosphate formed and its inhibition constant (Ki) for the particular viral or cellular DNA polymerase is predictive of the inhibitory activity of acyclovir on DNA replication [23]. Initial studies evaluating the efficacy of acyclovir against a broad variety of herpes viruses suggested efficacy against EHV-1 [24].

Acyclovir is reportedly able to inhibit replication of EHV-1 in vitro [b]. There are no controlled studies reporting on the efficacy of acyclovir in the treatment or prevention of EHM. However, animal model studies have demonstrated that EHV-1 is sensitive to inhibition by acyclovir in vivo. Acyclovir was effective at a dose of 100 mg/kg against equine herpesvirus type 1 infection in Syrian hamsters. The dose rate was sufficient to prevent any equine herpesvirus type 1 - induced mortality and inhibit viral multiplication, as judged by histopathological observations, clinical chemistry, and liver virus concentrations [25]. EHV-1 was sensitive to the nucleoside analogue penciclovir, a compound related to acyclovir, when tested in tissue culture; the ED50 was 1.6 µg/ml [26]. The results obtained with mice suggest that antiviral chemotherapy may be practical in the horse and that this possibility is worthy of further investigation in the natural host. EHV-1 was sensitive to BIOLF-62, viral median effective dose (ED50) concentrations of the drug being only 0.033 µg/ml. Such high antiviral potency and low cell toxicity indicate that BIOLF-62 might be useful in the treatment of infected animals [27].

Acyclovir is of potential interest to equine practitioners because it has come off patent and is potentially an affordable directed therapy for EHM. It is available in both oral and IV preparations. If the dose of 10 mg/kg, five times daily, is effective, estimated cost for oral therapy for a 450-kg horse is approximately $30.00 - $50.00/day. The IV formulation is more expensive. If used at 10 mg/kg IV, q 8 h, estimated costs would be approximately $300.00/day. The goal of treatment would be decreasing morbidity and mortality in affected horses, and total treatment cost may potentially be reduced by decreased losses and decreased requirements for intensive management of these cases. There are other potentially more efficacious antiviral medications, such as valacyclovir, that may become affordable for use in the horse in the future. Reported complications are minimal. Transient renal dysfunction has been reported following rapid IV administration in volume-depleted human patients [15].

5. Conclusions
EHM is a virus-induced central nervous system vascular necrosis with associated thrombosis, ischemia, and malacia. Prior therapy has been limited to supportive and anti-inflammatory treatments. Acyclovir is a potential, affordable, rational directed therapy for EHM.

Footnotes
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References

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