NOTE

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Time interval between the onset of type A influenza and consultation at the outpatient clinic in a community hospital: 1999–2000 epidemic

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Abstract We investigated the proportion of patients with laboratory-confirmed type A influenza who visited an outpatient clinic and who were suitable for receiving treatment with anti-influenza viral agents. Between December 1999 and March 2000, in a community hospital, 40 patients were diagnosed as having type A influenza by specific antigen detection ($n = 39$) and reverse transcriptase-polymerase chain reaction ($n = 1$). These patients with laboratory-confirmed type A influenza were enrolled in the study. We investigated the time interval between the onset of illness and visit to the outpatient clinic at the community hospital. The results indicated that 57.5% of the patients with type A influenza visited the hospital within 1 day of the onset of illness, and 77.5% visited the hospital within 2 days. The body temperature (mean $\pm$ SD) during the initial consultation was $38.9 \pm 0.8^\circ\text{C}$ ($n = 40$). Seventeen of the 40 patients (42.5%) were hospitalized. In conclusion, in the majority of patients, the time from onset of symptoms to consultation was appropriate for treatment with anti-influenza viral agents. A rapid antigen-detection assay, such as Directigen Flu A, is useful for early diagnosis and allows for early treatment with anti-influenza viral agents.

Key words Amantadine · Zanamivir · Oseltamivir · Neuraminidase inhibitor · Nosocomial infection · Rapid antigen-detection assay

Influenza is a respiratory viral infection that can lead to exacerbation of pre-existing diseases, cause various complications, and even cause death, particularly in high-risk

patients. In addition to amantadine hydrochloride (Novartis Pharma, Tokyo Japan), neuraminidase inhibitors such as zanamivir hydrate (Glaxo Smith Kline, Tokyo, Japan) and oseltamivir phosphate (Nippon Roche, Tokyo, Japan) are used for the treatment of influenza. The latter two medications have been covered by the national medical insurance in Japan only since February 2001. Although the effect of amantadine is limited to type A influenza, these anti-influenza viral agents are generally efficacious in alleviating the symptoms if they are administered within 2 days of the onset of influenza infection.^{1–6} However, only a few studies have examined the interval between onset of influenza infection and medical consultation.⁶ In the present investigation, we examined the period between onset of symptoms and visit to the outpatient clinic of a community hospital for antiviral treatment in patients with laboratory-confirmed type A influenza.

From December 1999 to March 2000, in an outpatient clinic of a primary and secondary care community hospital, 40 patients were confirmed as having type A influenza by laboratory tests. These patients were enrolled in the present investigation. The diagnosis of influenza infection was established in 39 patients by rapid antigen-detection assay. Type A influenza antigen was detected by Directigen Flu A (Nippon Becton Dickinson, Tokyo, Japan), using nasopharyngeal swabs obtained from the patients through the nasal cavity at the initial consultation. This procedure was conducted in those patients who sought medical advice in the outpatient clinic and reported the sudden appearance of fever exceeding 38°C , and in a patient with severe pain in the muscles of both thighs. In another patient, who developed acute respiratory distress syndrome (ARDS) and died after hospitalization, bronchial aspirates were examined for the type A influenza gene by reverse transcriptase polymerase chain reaction (RT-PCR) because of the unavailability of an antigen-detection kit.

The patients included 23 men and 17 women (age [mean $\pm$ SD], 46.3 ± 25.5 and 43.1 ± 24.4 years, respectively; whole group, 46.8 ± 24.9 years). Seventeen patients (42.5%) were subsequently hospitalized for treatment of influenza, and some patients were hospitalized for the treat-

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ment of complications. We investigated the time intervals, from the onset of the fever in the 39 patients and from the onset of the severe myalgia in the 1 patient, until their consultation with the physicians to determine whether the interval was appropriate for the administration of anti-influenza viral agents, including amantadine. The time intervals were determined retrospectively, based on the medical records. Data values were expressed as means $\pm$ SD. Differences in age and duration of administration of amantadine between survivors and patients who died were examined by Student's *t*-test. A *P* value of less than 0.05 was considered significant.

The distribution of the consultation times for patients with type A influenza by week of the year is shown in Fig. 1. The first patient with type A influenza visited the hospital in the fifty-second week of 1999, while 30 (75%) of the 40 patients visited the outpatient clinic from the fourth week to the sixth week of 2000. The time at which the maximum number of patients visited the hospital was similar to that determined by the national investigation (<http://idsc.nih.go.jp/index-j.html>). Between week 5 and week 6, type A influenza-specific antigen could not be detected, due to the unavailability of Directigen Flu A across Japan. Therefore, some cases were not counted.

Fig. 1. Distribution of consultation times by week of the year in 40 patients with type A influenza

The intervals between the onset of symptoms until initial consultation at the outpatient clinic are shown in Table 1. In 23 patients (57.5%), the interval was within 1 day of onset of symptoms, while in 8 patients (20%), the interval was within 2 days. Thus, 31 of the 40 patients (77.5%) visited the hospital within 2 days of the clinical onset of influenza. All patients except 1 developed sudden onset of high fever, and the mean body temperature at consultation was $38.9 \pm 0.8^\circ\text{C}$. One patient, an 82-year-old woman, had slowly progressive interstitial changes in both lungs due to sarcoidosis and had been treated with 10mg prednisolone. Her body temperature was 36.8°C on admission and she reported inability to stand up, due to severe pain in the thigh muscles. A rapid type A influenza antigen-detection test was performed because of suspicion of influenza myositis. The test was positive and the patient was admitted to the hospital and treated with amantadine.

A total of 33 patients (82.5%), including 14 hospitalized patients, were treated with amantadine HCl, at a dose of 100mg/day. The average duration of treatment was 4.3 ± 1.49 days ($n = 33$). Seven patients in the present study were not treated with amantadine. This group was treated with antipyretic agents only and survived well. In all 4 hospitalized patients who subsequently died because of complications, type A influenza antigen was detected, and this was followed immediately by the administration of amantadine.

Table 2 shows comparisons of the age of patients, the average duration from onset of symptoms to administration of amantadine HCl, and the duration of treatment with amantadine HCl in hospitalized patients who subsequently died ($n = 4$) and those who survived ($n = 13$). The average age of those who died was significantly higher than that of the survival group, but there was no significant difference between the groups with regard to the period between onset of symptoms and administration of amantadine, or with regard to duration of treatment.

Neuraminidase inhibitors were not commercially available in Japan during the period of our investigation. Other studies¹⁻⁶ have reported that anti-influenza viral agents, such as rimantadine hydrochloride,^{1,2} amantadine hydrochloride,¹ and neuraminidase inhibitors,³⁻⁶ are efficacious in alleviating the symptoms of influenza when treatment with these agents is begun within 2 days of the onset of illness. However, to our knowledge, very little is known about the proportion of Japanese patients who visit a community hospital within 2 days of the clinical onset of laboratory-confirmed influenza infection. Silagy and Watts⁶ reported

Table 1. Distribution of the intervals from onset of influenza symptoms to initial consultation

	Interval (days after onset of symptoms)					Mean $\pm$ SD
	1	2	3	4	5	
Total number of patients	23	8	7	1	1	1.53 ± 1.15
Cumulative number of patients	23	31	38	39	40	
Cumulative ratio (%)	57.5	77.5	95	97.5	100	
Hospitalized patients ($n = 17$)	8	6	2	0	1	1.59 ± 1.33
Survivors ($n = 13$)	7	4	1	0	1	1.46 ± 1.45
Deceased ($n = 4$)	1	2	1	0	0	2.00 ± 0.82

Table 2. Comparison of age, interval from onset of symptoms to administration of amantadine HCl, and duration of treatment with amantadine in patients who died and survivors

	Age (year)	Interval (days after onset)	Duration of treatment (days) ^b
Deceased (<i>n</i> = 4)	76 ± 4.9	2 ± 0.82	3 ± 1.6 (<i>n</i> = 4)
Range	70–82	1–3	1–5
Total number of survivors (<i>n</i> = 36)	59 ± 25.8	1.3 ± 1.4	4.5 ± 1.4 (<i>n</i> = 29)
Range	20–90	0–5	3–9
<i>P</i> value ^a	<i>P</i> < 0.05	NS	NS
Hospitalized survivors (<i>n</i> = 13)	55.4 ± 25.5	1.46 ± 1.45	5 ± 1.7 (<i>n</i> = 10)
Range	20–90	0–5	3–9
<i>P</i> value ^a	<i>P</i> < 0.05	NS	NS

NS, Not significant

^a Student's *t*-test was used for the analysis of differences between the survivors and the deceased groups^b Some patients were not treated with amantadine HCl

that 40% of clinically diagnosed influenza patients consulted physicians within 36h. Although the number of patients with laboratory-confirmed type A influenza was limited in our study, the majority (77.5%) of the patients consulted physicians within 2 days of the appearance of symptoms. The reason for such early consultation could be the sudden onset of high fever (mean body temperature, 38.9 ± 0.8°C). Understandably, the availability of medical services, including transportation and the location of the medical facility, and the government medical insurance system, influence the medical consultation behavior of patients. Therefore, the results of such investigations will vary based on the country and the available health care system. These factors possibly explain the shorter period between the appearance of symptoms and consultation in our study compared with that of Silagy and Watts.⁶ Therefore, in Japan, the results presented here indicate that, following laboratory confirmation of diagnosis of influenza by the rapid antigen-detection assay at the initial consultation, treatment with anti-influenza viral agents could be administered in the majority of patients.

In the present study, only patients with laboratory-confirmed type A influenza were treated with amantadine HCl. Other patients were treated with anti-pyrexia agents and showed satisfactory improvement. However, in spite of receiving immediate treatment with amantadine HCl, four elderly patients with other diseases died during hospitalization. The influenza antigen-detection kit is useful for the early diagnosis and initiation of treatment. Unfortunately, the kit was not available during part of the present study. In such a situation, we believe that anti-influenza viral agents should be administered to clinically diagnosed influenza

patients, especially elderly patients with other associated diseases. We believe that such therapy is appropriate for patients with acute respiratory syndrome.

In conclusion, we have demonstrated in the present study that a rapid antigen-detection assay, such as Directigen Flu A, is useful for the early diagnosis of influenza and allows early treatment with anti-viral agents. Our results also indicated that the majority of patients sought medical advice at a local community hospital within an appropriate period for treatment with anti-influenza viral agents.

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