—**Report on Experiments and Clinical Cases**—

Effect of Maclorides on Duration and Resolution of Symptoms and Complication of Pneumonia in Children with Influenza

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Abstract

We randomly administered cephalosporins or macrolides to 365 pediatric patients with influenza-like symptoms and compared the clinical course and complication rate of pneumonia. One hundred and fifty-four patients received cephalosporins (Group 1) and 211 received macrolides (Group 2). There were no significant differences in age, male/female ratio and body weight between the two groups. Macrolides alleviated fever significantly faster than cephalospoins (3.8±1.4 days vs 4.3±1.4 days), though maximum body temperature showed no significant difference between the two groups. Thirty-nine patients underwent laboratory examinations and twenty-nine had high influenza A (H3N2) virus haemagglutinate inhibition (HI) titer, six had high influenza B (B1) virus HI titer and four did not show any elevation of influenza virus HI titer. Thirteen patients in Group 1 and two patients in Group 2 suffered from pneumonia and the complication rate was significantly lower in Group 1 than in Group 2 (8.4% vs 0.9%). All of them recovered within two weeks and did not have any other complications.

Conclusion: Macrolides are more effective in reducing the time required to alleviate fever and complication rate of pneumonia than cepharosporines in children with influenza and influenza-like illness. These results indicate that macrolides may have therapeutic value for influenza virus infection. (J Nippon Med Sch 2002; 69: 53–57)

Key words: influenza, pneumonia, macrolides, cepharosporins

Influenza virus infection frequently causes severe acute respiratory infection and is sometimes accompanied by pneumonia, otitis media, meningitis and encephalitis[1–3]. Vaccination is effective to prevent the prevalence[4,5]. Currently, four antiviral agents (amantadine, rimantadine, zanamivir and oseltamivir phosphate) are approved for use in treating influenza[6–9]. These agents prevent viral replication and should be given within 48 hours of the first symptoms[6]. However, amantadine and rimantadine, which were active against influenza A virus only, appear to produce rapid drug resistant variants[10] and have central nervous system side effects[11]. Zanamivir and oseltamivir phosphate, which are neuraminidase inhibitors, are not indicated for use on children in Japan. Although antibiotics have not been administered to patients with influenza virus infection in principle[12], some reports show the usefulness of antibiotics to prevent complications and aggravation of symptoms[13,14]. This has been thought to result from

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their action in preventing concomitant or secondary bacterial infection[3] and protease secretion of some strains which facilitate viral replication[15,16]. But recent reports have indicated some symptoms and complications of influenza virus infection may result from cytokine storm[1,2,12,17] and macrolides, which are known as antibiotics with potent anti-inflammatory effects[18,19], alleviate pneumonia with influenza virus infection in mice[14].

We administered cephalosporins and macrolides to pediatric patients who came to our hospital with influenza or influenza-like illness during the 1997～1998 and 1998～1999 influenza seasons, and followed clinical their courses and complication rate of pneumonia.

Methods

Patients

The study was carried out in children with influenza-like illness who presented at Nissan Tamagawa Hospital during 1997～1998 and 1998～1999 influenza seasons. Patients were enrolled within 48 hours of the onset of fever. The criteria of enrolled patients were 1) with fever (≧38℃) lasting for 2 days or longer, 2) having routine examination every 2-3 days until the disappearance of symptoms, 3) without any congenital or chronic diseases. Also, patients with bacterial infection or immunization with influenza vaccine for the current season were excluded.

Study procedures

The parents were given an explanation of the medicines to be used and informed consents were obtained. The patients were randomly assigned to either the cephalosporins group (Group 1) or the macrolides group (Group 2). The patients were orally administered the medicines three times a day until their temperature returned to normal. The cephalosporins were Cefditoren pivoxil (CPDX-PI) at a dose of 9 mg/kg/day (maximum of 400 mg/day), Cefteram pivoxil (CFTM-PI) at a dose of 15 mg/kg/day (maximum of 400 mg/day) or Cefaclor (CCL) at a dose of 30 mg/kg/day. The macrolides were Erythromycin (EM) at a dose of 30 mg/kg/day or Clarithromycin (CAM) at a dose of 15 mg/kg/day (maximum of 300 mg/day). Some patients were given acetaminophen as relief medication but were informed not to use this routinely.

Patients were seen every two or three days and compliance was confirmed. A chest X-ray and blood tests including haemagglutinate inhibition (HI) antibody were conducted on those patients with abnormal sounds on chest auscultation or with fever lasting for 5 days or longer. The X-rays were read separately by a radiologist and a pediatrician to double-check the findings.

Data analysis

A Student-t test was performed between the two groups, and a Fisher test was used to test the difference in frequency of occurrence. AP value<0.05 was considered to be statistically significant.

Results

Three hundred and sixty-five patients with influenza-like illness were randomized into two groups. One hundred and fifty-four patients received cephlosporines (Group 1), consisting of 69 males and 85 females. Two hundred and eleven received macrolides (Group 2), consisting of 96 males and 115 females. In Group 1 the mean age was 5.9±3.8 years old (ranging from 4 months to 15.5 years of age) and in Group 2, 6.3±3.5 years old (ranging from 7 months to 14.8 years of age). There were no significant differences in age, male female ratio or body weight (**Table 1**). In Group 1, 43 received CPDX-PI, 85 received CFTM-PI and 26 received CCL. In Group 2, 63 received EM and 148 received CAM.

Group 2 patients were associated with significantly faster alleviation of fever than Group 1 patients (3.8±1.4 days vs 4.3±1.4 days, p=0.006). But the maximum body temperature showed no significant difference between the two groups (Table 1).

Fifty-four patients were on chest X-ray examination and fifteen were revealed to suffer from pneumonia. Thirteen patients received cefalosporines (Group 1) and two received maclorides (Group 2). The incidence of pneumonia in Group 2 was significantly lower than that in Group 1 (0.9% vs 8.4%,

Table 1 Clinical charactristics of 365 patients

	Group 1 Cephalosporins administration	Group 2 Macrolides administration	p value
No.(%) of male	69(45)	96(45)	NS*
No.(%) of female	85(55)	115(55)	NS*
total	154	211	
Age(years)	5.9±3.8	6.3±3.5	NS*
Body weight(kg)	20.9±11.6	22.6±17.3	NS*
Duration of fever	4.3±1.4	3.8±1.4	0.006*
Maximum temperature	39.6±0.6	39.1±0.6	NS*
No.(%) of associated pneumonia	13(8.4)	2(0.9)	0.002†

NS, not significant. Data are mean ± SD.
* ; unpaired student t test. † ; Fisher's exact test

Table 2 Cases of influenza-like illness accompanied by pneumonia

	Case	Age(years) and sex	Duration of fever(days)	CRP (mg/dl)	WBC (/mm^3)	Influenza virus HI titer
Group 1	1	1.4 F	7	3.17	8,800	A(H3N2) 2048
	2	2.5 M	6	0.11	5,700	A(H3N2) 4096
	3	1.5 F	7	0.53	7,600	A(H3N2) 2048
	4	6.0 F	6	5.53	12,300	B(1) 1024
	5	3.8 F	8	10.09	22,000	A(H3N2) 4096
	6	1.8 F	5	1.05	9,700	A(H3N2) 4096
	7	7.7 F	8	0.63	6,200	A(H3N2) 2048
	8	5.5 F	5	7.59	12,200	A(H3N2) 2048
	9	12.3 M	11	4.81	16,600	A(H3N2) 4096
	10	1.8 M	4	0.63	3,000	A(H3N2) 1024
	11	3.0 M	6	0.26	8,300	A(H3N2) 1024
	12	4.1 F	6	10.55	11,000	A(H3N2) 2048
	13	13.3 M	7	5.73	6,000	A(H3N2) 4096
Group 2	14	1.5 F	6	1.48	12,500	A(H3N2) 4096
	15	11.9 M	14	1.29	10,800	A(H3N2) 4096

Group 1 patients received cefalosporines and Group 2 patients received maclorides.
M ; male, F ; female, CRP ; C reactive protein, WBC ; white blood cell, HI ; haemo-agglutinative inhibition

p=0.002) (**Table 2**). Data on patients who concomitantly suffered from pneumonia is shown in Table 2. Chest-X ray films showed interstitial changes except patent 9, who had consolidation of the left upper lobe.

Thirty-nine patients underwent laboratory examinations and twenty-nine (74.4%) had high influenza A (H3N2) virus HI titer and six (15.4%) had high influenza B(B1) virus HI titer(≧1024). Four of them (10%) did not show any elevation of influenza virus HI titer.

None of the patients in either group had accompanying encephalitis, meningitis or otitis media.

Discussion

We had outbreaks of Influenza A (H3N2) in 1997～1998 and 1998～1999 seasons in Japan. One thousand and fifty-eight children with influenza-like symptoms visited Nissan Tamagawa Hospital during these two seasons and 365 of them who satisfied the criteria were enrolled in this study. Thirty-nine

patients(11%) were conducted blood tests and 90% of them had high influenza virus HI titer (H3N2 74.4 %, B1 15.4%). We could not perform convalescent antibody titer or isolation of virus because most of the patients were little children. But the influenza epidemic and the results of antigen titer led us to believe that the majority of the patients had influenza virus infection.

Some reports have stated that the complication rate of pneumonia in patients with influenza virus infection was 5～30%[13,20-23]. Maeda et al.[13] reported that the incidence of pneumonia was 16.3% in children with influenza-like illness who did not receive antibiotics and 2.4% in those who received sultamicillin in 1997～1998 season in Kobe. The incidence of pneumonia in Group 1 (8.4%) was lower than that in Maeda's group without antibiotics, and that in Group 2 (0.9%) was much lower.

In our patients with pneumonia, the laboratory data on Patient 10 clearly indicated viral infection (white blood cell count (WBC)＜5,000 /mm^3 and C reactive protein (CPR)＜1.0 mg/dl). Patients 4, 5, 8, 9 and 12 were suspected to have accompanying bacterial infection (WBC＞10,000 /mm^3 and CRP＞2.0 mg/dl), but diagnosis was difficult for all the other patients (5,000＜WBC＜10,000 /mm^3 and 1.0＜CRP ＜2.0 mg/dl)[12,23].

The causes of pneumonia accompanied by influenza virus infection are thought to be viremia, concomitant or secondary bacterial infections[12,24]. Recently, it has been reported that the several types of protease-producing bacteria cleave and activate the hemagglutinin of the influenza virus, which facilitates the proliferation of the virus in vivo[15,16]. Cephalosporines were administered to expect its bactericidal action. But maclorides were more effective in preventing pneumonia and in hastening the alleviation of fever, although their action is bacteriostatic. These results indicate that anti-inflammatory action of maclorides[14], rather than its antibacterial action, may have therapeutic value for influenza virus infection.

Macrorides are used as a therapeutic agents for chronic inflammation of the lower respiratory tract[18] and have been shown to have multiple biologic actions, such as inhibition of neutrophil chemotaxis[19,25], inhibition of interleukin-8[26], inhibition of interferon-γ[14] and antilymphocytic activity[27]. These effects were not observed in CCL or cephazorin. Sato et al[14] reported that maclorides administration reduced the mortality rate of influenza-infected mice with pneumonia, which resulted from suppression of the production of interleukin g and nitric oxide and superoxide. These tissue-damaging agents are elevated in respiratory tract epithelial cells and bronchoalveolar lavage in influenza virus infection[2,13,28,29].

The mechanism behind the appearance of symptoms and accompanying pneumonia in influenza virus infection still remains to be clarified. If cytokines have a significant roll in this mechanism, macrolides may work as a suppressive agent against tissue-damaging agents production. Our findings indicate that macrolides could be one of the useful therapeutic agents to alleviate fever and diminish the complication rate of pneumonia in children with influenza and influenza-like illness.

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(Received. September 17, 2001)
(Accepted. October 17, 2001)