Toxicon 110 (2016) 12–18

Contents lists available at ScienceDirect

Toxicon

journal homepage: www.elsevier.com/locate/toxicon

Retrospective survey to evaluate the safety and efficacy of Japanese botulinum antitoxin therapy in Japan

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ARTICLE INFO

Article history:
Received 7 September 2015
Received in revised form
9 November 2015
Accepted 18 November 2015
Available online 22 November 2015

Keywords:
Botulism
Retrospective survey
Side effect
Fatality rate

ABSTRACT

Japanese botulinum antitoxins have been used for more than 50 years; however, their safety and therapeutic efficacy are not clear. In order to analyze the available data on botulinum antitoxin therapy in Japan, we surveyed published reports about botulism cases in which botulinum antitoxins were used, and retrospectively analyzed the safety and efficacy of the therapy.

A total of 134 patients administered botulinum antitoxins were identified from published reports. Two cases of side effects (1.5%) were detected after antitoxin administration, both not fatal. The fatality rate was 9.4%, and more than 70% of the patients showed improvement in their symptoms and better clinical conditions than those not treated with antitoxins. These data suggest that the therapy with Japanese antitoxins is safe and highly effective.

1. Introduction

Botulism is a neuroparalytic disease caused by a neurotoxin produced by *Clostridium botulinum*. Food-borne botulism results from consumption of foods contaminated with botulinum neurotoxin (BNT), which is released while *C. botulinum* proliferates in food products. Food-borne botulism is a rare but fatal disease, which has killed many people worldwide, including patients in America, Europe, and Asia. There are eight antigenically distinct serotypes of BNT, A to H. A total of 444 outbreaks and 1087 patients have been reported in 46 years (from 1950 to 1996) in the USA where type A was the most common causative BNT followed by types E and B, while type F was rare (CDC, 1998). There also have been many cases of food-borne botulism in Canada; however, unlike in the USA, most of them were caused by type E BNT and were thought to be related to consumption of raw fish or marine mammals without prior thermal treatment (Leclair et al., 2013). In Japan, especially in the northern part, cases of type E food-borne botulism caused by consumption of fermented fish called “Izushi” and Izushi-like food have been reported since 1950. However, outbreaks of type A and B food-borne botulism resulting from ingestion of imported foods have been recently reported in various regions in Japan.

It has been established that the earliest possible administration of botulinum antitoxins is effective against food-borne botulism (Tacket et al., 1984). Connaught Laboratories in Canada developed a type E monovalent botulinum antitoxin in 1961 and a trivalent botulinum antitoxin for types A, B, and E in 1969, which have been successfully used for many patients in Canada and the USA (Dolman, 1974). In Japan, type E monovalent and type A, B, E and F tetravalent botulinum antitoxins were developed in 1961 and 1972, respectively, by Japanese manufacturers. Since then, both products have been supplied by Chiba Serum Institute before it closed in 2002. The Chemo-Sero-Therapeutic Research Institute (“Kaketsuken”) inherited the manufacturing techniques and licenses for these products from Chiba Serum Institute. The monovalent and tetravalent antitoxins have been supplied by Kaketsuken since 2009 and 2012, respectively, and used to treat patients with botulism.

The monovalent antitoxin developed in Japan contains 10,000 units of type E antitoxin, while the tetravalent antitoxin contains

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http://dx.doi.org/10.1016/j.toxicon.2015.11.010
0041-0101/

10,000 units of each type A, B, and E antitoxins and 4000 units of type F antitoxin. Both antitoxin preparations contain lyophilized horse immunoglobulins. In brief, the manufacturing process is as follows: plasma is collected from horses immunized by each type of toxoid obtained from formalin-detoxified purified BNT. Then, whole IgG purified by ammonium sulfate precipitation is digested by pepsin to obtain F(ab′)2 fragment of each type in undiluted solution. The solutions of types A, B, E, and F are diluted and mixed into bulk solution of the tetravalent antitoxin, and the solution of type E is diluted and poured into that of the type E monovalent antitoxin. The mixtures are lyophilized to yield the final products.

Although equine botulinum antitoxins have been used worldwide for a long time, no controlled studies have been conducted to evaluate their efficacy. Probable reasons for this are ethical difficulty in conducting a placebo-controlled study because of fatal nature of the disease and the scarcity of available efficacy data due to the rarity of the disease. Although botulinum antitoxins have been used in Japan for over 50 years, their safety and efficacy remain unclear because of the absence of clinical trials and clinical studies. The manufacturer is ultimately responsible for the quality of the products, and therefore, as an antitoxin supplier, we ought to reveal the safety (or the risk of side effects) and efficacy of botulinum antitoxin therapy. Moreover, the data collected on cases treated with botulinum antitoxins for over 50 years are considered to form a sample large enough to evaluate the safety and efficacy of this therapy. In this study, we researched published data on past cases of Japanese botulinum antitoxins application, analyzed retrospectively overall clinical results, and evaluated the efficacy and safety of botulinum antitoxin therapy in Japan.

2. Materials and methods

2.1. Retrospective survey of botulinum cases

In this investigation, we used in-house reports of prefectural institutes of public health across the country, the Guide to Botulism (1998–2000) issued by the antitoxin study group of the Ministry of Health, Labour and Welfare along with papers that cited the guide, and the Infectious Agents Surveillance Report (IASR) issued by the National Institute of Infectious Diseases (listed in Further reading section).

Based on the literature, we identified patients who received botulinum antitoxins during 52 years: from 1962 when the allocation of Japanese botulinum antitoxins started to 2014. As a result, we identified 134 patients who had been treated with botulinum antitoxin therapy.

We summarized patients' demographic and clinical characteristics including sex and age, symptoms, severity, and outcome of the disease (survival), serotype of the toxin that caused food-borne botulism, type and dose of administered antitoxins, improvement of symptoms after antitoxin therapy, and occurrence of side effects due to antitoxins. Patients with no records of side effects were considered as side effect-free. The severity of symptoms was determined if the symptoms were described as severe in the records, if the patient had dyspnea or breathing disorder, or if the case was fatal (CDC, 1998). Characteristics other than severity were considered if they were specified in the literature.

2.2. Classification of patients

Patients' classification is shown in Fig. 1. Group I comprises all patients who received botulinum antitoxins, Group II comprises patients considered eligible for efficacy evaluation of antitoxin therapy, and Group III comprises patients for whom treatment effects were described in the literature.

Safety evaluation was performed for all patients treated with botulinum antitoxin therapy (Group I).

The efficacy was evaluated with two indices: the fatality rate and improvement rate. We excluded 7 patients considered ineligible for the evaluation of antitoxin therapy efficacy (2 patients for whom serotypes of the causative toxin and administered antitoxin did not match, 4 patients who did not have botulism but received antitoxins prophylactically, and 1 patient with unknown outcome) and conducted efficacy evaluation for the remaining 127 patients (Group II) with the fatality rate as the index. Furthermore, we excluded 60 patients for whom treatment effect records were unavailable, and conducted efficacy evaluation for the remaining 67 patients for whom treatment effects were described in the literature (Group III); the symptom improvement rate was used as the index.

In addition, we evaluated the efficacy of antitoxin therapy in patients with severe botulism.

2.3. Analytical and statistical processing

We summarized the incidence of side effects, fatality rate, and symptom improvement rate for each group. We also classified the patients from several standpoints and performed Pearson's chi-squared test. Fisher's exact test was conducted if the number of patients in a category was 5 or less, because in this case, the approximation by chi-square distribution would not be accurate.

3. Results

3.1. Safety

The results of safety evaluation are shown in Table 1. Among the 134 patients who received antitoxin therapy, side effects were reported in 2 patients (1.5%), but were not fatal in both cases. These side effects were only reported in patients with type B food-borne botulism, and there were statistically significant differences in the incidence among BNT types A, B, and E. No significant differences were detected for other categories. Table 2 shows detailed information on the 2 patients with reported side effects. In one of them, an immediate allergic reaction occurred following additional antitoxin administration at day 7 after the start of antitoxin therapy. In the other patient, side effects such as rash and arthralgia occurred 6 days after the start of the therapy, and this patient was diagnosed with serum sickness.

3.2. Efficacy

We evaluated the efficacy in the patients classified into Groups II and III as well as in the patients with severe botulism.

3.2.1. Efficacy evaluation in groups II and III

Table 3 shows the results of efficacy evaluation in Groups II and III.

Among the 127 patients of Group II, 115 patients were survivors and 12 patients died (fatality rate, 9.4%). The fatality rate tended to be higher in men and the difference between sexes was statistically significant (Table 4). For other categories, no statistically significant association with fatality was detected.

Among the 67 patients of Group III, symptom improvements were observed in 52 patients, with the improvement rate of 77.6%. The improvement rate tended to be lower for type A botulism (Table 5). For other factors, including antitoxin type and dose, no association with the improvement rate was observed.

There was no significant difference in the mean age between survivors and non-survivors, and between patients with symptom