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Original Article

Doxofylline versus aminophylline for pediatric acute bronchial asthma and their effects on recurrence

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Abstract: Objective: The goal of this study was to explore the application and clinical effects of doxofylline and aminophylline in pediatric acute bronchial asthma and their effects on recurrence. Methods: Retrospective analysis was performed on medical records of 96 children with acute bronchial asthma, including 42 children treated with aminophylline (control group) and 54 children with doxofylline (observation group). The therapeutic effects, complication and recurrence rates of the two groups were observed after 7 days of treatment. At the same time, the duration of related symptoms and changes of pulmonary function indicators as well as blood gas analysis indicators before and after treatment in the two groups were compared. Results: The markedly effective rate and total response rate in the observation group were higher than those in the control group ($P<0.05$). The total incidence of complications in the observation group was significantly lower than that in the control group ($P<0.001$). After 3 months of follow-up, the recurrence rate of bronchial asthma in the observation group was notably lower than that in the control group ($P<0.05$), and the duration of wheezing, coughing and pulmonary wheezing rale in the observation group was obviously shorter than that in the control group (all $P<0.001$). After treatment, the levels of FVC, PEF and FEV1 in both groups were elevated (all $P<0.05$), and the levels in the observation group were higher than those in the control group (all $P<0.001$). Concurrently, SpO_2 and pO_2 levels were increased, but pCO_2 levels were decreased in both groups (all $P<0.05$). Additionally, SpO_2 and pO_2 levels in the observation group were higher while pCO_2 levels were lower than those in the control group (all $P<0.001$). Conclusion: Doxofylline is of better efficacy in pediatric bronchial asthma, which could more effectively shorten the duration of symptoms, improve the lung function and blood gas function, reduce the incidence of complications and recurrence, thereby being worthy of clinical application.

Keywords: Doxofylline, aminophylline, pediatric acute bronchial asthma, clinical effects

Introduction

Pediatric bronchial asthma is a heterogeneous asthma accompanied by variable expiratory flow limitation, which is mainly caused by chronic airway inflammation, with a variety of cells and cellular components involved. It mostly occurs in children before the age of 4 to 5 years old, accounting for about 70% to 80%, and is one of the most important causes of repeated coughing in children [1, 2]. With the changes in the social living environment and the increase of various environmental pollution, the incidence of bronchial asthma in children is also rising year by year, which has a great impact on children's learning and life as well as physical and mental health [3, 4]. Children with bronchial asthma need active clinical treatment to prevent irreversible airway stenosis and airway remodeling.

Relieving bronchospasm, improving pulmonary ventilation function and controlling infection are the principles of treatment for pediatric acute bronchial asthma [5]. Doxofylline and aminophylline are currently the first-line drugs for the clinical treatment of bronchial asthma, which can effectively relax the bronchus and relieve cough and wheeze [6]. With extensive use of aminophylline, some studies have reported that the effective blood concentration range of aminophylline is narrow and varied in different patients, which is easily to cause some adverse reactions in patients such as nausea and vomiting [7]. In recent years, some studies have reported that in the treatment of bronchial asthma, doxofylline combined with aminophylline therapy has a notable lower incidence of complications and even a better therapeutic effect compared with the treatment of aminophylline alone [8]. Another study reported that

the most common side effect was epigastric discomfort in 4 patients (8%) treated with aminophylline versus 2 patients (4%) treated with doxofylline, followed by headache, insomnia, nausea and nervousness. Moreover, doxofylline was also superior to aminophylline in improving the peak expiratory flow rate (1.12±0.73 (L/s) vs. 0.77±0.43 (L/s)), which caught the attention of researchers [9]. Although both doxofylline and aminophylline have been used in the treatment of bronchial asthma in children, the comparative studies of the two drugs are still scarce.

Therefore, this study retrospectively analyzed the medical records of children with acute bronchial asthma treated with doxofylline and aminophylline in Hubei University Hospital to explore and compare the therapeutic effect and safety of the two drugs.

Materials and methods

Study subjects

The medical records of 96 children with acute bronchial asthma, aged 2 to 10 years old, admitted to Hubei University Hospital from April 2015 to July 2016, were retrospectively analyzed, including 42 children treated with aminophylline (control group) and 54 children receiving treatment with doxofylline (observation group). The severity of bronchial asthma in children was analyzed according to the pulmonary function indicators as well as blood gas analysis indicators.

Inclusion and exclusion criteria

Inclusion criteria: All children met the 2014 WTO diagnostic criteria for pediatric bronchial asthma, such as cough or increased cough frequency, difficulty in lying supinely, obvious flaring of alae nasi, inability to sleep peacefully at night and rale in the lung [10]; no history of allergic diseases; no past history of respiratory diseases. Clinical data of all children were complete.

Exclusion criteria: Children who received previous treatment with theophylline drugs; the children who had abnormal bleeding or blood coagulation dysfunction combined with cardiocerebral vascular disease, liver and kidney disease, or digestive tract disease; the children who were transferred to another hospital during the treatment; the relatives of the children who did not cooperate with the treatment, and had mental disorders. This study was approved by the Ethics Committee of Hubei University Hospital, and informed consent was signed by patients or their families.

Treatment methods

All children enrolled in this research were given routine treatments, such as anti-inflammation, relieving asthma, easing cough, removing phlegm, and oxygen inhalation. The children in the control group were given aminophylline (Chongqing Yaoyou Pharmaceutical Co., Ltd.) intravenously on the basis of routine treatment at a dose of 5 mg/kg twice a day. The children in the observation group were given doxofylline (Shanghai Qinyi Nantong Pharmaceutical Co., Ltd.) intravenously on the basis of routine treatment at a dose of 5 mg/kg once a day. Children in both groups were treated continuously for 1 week. After the therapy, children were followed up for 3 months, and the recurrence rates were evaluated according to the symptoms.

Outcome measures

The therapeutic effects, complication rates and recurrence rates of the two groups were observed after 7 days of treatment. Furthermore, the duration of related symptoms, changes of pulmonary function indicators (forced vital capacity (FVC), the peak expiratory flow (PEF), forced expiratory volume in one second (FEV1); MSPFT-B pulmonary function instrument, Shanghai Hanfei Medical Instrument Co., Ltd.) and blood gas analysis indicators (oxygen saturation (SpO_2), arterial oxygen partial pressure (pO_2), arterial carbon dioxide partial pressure (pCO_2); GEM Premier3000 automatic blood gas analyzer, Shanghai Yuyan Scientific Instrument Co., Ltd.) before and after treatment in the two groups were compared and analyzed.

Evaluation criteria of therapeutic effects

The therapeutic effects were divided into three classes including markedly effective, effective and ineffective. Markedly effective means that the patient's condition was completely improved. The clinical symptoms such as cough, shortness of breath and rale in the lung disappeared completely, the body temperature returned to normal and no complications occurred. Effective referred to the basic im-

Table 1. General information of the subjects

	Control group (n=42)	Observation group (n=54)	χ^2/t	P
Gender (n, %)			0.000	0.979
Male	24 (57.14)	31 (57.41)		
Female	18 (42.86)	23 (42.59)		
Age (year)	4.8±1.6	4.9±1.6	0.304	0.762
Body weight (kg)	44.6±21.9	43.4±19.8	0.281	0.779
Height (cm)	143.9±19.8	140.5±18.4	0.869	0.387
Acute course of disease	1.92±0.71	1.85±0.67	0.495	0.622
Average course of disease	4.2±1.2	4.3±1.3	0.387	0.700
Degree of illness (n, %)			0.254	0.881
Mild	15 (35.71)	21 (38.89)		
Moderate	21 (50.00)	27 (50.00)		
Severe	6 (14.29)	6 (11.11)		
Exposure to secondhand smoke (n, %)			0.056	0.814
Yes	7 (16.67)	10 (18.52)		
No	35 (83.33)	44 (81.48)		
Specific IgE (n, %)			0.139	0.987
≥ 0.7 kU/L, <3.5 kU/L	6 (14.29)	9 (16.67)		
≥ 3.5 kU/L, <17.5 kU/L	15 (35.71)	19 (35.19)		
≥ 17.5 kU/L, <50 kU/L	14 (33.33)	18 (33.33)		
≥ 50 kU/L	7 (16.67)	8 (14.81)		

Table 2. Therapeutic effects in the two groups (n, %)

	Control group (n=42)	Observation group (n=54)	χ^2	P
Markedly effective	12 (28.57)	27 (50.00)	4.497	0.034
Effective	22 (52.38)	24 (44.44)	0.596	0.440
Ineffective	8 (19.05)	3 (5.56)	4.239	0.054
Total response rate	34 (80.95)	51 (94.44)	4.239	0.040

provement of the patient's condition. The clinical symptoms above were basically improved. Ineffective means that the clinical symptoms above were not improved after treatment, and the patient's condition even deteriorated. Total response rate = (markedly effective + effective)/total number of cases * 100% [11].

Statistical analysis

Data were analyzed with SPSS, version19.0 (Asia Analytics Formerly SPSS China). Count data are expressed as cases/percentage (n/%) and evaluated by the χ^2 test. Measurement data are expressed as mean ± standard deviation ($\bar{x}$±sd). The comparison between the two groups was performed by an independent t test. A paired t test was used for intragroup before-after comparison. P<0.05 was statistically significant.

Results

General information of the research subjects

There were 42 children in the control group, including 24 males and 18 females, with an average age of 4.8±1.6 years old. There were 54 children in the observation group, including 31 males and 23 females with an average age of 4.9±1.6 years old. There were no significant differences in sex distribution and age between the two groups (P > 0.05). Additionally, there were no distinct differences in other basic information such as body weight, height, and acute course of disease between the two groups (P > 0.05) as shown in **Table 1**.

Evaluation of therapeutic effects in the two groups

The evaluation of therapeutic effects after 1 week of treatment showed that there were no remarkable differences in the effective and ineffective rates in the two groups (P > 0.05), but the markedly effective rate and total response rate of the observation group were higher than those of the control group (P<0.05), as shown in **Table 2**.

Table 3. The total incidences of complications in the two groups (n, %)

Complications	Control group (n=42)	Observation group (n=54)	χ^2	P
Nausea	3 (7.14)	2 (3.70)	0.084	0.772
Vomit	4 (9.52)	0	3.246	0.072
Headache	5 (11.90)	2 (3.70)	1.294	0.255
Fidgetiness	4 (9.52)	1 (1.85)	1.477	0.224
Palpitation	5 (11.90)	2 (3.70)	1.294	0.255
Arrhythmia	2 (4.76)	1 (1.85)	0.049	0.825
The total incidence	23 (54.76)	8 (14.81)	17.243	<0.001

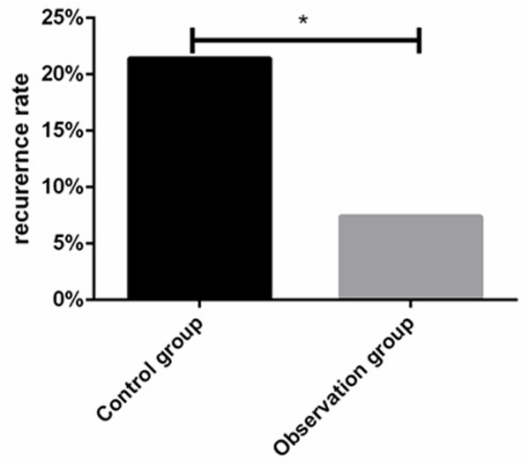

Figure 1. Recurrence rate after treatment in the two groups. The recurrence rate of bronchial asthma in the observation group was significantly lower than that in the control group, *P<0.05.

The total incidence of complications in the two groups

Adverse reactions occurred in both groups and were cured after receiving appropriate treatment intervention. The total incidence of complications in the observation group was notably lower than that in the control group (P<0.001). However, there were no statistically significant differences in the incidence of single complication between the two groups, including nausea, headache, fidgetiness, etc. (P > 0.05) as shown in **Table 3**.

The recurrence rate after treatment in the two groups

After 3 months of follow-up, the recurrence rate of the control group was 21.43% (9 cases), and that of the observation group was 7.41% (4 cases). The recurrence rate of bronchial asthma in the observation group was significantly lower than that in the control group (P<0.05) as shown in **Figure 1**.

The duration of related symptoms in the two groups

The durations of wheezing, coughing and wheezing rale in the lung in the observation group were obviously shorter than those in the control group (both P<0.001), as shown in **Table 4**.

The changes of pulmonary function indicators in the two groups

There were no statistical differences in the levels of FVC, PEF, or FEV1 between the two groups before treatment (all P > 0.05). After treatment, the levels of FVC, PEF, and FEV1 were increased in both groups (all P<0.05). Furthermore, the levels of FVC, PEF, and FEV1 in the observation group were all higher than those in the control group (all P<0.001), as shown in **Table 5**.

The changes of blood gas analysis indicators in the two groups

There were no statistical differences in the levels of SpO_2, pO_2 or pCO_2 between the two groups before treatment (all P > 0.05). After treatment, the levels of SpO_2 and pO_2 were elevated while the levels of pCO2 were lowered in both groups (all P<0.05). In addition, the levels of SpO_2 and pO_2 in the observation group were higher than those in the control group, and the pCO_2 level was lower than that in the control group (all P<0.001), as shown in **Table 6**.

Discussion

Pediatric bronchial asthma is a heterogeneous disease of the respiratory system caused by allergens, climate changes, mental factors, genetic factors, etc. It's pathogenesis has not yet been fully studied. Pediatric bronchial asthma relapses easily with a long treatment cycle. The core purpose of treatment is asthma control [12, 13].

Theophylline drugs, such as doxofylline and aminophylline, are the most commonly used methylxanthine drugs for relaxing bronchial smooth muscle, which play a role by increasing the levels of intracellular cyclic adenosine phos-

Table 4. The durations of related symptoms in the two groups

	Control group (n=42)	Observation group (n=54)	t	P
The duration of wheezing	4.71±0.42	2.25±0.36	30.871	<0.001
The duration of coughing	6.22±0.24	4.35±0.17	44.661	<0.001
The duration of wheezing rale in the lungs	4.78±0.24	3.85±0.21	20.218	<0.001

Table 5. The changes of pulmonary function indicators in the two groups

Indicators		Control group (n=42)	Observation group (n=54)	t	P
FVC (L)	Before the treatment	1.62±0.55	1.67±0.43	0.500	0.618
	After the treatment	2.10±0.25*	2.77±0.31*	11.411	<0.001
PEF (L/s)	Before the treatment	4.72±0.24	4.79±0.26	1.353	0.179
	After the treatment	5.46±0.32*	6.36±0.38*	12.320	<0.001
FEV1 (%)	Before the treatment	75.41±5.69	76.25±5.73	0.715	0.477
	After the treatment	86.44±6.08*	92.12±6.47*	4.380	<0.001

Note: FVC: forced vital capacity; PEF: peak expiratory flow; FEV1: forced expiratory volume in one second. In comparison with the same group before the treatment, *P<0.05.

Table 6. The changes of blood gas analysis indicators in the two groups

Indicators		Control group (n=42)	Observation group (n=54)	t	P
SpO_2	Before the treatment	82.75±4.73	83.26±4.81	0.519	0.605
	After the treatment	90.04±5.18*	98.30±5.87*	7.222	<0.001
pO_2 (mm Hg)	Before the treatment	75.69±4.14	76.23±4.17	0.631	0.529
	After the treatment	84.54±4.85*	95.62±5.03*	10.875	<0.001
pCO_2 (mm Hg)	Before the treatment	46.22±2.47	45.73±2.38	0.984	0.328
	After the treatment	42.25±1.11*	35.73±1.02*	29.892	<0.001

Note: SpO_2: oxygen saturation; pO_2: arterial oxygen partial pressure; pCO_2: arterial carbon dioxide partial pressure. In comparison with the same group before the treatment, *P<0.05.

phate and cyclic guanosine phosphate [14, 15]. However, with the use of new drugs such as glucocorticoids and beta-agonists, the efficacy and safety of theophylline drugs such as aminophylline in respiratory diseases have also been questioned. In recent years, studies have reported that the asthma relieving effect, safety and tolerability of doxofylline are better than aminophylline [16, 17], but no consensus has been reached on this subject. Therefore, the roles of doxofylline and aminophylline in pediatric bronchial asthma were analyzed in this study, and their values of clinical application were evaluated again.

First, the treatment effects of two drugs were analyzed in pediatric bronchial asthma. The results showed that the markedly effective rate was 50.00%, and the total response rate was 94.44% in the observation group, which were higher than the control group with a markedly effective rate of 28.57% and a total response rate of 80.95%. Therefore, it was indicated that doxofylline was superior to aminophylline in the treatment of pediatric bronchial asthma. Second, safety is an important indicator for evaluating the effect of drug treatment. From the results of analysis, the total incidence of complications in the observation group was found to be 14.81%, which was significantly lower than the control group with an incidence of 54.76%, indicating that the safety of doxofylline in the treatment of pediatric bronchial asthma was also better than that of aminophylline. Moreover, the recurrence rate within 3 months in the observation group was clearly lower than that in the control group. Lastly, the changes of lung function and blood gas function in the two

groups was analyzed. The results showed that although the FVC, PEF, FEV1, SpO_2, pO_2, and pCO_2 of the two groups were effectively improved, it was obvious that the improvement of these indicators in the observation group was significantly better than that in the control group. These results suggest that doxofylline is superior to aminophylline in improving lung function and blood gas function in pediatric bronchial asthma, which again indicates that the therapeutic effect of doxofylline is better than that of aminophylline.

Doxofylline and aminophylline mainly reduce the airway hyperresponsiveness and relieve bronchospasm by relaxing the bronchus. Doxofylline is a new type of methylxanthine drug similar to aminophylline, the mechanism of which is related to the inhibition of phosphodiesterase activity. However, doxofylline has a lower affinity for adenosine receptors than aminophylline and is capable of reducing the stimulation of the cardiovascular system, the central nervous system and other systems, thereby decreasing the development of complications, which may be one of the reasons for its better safety [18, 19]. Some studies have also reported the excellent therapeutic effect of doxofylline. In a related report, it was found that the therapeutic effect of doxofylline on bronchial asthma and the improvement of lung function were better than aminophylline. The total response rates of doxofylline group and the aminophylline group were 91.07% and 76.79%, respectively, and the difference between the two groups was statistically significant. After treatment, the FVC was 2.24±0.63 L, FEV1 was 1.59±0.47 L, the lung capacity was 2.94±0.77 L, and the incidence of adverse reactions was 10.71% in the doxofylline group, which was all better than those in the control group [20]. In a clinical investigation of pediatric bronchiolitis, it was also found that the efficacy and safety of doxofylline were superior to aminophylline. The total response rate was 96.7% and the incidence of adverse reactions was 11.7% of doxofylline treatment; the total response rate was 76.7% and the incidence of adverse reactions was 40.0% of aminophylline treatment [21]. A report on chronic obstructive pulmonary disease showed that compared with aminophylline, doxofylline had a more ideal clinical effect in the treatment of acute exacerbation of chronic obstructive pulmonary disease. Doxofylline has an effective rate of 91.2% higher than 70.6% of aminophylline, which could effectively improve patients' lung function, reduce adverse reactions (11.8% vs. 32.4%) and enhance the safety of drug [22]. A double-blind study on asthma treatment also reported that doxofylline was an effective substitute for aminophylline with better efficacy and safety [23]. Although there are few reports on pediatric bronchial asthma, these studies have confirmed the higher application value of doxofylline in respiratory diseases compared with aminophylline. However, there are also some deficiencies in this study. Bronchial asthma is a pulmonary disease with high recurrence rates. Therefore, the long-term therapeutic effects of doxofylline and aminophylline treatment cannot be completely confirmed by follow-up for only three months. In addition, the sample size of this study is also small, which requires us to include more clinical data. It is hoped that this study could encourage more scholars to conduct multi-center experiments with larger sample size for in-depth research.

In conclusion, the results of this study suggest that compared with aminophylline, doxofylline has better clinical effects in pediatric bronchial asthma. Doxofylline can effectively shorten the duration of symptoms in children, improve lung function and blood gas function, reduce the incidence of complications and recurrence, which is worthy of clinical application.

Disclosure of conflict of interest

None.

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