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Abstract A retrospective study of the 2003–2004, 2004–2005, and 2005–2006 influenza seasons was done to investigate the effectiveness of amantadine and oseltamivir for treating influenza A. Commercial antigen detection kits were used for diagnosis and data were collected from 44 clinics throughout Japan, using an Internet-based system. Oseltamivir was administered to 2775 patients and amantadine to 781 patients. The durations of fever, from the time of the first drug administration and from the onset of fever, were calculated for each patient. In the 2005–2006 season, the duration of fever from the first drug administration was longer for patients who received amantadine than for those who received oseltamivir when the patients were grouped by the time from onset of fever to the start of treatment ($P < 0.001$ for groups administered at 0–12, 13–24, 25–36 h from the onset) and by patient age ($P < 0.001$ for under 16 years and $P < 0.05$ for 16–64 years). Mean values of duration of fever from the first drug administration were 31.3 h, 31.3 h, and 31.9 h for oseltamivir therapy, and 33.3 h, 42.7 h, and 53.3 h for amantadine therapy, in the 2003–2004, 2004–2005, and 2005–2006 seasons, respectively. Reduction in the effectiveness of amantadine over the three influenza seasons were also observed in each age group of 0–6, 7–15, and 16–64 years. The studied season was an independent factor associated with the effectiveness of amantadine by multiple regression analysis. In conclusion, the effectiveness of oseltamivir did not change, but the effectiveness of amantadine was progressively reduced over the three influenza seasons.

Key words Influenza · Oseltamivir · Amantadine · Drug resistance · Rapid diagnosis

Introduction

Amantadine, an M2 protein inhibitor, has been widely prescribed for the treatment of influenza. We reported that the effectiveness of amantadine was equivalent to that of oseltamivir in the 2002–2003 influenza season in Japan. Recently, an increased prevalence of amantadine-resistant influenza A virus has been reported. In February 2006, Bright et al. reported the screening of 209 influenza A/H3N2 virus samples, isolated from patients in 26 states in the United States, of which 193 (92.3%) contained an amino acid change from serine to asparagine at position 31 of the M2 gene, which is known to be correlated with amantadine resistance. They also reported that two of eight influenza A/H1N1 viruses contained the same mutation. The Centers for Disease Control (CDC) had announced, on January 14, 2006, a recommendation for the use of antivirals, suggesting that doctors not prescribe amantadine for influenza. In Japan, few epidemiological studies of amantadine-resistant virus have been published, and amantadine continued to be prescribed for influenza A through the 2005–2006 influenza season. In the present study, a large number of patients with influenza A treated with oseltamivir or amantadine were analyzed, including children and adults. An analysis was done of the duration of fever in patients treated with oseltamivir, and those treated with amantadine, against influenza A, over three influenza seasons, 2003–2004, 2004–2005, and 2005–2006.
Methods

Study procedures

Family doctors, pediatricians, and physicians at 44 clinics that belong to the Influenza Study Group of the Japan Physicians Association participated in the study. Patients were enrolled from November 19, 2003, through May 23, 2006. Patients who reported to any of these clinics, located throughout Japan, with influenza-like illness manifesting such symptoms as a body temperature of 37.5°C or more, upper respiratory tract symptoms, and systemic symptoms received a diagnosis of influenza A, based on the results of commercial antigen detection kits. Among the patients with influenza confirmed by antigen detection kits, those who received oseltamivir or amantadine within 48 h after the onset of symptoms were registered in this study after providing informed consent. For patients with influenza, the decision on whether or not to administer oseltamivir or amantadine was left to the discretion of the clinician, who considered the background and characteristics of the patient, such as the presence of other existing diseases, patient age, and patient preference.7–11 In the 2005–2006 season, most doctors administered oseltamivir according to the CDC recommendation. However, amantadine was administered, under careful observation, by some doctors. A few patients were changed to oseltamivir after starting amantadine therapy if the fever had not resolved within 48 h of the start of therapy.

Laboratory tests

Specimens from throat swabs, nasal swabs, or nasal aspirates were subjected to antigen detection, virus isolation, and polymerase chain reaction (PCR). Commercial antigen detection kits based on immunochromatography were mainly used. A kit based on an enzyme immunoassay (EIA) was used in some cases. The names of the kits and their reported sensitivities and specificities for influenza A are described elsewhere.7,12–20 Virus isolation was done by standard methods, using Madin-Darby canine kidney cells. The virus subtype, influenza A/H3N2 or A/H1N1, was determined by hemagglutination inhibition test and/or PCR using subtype-specific primer sets.

Data collection

Oseltamivir or amantadine was administered orally twice per day for 5 days (oseltamivir, 75 mg for adults and for children who weighed 37.5 kg or more, and 2 mg/kg for children who weighed less than 37.5 kg; amantadine, 50 mg for adults or 2.0–4.0 mg/kg for children). Patients took the initial dose of oseltamivir or amantadine at the clinic or at home and entered the time of the initial administration of the drug on a questionnaire. Age, sex, vaccination status, and the highest body temperature during the course of the disease were recorded. The date and time of the onset of fever, the date and time of the first administration of oseltamivir or amantadine, and the resolution of fever were recorded by the physician, patient, or an attending family member. The first time that a patient reported a fever (temperature ≥37.5°C) was defined as the time of onset. Patients were asked to measure body temperature at least three times per day (8:00 a.m., 2:00 p.m., and 8:00 p.m.); the time at which a body temperature of less than 37.5°C was attained was defined as the time that the patient became afebrile. All data were collected using an internet-based protocol, in which participating physicians sent their data to a central computer system via the internet, as described elsewhere.1,7,21 The time from the first administration of drugs to the resolution of fever, and the duration of fever between the onset of fever and resolution were calculated automatically in the database.7

Statistical analysis

Student’s t test was used for between-group comparisons of the time to onset of fever and the duration of fever. To address factors that might influence the duration of fever from the first administration of amantadine, multiple regression analysis was done. The analyzed factors were patient age, sex, vaccination status, peak body temperature, time to administration of the first dose after the onset of fever, and the influenza season. A P value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 3556 patients with influenza A were enrolled; 2775 were treated with oseltamivir and 781 were treated with amantadine. Of 321 patients in the 2005–2006 season who initially received amantadine, 56 changed to oseltamivir 2 to 4 days after the first dose of amantadine on the recommendation of their physician. The demographic characteristics of the patients enrolled in the three influenza seasons are summarized in Table 1. No significant between-group differences were found for the three seasons, or for the ratio of female to male subjects, or for vaccination status between oseltamivir and amantadine. The values for mean highest body temperature and the mean time from onset to the first drug administration were comparable in the patients treated with oseltamivir and amantadine in the three influenza seasons.

The commercial antigen detection kits used were Capilia FluA, B or Capilia Flu A+B (Tauns, Numazu, Japan, and Nippon Becton Dickinson, Tokyo, Japan) for 2653 patients, Espline Influenza A&B-N (Fujirebio, Tokyo, Japan) for 70 patients, FluA, B or Capilia Flu A+B (Tauns, Numazu, Japan, and Nippon Becton Dickinson, Tokyo, Japan) for 630 patients, Infl AB Quick “SEIKEN” (Denka Seiken, Tokyo, Japan), for 70 patients; and other kits for 203 patients. All 79 patients for whom the viral type was determined in the 2003–2004 season had influenza A/H3N2. In the 2004–2005 season, 58 of 60 patients (96.7%) had influ-