

Prospective Survey on Safety Evaluation of Injectable Methylxanthines in Japan

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ABSTRACT

Background: Injectable methylxanthines are useful drugs in the treatment of asthma. The Asthma Prevention and Management Guidelines (JGL) that are followed in Japan recommend the use of sustained-release theophylline to control the disease and use of injectable methylxanthines to alleviate symptoms. In contrast, the guidelines followed in the west do not promote theophylline use due to safety concerns, and the use of injectable methylxanthines in particular are not recommended. We thus conducted a study on adult patients with bronchial asthma or chronic obstructive pulmonary disease treated with theophylline and injectable methylxanthines in Japan in order to assess the safety of these drugs.

Methods: 876 patients were surveyed at 55 medical institutions by the Committee on the Safety of Sustained-Release Theophylline and Injectable Methylxanthines (CST) of the Committee for Asthma Prevention and Management Guidelines of the Japanese Society of Allergology (JSA). 682 of the patients were evaluated for safety.

Results: Adverse reactions including facial flushing, palpitations, headache, tinnitus, diaphoresis, nausea, vomiting and tachycardia were reported by only 2 (0.29%) of the 682 patients, but none of these were serious.

Conclusions: The results confirm that injectable methylxanthines are safe, when used in accordance with the JGL.

KEY WORDS

adverse drug reaction, asthma, COPD, injectable methylxanthines, safety

INTRODUCTION

Injectable methylxanthines have been used in the treatment of asthma. Herrmann¹ administered aminophylline, an ethylenediamine salt of theophylline and a methylxanthine, intravenously to patients with clustering asthmatic attacks, and reported on the clinical efficacy in 1937. Aminophylline injection (Neophyllin[®]) was first marketed in Japan in 1950, and it is now widely used as a therapeutic drug for bronchial asthma. Aminophylline is a recommended first choice drug for acute attacks in patients with moderate or serious symptoms when inhalation of β_2 -agonist is not effective according to the Asthma Prevention and Management Guidelines (JGL).²

The attitude toward theophylline, another methylxanthine, as a therapeutic drug as set down in the therapeutic guidelines for asthma in the US, Canada, UK and other European countries differs from that in Japan, and its use is considerably limited in these countries. The reason for this seems to be due to the fact that the therapeutically effective margin of theophylline is narrow and despite evidence of its efficacy, there is concern about onset of serious adverse reactions likely to be caused by elevation of blood concentration above the practical range.

More than 10 million ampules of injectable aminophylline are prescribed annually in Japan, and no major problems have been found clinically other than health hazards due to overdose. Yet, while postmar-

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keting safety surveillance of new drugs is now mandatory in Japan, aminophylline injection being an older drug that was first marketed in 1950 has no postmarketing safety data. Therefore, the CST in the JSA decided to conduct a safety study on aminophylline and theophylline (Theodrip®) injections in adults to acquire such data.

This study was performed to determine the onset of adverse reactions, particularly serious adverse reactions caused by aminophylline and theophylline. The study targeted adult patients ranging in age from 15 to 64 years of age with bronchial asthma or chronic obstructive pulmonary disease (COPD) in Japan and was conducted by physicians certified by the JSA.

METHODS

SURVEY DESIGN

This survey was conducted in 55 institutions to which JAS-certified physicians were affiliated. The target symptom was dyspnea in patients with bronchial asthma or COPD. The age of patients was restricted to 15 years of age or more but less than 65 years of age. The duration of the survey was set at 1 month within the period from September 1 through December 31, 2001 as pre-designated by each participating institution. All patients that received the injectable methylxanthines were monitored for adverse reactions during the observation period. The target adverse reactions were those that occur during intravenous infusion or within 6 hours after a bolus administration. The doses of the injectable methylxanthines are the doses that are expected to be effective against acute attacks in daily therapy.

SURVEY ITEMS

The following items were recorded in the survey: gender, age, reason for use, component name, administration date, daily dose, mode of administration, concomitant use of other drugs and the presence of adverse reactions. If an adverse reaction was observed, the type of adverse reaction, date and time of onset after the start of administration, seriousness, and blood theophylline concentration were recorded.

The seriousness of adverse reactions was evaluated according to the following criteria in accordance with the ICH guidelines (Table 1).

RESULTS

NUMBER OF PARTICIPATING PATIENTS

The institutions which participated in this survey are shown in Table 2. Injectable methylxanthines were administered to 876 patients in 55 institutions during the observation period, and completed questionnaires were collected from these patients. A total of 194 patients were excluded from the evaluations due to violations of the inclusion or exclusion criteria. Specifically, 124 patients fell outside the designated age

Table 1 ICH Definition of the Seriousness of Adverse Reactions *

Serious:
1. Results in death or injury
2. Is life-threatening or may result in injury
3. Requires hospitalization or prolongation of existing hospitalization
4. Results in congenital disease or abnormality in the next generation
5. Other events that may require intervention to prevent one of the outcomes listed in definitions 1 – 4
Moderate: Neither severe nor mild
Mild: When symptoms are judged by the attending physician to be mild and recovery is rapid.

(* ICH: International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)

group, 39 had answered the questionnaire twice, 12 received the drugs at times that were outside the designated observation period, 9 either had conditions or diseases other than the targeted one or had received different drugs, and 10 whose age or presence of adverse reactions were not recorded. The recorded data from 682 patients was ultimately used in the evaluation of safety.

PATIENT BACKGROUNDS

The backgrounds of the 682 patients whose data were used to evaluate the safety of the drugs are shown in Table 3. The patients consisted of 294 males (43.1%) and 388 females (56.9%). The reasons for use were bronchial asthma in 673 patients (98.7%) and COPD in 9 patients (1.3%). The drugs were used for the treatment of dyspnea due to bronchial asthma in most patients. The mode of administration was intravenous infusion in all patients, and aminophylline was administered to 610 patients (89.4%) and theophylline to 77 (11.3%). The dose of aminophylline most frequently employed was 250 mg to 264 patients and 125 mg to 250 patients while theophylline was administered at a dose of 200 mg to 68 patients. Concomitant use of other drugs was recorded in 653 patients (95.7%) with steroids used by 618 patients (94.6%), β -agonists by 488 (74.7%) and oral methylxanthines by 357 (57.4%).

ONSET OF ADVERSE REACTIONS

None of the 682 patients evaluated for safety experienced serious adverse reactions, and only 2 patients (0.29%) had non-serious (mild or moderate) adverse reactions. The details of the onset of adverse reactions in these 2 patients are described below. Since adverse reactions were observed in only 2 patients, a stratified analysis by patient background was not carried out. There are many patients who use oral theo-

Table 2 Institutions that Participated in the Survey (in alphabetical order)

Asahi Chuo Hospital	Nihon University Itabashi Hospital
Chiba University	Okayama Red Cross General Hospital
Chukyo Hospital	Osaka City University Medical School
Doai Memorial Hospital	Rosai Hospital for Silicosis
Dokkyo University School of Medicine	Saitama Medical School
Ehime Prefectural Central Hospital	Sendai National Hospital
Fujita Health University School of Medicine	Sendai Open Hospital
Fukushima Medical University	Shimonita Kosei Hospital
Hitachi Totsuka General Hospital	Shizuoka Red Cross Hospital
International Medical Center of Japan	Showa General Hospital
Ishikawa Prefectural Central Hospital	Showa University Fujigaoka Hospital
Iwate Medical University	Showa University School of Medicine
Japanese Red Cross Medical Center	Teikyo University School of Medicine
Jobu Hospital for Respiratory Disease	Toho University School of Medicine, Sakura Hospital
Kameda General Hospital	Tohoku Rosai Hospital
Kariya General Hospital	Tohoku University School of Medicine
Kihara Hospital	Tokyo Kyosai Hospital
Kinki University School of Medicine	Tokyo Medical and Dental University
Kurume University	Tokyo Metropolitan Hiroo General Hospital
Maebashi-Kita Hospital	Tone Chuo Hospital
Mazda Hospital	Tosei General Hospital
Meitetsu Hospital	Toyoko Hospital, St. Marianna University School of Medicine
Nagoya Ekisaikai Hospital	Toyota Memorial Hospital
Nara Hospital Kinki University School of Medicine	Yokohama City Seibu Hospital, St. Marianna University School of Medicine
National Fukuoka-Higashi Hospital	Yokohama City University School of Medicine
National Okayama Medical Center	Yugawara Kosei-Nenkin Hospital
National Sagamihara Hospital	Yukawa Naika Clinic
National Sanatorium Minami Okayama Hospital	

phylline before administering aminophylline, therefore if theophylline is given for the first time, there is a low possibility of the onset of adverse reactions such as digestive symptoms which readily occur.

No serious adverse reactions were reported in the 194 patients that were excluded from the evaluation of safety. One patient, a 71-year-old woman, did show slight trembling of both knees.

PATIENT 1

The patient was a 57-year-old female. She received 250 mg of aminophylline diluted in 500 ml of diluent solution by intravenous infusion over 2 hours as treatment for acute aggravation of bronchial asthma. A β -agonist (skin patch), a steroid (inhalation) and sustained-release theophylline (300 mg/day) were used concomitantly as part of the long term management. At 2 hours after the start of aminophylline infusion, facial flushing, palpitations, headache, tinnitus and diaphoresis developed; but all of the symptoms were mild. Blood theophylline concentration at the time of onset of these adverse reactions was not measured. The patient did have a past history of facial flushing and palpitations with aminophylline. The at-

tending physician commented that the adverse reactions occurred due to acceleration of the infusion rate by the patient herself.

PATIENT 2

The patient was a 21-year-old male. He presented with acute aggravation of bronchial asthma at a nearby hospital, and was treated with a total dose of about 1000 mg of aminophylline. He subsequently visited an institution participating in this survey because there was no improvement in the symptoms. At the time of this visit, he was vomiting. A 125 mg dose of aminophylline was additionally infused on that day, and aminophylline was administered at a dose of 500 mg/day from the next day for a total of 6 days. A β -agonist (inhalation), a steroid (intravenous injection) and epinephrine were used concomitantly to relieve the patient from asthma exacerbations. The patient had palpitations, nausea, vomiting and tachycardia at 2 hours after the start of aminophylline infusion on the first day of administration. However, all the symptoms were moderate, and blood theophylline concentration at the time of onset of the adverse reactions was 19.5 $\mu\text{g/ml}$.

Table 3 Background of Patients Evaluated for Safety (682 patients)

Item			Number of patients			
Sex	Male	294 (43.1%)	Concomitant drugs	Not used	29 (4.3%)	
	Female	388 (56.9%)		Used	653 (95.7%)	
Age (years)	15 ≤	< 23 (3.4%)	β-Agonist		488 (74.7%)	
	20					
	20 ≤	< 105 (15.4%)		Inhalation	357 (54.7%)	
	30					
	30 ≤	< 119 (17.4%)		Intravenous injection	5 (0.8%)	
	40					
	40 ≤	< 136 (19.9%)		Patch application	123 (18.8%)	
	50					
	50 ≤	< 188 (27.6%)		Steroid	Oral	135 (20.7%)
	60					618 (94.6%)
Name of disease (reason for use)	60 ≤	< 111 (16.3%)	Inhalation		302 (46.2%)	
	65					
Mode of administration	Bronchial asthma	673 (98.7%)	Intravenous injection		450 (68.9%)	
	COPD	9 (1.3%)		Oral	150 (23.0%)	
Dose (mg/day)	Infusion	682 (100.0%)	Epinephrine		16 (2.5%)	
	Bolus	0 (0.0%)		Antibacterial drug		78 (11.9%)
	Aminophylline	610 (89.4%)	Macrolide		41 (6.3%)	
	125	250 (36.7%)	New quinolone	10 (1.5%)		
	200	60 (8.8%)	Others	29 (4.4%)		
	250	264 (38.7%)	Other methylxanthines	375 (57.4%)		
	300 ≤	36 (5.3%)		Oral	366 (56.0%)	
	Theophylline	77 (11.3%)	Suppository	0 (0.0%)		
	< 200	2 (0.3%)	Not described	9 (1.4%)		
	200	68 (10.0%)				
250 ≤	7 (1.0%)					

Note) Rates by type of concomitant drug are the ratios to the number of patients using concomitant drugs (653 patients).

DISCUSSION

To date there are no available reports on clinical studies conducted to examine the safety of injectable methylxanthines, however, the following adverse reactions have been reported in the literature where their efficacy was compared with a control group. Carlos *et al.* compared an aminophylline 5.6 mg/kg group, a matching placebo group and a hydrocortisone-salbutamol combination group, and reported that the incidence of nausea and headache in the aminophylline group was higher than that in the other groups.³ Wrenn *et al.* looked at an aminophylline 5.6 mg/kg group, a matching placebo group, and a methylprednisolone-metaproterenol combination group, and reported a high frequency of nausea in the aminophylline group.⁴ Carrier *et al.* compared an aminophylline group with an oral theophylline-epinephrine combination group, and reported a high frequency of headache, nausea, vomiting and tachycardia in the aminophylline group.⁵ Siegel *et al.* compared an aminophylline (5.6 mg/kg)-metaproterenol

combination group with a metaproterenol monotherapy group, and reported high rates of nausea, vomiting, anxiety, tremor and palpitations in the aminophylline combination group.⁶

From the experience with theophylline and injectable methylxanthines in Japan to date, based on anecdotal evidence, it seems that serious adverse reactions rarely occur, particularly in adults. However, there is no scientific evidence based on strict surveys to support this contention.

In the present survey, adverse reactions were reported by 2 (0.29%) of the 682 patients evaluated for safety, but none of them were serious. As previously mentioned, the adverse reactions were facial flushing, palpitations, headache, tinnitus and diaphoresis in Patient 1, and palpitations, nausea, vomiting and tachycardia in Patient 2. All of these symptoms are adverse reactions that are associated with injectable methylxanthines, and the present results agreed well with the aforementioned results obtained from other studies conducted in other countries. The adverse reactions that were observed in Patient 1 occurred pre-

sumably due to acceleration of the infusion rate by the patient herself during the administration. Patient 2 had been treated with a total of approximately 1000 mg of aminophylline prior to hospitalization at the participating institution, and the adverse reactions that were observed could have been due to an overdose, which was supported by a blood concentration of theophylline 19.5 µg/ml.

JGL describes the use of injectable aminophylline as follows: "For the treatment of attacks showing moderate symptoms, continuous mild symptoms or more serious symptoms, dilute about 6 mg/kg of aminophylline with 200 to 250 ml of an isotonic solution for infusion, and infuse half in 15 minutes and the remaining half in 45 minutes. If toxic symptoms such as headache, nausea, vomiting, tachycardia and arrhythmia occur during infusion, immediately discontinue administration. Blood theophylline concentration should be monitored during treatment. This aminophylline dose has been chosen based on the premise that a sufficient amount of theophylline was not administered before the onset of the attack, and the theophylline clearance is normal. When more than 600 mg/day of theophylline has been administered, or when the blood theophylline concentration is 8 µg/ml or higher, reduce the dose of aminophylline to half. Do not administer aminophylline alone but in combination with a steroid and epinephrine." In the present survey, the most frequently administered dose was 250 mg of aminophylline as recommended by the JGL, followed by a dose of 125 mg. It was inferred that the dose of aminophylline was decreased to 125 mg because an oral xanthine drug had been used in 56.0% of the patients. The mode of administration was intravenous infusion for all the patients. Theophylline was administered at a dose of 200 mg in almost all of the patients since only the 200 mg dose of theophylline injection is available.

We found that the frequency of adverse reactions caused by injectable methylxanthines was very low, as demonstrated by the results described above, and no serious adverse reactions were reported. Therefore, these data may suggest that injectable methylxanthines are highly safe drugs when used appropriately. It should be noted that this survey was con-

ducted at medical institutions staffed by JSA-certified physicians who fully understand the JGL and package inserts, and their participation may have greatly contributed to the favorable results. However, the results seem to confirm that injectable methylxanthines are safe, when used in accordance with JGL and instructions provided in package inserts which would be true when used even by physicians who are not JSA-certified.

The price of the aminophylline injection is ¥94 to ¥97 (about \$0.9) per ampule and that of the theophylline injection is ¥269 (about \$2.5) per bag as of August 1, 2003. These drugs are less expensive than other available drugs for the treatment of asthma, and therefore, we can recommend their use for the treatment of bronchial asthma or COPD from the standpoint of medical costs.

Injectable methylxanthines are safe drugs when used in accordance with the JGL and instructions provided in package inserts.

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