Curative efficacy and safety of peramivir in the treatment of children suspected with influenza

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Abstract
The data from a total of 200 children with suspected influenza virus infection were assessed at the febrile clinic of Women and Children’s hospital in Ganzhou of Jiangxi province from January 2018 to March 2019, and the patients were belonged to two groups (peramivir treatment group and oseltamivir treatment group). At the same time, 100 patients without special treatment were evaluated as the control group. We observed the patients’ fever relief time, pharyngeal pain relief time, nasal congestion relief time, runny nose symptoms relief time, days of hospitalization, days of medication, cost of medication, and adverse reactions in the three groups. We analyzed and compared the efficacy and adverse reactions of peramivir and oseltamivir in the treatment of children suspected with influenza. The recovery of body temperature, relief of cough, days of medication, and hospitalization period in the peramivir group were significantly shorter compared to the oseltamivir and control groups. The mean times to alleviation of fever in the three groups were 18.28 ± 17.74 h (peramivir group), 48.20 ± 34.28 h (oseltamivir group), and 72.56 ± 25.78 h (control group). The mean times to alleviation of cough in the three groups were 49.77 ± 27.58 h (peramivir group), 68.53 ± 32.54 h (oseltamivir group), and 59.38 ± 31.26 (control group). The cost of the peramivir group was significantly higher than that of the oseltamivir and control groups. The incidence of drug reactions in the peramivir group was significantly lower than that in the oseltamivir group. The rate of antibiotic usage in the peramivir group was significantly lower than that in the oseltamivir and control groups. Peramivir can significantly alleviate symptoms and reduce the use of antibiotics in children with suspected influenza. Peramivir has demonstrated good efficacy, high safety, and good compliance in treating children with suspected influenza infection.

Keywords
children, influenza, oseltamivir, peramivir, suspected influenza infection

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Introduction
Influenza is well recognized as an acute respiratory disease caused by the influenza virus, which is susceptible to a high incidence of influenza-like symptoms in the epidemic population. Influenza is, for the most part, self-limited and is typically accompanied by fever, shivering, headache, myalgia, and so on. However, some people such as the elderly, young children, and pregnant and lying-in women can easily progress to severe stages of the disease and even death because they are particularly prone to complications, including pneumonia, nervous system injury, and cardiac damage.1,2 Several
studies have reported that children are susceptible to influenza viruses and that they are also primarily the main community transmission groups. The US Centers for Disease Control and Prevention (CDC) estimated that there were between 32.0–43.4 million influenza illnesses, 401,000–706,000 hospitalizations, and 27,300–49,000 influenza-associated deaths during 2018–2019. A recent systematic review estimated that 99% of influenza-related deaths among children under the age of 5 years occurred in resource-limited settings, and that the incidence of severe acute lower respiratory tract infections among infants aged 0–11 months appeared to be greater in low-resource setting. During 2010–2014, influenza resulted in approximately 279,047 illnesses, 36,276 medical visits, 1,612 hospitalizations, and 755 deaths in infants aged 0–5 months in Kenya. In China, 195,723 patients were reportedly infected with the flu virus and there were 8 deaths in 2015; 306,682 patients were infected with the flu virus and there were 56 deaths in 2016; 456,718 patients were infected with the flu virus and there were 41 deaths in 2017; and 768,291 patients were infected with the flu virus and there were 144 deaths in 2018. Presently, laboratory diagnostic technology is not widely used to determine the viral etiology of the influenza virus. It is not common to use reverse transcription polymerase chain reaction (RT-PCR) technology to detect influenza viruses in some hospitals. Therefore, it is not easy to get the virology results in the early stage of the illness. If we confirm the influenza based on laboratory tests and consider the application of specific anti-influenza agents, we will inevitably lose the chance of the best treatment. According to expert consensus on influenza antiviral therapy and prevention, the decision to initiate antiviral therapy does not need to wait for laboratory confirmation. Early diagnosis and treatment are key to improving the cure rate of influenza and reducing the mortality rate. Children with suspected or documented influenza infection benefit from early antiviral treatment using neuraminidase inhibitors that can shorten illness duration, decrease symptom severity, and lower the risk of complications leading to hospitalization and death. Effective and well-tolerated treatments are required to reduce the impact of influenza on individuals and society. Peramivir is a new generation of anti-influenza agents for children and adults. Peramivir is the most recent neuraminidase inhibitor to receive Food and Drug Administration (FDA) approval (September 2017) for the treatment of uncomplicated influenza in outpatients who are at least 2 years old. This agent should be considered for treating children who are being managed as outpatients and those with influenza who cannot tolerate oral oseltamivir or inhaled zanamivir. This study retrospectively evaluated the efficacy and safety of peramivir in the treatment of children with suspected influenza infection.

Materials and methods

**Inclusion criteria**

(1) During the flu season, children had the following influenza symptoms—fever (axillary temperature ≥ 37.5°C), at least two moderate-to-severe symptoms of a total of seven symptoms (headache, muscle or joint pain, feverishness or chills, fatigue, cough, sore throat, and nasal stuffiness). It also met the influenza diagnostic criteria as specified in the “Influenza Guidelines for Diagnosis and Treatment” and recommended by the Chinese Medical Association’s respiratory pathology branch in 2011. (2) Illness typically appeared within 48 h of onset of symptoms. (3) The peripheral serum results showed a total number of white blood cells as normal or decreased. (4) The patient had no other antiviral medication history. (5) This study was approved by the Hospital Ethics Committee, and all family members agreed to participate in the study and provided their written informed consent.

**Exclusion criteria**

(1) Those who had been vaccinated with the influenza virus within 2 months. (2) Systemic use of steroids or other immunosuppressant agents. (3) Evidence of bacteria, Mycoplasma, Chlamydia, and co-infection. (4) Evidence of severe infection and complicated cases. (5) Children with dysfunction, convulsions, and underlying diseases such as heart, lungs, kidneys, and brain were excluded.

**Study patients**

A total of 968 children with suspected influenza virus infection were evaluated at the febrile clinic of Women and Children’s hospital in Ganzhou of
Jiangxi province from January 2018 to March 2019. A total of 200 patients, who were eligible and met the study criteria, belonged to two groups (the peramivir treatment group and the oseltamivir treatment group). At the same time, 100 patients without special treatment were designated as the control group. We retrospectively analyzed the efficacy of the two drugs.

**Sample size**

To study the efficacy of peramivir and oseltamivir in influenza like patients, pre trials found that peramivir was 80% effective and oseltamivir was 60% effective. We calculated the sample size by comparing the two sample rates. Operation procedure with Pass software was as follows: Procedures—Proportions—Two independent—Testing using Proportions—Run. Then we got the sample size.

**Methods**

**Clinical data statistics**

The clinical data of the children were collected, including general information, current medical history, birth history, past history, vaccination history, family history, symptoms, signs, auxiliary examinations, and diagnosis. The patients’ symptoms, signs, and laboratory results were recorded during treatment and follow-up. All of the patients began to record their daily body temperature, symptoms, oral antipyretic medications, and drug reactions from the first day until their body temperature and flu-related symptoms returned to normal. All outpatients were monitored by telephone or face-to-face follow-up visits in the outpatient clinic; their symptoms were recorded until all of their symptoms had been alleviated or had disappeared for a period of up to 24 h. The observation indicators for hospitalized children were as follows: (1) observe the fever relief time in the peramivir group and the oseltamivir group from the start of the medication use to the maintenance of normal body temperature (<37.3°C) and for 24 h or more. (2) Note symptom relief with respect to cough and/or sore throat, stuffy nose, catarrh, runny nose, headache, fatigue, and body muscle and joint pain for 24 h or more. (3) Observe the incidence of adverse reactions. (4) Keep track of antibiotic use.

**Influenza virus detection**

Nasopharyngeal swabs were collected for virus detection using A and B influenza virus antigen rapid detection kits (clereview®Exact Influenza A&B, America, Alere, 2016040202). Nasopharyngeal aspirates from the patients were collected using a standardized technique and a disposable sterilized cotton swab. The specimens were maintained at 4°C for a maximum of 4 h, and they were analyzed further at our hospital laboratory. The viral RNA was extracted from 200-μL aliquots of the nasopharyngeal aspirate samples using the QIAamp MinElute Virus Spin Kit (Qiagen, Hilden, Germany). The RNA was applied as the template for cDNA synthesis using the SuperScript III First-Strand Synthesis System (Invitrogen, CA, USA). The cDNA products were used for subsequent testing of the flu virus by PCR.

**Statistical analyses**

Data were analyzed by the SPSS 17.0 software package. Quantitative variables were described using mean ± standard deviation while categorical variables were described using frequency and percent. Statistical significance was assessed by the Chi-square test or Fisher’s exact test for categorical variables, as well as the t-test and ANOVA for continuous variables. A two-sided $P<0.05$ was considered statistically significant.

**Results**

**Study population**

A total of 300 patients were included in this study. There were no statistically significant differences in sex and age between the three groups ($P > 0.05$). (Please see in Table 1).

**Efficacy based on clinical symptoms**

The mean times to alleviation of fever in the three groups were $18.28 \pm 17.74$ h (peramivir group), $48.20 \pm 34.28$ h (oseltamivir group), and $72.56 \pm 25.78$ h (control group). There were statistical differences between the three groups ($P < 0.001$). The alleviation time of fever in the medication group was shorter than that in the untreated control group. The fever remission time in the peramivir
group was significantly shorter than that in the oseltamivir group \((P < 0.001)\).

The mean times to alleviation of cough in the three groups were 49.77 ± 27.58 h (peramivir group), 68.53 ± 32.54 h (oseltamivir group), and 59.38 ± 31.26 h (control group). There were statistical differences between the peramivir and oseltamivir groups \((P = 0.034)\). There were statistical differences between the peramivir group and the control group \((P = 0.041)\). There was no significant difference in cough remission time between the oseltamivir group and the control group \((P = 0.56)\).

The mean times to alleviation of catarrh symptom (nasal obstruction, running, and so on) were 4.23 ± 1.33 days (peramivir group), 4.89 ± 1.48 days (oseltamivir group), and 6.88 ± 1.56 days (control group). There was no statistical significance between the peramivir and oseltamivir groups in the time of remission of catarrh symptom \((P = 0.67)\). The alleviation time of catarrh symptom in the medication group was shorter than that in the untreated control group.

The mean times of hospitalization and drug used in the peramivir and oseltamivir groups were 3.87 ± 1.57 days and 4.26 ± 2.46 days \((P = 0.042)\). The cost of the peramivir group was significantly higher than that of the oseltamivir and control groups \((P < 0.001)\).

Safety

The primary adverse effects were gastrointestinal reactions such as vomiting and diarrhea, as well as leukopenia, platelet elevation, and rash. Most of the adverse events were mild or moderate in severity. The incidence of gastrointestinal reactions was observed in six (6%) patients in the oseltamivir group and two (2%) patients in the peramivir group \((P = 0.59)\). Decreases in neutrophil counts were observed in three patients in the peramivir group.

| Table 1. Comparison of demography, symptom relief and adverse reactions among three groups. |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----|
| Peramivir \(n = 100\) | Oseltamivir \(n = 100\) | Control \(n = 100\) | \(P\) |
| Sex (men) | 61 (61%) | 58 (58%) | 55 (55%) | 0.76 |
| Age (month) | 32.68 ± 27.43 | 37.37 ± 21.95 | 34.45 ± 25.55 | 0.11 |
| Fever relief time (hour) | 18.28 ± 17.74 | 48.20 ± 34.28 | 72.56 ± 25.78 | \(P = 0.00\) |
| Cough relief time (hour) | 49.77 ± 27.58 | 68.53 ± 32.54 | 59.38 ± 31.26 | \(P = 0.034\) |
| Catarrh symptom relief time (day) | 4.23 ± 1.33 | 4.89 ± 1.48 | 6.88 ± 1.56 | \(P = 0.67\) |
| Hospitalization days (day) | 3.87 ± 1.57 | 4.26 ± 2.46 | 0 | \(P = 0.042\) |
| Days of medication (day) | 3.87 ± 1.57 | 4.26 ± 2.46 | 0 | \(P = 0.042\) |
| Drug cost (yuan) | 591 ± 135.6 | 143.23 ± 35.4 | 36.78 ± 18.79 | \(P = 0.00\) |
| Adverse reactions | 16 (16%) | 38 (38%) | 0 | \(P = 0.017\) |
| Gastrointestinal reactions such as nausea, vomiting and diarrhea | 2 (2%) | 6 (6%) | 0 | \(P = 0.59\) |
| Leukocyte or neutrophil decrease | 3 (3%) | 10 (10%) | 0 | \(P = 0.046\) |
| Platelet elevation | 10 (10%) | 20 (20%) | 0 | \(P = 0.037\) |
| Rash | 1 (1%) | 2 (2%) | 0 | – |
| Influenza virus positive | 33 (33%) | 35 (35%) | 0 | \(P = 0.78\) |
| Use of antibiotics | 8 (8%) | 40 (40%) | 38 (38%) | \(P = 0.00\) |
| Leukocyte count at admission \(10^9/L\) | 6.39 ± 3.15 | 6.11 ± 5.00 | – | \(P = 0.19\) |
| Percentage of neutrophils at admission (%) | 46.34 ± 15.43 | 48.36 ± 19.04 | – | \(P = 0.71\) |
| C-reactive protein at admission (mg/L) | 4.28 ± 6.79 | 8.00 ± 21.97 | – | \(P = 0.03\) |

\(^a\)Peramivir group, \(^b\)Oseltamivir group, \(^c\)Control group.
and 10 patients in the oseltamivir group ($P=0.046$). A decrease in the neutrophil count also occurred in patients who did not receive antiviral treatment. Platelet elevation was observed less in the peramivir group than in the oseltamivir group ($P=0.037$). The incidence of rash was observed in one patient in the peramivir group and two patients in the oseltamivir group. The total incidence of adverse drug reactions in the peramivir group was significantly lower than that in the oseltamivir group ($P=0.017$). All of the adverse reactions did not receive special treatment; they were gradually alleviated and disappeared as the condition improved.

**Virological characteristics**

Among these patients with suspected influenza, the detection rate of influenza was only one third. There was no statistical difference between the peramivir and oseltamivir groups ($P=0.78$). But there was a significant difference in the use of antibiotics. The usage rate of antibiotics in the peramivir group, oseltamivir group, and control group was 8%, 40%, and 38%, respectively. The usage rate of antibiotics in the peramivir group was significantly lower than that in the oseltamivir and control groups ($P=0.00$). There was no difference in antibiotic use between the oseltamivir group and the control group ($P=0.87$).

**Discussion**

**Current status of influenza treatment**

In the temperate zone, influenza is widespread between late autumn and early spring. Antiviral medications with activity against influenza viruses are important in controlling influenza. We compared intravenous peramivir, a potent neuraminidase inhibitor, with oseltamivir in patients with seasonal influenza virus infection. Oseltamivir, the leading anti-influenza agent, has been evaluated, for the most part, in otherwise healthy adults with uncomplicated influenza whose treatment was initiated within 48 h of symptom onset. Children with suspected or documented influenza virus infection or serious diagnosed diseases and oral medication difficulties. Peramivir has demonstrated a high level of safety and few adverse reactions, as reported previously. There was a significant difference in platelet elevation between peramivir and oseltamivir, which was consistent with findings in the literature. Although the total cost of hospitalization in the peramivir group was higher than that in the oseltamivir group, the use of peramivir has increased significantly. The time to virus clearance was significantly shorter with peramivir than with oseltamivir. One study strongly suggested that using early antiviral treatment in patients at high risk for developing complications is effective in decreasing the incidence of secondary complications leading to hospitalization.

During the H1 N1 epidemic in 2009, the US FDA approved the use of peramivir in treating children. Many studies have reported that children appear to tolerate this agent well. In this study, the efficacy of the peramivir group was significantly better than that of the oseltamivir group and the negative control group within 48 h of onset. In the case of hypothermia and cough relief, the peramivir group had a significantly better response time compared to the oseltamivir group. In terms of nasal congestion, salivation, and other catarrhal symptoms, the two groups were equally effective. Similar to the reports in the literature, peramivir has a strong affinity for influenza virus neuraminidase. The symptoms were alleviated and the disease was controlled within 3 days. For children with confirmed or suspected influenza, the early diagnosis and early application of the specific anti-influenza drug (peramivir) are keys to improving the cure rate of influenza and reducing the mortality rate. Ideally, treatment should be started within 48 h of symptom onset.

Peramivir, which is currently the only intravenous preparation of neuraminidase inhibitors, is more suitable for infants and young children. Peramivir should be actively used as early as possible in children with highly suspected influenza virus infection or serious diagnosed diseases and oral medication difficulties. Hikita has demonstrated that peramivir was very effective in the treatment of influenza in children. However, its safety has not been observed and evaluated in this study.

**The safety of peramivir**

There were several limitations in this study. Because this was a retrospective study, we did not collect nasopharyngeal swabs on the last day of symptoms or at the end of the antiviral treatment,
and we were unable to discuss the efficacy of the treatment proposed. We did not evaluate the efficacy of treatment with anti-flu medications in patients who were severely ill.

In summary, peramivir can significantly and rapidly relieve symptoms, has fewer adverse reactions, and demonstrates good safety and compliance in treating children suspected with influenza. In addition, the use of antiviral treatment of children infected with the influenza virus or with suspected influenza infection in the outpatient setting should be strongly considered. Our study has shown that this new-generation anti-influenza agent has facilitated the treatment of children with clinically suspected influenza infection and has provided a reference for the rational clinical application of peramivir.

Conclusion

Peramivir can significantly alleviate symptoms and reduce the use of antibiotics in children with suspected influenza. Peramivir has demonstrated good efficacy, high safety, and good compliance in treating children with suspected influenza infection.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

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Informed consent

Signed consent was obtained from each child’s parents or foster parents. Written informed consent was obtained from all subjects before the study.

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