International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Canine Distemper and Circumstantial Unconventional Use of Anti-Viral Drug, Favipiravir; An Attempt to Avert Euthanasia

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Abstract: ***Canine distemper affects several terrestrial and marine mammalian genera in different families but till date no specific anti-viral line of treatment has been acknowledged in routine protocol by veterinary fraternity. With consistent genetic evolution, changing scenario of infectious diseases and reports of vaccine failure, amendments are required in the system of dealing with such diseases which may possibly extend into human as host. This account mentions circumstantial administration of anti-viral drug, favipiravir to canine distemper afflicted pup in an attempt of rescue over euthanasia.***

Keywords: Canine distemper, Evolution, Virulence, Euthanasia aversion, Anti-viral remedy, Survival

1.The Virus and its attributes

Canine distemper virus is a large single stranded, negative sense RNA virus in genus *Morbillivirus* of family Paramyxoviridae. The genome consists of six structural genes coding for- a single envelop associated protein [Matrix, M], two glycoproteins (Haemagglutinin (H), Fusion (F) proteins), two transcriptase associated proteins- Phosphoprotein (P), Large protein (L); Nucleocapsid protein (N) and two non-structural genes for V protein which has a role in virulence of virus and C protein which is critical in viral RNA synthesis (Röthlisberger et al., 2010; Siering et al., 2021; da Costa et al., 2021).

H and F proteins have lead role in the process of host recognition, infection and disease advancement. The hemagglutinin protein (H) presents a decisive role in the antigenic recognition and the viral interaction with signaling lymphocyte activation molecule (SLAM) and nectin-4 molecule which are the host cell receptors present on T and B lymphocytes, specific dendritic cells and macrophages (Seki et al., 2003; Pratakpiriya et al., 2017; Sawatsky et al., 2018; Rendon-Marin et al., 2019). Nectin-4 is an epithelial cell receptor for canine distemper virus, present on organs of host and is also involved in the neuro-virulence (Pratakpiriya et al., 2012). Since the H protein initiates infection, the host may be protected from the canine distemper virus by eliciting a strong immune response against H protein (Wang et al., 2014; Bhatt et al., 2019). The H protein of canine distemper virus induces cytotoxic T lymphocyte (CTL) antiviral activity in animals and is a crucial candidate for developing effective vaccines (Rendon-Marin et al., 2019). If the decisive act of recognition and attachment by H protein succeeds, the F protein of canine distemper virus facilitates membrane fusion and entry of viral genome into host cell (Plattet et al., 2005).

Seven diverse lineages of canine distemper are documented globally so far; based on sequence analysis of the H gene; they are Asia-1, Asia-2, America-1, America-2, Arctic-like, European wildlife and Europe. Further lineages including African and South American strains have been suggested, and identification of even more lineages is possible. It is also mentioned by the analysts that the traditional vaccine strains of canine distemper virus- Snyder Hill, Onderstepoort and Lederle are comprised in the America-1 lineage (MacLachlan and Dubovi, 2016).

2.Propagation and manifestation

Canine distemper virus is highly contagious; transmitted through aerosol and contact with body fluids of diseased animal. Virus enters new host through nasal-oral route; initially proliferates in tonsils and lymph nodes in vicinity and, spreads systemically through lymph resulting in immunosuppression (Sawatsky et al., 2018). Clinically or sub-clinically infected animals may also shed virus for several months (Willi et al., 2015; Lanszki et al., 2021). A weak immune response results in symptoms like listlessness, appetite loss, fever. Symptoms aggravate with further advancement of disease and demonstrate mucopurulent ocular and nasal discharge, cough, laboured breathing, vomit and diarrhea which may turn into hemorrhagic form. Neurological symptoms may occur concurrently or may follow the other symptoms. Nervine symptoms may begin with spasms (mild twitching along the temple and jaw line), chorea and may extend to convulsions when the disease progresses in the central nervous system resulting in complications such as demylenating encephalitis (Vandevelde and Zurbriggen, 2005; Pan et al., 2013; Klemens et al., 2019). An immune-compromised host may develop secondary bacterial lung infection and other systemic complications as well (Headley et al., 1999; Rendon-Marin, 2019).

3.Expanding host range and vaccine efficacy

Wide host range of canine distemper virus has been reported including several families of mammals; from domestic dogs to primates and further extending to marine

mammals (Beineke et al., 2015; Stokholm et al., 2021). With evolution, expanding host range and genetic proximity of canine distemper virus with measles virus, the possibility of human enlisting as a host cannot be ruled out (Tatsuo et al., 2001; Wang et al., 2012; Otsuki et al., 2013; Rendon-Marin et al., 2019; Uhl et al., 2019). Vaccine failure has also been reported in case studies of canine distemper (Galán et al., 2014). A highly virulent canine distemper virus strain was isolated from vaccinated mink in China (Liu et al., 2021). Diversity, evolution through high mutation rates and genetic recombination in the viral genome have put efficacy of vaccines in suspicion (Shi et al., 2021). Researchers suggest that recombination might also occur between vaccine and field (pathogenic) strains of the virus, signifying that vaccination for canine distemper might play a role in influencing virus evolution (da Fontoura et al., 2016). Onderstepoort, Lederle and Rockborn are vaccine strains of canine distemper virus reported to be approved for use in India (CDSCO, 2018). Despite reports of vaccine failure, vaccination remains the foremost method of restricting spread of disease. But regular monitoring for vaccine breach; molecular scrutiny and investigations into developing safer and more competent vaccines must continue across the globe (Demeter et al., 2010; Dong et al., 2015; Anis et al., 2018).

4.Management of canine distemper

1. **Prophylaxis**-Vaccination of healthy owned, semi-domiciliated, stray and wild animals under government policies is one method of reducing risk of canine distemper.
2. **Supportive/ symptomatic treatment of diseased animal**-As far as analyzed from available literature including case reports (Tariq et al., 2013; Xue et al., 2019; Creevy, 2020) and discussions with veterinarians, no direct anti-viral therapy was used in routine protocol to control canine distemper and the same condition persists in present times. Supportive therapy is generally administered which includes intravenous fluids, vitamins, anti-bacterial drugs to avoid secondary infections, anti-convulsant and anti-pyretic agents based on the symptoms. In some papers (Rodeheffer et al., 2007; Bonning, 2020), it has been reported that high dose of retinol (vitamin A) causes hindrance in proliferation of canine distemper virus and aids in sustaining vital metabolic functions for survival of host. Yao (2010) also mentioned the importance of retinol in canine distemper in animal as well as measles in human.
3. **Homeopathic supplementation/ alternate therapies**-Homeopathic *Distemperinum* nosodes (Jervis, 1929; Cooney, 2017) and other homeopathic dilutions such as *Conium maculatum* (Naveenkumar et al., 2019) are suggested to boost immunity and to control symptoms. More data on natural methods is available in public domain.
4. **Immunoglobulin administration**-Zhang et al. (2021) used donkey-derived anti-canine distemper virus-IgG, as a passive immunotherapy agent and concluded that it effectively increased survival rates of the experimental canine distemper virus-infected dogs. Presently, purified hyper-immune immunoglobulin (IgY) against canine distemper is commercially available to ensure passive immunization of dogs, for therapeutic and prophylactic use (Canglob D Forte, DYNTEC, Czech Republic).
5. **Euthanasia on poor prognosis**-Under incidents of severe symptoms when supportive therapy fails, the veterinarians usually suggest euthanasia (Galán et al., 2014).
6. **Use of anti-viral drugs**-Difficult availability, high cost, apprehensions of ill effects, technical and official hurdles have distanced the practitioners from prescribing specific anti-viral drugs over generalized supportive therapy despite certain researches showing effectiveness of anti-viral drugs against canine distemper in *in-vitro* experiments. Two of the anti-viral agents are discussed here; (a) Ribavirin and (b) Favipiravir.

Ribavirin-Ribavirin is a 1-ribosyltriazole that is the 1-ribofuranosyl derivative of 1, 2, 4-triazole-3-carboxamide. A synthetic guanosine analogue; that is an inhibitor of viral RNA-dependent RNA polymerase and possesses a broad spectrum of activity against DNA and RNA viruses [Ribavirin, NCBI, 2022]. It is ineffective against major viral encephalitis because of its failure to cross the blood-brain barrier. Researchers mention that its penetration into central nervous system may be increased by use of carrier molecules such as alpha-cyclodextrin (Jeulin et al., 2009). Similarly, ribavirin triacetate, a lipophilic derivative of ribavirin was reported to be more effective in protecting animals from encephalitis and that ribavirin concentration in brain was higher when administered as aerosol rather than through other routes (Gilbert et al., 1991). Ribavirin has been used to treat canine distemper in dogs, with nervine symptoms, under clinical conditions but with partial success, signifying that treatment in early stages would be more efficacious (Viana and Teixeira, 2015). In another case, ribavirin has also been used in combination with routine supportive treatment to treat canine distemper under clinical trials with hopeful results (Değirmençay, 2017).

Favipiravir- Favipiravir is a pyrazine-carboxamide derivative; favipiravir is converted to the ribofuranosyl-triphosphate derivative by host enzymes and selectively inhibits the viral RNA-dependent RNA polymerase thus presenting activity against RNA viruses [Favipiravir, NCBI, 2022]. Favipiravir has been tested under *in vitro* condition against canine distemper virus with optimistic results. Researchers reported that when favipiravir was given at fixed time intervals after virus infection in Vero cells and DH82 cells, it showed efficacious antiviral action (Zhu et al., 2018; Xue et al., 2019; Ibrahim and Al-Garawi, 2021). Favipiravir has been studied in terms of COVID-19 pandemic as it was one of the important therapeutic agents in the pandemic duration (Richardson et al., 2020). It was readily available during this period to treat corona virus afflicted patients (Mukherjee, 2021) but there is insufficient literature in public domain regarding its application in canine distemper.

5.Circumstantial evidence of antiviral drug efficacy in canine distemper (*in vivo*)

The city of Jabalpur (M. P., India) has dense dog population (Sharma, 2022). Sporadic cases of canine distemper were recorded in the period of year 2017 to 2018 under research project (SERB/YSS/2015/000800) of first author at Jabalpur city and suburb but in the period December 2021 to April 2022, it was observed that canine distemper was widespread in Jabalpur city. Several pups and young dogs died of this disease alone in the city.

The disease first affected stray dogs and further crept into semi-domiciliated and owned dogs of indigenous and exotic breeds. In most cases diagnosis was based on observation of symptoms rather than Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) test or serological tests; owing to expenses and limited resources. Nasal discharge, cough, conjunctivitis were often marked as the initial symptoms; pneumonia, diarrhoea, nervine symptoms developed later. In some cases, nervine symptoms developed first while gastro-enteric and pulmonary symptoms appeared later depending on the progression of disease.

Under prevailing circumstances, euthanasia was usually advised by practitioners in cases with advancing symptoms. Keeping in view, the poor prognosis and result in such cases where pups are destined to succumb to the disease, an alternate approach was adopted. And, an antiviral drug was attempted in order to give a canine distemper afflicted pup an opportunity to combat for life.

At the crucial time of need, the locally available antiviral agent, favipiravir (Fabiflu, Glenmark company) was administered to a female pariah pup aged *ca.* eight to ten weeks, weighing *ca*. two kilograms, exhibiting symptoms of conjunctivitis with oculo-nasal discharge, dyspnea, haemorrhagic gastro-enteritis, myoclonus twitching of jaw and temple, enamel hypoplasia, anorexia, fever, crying, crusted nasal dermis and foot pads, with course of time.

The symptoms satisfactorily indicated canine distemper. Favipiravir was administered at initial dose of 40 mg/ kg/ *bid*, on day 1, reduced to 20 mg/ kg/ *bid* for day 2 to day 10. On assessing good prognosis; and apparently no serious adverse effects, the drug was administered for further five days at 20 mg/ kg/ *od*. The conventional supportive therapy was also given in parallel but caution was taken not to administer any immunosuppressant agents. All symptoms resolved except nervine symptoms. After seven months of this treatment, the animal is continuing a regular active life with adaptable nervine impairment.

On the basis of this circumstantial evidence, a detailed study under standard protocols is yet to be initiated, possibly, at the hospital of second author.

6.Discussion

The discretion to attempt favipiravir was based on the fact that it has been used safely in paediatric human patients (Gulhan and Ozkaya-Parlakay, 2020; Ozsurekci et al., 2021). The dose was also determined with reference to paediatric case report for 47-day-old newborn human patient with severe viral pneumonia (Moolasart et al., 2020). Favipiravir deliberation results, toxicity and lethal dose datasheet have also been referred to. It is pertinent to mention that dog was one of the experimental models in favipiravir toxicity test (Favipiravir, PMDA, 2014). Also on comparing developmental stages of dog and human, it is noted that physiology of dog develops faster than human and dog has a competent physiological stress recovery system (Lensen et al., 2019; Wang et al., 2020).

In an effort to avert euthanasia, a deviation from usual course of action was deliberated at the crucial phase of disease. Enough literature was not available for dose calibration but evidences here suggest that favipiravir proved effective in containing multiplication of distemper virus in the body. But, due to poor penetration across the blood brain barrier (Virojanapirom et al., 2016; Yamada et al., 2019; Richardson et al, 2020), its effect on viruses present in central nervous system could not be anticipated. Rather, there was no improvement seen in the nervine symptoms but the impairment paused after an initial phase of deterioration in this case. Thus, efforts of conventional or un-conventional treatments should be made in the initial stages of infection for hopeful prognosis. Late observations and late decisions may fail any life-saving attempt.

While the antiviral agent hinders viral replication, the immune system takes this opportunity to raise immune response against the already present viral antigens in the body. Favipiravir cannot be used as a prophylactic agent. Also, it is necessary to uphold that the drug does not destroy the virus it only deters replication of virus (Furuta et al., 2017). Thus administering favipiravir or any other viro-static drug is useful only after infection is accomplished and immune system is sensitized (Krumm et al., 2014; MacKenzie, 2014). Favipiravir is effective in containing viral multiplication even at the stage of viremia involving multiple organs; but, hindrance in crossing blood brain barrier at therapeutic doses is a major obstacle in treating viral proliferation in central nervous system (Richardson et al, 2020).

7.Conclusion

Canine distemper represents a '*tug of war'* between the virus and the host immune system. An anti-viral agent gives an advantage to the host immune system in this struggle by hindering multiplication of the virus. Therefore, it is suggested that weightage be given to timely assessment and use of appropriate antiviral agents over euthanasia; as per prevailing conditions in cases of canine distemper. Also, that the virus is steadily evolving, extending its host range and presenting challenge to available vaccines hence indicating towards need of novel strategies to restrict this disease.

Supplementary Data

Videos of the Canine distemper survivor pup are available at Harvard Dataverse-

Sharma, Poornima, 2022, "Seoni-Asian pariah pup that survived canine distemper",

https://doi.org/10.7910/DVN/DX9USH, Harvard Dataverse, V1

Author Contributions

First Author: Review and circumstantial attempt of remedy.

Second Author: Preliminary diagnostic analysis.

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