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A Pharmacokinetic and Pharmacodynamic Approach for Dosing Valacyclovir Against Equine Herpesvirus Type 1 Infections

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In veterinary medicine, vaccination is the most designated weapon in the battle against viral infections. Antiviral drugs are of interest in the inhibition of viral replication and clinical signs and are currently a topic of increased interest in veterinary medicine.

Equine herpesvirus 1 (EHV1) may result in several clinical syndromes in horses. The respiratory disease is usually silent (Foote et al., 2006), but a new sporadic form of EHV1 results in respiratory distress and possibly, death of the affected horses (Del Piero and Wilkins, 2001). EHV1 is also the most important cause of infectious abortion worldwide and infection late in gestation may result in neonatal foal disease. EHV1 also causes important emotional and economic losses due to nervous system disorders.

Acyclovir has already been used during outbreaks of nervous system disorders (Friday et al., 2000) and for the treatment of neonatal EHV1 infections (Murray et al., 1998). However, the therapeutic benefit is difficult to evaluate since no untreated control animals were included.

Most important for the use of antivirals in veterinary medicine is a thorough knowledge of the pathogenesis of the virus in the animal and of the pharmacokinetic and pharmacodynamic properties of the compounds. Before using acyclovir, or in extenso any antiviral for the treatment of EHV1 infections, one should make some considerations.

1. The efficacy of acyclovir against the virus should be demonstrated in vitro

There is a great variation among the several herpesviruses in their susceptibility to acyclovir. Feline herpesvirus 1 is susceptible to acyclovir; however, high concentrations are needed to reduce the numbers of plaques in vitro, resulting in high EC$_{50}$-values (50% effective concentration). In contrast, acyclovir has a good efficacy against suid herpesvirus 1 (Rollinson and White, 1983) and EHV1 (Rollinson and White, 1983; Garré et al., 2007a).
2. An appropriate dosage regimen should be designed
Dosages cannot be simply extrapolated from dosages recommended in human medicine. Therefore, the pharmacokinetics of acyclovir should be determined in horses. The pharmacokinetics after a single intravenous infusion and after single oral administration have been described by Wilkins et al. (2005), Bentz et al. (2006) and Garré et al. (2007b). Rapid infusions of acyclovir appear to be more commonly associated with development of adverse effects in humans, and apparently also in horses. Therefore, IV infusion of acyclovir to horses is restricted to veterinary clinics and has limited applicability at equestrian centres during an outbreak. Oral administration of acyclovir is associated with high variability in plasma concentration-time profiles and a very low bioavailability of about 7% (Bentz et al., 2006; Garré et al., 2007b). This excludes the therapeutic use of oral acyclovir in horses. Oral administration of the prodrug, valacyclovir, is associated with higher bioavailability (Garré et al., 2007b), resulting in higher plasma concentrations. By combining the concentration-time data after oral administration of valacyclovir and the in vitro EC\textsubscript{50}-values of EHV1, we designed a dosage schedule that makes it possible to obtain plasma concentrations above the EC\textsubscript{50}-value of EHV1 for the majority of the treatment period (Garré et al., 2009a).

3. The diffusion of the drug into relevant tissues should be studied
Before treating an animal with an antiviral, it should be investigated if the drug is able to reach the cells, tissues and/or organs where it has to exert its antiviral activity. In humans, it is described that acyclovir is able to diffuse into saliva, vaginal secretions and cerebrospinal fluid. Since we found a volume of distribution of acyclovir of 9.81 L/kg in the horse, it is likely that the drug reaches target cells and/or tissues (Garré et al., 2007b).

4. The toxicity of the drug should be evaluated before it is used in animals
Acyclovir has proven to be safe in humans during almost 30 years. It is not carcinogenic or teratogenic which is important for the use in pregnant mares. However, intravenous infusion of acyclovir is associated with renal impairment in humans when it is administered at high doses or as rapid infusion. At a dose of 10 mg/kg administered as a 1 hour infusion, no effect was seen on the renal function of horses (Garré et al., 2007b).

5. The efficacy of the drug should be evaluated in a controlled infection experiment
We investigated the therapeutic efficacy of valacyclovir against EHV1 in a controlled study with EHV1-negative ponies (Garré et al., 2009b). Although suffi-
cient plasma concentrations could be reached, clinical signs, viral shedding and viremia were similar in valacyclovir-treated and untreated ponies. The treatment was started 1 hour before inoculation. If the treatment would have been started 24 hours before inoculation, an effective concentration of acyclovir might be present in the nasal mucosa at the time of inoculation. This may result in an effect on viral replication in the upper respiratory tract and thus, nasal shedding, respiratory symptoms and the onset of viremia. This could imply that acyclovir only has an application as a prophylactic drug.

References