Review

Summary of Drugs for Canine Parvovirus

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Article

Summary of Drugs for Canine Parvovirus

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Simple Summary: Infection of parvovirus in dogs is becoming more common, high morbidity and mortality are increasing, and due to the high cost of treatment, most families will choose to forgo treatment, leaving dogs dying in great pain. There is no specific drug that makes infection with this virus an incurable disease and a cancer in dogs. The purpose of this review is to alleviate the pain of some dogs, reduce symptoms such as pain and diarrhea, and hope to provide the necessary value for the development of new drugs.

Abstract: Canine parvovirus (CPV) infection is a widespread ailment among young dogs globally, characterized by high morbidity, mortality, and significant infectivity. Due to its grim prognosis, it is often likened to canine "cancer" with a medium-term mortality rate of 46.43% and late-stage mortality reaching up to 100%.Current treatment modalities primarily encompass fluid therapy, antiemetics, antimicrobial medications, pain relievers, and enteral nutrition. However, the absence of specific internationally recognized medications necessitates substantial care expenses. This review aims to elucidate recent advancements in pharmacological interventions for mitigating CPV infection symptoms, underscoring the potential of novel pharmaceutical technologies in veterinary medicine to enhance clinical outcomes for afflicted animals and their caregivers，lay a theoretical foundation for the development of specific drugs.

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Introduction

Dogs are assuming an increasingly pivotal role in human society, propelled by rapid economic development and their unique ability to instill a sense of responsibility through caregiving needs and companionship. This review explores the significance of dogs in modern society and delves into the molecular intricacies of Parvovirus. Derived from the Latin "parvo" meaning small, represent a capsid-free, single-stranded DNA virus comprising 5,000 nucleotides(Cotmore & Tattersall, 1984; Shade, Blundell, Cotmore, Tattersall, & Astell, 1986; Wu & Rossmann, 1993).Canine myocarditis and enteritis are brought on by the canine parvovirus (CPV). Since it is not a local infection, the afflicted animal's organs are affected in multiple ways. Even if they survive, survivors may get other dangerous diseases like gastroenteritis(Kilian et al., 2018).In the Parvoviridae family, a wide array of viruses exists, including notable examples such as the feline panleukopenia virus, parvovirusine, Aleutian mink virus, and porcine parvovirus. These viruses, each with distinct characteristics and effects, contribute to the diversity within the Parvoviridae family(Bloom, Kanno, Mori, & Wolfinbarger, 1994; Molitor TW, 1990a, 1990b; Parrish, 1995) .The virus commonly infects infants, young children, and fetuses(Brown, Mori, Cohen, & Field, 1991) .The single-stranded DNA (ssDNA) virus B19V belongs to the genus Parvovirus B19, within the family Erythrovirus, Parvoviridae, and Parvovirinae(Gigi & Anumba, 2021; Landry, 2016; Rogo, Mokhtari-Azad, Kabir, & Rezaei, 2014).

Until now, only primary cells derived from human bone marrow, fetal liver, peripheral blood, and umbilical cord blood have demonstrated the ability to support B19 replication in vitro(Ozawa, Kurtzman, & Young, 1986, 1987; Schwarz et al., 1992; A. Srivastava et al., 1990; A. Srivastava & Lu, 1988; C. H. Srivastava, Zhou, Munshi, & Srivastava, 1992; Yaegashi et al., 1989).Blood products, including pooled factor VIII and factor IX concentrates, can also serve as a transmission

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route for parvovirus B19(Azzi, Morfini, & Mannucci, 1999).Parvovirus B19 infection is associated with several conditions, including encephalopathy, epilepsy, meningitis, myocarditis, dilated cardiomyopathy, and autoimmune hepatitis.(Heegaard & Brown, 2002)Despite years of study, the validation of virus-host interactions remains incomplete, and numerous new observations continue to raise additional challenges, necessitating the application of advanced technologies(Goodwin, McPherson, & McCombie, 2016).CPV enteritis is reported to exhibit higher prevalence rates among English Springer Spaniels, American Pit Bull Terriers, and German Shepherds(Glickman, Domanski, Patronek, & Visintainer, 1985).

CPV is an acute intestinal disease primarily affecting dogs, caused by canine parvovirus, typically manifesting in puppies aged between 6 weeks to 6 months, characterized by severe symptoms and high mortality rates. Adult dogs are less frequently affected(Qi, Zhao, Guo, & Sun, 2020).Microviruses primarily target intestinal epithelial cells and cardiomyocytes, resulting in a clinical phenotype primarily characterized by enteritis and myocarditis. Common symptoms include lethargy, loss of appetite, vomiting, and diarrhea. Diarrhea may manifest as soft, mucus-laden, liquid, or even hemorrhagic(Goddard & Leisewitz, 2010).

Various diagnostic tests have been developed to detect microbial infections, including traditional methods, immunological methods, and molecular methods(Tuteja, Banu, & Mondal, 2022).The most commonly utilized test is RT-PCR (real-time polymerase chain reaction), employing the TaqMan method for detecting CPV-2 DNA in specimens. This technique ensures rapid and definitive identification of the virus, facilitated by the application of the small groove-binding agent (MGB) probe technique(Decaro et al., 2005; Nandi & Kumar, 2010).

CPV was first reported as a viral diarrhea pathogen in dogs in the United States and other countries in 1978. Since its appearance in 1978, it has been considered an important pathogen both domestically and in the wild and has spread throughout the world. Asia, Australia, New Zealand, America, and Europe have all reported on it. In dogs, CPV-2 is the cause of both myocarditis and acute hemorrhagic stroke(Tuteja et al., 2022).The introduction of various CPV strains over time, such as CPV-2a, CPV-2b, and CPV-2c, coupled with infections affecting both domestic and wild canines, has significantly complicated the disease landscape(Nandi & Kumar, 2010).

In developed nations, CPV has been extensively researched and well-documented, with China notably contributing to the body of knowledge on the disease. These nations have accumulated considerable experience and established robust operational systems, offering valuable insights for countries like ours to leverage in understanding global trends and research advancements. Presently, there exists no specific medication for CPV globally, and clinical symptom management remains the primary approach. However, treating CPV poses challenges due to the canine digestive system's variability in gastric pH and extensive surface area of the small intestine, both influencing drug efficacy. Furthermore, factors such as breed, sex, age, and diet can impact physiological responses, necessitating consideration of multiple variables in drug development(Song, Peressin, Wong, Page, & Garg, 2016; Wu & Rossmann, 1993).

The following is a summary of the clinical symptoms targeted by various types of drugs, aimed at providing supportive evidence for CPV drug development.

1. Antiemetic

Canine parvovirus (CPV) infection can trigger vomiting, potentially disrupting electrolyte and acid-base balance to the extent of causing severe dehydration or even coma. Continuous vomiting necessitates the avoidance of food and drink abstention, with anti-emetics serving as a viable option for relief. Studies indicate the efficacy of chlorpromazine and metoclopramide (Gastrodia) in alleviating vomiting symptoms(Yalcin & Keser, 2017).Chlorpromazine belongs to the class of thiazide antipsychotics, acting by blocking dopamine D2 receptors to alleviate symptoms and improve overall conditions in patients with psychosis. Additionally, it binds to dopamine receptors, providing an antiemetic effect on the vomiting center and reducing nausea and vomiting. Similarly, metoclopramide exerts its antiemetic effect through dopamine blockade. Ondansetron, a highly

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potent and selective 5-HT3 receptor antagonist, offers robust analgesic effects. Other drugs utilized for similar purposes include scopolamine and domperidone. See Table 1 for details.

Table 1. Antiemetic choices and some adverse reactions for CPV.

Classificatin	**Mechanism**	**Representative drugs (Time on market)**	**Adverse reaction**
5-HT3 receptor antagonist	Selective blockade of central and peripheral 5-HT3 receptors	Ondansetron (1986) Gransetron (1991)	Headache
Gastrointestinal motility drugs	Blocking central and peripheral dopamine D2 receptors	Metoclopramide(1985) Domperidone(1985)	Breast pain
Antacid	InhibitsH+,K+-ATPase activity and inhibits the terminal link in gastric acid production	Omeprazole(1988) Cimetidine(1994)	Abdominal pain. Constipation.Headache
Glucocorticoid	Inhibits capillary dilation, reduces exudation and oedema	Dexamethasone(1995) Prednisone(1995)	Metabolic disorder. Weight gain
NK-1 receptor antagonist	Inhibition of substance P(chromophobic vagus nerve, solitary bundle nucleus,CTZ)	Arepitant (2013) Rolapitan (2015)	Indigestion. Diarrhea
Anticholinergic drugs	Reduces vagal excitability and relieves gastrointestinal spasm to prevent vomiting	Benadry (1982) Scopolamine (1979)	Thirsty.Constipation
Butyrylbenzenes	Inhibits the central CTZ, producing a strong anti-emetic effect	Haloperidol (1967) Droperidol(1986)	Generating dependence
Antihistamines	Inhibition of the vomiting centre.	Promethazine (1985) Chlorpheniramine (1982)	Diarrhoea.Pain in the muscles

The table includes the classification, mechanism, representative drugs, adverse reactions of Antiemetics.

2. Fluid Therapy - Establishing Vascular Access

Vomiting can lead to electrolyte imbalances and dehydration, which can be identified by changes in the dog's behavior, such as lethargy and rapid breathing, or by monitoring their weight.

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Restoring electrolyte and fluid balance is a crucial aspect of dehydration treatment. Infected dogs should receive treatment with broad-spectrum antibiotics, including options such as ampicillin, chloramphenicol, erythromycin, gentamicin, among others(Mazzaferro, 2020). Symptomatic treatment involving steroids, broad-spectrum antibiotics, and fluid and electrolyte therapy can be life-saving for animals affected by CPV. Immediate initiation of fluid therapy upon identification of symptoms is crucial for maintaining hydration and combating the virus. The placement of a jugular vein catheter not only provides intravenous access but also facilitates blood sampling for glucose, acid-base, and electrolyte monitoring without the need for repeated catheterization. Regular monitoring of blood pressure, acid-base balance, and the dog's mood is essential during intravenous fluid administration. Strict aseptic techniques must be employed during intravenous infusion to prevent cross-infection. In cases where serum glucose levels drop below 60 mg/dl, intravenous glucose supplementation is recommended, followed by the addition of 2.5% to 5% glucose to crystalloids(Venn, Preisner, Boscan, Twedt, & Sullivan, 2017).While some studies suggest that oral rehydration fluids can offer supportive treatment, it's important to note that they should never substitute intravenous therapy, especially in cases of severe blood loss or hypovolemia. Intravenous fluid administration remains paramount in such critical conditions to ensure rapid recovery and stabilization of the animal's condition(Mazzaferro, 2020).

Crystalloid solutions play a vital role in restoring electrolyte and acid-base balance in patients with CPV enteritis. While acid-base levels typically remain within normal ranges for most patients, the extent of hydrochloric acid loss may vary(Yalcin & Keser, 2017).

3. Antibacterial Drugs

Patients afflicted with CPV enteritis face an elevated risk of bacterial infection attributed to compromised intestinal villi and immune system impairment.(Miranda & Thompson, 2016b) The most common is E. coli - an important component of the normal intestinal flora, non-pathogenic, gram-negative (G-) bacteria, but in some cases causing disease. They are classified according to their biological characteristics as enteropathogenic E. coli, enterotoxigenic E. coli, intestinal erosive E. coli, intestinal hemorrhagic E. coli, intestinal adherent E. coli and diffuse adherent E. coli. Infection with E. coli causes symptoms of diarrhoea and extra-intestinal infections. Once infected with the bacteria, antibiotics should be used symptomatically(Schirò et al., 2022). The administration of antibiotics in puppies with CPV enteritis may disrupt cell development by interfering with other essential chemicals. Additionally, these puppies often harbor pathogens, including gastrointestinal parasites. Therefore, considering this, antiparasitic therapy should be initiated as soon as the patient demonstrates tolerance to oral treatment(Pereira et al., 2018).

4. Pain Medication

Due to the parvovirus there can be abdominal pain, stomach pains and general muscle aches and pains. Painkillers are great for relieving this pain and making it less painful. There are five categories of painkillers: the first drug is non-steroidal anti-inflammatory， such as aspirin and ibuprofen; the second are central painkillers, with tramadol being representative, and morphine; the third are narcotic painkillers, with opioids such as dulcolax being very effective, which can be addictive and should therefore be used with caution; the fourth are antispasmodic painkillers, for the treatment of gastrointestinal and smooth muscle pain, with atropine and scopolamine being typical drugs The fifth group is the anti-anxiety analgesics, represented by Valium. See Table 2 for details. Lidocaine is known to promote gastrointestinal motility and possesses analgesic properties. In addition to its central antiemetic effects, maropitant offers visceral analgesia in puppies affected by CPV enteritis. However, it's important to note that alpha-2 agonists can induce excessive vasoconstriction, thereby restricting gastric emptying(Nandi & Kumar, 2010).

Table 2. Anodyne choices for CPV.

Classification	Mechanism	Representative drugs	Adverse reaction

 doi:10.20944/preprints202408.1506.v1

		(Time on market)	
Nonsteroidal Antiinflammatory Drugs	Inhibition of prostaglandin synthesis	Aspirin.(1989)	Gastrointestinal reactions
Central analgesic	Inhibition of central opioid receptors	Tramadol(1977)	Sweating and nausea
Narcosis analgesic	Pain relief through anaesthesia of the pain centre	Morphine(1941)	Development of drug resistance
Antispasmodic analgesic	Relieves smooth muscle spasm of the gastrointestinal tract	Nifedipine.(1981)	Transient low blood pressure in the morning
Painkiller narcotic	Eliminates neurotransmission in the body and is able to inhibit the nervous system	Diazapam(1963)	Drowsiness

The table includes the classification, mechanism, representative drugs, adverse reaction of painkillers.

5. Outpatient

Patients diagnosed with CPV face a challenging prognosis, often leading to fatal outcomes if not promptly and aggressively treated. Surveys indicate that the cost of CPV treatment is prohibitively high, exceeding the financial means of the average family. Consequently, many families may opt to forgo treatment altogether or initially seek care at general outpatient clinics before ultimately discontinuing treatment due to financial constraints. However, outpatient treatment options can provide rapid relief from the disease, with healthcare professionals offering regular monitoring to prevent deterioration of the patient's condition(Cotmore & Tattersall, 1984).Upon confirmation of microbial infection during outpatient treatment, the primary approach involves intravenous cauterization and fluid therapy until symptom alleviation, with glucose infusions administered in cases of hypoglycemia. Following the restoration of intravascular volume and perfusion, affected puppies typically receive a single dose of cephalexin (8 mg/kg subcutaneously), maropitant (1 mg/kg subcutaneously every 24 hours), buprenorphine (0.02 mg/kg), and high fructose corn syru(Mazzaferro, 2020).

6. Antidiarrheal Drugs

SC-27166 represents the culmination of ongoing research endeavors aimed at identifying selective and orally active antidiarrheal agents. Comparative studies revealed that, at equivalent doses, SC-27166 exhibited significantly lower suppression of abstinence-induced jumping compared to both loperamide and diphenoxylate. Furthermore, SC-27166 demonstrated no discernible anticholinergic effects(Dajani et al., 1977).A new approach to the treatment of diarrhea. Further studies have demonstrated that racecadotril does not promote bacterial overgrowth in the small intestine(Schwartz, 2000).

7. Antiviral Therapy

Although vaccination is effective in preventing CPV, the antiviral drugs are still required since antigenic variation and maternal immunity may lead to CPV vaccination failure, with the widespread use of inactivated or live-attenuated vaccines. Oseltamivir phosphate is a drug precursor for the active metabolites of oseltamivir, its active metabolite (oseltamivir carboxylate) is a specific influenza virus neuraminidase inhibitor. It has been shown that oseltamivir as an antiviral is effective in

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reducing the bacterial increase in the gut, and reducing the symptoms of leukopenia , but the side effects are yet to be studied , the drug can be used in Europe and Australia, but is not approved in the United States(Savigny & Macintire, 2010) .Several studies have provided evidence of the efficacy of recombinant feline interferon inhibitor in the treatment of CPV in cats. Approved as a therapeutic agent for canine parvovirus infection in Japan in 1997,it functions by binding to interferon receptors located on the surface of canine cells, thereby eliciting antiviral and immune responses(Minagawa, Ishiwata, & Kajimoto, 1999) . A study has demonstrated the effective antiviral activity of Nitazoxanide, Closantel Sodium, and Closantel in the treatment of CPV by PCR and indirect immunofluorescence assay (IFA) (Zhou et al., 2019) .Serum has also been shown to be effective as an antiviral treatment for CPV, and the administration of serum-derived transfer factor (TF) to puppies with CPV has been shown to reduce group mortality, although it does not directly kill microviruses(Willeford, Shapiro-Dunlap, & Willeford, 2017).

8. Hemostatics

Hematochezia is also characteristic of CPV.Prescription 1: aminotoluenic acid injection, 2~10mL, intravenously; Prescription 2: phenylethylamine injection, 2~4mL times, intramuscular injection; Prescription3: VK1 injection, 10-30mg/time, intramuscular injection;Prescription 4: Anluo Blood injection, 1~2mL times, intramuscular injection.For pets with severe bleeding symptoms for a long time, anti-fibrinolytic drugs such as amino-toluenic acid can be used to accelerate the blood coagulation process to achieve the purpose of rapid hemostasis(Cotmore & Tattersall, 1984).

9. Other Drugs

Experimental studies have also shown that ORF (oral recuperation fluid) conditioner promotes gastrointestinal health during the recovery phase from microvirus infections. Moreover, it aids in the provision of enteral nutrition without inducing malnutrition during the course of the disease.(Tenne et al., 2016)In puppies under six months of age with canine parvovirus enteritis (CPE), administration of 0.5 mg/day over a five-day period has been shown to reduce clinical signs, improve survival rates, and modulate inflammatory cell parameters(Muñoz et al., 2021) .As a common terminus of the activation pathway initiated by erythropoietin (Epo), pimozide inhibits STAT5 phosphorylation, thereby suppressing B19V replication(Ganaie et al., 2017).Studies have indicated the antioxidant properties of N-acetylcysteine (NAC) in dogs afflicted with canine parvovirus (CPV) infection. NAC treatment has been shown to gradually ameliorate leukocyte, neutrophil, monocyte, and eosinophil counts in CPV-infected dogs. Moreover, NAC administration significantly elevates glutathione S-transferase (GST) activity while concurrently reducing nitrite + nitrate (NOx) and malondialdehyde (MDA) concentrations in mildly infected dogs compared to those receiving supportive therapy(Gaykwad, Garkhal, Chethan, Nandi, & De, 2018).

10. Canine Parvovirus Vaccination-Prevent Effectively.

The most effective strategy for preventing the spread of canine parvovirus (CPV) in dogs is vaccination. Modified live virus (MLV) vaccines are commonly used to prevent CPV infection by eliciting robust antibody- and cell-mediated immune responses. This vaccination approach confers strong and long-lasting immunity against subsequent CPV challenges(Day, Horzinek, & Schultz, 2007).But there are also many reasons for vaccination failure(Altman, Kelman, & Ward, 2017).The new vaccines are mainly genetic engineering vaccines (DNA vaccine, genetically modified crops vaccine), nucleic acid vaccine (RNA vaccine and DNA vaccine), virus subunit vaccine, the cIL-2 and cIL-7 genes also showed the significant synergic effects on enhancing the immunogenecity of CPV VP2 DNA vaccine(Chen et al., 2012).A recent study showed that most dogs will become infected with field strains of CPV-2 shortly before or after vaccination(Decaro et al., 2007).Dogs may develop certain diseases following vaccination,(Miranda & Thompson, 2016a) so at the moment we are far from disease eradication, it is a long way to research.

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Discussion

In conclusion, dogs serve as loyal companions to humans, yet canine infection with canine parvovirus (CPV) presents a complex and challenging condition. Once contracted, CPV infection progresses rapidly, often culminating in death In recent years, researches on CPV drugs have revealed that treatment for this disease is symptomatic and there is no specific drug available, but previous articles and experiments have given us good insights and are worthy of further investigation. The development of sensitive, specific and easy-to-use diagnostic methods or assays will remain an important area of research in the future. In addition, there is a need to assess the ability of existing vaccines to protect against mutant strains and, on this basis, to clarify the need to develop vaccines against new antigenic types and to explore the possibility of new genetically engineered vaccines to prevent the disease. In terms of mechanistic studies, the pathogenicity of the mutant strains and the risk of cross-host transmission still need to be further evaluated. To achieve a comprehensive understanding of the pathogenicity of viruses, it is imperative to identify their cellular interacting partners and characterize their interactions with all viral components, including packaged genomes(Kailasan, Agbandje-McKenna, & Parrish, 2015).

There is also the issue of the price of CPV treatment, and businesses should reduce the price of treatment appropriately to maximize the survival rate of CPV dogs. The high price may mean that things are more expensive than they are, and ultimately, the development of potent drugs should be a priority. The average cost was €68,942 per B19V infection prevented, €294,470 per case prevented and €3,096,102 per fatal case. With a low negative cost estimate, the risk of low B19V in blood donors is 0.005% per year. In comparison, the rate of parvovirus infection in seronegative pregnant women in the Netherlands is 2.4% per year(van Hoeven, Janssen, Lieshout-Krikke, & Molenaar-de Backer, 2019).

There are many ways to prevent such diseases at all times while controlling them. Prompt symptom treatment by a veterinarian, restoration of fluids and antibiotics to prevent bacterial infection will improve the survival rate of infected puppies, but vaccination should be considered the best way to control the disease in dogs(Mazzaferro, 2020).As the economy expands and the population of dog owners grows, there is a significant increase in the prevalence and mortality of CPV, causing unprecedented harm to dog enthusiasts. There is a need for improvement in existing vaccines, further exploration of vaccine development, as well as education for dog owners on CPV. Most importantly, there is an urgent need for the development of new and effective drugs.

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