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VIEWPOINT

Pharmaceutical care recommendations for antiviral treatments in children with coronavirus disease 2019

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Up to now, no antiviral therapeutic regimens with exact efficacy are recommended to be used in children with coronavirus disease 2019 (COVID-19). *Interim Guidance for Diagnosis and Treatment (the sixth edition) of COVID-19* [1] only provided potential antiviral treatments in adults. According to the current guidelines for management in adults and children and available resources in antiviral drugs, we herein discussed the pharmaceutical care of the five antiviral treatments (IFN-α, lopinavir/ritonavir, ribavirin, chloroquine diphosphate and arbidol) in children with COVID-19 (Table 1).

IFN-α

IFN-α is a broad-spectrum antiviral drug, which could inhibit the synthesis of viral RNA and inhibit viral replication and spread. IFN-α, combined with ribavirin, which could reduce viral replication, moderated the host response and improved clinical outcome in MERS-CoV infected rhesus macaques [2]. In China, IFN-α is available in injections, sprays, gels, etc. IFN-α nebulization or spray are commonly used in children for treating bronchiolitis [3, 4], herpes angina [5, 6], hand-foot-mouth disease [7, 8], etc. In the experts' consensus statements, it could be also used for treatment of COVID-19 in children [9], IFN-α is the only antiviral drug which is clearly recommended to be used in children with COVID-19.

IFN-α nebulization can be given at a dosage of 200,000–400,000 IU/kg or 2–4 μg/kg (in 2 mL sterile water) two times daily for 5–7 days. IFN-α2b spray can be used for high-risk populations who have a close history of contact with suspected infected patients or those with only upper respiratory tract symptoms in the early phase. One to two sprays can be used on each nostril, and 8–10 sprays on the oropharynx. The dose of IFN-α2b injection is 8000 IU, once every 1–2 h, 8–10 sprays/day for 5–7 days. Intramuscular injection of high-dose IFN-α (> 2 μg/kg/time) could cause myelosuppression in children [10]. Overdose of IFN-α also could cause liver enzyme abnormalities, renal failure, bleeding, etc. It should be cautious while prescribing for children.

IFN-α is contraindicated in patients with abnormal liver function. In children with creatinine clearance (CrCl) below 50 mL/min, IFN-α is prohibited. IFN-α is also contraindicated in children with histories of mental illness, severe or unstable heart disease, or aplastic anemia. IFN-α nebulization should be used with caution in neonates and infants younger than 2 months [10]. Adverse reactions of IFN-α mainly include low-grade fever and flu-like symptoms (both in children with intramuscularly injection) [11]. Growth and development inhibition is more common when combining IFN-α with ribavirin. Suicidal ideation is more common in children (mainly adolescents) compared with adults (2.4% vs. 1%) [12]. To our knowledge, IFN-α has few drug interactions. However, IFN-α should be used with caution while combining with sleeping pills and sedatives.

Lopinavir/ritonavir (LPVr)

LPVr is mainly used for treating HIV. Based on the clinical experiences in treating SARS [13] and MERS [14], LPVr is proposed to treat COVID-19. LPVr is available in oral tablets and solutions. LPVr oral solution is more suitable for children with a body surface area less than 0.6 m^2 or those who are unable to swallow tablets. LPVr oral solution contains approximately 42% (v/v) ethanol and 15% (w/v) propylene glycol, which is not recommended in premature infants within 42 weeks and neonates within 14 days based

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Table 1 Dosage regimen and precaution of antiviral drugs in children

Drugs	Age available	Dosage regimen of COVID-19 in children	Precaution/contraindication
IFN-α	Nebulization: using with caution in neonates and infants younger than 2 months	Nebulization: 200,000–400,000 IU/kg or 2–4 μg/kg in 2 mL sterile water, twice daily for 5–7 days Spray: 1–2 sprays on each nostril and 8–10 sprays on the oropharynx, once every 1–2 h, 8–10 sprays/day for 5–7 days	Contraindication: CrCl < 50 mL/min; histories of mental illness, severe or unstable heart disease, or aplastic anemia
LPVr	China: OS ≥ 6 months, T ≥ 2 years USA: OS ≥ 14 days, T ≥ 6 months	Body weight (kg) 7–15: 12 mg/3 mg/kg/time, twice daily for 1–2 weeks 15–40: 10 mg/2.5 mg/kg/time, twice daily for 1–2 weeks > 40: 400 mg/100 mg/time, twice daily for 1–2 weeks	Contraindication: patients with severe hepatic insufficiency Not be recommended: children with jaundice
Ribavirin	China: oral dosage forms ≥ 6 years USA and Europe: oral dosage forms ≥ 3 years	Intravenous infusion at a dose of 10 mg/kg every time (maximum 500 mg every time), 2–3 times daily	Not be recommended: CrCl < 50 mL/min Should be discontinued: SCr > 2 mg/dL Warning: hemolytic anemia
CD	Using with caution	No recommendation	Acute poisoning is usually fatal with a dose of 50 mg/kg
Arbidol	≥ 2 years for influenza in Russia	No recommendation	Using with caution in patients with liver dysfunction

IFN-α interferon-α, *LPVr* lopinavir/ritonavir, *CD* chloroquine diphosphate, *COVID-19* coronavirus disease 2019, *CrCl* creatinine clearance, *SCr* serum creatinine, *OS* oral solutions, *T* tablets

on drug instructions in the USA [15]. In China, LPVr oral solution is suitable for children aged 6 months or older [16]. Differences in age limitation maybe due to different excipients and the manufacture process used. The dosage regimen of LPVr was recommended as follows [17]: LPVr tablets (200 mg/50 mg): 12 mg/3 mg/kg every time for the children with 7–15 kg body weight (BW); for those with BW of 15–40 kg, 10 mg/2.5 mg/kg every time; for those with BW of 40 kg or more, 400 mg/100 mg can be administrated every time. LPVr tablets are administered twice daily for 1–2 weeks.

Lopinavir (LPV) is mainly metabolized by the liver, so LPVr should be used with caution in patients with mild to moderate hepatic insufficiency, and contraindicated in patients with severe hepatic insufficiency. In addition, LPVr could cause increased PR interval, second- or third-degree cardiac block [18]. LPVr should be used with caution in children with congenital QT interval extension syndrome or hypokalemia. The most common adverse reactions of LPVr include diarrhea (adults 19.5%; children 12%), vomiting (adults 6.8%; children 21%), rash (adults 5%; children 12%), etc. [19]. Children are more likely to present with adverse reactions such as rash and vomiting, these symptoms should be closely monitored in children. For LPVr, lopinavir is a substrate of CYP3A enzyme, and ritonavir is a strong inhibitor of CYP3A enzyme. LPVr should be cautiously used while combining with drugs metabolized by CYP3A enzyme or drugs affecting CYP3A enzyme activity. For children with jaundice, LPVr may increase free bilirubin and exacerbate jaundice. Therefore, LPVr should not be used in children with jaundice.

Ribavirin

Ribavirin is a broad-spectrum antiviral drug, which has inhibitory effects on RNA viruses and DNA viruses. Different dosage forms and age restrictions of ribavirin can be seen in China and other countries. In China, ribavirin is available in injections, oral dosage forms (capsules, granules, tablets), aerosols, etc. Clinical trials for oral dosage forms have not been carried out in children under 6 years in China, so oral ribavirin is not recommended to be used in children younger than 6 years in China. Ribavirin is available in oral dosage forms in USA and European countries and inhalation in USA. In these countries, the oral dosage forms are only recommended to be used in children aged 3 years or older. Intravenous infusion of ribavirin injections at a dose of 10 mg/kg every time (maximum 500 mg every time), 2–3 times daily was recommended for children with COVID-19 [17].

Ribavirin should be used with caution in patients with abnormal liver function. In patients with creatinine clearance (CrCl) below 50 mL/min, ribavirin is not recommended. In patients with serum creatinine (SCr) higher than 2 mg/dL, ribavirin should be discontinued. The most common adverse reactions of ribavirin in children include fever (80%), headache (62%), neutropenia (33%), fatigue (30%), etc. [20].

Ribavirin should be noted to enter red blood cells and can be largely accumulated, which could lead to hemolytic anemia [21, 22]. Large doses of ribavirin could cause decreased hemoglobin and serious heart damage. Children with heart diseases should be suggested to avoid using ribavirin. If necessary, ribavirin should not be given at a high dose and the hemoglobin and hematocrit should be closely monitored.

Chloroquine diphosphate (CD)

CD is an optimized drug based on the structure from a classic antimalarial drug named quinine which is mainly used for malaria, parenteral amoebiasis, etc. CD has shown apparent efficacy in treating COVID-19 in adult clinical trials [23]. CD is available in oral tablets and injections. CD tablets were recommended for oral administration in 18–65 years of infected adults at a dose of 0.5 g every time, twice daily [1], for 7 days. For BW ≤ 50 kg patients, CD dosage needs to be decreased to 0.5 g, once daily, during 3–7 days after administration in later released file [24]. There is no dosage recommendation of CD in COVID-19 children so far. Acute poisoning of CD is usually fatal with a dose of 50 mg/kg according to the instruction. A report regarded chloroquine concentration > 25 μmol/L as a fatal predictor [25]. Extreme caution should be followed while prescribing CD for children.

CD should be used with caution in patients with heart diseases, liver or kidney dysfunction, hematoporphyria, mental illness. There are mild adverse reactions of CD in treating malaria, including dizziness, headache, loss of appetite, etc. [26]. At higher doses of CD, the main adverse reaction is ocular toxicity, which could affect vision. If eye discomfort or visual abnormality occurs, CD should be discontinued. Other adverse reactions of CD include arrhythmia, drug-induced psychosis, leukopenia, etc. CD is mainly metabolized by liver and the burden of liver could be aggravated while combining with the other drugs (e.g., chlorpromazine) metabolized by liver. CD has a direct inhibitory effect on neuromuscular junctions, which could be aggravated while combining with drugs (e.g., clindamycin, streptomycin, gentamicin, etc.). Combination of CD with heparin could increase bleeding risk. For the patients with digitalization, CD could cause cardiac block. Other drug interactions (with indomethacin, thyroxine, isoniazid, etc.) also need to be noted.

Arbidol

Arbidol (umifenovir) is a broad-spectrum antiviral compound approved in Russia and China for prophylaxis and treatment of influenza. This compound shows activities against numerous DNA and RNA viruses [27]. Arbidol was found to be effective to SARS-CoV-2 in vitro [28]. Arbidol is available in oral dosage forms in China and Russia [29]. The dosage regimen of arbidol (0.2 g every time, twice daily, not be given over 10 days) in adults with COVID-19 was recommended [1]. There is no recommendation of dosage regimen of arbidol in children with COVID-19 so far.

Arbidol is mainly metabolized by the liver, it should be used with caution in patients with liver dysfunction. Adverse reactions include nausea, diarrhea, dizziness, elevated serum aminotransferase, etc. The average plasma protein binding (PB) rate of arbidol is 89.2–91.6%. Arbidol could compete with drugs of higher PB rate for plasma protein, leading to increased concentration of combined drugs.

In conclusion, all antiviral drugs are only tried to be used for treating COVID-19. Antiviral drugs should be used after weighing advantages and disadvantages with caution in children. For those with mild symptoms, low dosage of IFN-α nebulization can be used. In addition, LPVr is a choice for COVID-19 children. Ribavirin is usually used as a combined drug. The combination of three or more antiviral drugs at the same time is not recommended.

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