UNIVERSITY of GUELPH

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Centre for Public Health and Zoonoses

Use of acyclovir in raccoons for the treatment of canine distemper virus infection

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Background

Canine distemper is an endemic disease in Canada and frequently affects raccoons. Often, raccoons with clinical signs consistent with distemper are presented to rehabilitation centres and concern has been raised recently about use of the antiviral drug acyclovir for treatment of suspected distemper. This document aims to review the issues pertaining the potential efficacy of acyclovir (and antiviral therapy, in general) in raccoons, as well as potential concerns regarding the use of acyclovir in raccoons in rehabilitation facilities.

Acyclovir

Acyclovir is a nucleoside (purine) analogue antiviral drug that acts through inhibition of replication of viral DNA. In humans, its main use is to shorten the clinical course of herpesvirus infections, including herpes simplex viruses and varicella zoster virus. It also has moderate activity against Epstein-Barr virus (human herpesvirus 4), but has lesser activity against cytomegalovirus, despite it being another herpesvirus.[1] Therefore, it's spectrum of activity is largely confined to a subset of herpesviruses. It's impact on other viruses has been evaluated and activity is limited as to be functional, acyclovir must be phosphorylated to the active form, a process that is selectively catalyzed by cells expressing herpesvirus infection-associated thymidine kinases. It has poor oral bioavailability in humans (15-30%) but can be administered orally for some diseases. Otherwise, it is administered parenterally (by injection) or topically.

Acyclovir is uncommonly used in animals. It has been investigated for treatment of equine herpesvirus infections, but is rarely used because of lack of evidence of efficacy, poor oral bioavailability and availability of somewhat better antiviral options. A very weak study of dogs suggested some potential efficacy for prevention of canine parvovirus infection when used prophylactically,[2] but care must be taken when interpreting this study and no subsequent

data have emerged supporting potential effectiveness of this drug for this application.

Canine distemper virus

Canine distemper virus (CDV) is a highly transmissible virus that primarily infects canids and raccoons, but has fairly broad potential host range. It is a single stranded RNA virus from the Paramyxoviridae family, related to human measles virus. As an RNA virus, it is fundamentally different from the narrow range of DNA viruses that acyclovir targets.

Efficacy of acyclovir against canine distemper virus and related viruses

There is no evidence that replication of CDV is affected by acyclovir. As a drug that targets a limited range of DNA viruses, activity against an RNA virus would be unlikely. Measles is a closely related virus to CDV, so information about susceptibility (or lack thereof) of CDV to antivirals can be reasonable inferred from data about measles virus. Despite the severity of measles in humans and intensive investigation, to date, there is no antiviral therapy that has been shown to be effective against that virus. Ribavirin is an antiviral that has some promise for treatment of measles, based on in vitro susceptibility of the virus. However, clinical trials have not been performed to assess *in vivo* efficacy. This drug is completely unrelated to acyclovir. No other available antivirals have shown adequate promise for treatment of measles.

Safety

A variety of adverse reactions to acyclovir can occur in different animal species, including vomiting, nephrotoxicity, diarrhea, encephalopathy and low injection site reactions. The nephrotoxicity risk appears to be increased with rapid IV injection and suboptimal hydration. Injectable acyclovir has a high pH (~11) and should be administered by slow intravenous infusion. In humans, infusion over 1 hour is typically performed. Oral treatment has a lower apparent risk of adverse effects, likely because of lower oral bioavailability (and therefore lower systemic levels. However, toxicity can still occur following oral treatment.

Acyclovir in raccoons

No data are available about the pharmacokinetics or safety of acyclovir in raccoons. In humans and horses, oral bioavailability is poor and there is no information about oral bioavailability in raccoons; however, there is no reason to suspect that bioavailability would be better in raccoons.

Do antiviral drugs work against CDV?

There is no evidence of efficacy of acyclovir against CDV in raccoons or any other species. While there has been limited investigation, that is probably in large part because there is no reasonable expectation of efficacy based on the drug's spectrum of activity. Perhaps more important is the lack of any demonstrable efficacy against measles virus in humans, given the close relationship between measles virus and CDV. Despite the importance and potential severity of measles, there is no clear effective anti-viral treatment. Ribavirin is sometimes used for treatment of measles in people who are immunocompromised or who have severe disease, or for prophylaxis is high risk exposure situations.[3-5] Efficacy data are limited. Acyclovir is a widely available antiviral and if there was any evidence of efficacy against measles or related viruses like CDV, it would presumably be a commonly used treatment for measles.

There is preliminary information about a small number of antiviral drugs and CDV. Ribavirin can inhibit CDV *in vitro* and may have some promise as a therapeutic;[6-8] however, clinical data are lacking and this drug is likely cost prohibitive in animals. Favipiravir, a drug that targets some RNA viruses, has also been shown to inhibit CDV in vitro.[9] In vivo data are currently lacking. Neither drug is related to acyclovir.

What are potential concerns with treating raccoons with acyclovir?

Beyond the presumed futility of acyclovir for treatment of distemper, risks to raccoons are unclear. There are no studies that have evaluated proper dosing or safety in raccoons. While drug doses are often similar between different mammalian species and extrapolation can be reasonable, there are many exceptions where doses need to higher, lower or given at different intervals in different species. Toxicity risks can be particularly variable between species, and acyclovir is not recommended for use in cats because of the apparently increased risk of toxicity (renal, hepatic and bone marrow). Toxicity incidence, risk and avoidance have not been investigated in raccoons. In other species, nephrotoxicity and neurotoxicity are potential concerns. Nephrotoxicity may not be readily detected in raccoons if there is little to no monitoring (e.g. monitoring blood parameters or urine). Neurotoxicity could be misinterpreted as neurological consequences of CDV infection or rabies. The incidence and relevance of these issues is unknown.

What are other potential concerns?

Other concerns with treatment of raccoons with acyclovir are probably limited. Acyclovir accumulation in the environment could occur after release through excretion of the drug, mainly in feces. Given the likely short half-life in other species, this is probably of limited risk unless animals are released very soon after treatment (within a day). Even if there is acyclovir shedding in feces, the environmental risks are presumably negligible.

As a prey species, the potential impact on predators must also be considered. With a short half-life and poor bioavailability, drug levels in raccoons ingested by predators would be very low, even if the raccoon was treated shortly before release. This probably poses negligible risk.

Antiviral resistance has been minimally investigated compared to antibiotic resistance. Acyclovir resistance appears to be rare in humans but can occur. Risks posed by treated raccoons are negligible. For a risk to be present, resistance would have to develop during short term treatment and the virus would have to be transmitted to another host. Heavy use of acyclovir could theoretically lead to a risk of acyclovir resistance emergence in susceptible viruses in a rehabilitation facility. Given its limited activity against CDV, acyclovir resistance in CDV would be unlikely (since it is already essentially intrinsically resistant). Resistance could develop in susceptible DNA viruses that could be circulating in the raccoon population, but the likelihood of this is unclear and probably very low. Human health risks are likewise negligible. For a concern to be present, resistance would have to develop in a zoonotic pathogen in a raccoon, with subsequent transmission to a susceptible human, and, in a situation where acyclovir (or a related drug where cross-resistance might be an issue) is used to treat that disease in humans. There is no evidence of a zoonotic reservoir for herpes simplex virus and varicella zoster virus, the two main viruses that acyclovir is used to treat. However, applying the precautionary principle, the US National Wildlife Rehabilitators Association Veterinary Committee has recommended that oseltamivir (Tamiflu™) not be used in wildlife because of public health concerns associated with resistance. The issues with influenza and oseltamivir are somewhat different than acyclovir and distemper, but similar application of the precautionary principle in use of antivirals in wildlife is reasonable, as was done by the Canadian Wildlife Health Cooperative in their report *Disease risks associated with translocation of wildlife – information for veterinarians and wildlife rehabilitators in Ontario*. In that, they state "Anti-viral medication should not be used for the prevention or treatment of viral infections in wildlife patients due to public health risks associated with the development of drug resistance."

The costs of acyclovir treatment are also a concern in a rehabilitation context, in

which funds are typically limited and would be more reasonably spent on other aspects of care rather than a therapy that has no evidence of efficacy.

Development of treatment approaches for wildlife diseases

Treatment approaches and regimens for wildlife are often adapted from those for domestic animals. That is a reasonable approach in many circumstances, but differences in animal host biology and disease properties can limit the effectiveness of extrapolation of domestic animal data. Clinical observations can be useful for generating hypotheses and developing sound clinical studies, but do not replace such studies. Ideally, clinical observations form an evidence base that is scrutinized to assess whether a causal relationship is probable or plausible, with potential progression to proper design of experimental or field studies that consider animal health, animal welfare, public health and ecosystem health aspects in a broader risk assessment.

Ideally, controlled experimental or field studies are performed to evaluate specific treatments, treatment regimens and treatment conditions. Yet, limited research has been performed on distemper in raccoons, or more broadly, treatment of infectious diseases in wildlife in general. There are many reasons for this, including limited funding, logistical challenges, limited numbers of people with adequate expertise in the area and questions about the cost-benefit of treatment of various transmissible wildlife disease.

Anecdotes often form the basis of opinion in the absence of sound evidence. However, it is well established that anecdotes can be misleading. What a person perceives as an effective treatment may be the result of other unidentified factors, natural variation in disease, response despite (not because of) a provided treatment or unintentional (unconscious) bias. For these reasons, proper experimental design is required to assess treatments, to maximize identification of effects (good or bad) and maximize confidence in the data. Alongside that, there must also be consideration of animal welfare components when using untested treatments that might result in adverse events. For these reasons, evaluation of new treatments is best performed by (or in collaboration with) researchers with experience in disease and study design, with animal care approval and oversight, and in compliance with regulations including the Ontario Animals For Research Act.

Unstructured ‘research’ on canine distemper in raccoons based on anecdotal observations from uncontrolled study poses multiple risks, including adverse drug reactions in treated raccoons, maintaining infected animals in a facility that might pose a risk of infection to other animals in the facility and release of animals that may still be shedding

infectious virus (and therefore act as a reservoir of infection for other animals). Canine distemper virus shedding and disease patterns are not well described in raccoons. In dogs, infected animals can shed the virus for prolonged periods of time (e.g. weeks), posing a risk to others during this period. Further, dogs with acute distemper can apparently recover but then later develop sequelae such as neurological disease. Releasing raccoons that may subsequently develop complications, particularly neurological disease, raises animal welfare concerns, can also complicate rabies surveillance, which is a significant public health concern.

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