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Synthesis of Phosphorimidate Derivatives of Acyclovir with Antiviral Activity *in Vitro*

Payal M Oak*

Department of Pharmacology, Gourishankar Institute of Pharmaceutical Education and Research, Maharashtra, India

***Corresponding author:** Payal M Oak, Department of Pharmacology, Gourishankar Institute of Pharmaceutical Education and Research, Maharashtra, India, E-mail: payaloak@yahoo.com

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Description

Canine parvovirus is a very transmissible, severe and often deadly infectious disease of dogs caused by Type II Canine Parvo Virus (CPV-2). According to a recent report, acyclovir has been effective candidate against parvovirus infection, however, a continuous spread of CPV-2 infections is observed, even in shelters where an appropriate vaccination program is applied, and this is a reason to provide antiviral drug therapy. The aim of the present study was to the development of antiviral drugs with the determination of the effect of concentration of new chemical entities and analyzes acyclovir analogous against CPV-2 strains. A sensitive *in vitro* assay capable of measuring the infectivity of CPV-2 was employed to determine the efficacy of different concentrations of 9-(2-hydroxyethomethyl) guanine phosphor mono morpholidate. We successfully show that new compound inhibits CPV-2 replication by exhibiting 50% inhibitory concentrations in the low micro molar range.

Canine Parvo Virosis (CPV-2) is a very spreadable, severe and frequently mortal infectious disease that occurs in both domestic and wild dogs. CPV-2, the etiological agent of canine parvovirosis, goes to the parvoviridae family and parvovirinae subfamily and it is included in carnivore protoparvovirus species together with raccon sparvovirus, feline parvovirus and minkenteritis virus. CPV-2 is a small around 25 nm diameter, non-enveloped virus composed of three major proteins surrounding a single-stranded linear DNA genome. Usually, CPV-2 infects 2 weeks-12 weeks mature pups, particularly during the failure of Maternally Derived Antibodies (MDA). Commonly, adults are resistant to CPV-2 infection due to reduced vulnerability or presence of immunity encouraged either by vaccination or previous infections. The transmission route is or nasal through direct or indirect contact with the feces of infected dogs or contaminated fomites indirect contact is facilitated by the environmental resistance of the virus. Diagnosis is conducted by real-time PCR and NGS nowadays *via* detection of the CPV-2 DNA in feces of infected pups. The virus is inactivated 60 seconds at 100°C while resists up to 7 hours at 80°C and 72 hours at 56°C, in addition, CPV-2 resists for 14 days-21 days at 37°C and sometimes 6 months at room temperature. A recent report shows that CPV-2 is resistant to most disinfectants while is sensitive to oxidizing agents, formalin, hydroxylamine, halogens, β-propiolactone. Along with above compounds Acyclovir is showing effect against CPV in the infection in puppies. Acyclovir is guanine analog frequently used antiviral chemotherapy of low cytotoxicity and mainly used for treatment of Herpes Simplex Virus (HSV) infection. The purposes of this study were to record the therapeutically evaluation of an acyclovir as a prophylactic pharmacological agent for canine parvovirus. The aim of the present study was to determine the effect acyclovir analogous with different concentrations and time frame against several CPV-2 strains *in vitro*.

Study of Dulbecco's Modified Eagle's

ACV was obtained as a gift sample from Merck, India. A72 adherent canine tumor cell line was obtained from American type culture collection. A72 cells were maintained in high glucose dulbecco's modified eagle's medium supplemented by 10% fetal calf serum (and 1% L-Glutamine, 1% Penicillin-Streptomycin (Sigma Aldrich)). A72 cell line was incubated in humidified atmosphere with 5% CO_2. CPV-2 strain was used in the study, strain. The viruses were spread on A-72 cells to obtain stock viruses for the subsequent experiments. Each stock virus was titrated on A-72 cells. Briefly, after an incubation period of 48 hours, the infected cells were fixed with cold acetone and tested using CPV-2-specific canine antibodies and rabbit anti-dog IgG conjugated with fluorescein isothiocyanate (SigmaAldrich). Viral titer, determined on A-72 cells, was tissue culture infectious doses TCID for strain. Phosphorus oxychloride was added to a suspension of ACV in triethylphosphate precooled. The mixture was kept for 4 hours. Then, it was treated with the amidating agent and N-di-isopropylethylamine in 1% aqueous dioxane. The reaction was maintained for 2 hours, neutralized by a saturated to solution pre-cooled, and extracted with ether. The aqueous extract was applied onto a DEAE-Toyopearl column and eluted with a linear gradient. The target fraction was concentrated by evaporation under vacuum; the residue was diluted with water, re-evaporated and additionally chromatographed on RP-18 column and eluted with a linear gradient of acetonitrile. The fraction containing the target product was freeze-dried from water. It was diluted with sterile distilled water to the final concentration.

Cellular Thymidine Kinase of Antiviral Drugs

The advance of antiviral drugs is still in its beginning with rapid changes and progressive milestones come across almost daily. The last 30 years have been the most dynamic in the history of viral infections and their management. Unfortunately, antiviral drugs have been active for only a few groups of viruses up until now. Maximum antiviral drugs do not provide a cure, but rather allow control of the contamination. However, the limitations of chemotherapy, with the high costs of drugs, make the need for anticipation even more urgent. Concerning the effect of acyclovir on treatment of CPV2 in experimentally diseased puppies. It was successes in preventing of CPV2 replication in puppies and virus recovering, which revealed absences of viral particles in fecal swabs, leukopenia, lymphopenia and hypoproteinemia in compared to second group and this supported by Piret, who mentioned that the acyclovir diverges from earlier nucleoside analogs in covering only a partial nucleoside structure, the sugar ring is replaced with an open-chain structure. It is selectively converted into 9-(2-hydroxyethomethyl) guanine phosphor (mono) morpholidate which is far more effective in phosphorylation than cellular thymidine kinase. Subsequently, the monophosphate form is

further phosphorylated into the active triphosphate form, 9-(2-hydroxyethomethyl guanine phosphor mono morpholidate, by cellular kinases. Chain termination resulting and assimilate with viral DNA. It has also been shown that viral enzymes cannot remove 9-(2-hydroxyethomethyl) guanine phosphoro mono morpholidate from the chain, which results in inhibition of further activity of DNA polymerase. Detectable antiviral effect against canine virus and it was valuable to reduce the severity of CPV-2.

To assess the toxic effect of the substance on the cell lines used, the MTS solution was used. Using this tetrazolium salt, the metabolic activity could be measured by measuring the absorption at 490 and thus the vitality of the cells was concluded. For this test, A-72 cells were seeded in a 96 well "plate with culture medium and the substances to be tested in the final concentrations in triplets on the cells. The substances dissolved in DMSO were diluted in the cell culture medium from the stock solutions. The same volume of DMSO was used as the control. The cells were cultured for four days with the substances in the incubator at 5% CO_2. After four days, of MTS solution per well were added to the cells and the cells were incubated with the MTS solution for 2 hours in the incubator. Subsequently, the absorbance at 490 nm was measured.