

A Prospective Survey on Safety of Sustained-Release Theophylline in Treatment of Asthma and COPD

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ABSTRACT

Background: Theophylline is a useful drug for the treatment of asthma. The Asthma Prevention and Management Guidelines (JGL) recommend use of sustained-release theophylline products as controllers and of injectable aminophylline products as relievers. The Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention, the NHLB/WHP Workshop Report 1995 (GINA, 1995) and guidelines in Western countries recommend sustained-release theophylline, but not as positively as in the JGL. The aim of this survey was to determine the occurrence of serious adverse reactions.

Methods: The survey was conducted in 66 institutions staffed by physicians certified by the Japanese Society of Allergology (JSA). The target diseases were asthma and COPD including chronic bronchitis and pulmonary emphysema, which are indications for use of sustained-release theophylline products in Japan.

Results: 3,921 patients were included in the safety evaluation. No serious adverse reactions were observed among the patients in this survey, although 54 patients (1.38%) exhibited non-serious adverse reactions. The incidence of adverse reactions was found to be high in patients who had begun use of sustained-release theophylline products at the time of registration in this survey, and in patients who were concomitantly taking macrolide antibiotics.

Conclusions: The present survey demonstrates that sustained-release theophylline is safe, as long as used appropriately, although adverse reactions tend to develop early after initiation of administration.

KEY WORDS

adverse drug reactions, asthma, COPD, safety evaluation, sustained-release, theophylline

INTRODUCTION

Theophylline has long been used as a bronchodilator. Sustained-release theophylline products have been used for continuous suppression of asthmatic symptoms such as wheezing and dyspnea because of the long duration of their efficacy. Recently, the anti-inflammatory effects of theophylline such as suppression of infiltration of T-cells and eosinophils into the airway, inhibition of proliferation of T-cells, production of cytokines, and induction of apoptosis of eosinophils and neutrophils have been reported.¹⁻⁶ Enhancement of histone deacetylase (HDAC) activity has also been reported.⁷ Such anti-inflammatory ef-

fects have become the focus of interest as a new aspect of theophylline efficacy.

The bronchodilator activity of theophylline is dose-dependent,⁸ and its therapeutic range is set at 5 to 20 mcg/mL. Anti-inflammatory effects are observed at 5 mcg/mL and above. The Asthma Prevention and Management Guidelines⁹ developed in Japan set the target blood theophylline concentration at 5 to 15 mcg/mL and recommended that sustained-release theophylline products be used as controllers in persistent asthma of mild to severe severity.

In contrast, the Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention, the NHLB/WHP Workshop Report 1995 (GINA,

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1995), which was prepared as an international guideline in 1995,¹⁰ recommends the use of sustained-release theophylline products and injectable methylxanthine products, but theophylline products are not recommended as first-line medication because of fears about the possible occurrence of serious adverse reactions.

Sustained-release theophylline products have also been used in the treatment of COPD including emphysema and chronic bronchitis. Sustained-release theophylline products are designated as supplemental drugs in the Japanese COPD guidelines.¹¹ These guidelines state that these drugs should be used only when inhalational therapy with anti-cholinergic drugs and β 2-agonists is insufficient. The Global Initiative for Chronic Obstructive Lung Disease¹² states that inhalation bronchodilators are preferable to sustained-release theophylline products in terms of possible adverse reactions, despite an acknowledgment of the effectiveness of sustained-release theophylline products.

We believe, however, that the safety of sustained-release theophylline has been demonstrated based on the actual widespread use of sustained-release theophylline products in Japanese adult patients. However, no survey supporting the safety of these products has been conducted. Thus, we conducted a prospective survey to determine the occurrence of serious adverse reactions induced by or related to sustained-release theophylline products, in adult patients ranging from 15 to 64 years of age with asthma or COPD in Japan at institutions staffed with physicians certified by the Japanese Society of Allergology (JSA). The aim of this survey was to finally confirm the safety of sustained-release theophylline products.

METHODS

SURVEY METHODS

The survey was conducted in 66 institutions staffed by physicians certified by the JSA. The target diseases were asthma and COPD including chronic bronchitis and pulmonary emphysema, which are indications for use of sustained-release theophylline products in Japan. The subjects ranged in age from 15 to 64 years. The period of patient registration was 1 month set separately and in advance by each participating institution between September 1 and December 31 in 2001. The observation period was 1 month after the registration of each patient, and adverse reactions observed during the observation period were recorded.

SURVEY ITEMS

The following items were surveyed: sex, age, date of registration, diseases (reason for use), dose and term administration, concomitant drugs (therapy and medication), adverse reactions and blood theophylline concentration (if present, type of the adverse re-

Table 1 ICH definition of seriousness of adverse reactions *¹³

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 the definition 1 – 4.

Moderate: Neither severe nor mild

Mild: When symptoms are judged to be mild by the physician-in-charge and easily recoverable.

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

action, seriousness and date of occurrence), and course and treatment for adverse events, vital signs, results of general and biochemical hematological examinations and urine examinations performed before, during and after the administration of theophylline (required in cases of a serious adverse reaction). Adverse events were reviewed by the physician at the visit to the clinic. The seriousness of adverse reactions was evaluated according to the following criteria in accordance with the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) criteria (Table 1).¹³

RESULTS

BREAKDOWN OF PATIENTS

The 66 institutions where the survey was conducted are shown in Table 2. A total of 4,983 patients from these institutions participated in this survey out of which 1,062 patients were excluded. Specifically, 739 patients fell out of the designated age range (under 15 years and over 65 years), 177 were not observed for the total observation period (25 days or less), 55 violated the registration protocol such as being registered outside the registration period, 49 were registered twice, 33 did not suffer from the targeted disease and 9 failed to come back to the hospital. Ultimately 3,921 patients were included in the safety evaluation.

PATIENT BACKGROUND FACTORS

The background factors of patients who were the target of safety evaluation and occurrence of adverse reactions are shown in Table 3. There were 1,967 males (50.2%) and 1,954 females (49.8%). The largest number of patients were in their 50s at 1,190 (30.3%), and patients who were 40 years of age or older numbered 2,710 (69.1%). The disease (reason for use) was

Table 2 Institutions that participated in the survey (in alphabetical order)

Aichi Medical University	Nihon University Itabashi Hospital
Asahi Chuo Hospital	Niigata University
Chiba University	Ogaki Municipal Hospital
Chukyo Hospital	Okayama Red Cross General Hospital
Doai Memorial Hospital	Okayama University
Dokkyo University School of Medicine	Osaka City University Medical School
Ehime Prefectural Central Hospital	Rosai Hospital for Silicosis
Fujita Health University School of Medicine	Saitama Medical School
Fukushima Medical University	Sendai National Hospital
Gunma University School of Medicine	Sendai Open Hospital
Hanzomon Hospital	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
Kameda General Hospital	Toho University School of Medicine, Sakura Hospital
Kariya General Hospital	Tohoku Rosai Hospital
Kihara Hospital	Tohoku University School of Medicine
Kinki University School of Medicine	Tokyo Kyosai Hospital
Kurume University	Tokyo Medical and Dental University
Maebashi-Kita Hospital	Tokyo Metropolitan Hiroo General Hospital
Mazda Hospital	Tone Chuo Hospital
Meitetsu Hospital	Tosei General Hospital
Nagoya Ekisaikai Hospital	Toyoko Hospital, St. Marianna University School of Medicine
Nagoya University	Toyota Memorial Hospital
Nara Hospital Kinki University School of Medicine	University of Tokyo
National Fukuoka-Higashi Hospital	Yokohama City Seibu Hospital, St. Marianna University School of Medicine
National Minami-Fukuoka Chest Hospital	Yokohama City University School of Medicine
National Numata Hospital	Yugawara Kosei-Nenkin Hospital
National Okayama Medical Center	Yukawa Naika Clinic
National Sagamihara Hospital	
National Sanatorium Minami Okayama Hospital	

asthma in 3,659 patients (93.3%), COPD in 203 patients (5.2%), and asthma + COPD in 59 patients (1.5%).

At the time of registration, 2,856 patients (72.8%) had been receiving sustained-release theophylline products for 1 year or more. The dose of sustained-release theophylline products was 400 mg/day or less in 3,398 patients (86.7%), and between 301 and 400 mg/day in 2,413 (61.5%) of these. The mean dose ($\pm$ S.D.) was 382.4 ± 132.4 mg/day (100 to 1,600 mg/day) (not shown in the table).

Among the patients included in the safety evaluation, blood theophylline concentration was measured in 81 patients who were treated with sustained-release theophylline continuously, and the observed round-the-clock (RTC) concentrations were 1.83 to 19.79 mcg/mL (mean $\pm$ S.D.: 8.84 ± 3.47 mcg/mL). Only 3 patients with blood concentrations of 15.93,

17.3 and 19.97 mcg/mL had concentrations higher than the target blood concentration recommended by the Asthma Prevention and Management Guidelines (JGL), but none exceeded the possible toxic concentration of 20 mcg/mL.

A total of 3,679 patients took other drugs concomitantly, mainly corticosteroids (3,156 cases, 85.8%) and β -agonists (2,256 cases, 61.3%).

OCCURRENCE OF ADVERSE REACTIONS

No serious adverse reactions were observed among the 3,921 patients included in the safety evaluation. Seventy-one non-serious adverse reactions were observed in 54 patients (adverse reaction incidence rate: 1.38%). The main non-serious adverse reactions were nervous system disorders (14 incidents: 0.36%) such as tremor and hypertonia, gastrointestinal disorders (14 incidents: 0.36%) such as nausea and dyspep-

Table 3 Background factors of patients included in the safety evaluation and occurrence of adverse reactions

Factor	No. of patients	(%)	Adverse drug reaction		<i>P</i> (χ^2 test)	Factor	No. of patients	(%)	Adverse drug reaction		<i>P</i> (χ^2 test)
			No. of patients	(%)					No. of patients	(%)	
Total number of patients	3,921		54	(1.38)		Concomitant drugs					
Gender						None	242	(6.2)	2	(0.83)	N.S.
Male	1,967	(50.2)	29	(1.47)	N.S.	Any	3,679	(93.8)	52	(1.41)	—
Female	1,954	(49.8)	25	(1.28)		β 2-agonist	2,256	(61.3)	33	(1.46)	
Age (years)						Inhaled	1,310	(35.6)	26	(1.98)	
15 ≤ <20	83	(2.1)	0	(0.00)	N.S.	Oral	969	(26.3)	6	(0.62)	
20 ≤ <30	449	(11.5)	4	(0.89)		Patch	522	(14.2)	3	(0.57)	
30 ≤ <40	679	(17.3)	9	(1.33)		Corticosteroid	3,156	(85.8)	47	(1.49)	—
40 ≤ <50	710	(18.1)	14	(1.97)		Inhaled	3,023	(82.2)	47	(1.55)	
50 ≤ <60	1,190	(30.3)	17	(1.43)		Oral	500	(13.6)	2	(0.40)	
60 ≤ <65	810	(20.7)	10	(1.23)		Anti-allergic drugs ¹⁾	1,822	(49.5)	15	(0.82)	—
Diseases						Anti-microbial agent	249	(6.8)	10	(4.02)	—
Asthma	3,659	(93.3)	50	(1.37)	N.S.	Macrolide	206	(5.6)	10	(4.85)	
COPD	203	(5.2)	3	(1.48)		New quinolone	14	(0.4)	0	(0.00)	
Asthma + COPD	59	(1.5)	1	(1.69)		Others	18	(0.5)	1	(5.56)	
Period of administration before registration						Other methylxanthine products	51	(1.4)	3	(5.88)	—
No administration	94	(2.4)	7	(7.45)	***	Oral ²⁾	24	(0.7)	0	(0.00)	
<1 month	227	(5.8)	4	(1.76)		Injected	24	(0.7)	3	(12.5)	
1 month ≤ <6 months	437	(11.1)	4	(0.92)		Suppository	0	(0.00)	0	(0.00)	
6 months ≤ <1 year	307	(7.8)	4	(1.30)		Not described	3	(0.08)	0	(0.00)	
1 year ≤	2,856	(72.8)	35	(1.23)							
Dose of theophylline (mg/day)											
≤200	853	(21.8)	16	(1.88)	N.S.						
201 ≤ <300	132	(3.4)	2	(1.52)							
301 ≤ <400	2,413	(61.5)	33	(1.37)							
400 <	523	(13.3)	3	(0.57)							

N.S.: not significant *** : $P < 0.001$

Note) The percentages of concomitant drugs by type are the percentages of total number of patients who used concomitant drugs (3,679 patients).

¹⁾ Anti-allergic drugs: DSCG, leukotriene modifiers, second-generation antihistamines (H1-antagonists) and other oral antiallergic compounds

²⁾ Other methylxanthine products (oral): short acting methylxanthine products (aminophylline, choline theophylline, diprophylline)

sia, and abnormal laboratory test results (29 incidents: 0.74%) such as hyperuricemia (Table 4).

Among the patients who exhibited adverse reactions, an RTC blood theophylline concentration was present in 29 patients, and the concentration ranged from 2.9 to 17.3 mcg/mL (mean ± S.D.: 8.76 ± 3.48 mcg/mL); only 1 patient exhibited a concentration higher than the target blood concentration recommended by the JGL of 15 mcg/mL.

OCCURRENCE OF ADVERSE REACTIONS BY PATIENT BACKGROUND FACTORS

The occurrence of adverse reactions observed in the 3,921 patients included in the safety evaluation are shown in Table 3.

The incidence of adverse reactions in patients who started receiving sustained-release theophylline prod-

ucts at the time of registration was 7.45% and significantly higher than that in patients who had been receiving sustained-release theophylline products before registration ($p < 0.001$).

The incidence of adverse reactions among patients taking concomitant drugs was high in patients receiving macrolide antibiotics (4.85%) and patients receiving injectable methylxanthine products (12.5%). Among the patients who started receiving administration at the time of registration, 12 adverse reactions were observed in 7 patients (Table 5) with 4 cases of nausea and 2 each of palpitations and tremor. The number of days to the time of onset of adverse reactions was within 5 days after the start of administration in 5 of 7 patients.

Twelve adverse reactions were observed in 10 of the 206 patients receiving concomitant macrolide an-

Table 4 List of adverse reactions

Number of patients exhibiting adverse reactions: 54	
Abnormal laboratory tests	29 incidents
Hyperuricemia (16), blood uric acid increased (4), blood creatine phosphokinase increased (6), aspartate aminotransferase increased (2) and alanine aminotransferase increased (1)	
Nervous system disorders	14 incidents
Tremor (6), hypertonia (2), dizziness (2), insomnia (2), hypoaesthesia (1) and headache (1)	
Gastrointestinal disorders	14 incidents
Nausea (6), indigestion (3), bloating (3), vomiting (1) and diarrhea (1)	
Cardiovascular disorders	9 incidents
Palpitations (9)	
Metabolic and nutritional disorders	2 incidents
Appetite decreased (1) and anorexia (1)	
Skin and subcutaneous tissue disorders	2 incidents
Pruritus (2)	
General disorders	1 incident
Malaise (1)	

tibiotics (Table 6) with 2 cases of nausea, 1 each of tremor, dyspepsia and palpitations, and 7 of abnormal laboratory test results such as hyperuricemia.

DISCUSSION

No serious adverse reactions were observed among the 3,921 patients included in the safety evaluation in this survey. A possible reason for the absence of serious adverse reactions is that this survey was conducted in institutions with physicians who were experts in the treatment of asthma and COPD and certified as specialists by the JSA. Furthermore, the standard dose for use as a controller is 400 mg/day and the target blood concentration is 5 to 15 mcg/mL according to the JGL. A total of 3,398 patients (86.7%) received doses of 400 mg/day or less. The mean blood concentration in 81 patients who underwent RTC measurement of blood theophylline concentration was 8.84 ± 3.47 mcg/mL (1.83 to 19.79 mcg/mL). Only 3 patients exhibited concentrations higher than 15 mcg/mL, and none exhibited concentrations higher than 20 mcg/mL, the potentially toxic level.

Treatment with sustained-release theophylline can be considered safe as long as treatment is conducted in accordance with the JGL guidelines of a target blood concentration level of 5 to 15 mcg/mL. Even if the clearance rate is adversely affected for any reason, it is still highly unlikely that the blood theophylline concentration would hit the potentially toxic level of 20 mcg/mL.

Non-serious adverse reactions were found in 1.38% of cases, and the main reactions were nervous system disorders such as tremor and hypertonia, gastrointestinal disorders such as nausea and dyspepsia, and ab-

normal laboratory test results such as hyperuricemia. Of 54 adverse reactions, an RTC blood theophylline concentration was present in 29. Concentrations ranged from 2.9 to 17.3 mcg/mL, and only 1 patient exhibited a concentration higher than 15 mcg/mL and also exhibited mild hyperuricemia. In several of clinical trials of preparations of sustained-release theophylline in Japan, a total of 517 subjects received the preparations.¹⁴⁻¹⁶ No serious side effects were reported, and 10.06% (52/517) of the subjects showed non-serious side effects. The reason of higher incidences of non-serious side effects in other clinical trials is not clear, since the survey methods were different from those used in the present study. Another possibility is that around 70% of subjects in this survey had been on sustained-release theophylline at the start of the survey and might have developed tolerance to these preparations before the survey. Weinberger reported complaints during chronic therapy in 1-2%^{17,18} of patients, which is similar to the percentage in the present survey. It should be noted that this study was intended to study the occurrence of "serious side effects" and not that of "non-serious side effects".

Patients who started receiving sustained-release theophylline at the time of registration exhibited a significantly higher incidence of adverse reactions, namely 7 of 94 patients. The adverse reactions observed were already known and 5 of 7 continued medication (Table 5). Safe administration is possible with attention paid to development of adverse reactions in the early period of treatment.

Seventy three percent of the patients had received sustained-release theophylline and patients who showed serious side effects might have been excluded for the use of sustained-release preparations. However, the above-mentioned clinical trials in Japan and double-blind clinical trials in the United States/Europe did not report serious side effects when patients were given sustained-release theophyllines. In these trials no sustained-release theophylline was given before the trials.¹⁹⁻²⁵

The incidence of adverse reactions in patients concomitantly receiving macrolide antibiotics was 4.85% (10/206 patients) which is higher than that observed in patients receiving other concomitant drugs. Macrolide antibiotics inhibit CYP1A2 and may increase blood theophylline concentration.²⁶ However, none of 10 patients in the current survey who concomitantly received macrolide antibiotics and experienced an adverse reaction, exhibited a blood theophylline concentration of over 20 mcg/mL, which may cause an adverse reaction.⁸ Only the 1 patient who had a blood theophylline concentration of 17.3 mcg/mL actually had a target blood concentration higher than that recommended by the JGL. Administration of sustained-release theophylline was not discontinued in any of the 10 patients with adverse reac-

Table 5 Outline of occurrence of adverse reactions (patients who began receiving theophylline administration at the time of registration)

Sex, age (years) Reason for use	Dose of theophylline	Concomitant drugs	Name of adverse reaction (severity) Time of occurrence of adverse reaction (treatment)	Theophylline concentration in RTC
1. Female, 26 Asthma	400 mg/day	β 2 (inhaled), CS (inhaled, oral)	Nausea (mild) Day 1 of administration (continued)	11.2 mcg/mL
2. Female, 21 Asthma	400 mg/day	β 2 (inhaled), CS (inhaled)	Nausea, dizziness (dizziness on standing up, giddiness), palpitations, tremor (moderate) Day 1 of administration (discontinued)	Not measured
3. Female, 53 Asthma	400 mg/day	β 2 (inhaled), CS (inhaled, injected), Mc, Am (injected)	Tremor, nausea (moderate) Day 2 of administration (dose-decreased)	13.8 mcg/mL
4. Female, 31 Asthma	400 mg/day	β 2 (inhaled), CS (inhaled)	Palpitations (mild) Day 4 of administration (dose-decreased)	Not measured
5. Female, 44 Asthma	400 mg/day	β 2 (inhaled), CS (inhaled), Mc, Am (injected)	Nausea (moderate) Day 5 of administration (dose-decreased)	Not measured
6. Female, 27 Asthma	400 mg/day	CS (inhaled)	Headache (slight) Day 15 of administration (discontinued)	Not measured
7. Male, 62 COPD	200 mg/day	Mc	Hyperuricemia (mild) Day 29 of administration (continued)	6.9 mcg/mL

β 2: β 2-agonist CS: corticosteroid Mc: macrolide Am: aminophylline

Table 6 Outline of occurrence of adverse reactions (patients concomitantly receiving macrolide antibiotics)

Sex, age (years) Reason for use	Dose of theophylline Period of administration before registration	Concomitant drugs other than macrolide	Name of adverse reaction (severity)	Treatment	Theophylline concentration in RTC
1. Female, 53 Asthma	400 mg/day Administration started at the time of registration	β 2 (inhaled), CS (inhaled), Am (injected)	Tremor, (moderate) Nausea (moderate)	Dose-decreased	13.8 mcg/mL
2. Female, 44 Asthma	400 mg/day Administration started at the time of registration	β 2 (inhaled), CS (inhaled), Am (injected)	Nausea (moderate)	Dose-decreased	Not measured
3. Male, 30 Asthma	400 mg/day Less than 1 month	β 2 (inhaled), CS (inhaled), Aa, cephem	Dyspepsia (mild) (possibly due to cephem)	Continued	8.6 mcg/mL
4. Male, 58 Asthma	400 mg/day 1 year or more	β 2 (oral) CS (inhaled), Aa	Palpitation (mild)	Continued	9.2 mcg/mL
5. Male, 62 COPD	200 mg/day Administration started at the time of registration	None	Hyperuricemia (mild)	Continued	6.9 mcg/mL
6. Male, 61 COPD	200 mg/day 1 month – half a year	CS (inhaled)	Hyperuricemia (mild)	Continued	17.3 mcg/mL
7. Male, 62 COPD	200 mg/day Half a year – 1 year	CS (inhaled)	Hyperuricemia (mild) AST (GOT) increased (mild)	Continued	8.6 mcg/mL

tions. This problem could probably be avoided by adjusting the dosage to bring the blood concentration level within the standard set by the JGL.

The incidence of non-serious adverse reactions among the 733 patients not included in the safety evaluation because they were over 65 years of age

was 0.8% (6/733). The mean dose was 348.3 mg/day for these patients, which is lower than among the patients included in the evaluation (382.4 mg/day). This difference in dosage can probably be attributed to adjustments in dosage which took into consideration lowered metabolism found among the elderly.

As the aim of this survey was to confirm the safety of sustained-release theophylline products, we did not survey the effectiveness of these products. However, we assumed that effective dosages had been administered in regular treatments according to the JGL guidelines in the surveyed cases. Accordingly, we believe that there were no particular problems regarding the effectiveness of these products in this survey.

Finally, the price of sustained-release theophylline products is lower than that of other therapeutic drugs for asthma. Therefore, the most recent issue of GINA 2002²⁷ recommended the wide use of sustained-release theophylline products from the standpoint of medical economy.

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