Original Article

Methylxanthine use for acute asthma in the emergency department in Japan: a multicenter observational study

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Aim: Methylxanthines are no longer recommended for emergency department (ED) patients with acute asthma according to international guidelines. We aimed to describe the current methylxanthine use for acute asthma and to determine factors related to its use in the ED.

Methods: We undertook a multicenter retrospective study in 23 EDs across Japan. From each participating hospital, we randomly identified 60 ED patients aged 18–54 years with acute asthma from 2009 through 2011. We examined the associations of ED and patient characteristics with methylxanthine use by constructing a multivariable logistic regression model adjusting for a predefined set of ED- and patient-level factors.

Results: Among 1,380 patients, methylxanthines were used for 79 patients (5.7%, 95% confidence interval [CI], 4.6–7.0%). The proportion of methylxanthine treatment varied substantially among EDs, ranging from 0% to 26.1%. In the multivariable analysis, the number of annual ED patients with acute asthma (odds ratio [OR] per 100 increase in annual asthma patients, 0.12; 95% CI, 0.04–0.34; $P < 0.001$) and having a protocol for asthma treatment (OR 2.91; 95% CI, 1.06–8.00; $P = 0.04$) at the ED level, and systemic corticosteroid use (OR 6.39; 95% CI, 3.34–12.22; $P < 0.001$) at the patient level were associated with likelihood of methylxanthine use.

Conclusions: In this multicenter study, approximately 6% of ED patients with acute asthma were treated with methylxanthines, with a wide variation across EDs. The number of annual ED patients with acute asthma was significantly associated with a lower likelihood of methylxanthine use, whereas having an ED asthma treatment protocol and systemic corticosteroid use in the ED were associated with a higher likelihood of methylxanthine treatment.

Key words: Acute asthma, emergency department, guidelines, methylxanthine, multicenter study, practice variation

INTRODUCTION

ASTHMA IS A common disease that affects approximately 330 million people worldwide[1] and 5 million people in Japan.[2] Additionally, acute asthma accounts for a significant proportion of the public health burden. As many patients with acute asthma present to emergency departments (EDs) and are hospitalized through the ED,[3] understanding the current practice for acute asthma in the ED is important to provide high-quality care and to reduce patient's morbidity and mortality (e.g., ED revisit, hospital admission, and in-hospital death).

Methylxanthines (e.g., aminophylline) have been used for moderate to severe acute asthma in Japan[4] based on the data of a small randomized controlled trial ($n = 53$) carried out in 1996.[5] However, current international guidelines of asthma[6,7] no longer recommend treatment with methylxanthines in ED patients with acute asthma because of the lack of high-quality evidence supporting their efficacy and the risk of adverse events including vomiting, seizures, and

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arrhythmias.[6,8] In this context, recent studies have also reported decreases in methylxanthine use for ED patients with acute asthma in other developed nations.[9,10] Furthermore, similar practice changes have been reported in the primary care setting in Japan.[11] Nevertheless, despite the clinical importance, there has been no study that investigates the current methylxanthine use for acute asthma in Japanese EDs.

To address the knowledge gap in published reports, we aimed to describe the current practice on methylxanthine use for acute asthma in the ED by using a multicenter dataset of patients with acute asthma from 23 EDs in Japan. Additionally, we further examined the factors associated with methylxanthine use in the ED.

METHODS

Study design and setting

THIS IS A secondary analysis of multicenter chart review study to characterize patients with acute asthma and their management in EDs across Japan. The study design, setting, participants, methods of measurement, and measured variables have been reported previously.[12] Briefly, this study was coordinated by the Japanese Emergency Medicine Network (JEMNet), a consortium of 23 academic and community medical centers from different geographic regions across Japan (http://jemnet.asia/wp). All 23 EDs were staffed by ED-based attending physicians. All patients were managed at the discretion of the treating physician. The Institutional Review Board of each participating center and Massachusetts General Hospital (Boston, MA, USA) approved the study with a waiver of written informed consent before data collection.

Participants

The abstractors at each site identified all ED visits with the principal discharge diagnosis of asthma by using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM)[13] code J45.xx from January 2009 to December 2011. Inclusion criteria were visits made by patients aged 18–54 years with a history of physician-diagnosed asthma prior to the index visit, who presented to the ED with acute asthma.[12,14] We excluded: (i) visits made by patients with a history of physician-diagnosed chronic obstructive pulmonary disease, emphysema, or chronic bronchitis, (ii) transfer visits, (iii) repeat visits by the same subject, or (iv) visits not prompted largely by acute asthma. In the case of repeat visits, only the first ED visit during the study period was included.

Data measurement

Data collection

Onsite chart abstractors reviewed 60 randomly selected ED charts from January to December 2011. Sites with fewer than 60 eligible ED visits during this period also reviewed eligible ED visits from the calendar years 2009 and 2010 to reach the target number of 60 charts. All chart abstractors were emergency physicians or emergency medicine residents. Abstractors were trained with a 1-h lecture, and then the abstractors completed practice charts, which were examined versus a "criterion standard." If an abstractor's accuracy was <80% per chart, the individual was retrained. All forms were reviewed by site investigators and submitted to a secure, web-based, electronic database. Finally, all data were reviewed by the JEMNet Coordinating Center, and site investigators were queried about missing data and discrepancies identified by manual data checks.

Emergency department-level covariates

The collected ED-level covariates included the number of annual ED visits, number of annual ED patients with acute asthma, number of ED beds, number of full-time emergency physicians, affiliation with an emergency medicine residency program, having an bundle for asthma treatment, having a protocol for asthma treatment, and urban–rural distinction. Rural and urban distinction was made according to the criteria of the Japanese Ministry of Land, Infrastructure, Transport, and Tourism.[15]

Patient-level covariates

By using a standardized form, the trained site investigators abstracted the patient-level data, including demographics, asthma history, current asthma medications, patient presentation (e.g., duration of symptoms, initial oxygen saturation, and complicated infection), treatment in the ED, and ED disposition (e.g., hospital admission). This standardized form has been used in multiple US-based studies undertaken by the Emergency Medicine Network.[16–23]

Statistical analysis

Summary statistics at both the ED and patient levels were presented as proportions with 95% confidence intervals (CI) and medians with interquartile ranges (IQR) as appropriate, according to methylxanthine use in EDs. Next, to determine the associations of ED and patient characteristics with methylxanthine treatment for acute asthma, we fitted a

multivariable generalized linear mixed (random-effect) model using methylxanthine use as a binomial response, adjusting for patient clustering within hospitals. We included a predefined set of ED-level factors (the number of annual ED patients with acute asthma, having bundle for asthma treatment, having protocol for asthma treatment) and patient-level factors (age, history of hospital admission for asthma, current use of oral methylxanthines, duration of symptoms, initial oxygen saturation, concurrent infection, and systemic corticosteroid use in the ED). The number of annual ED patients with acute asthma was considered as a continuous variable for increments of 100 annual ED patients. To address missing data, we used multiple imputations with the chained equation method[24] to generate and analyze 20 multiply imputed datasets. The percentage of missing values across the 11 variables varied between 0% and 38% (Table S1). In brief, the missing values were imputed under fully conditional specifications[25] using the covariates of the multivariable models above, sex, current smoking status, current use of inhaled corticosteroids, current use of leukotriene modifiers, dose of inhaled β-agonists in ED, and ED disposition. The imputed values were estimated with multiple regression applied to each imputed dataset separately. These estimates and their standard errors were combined using Rubin's rules.[24] In the sensitivity analysis, we also repeated the analysis using only the patients without any missing data. The analysis was undertaken using JMP 11.0 (SAS Institute Japan, Tokyo, Japan); imputation was carried out by using R 2.13.1 (R Foundation for Statistical Computing, Vienne, Austria) with the default strings of the *mice* 2.12 package.[26] All *P*-values were two-tailed, with $P < 0.05$ considered statistically significant.

RESULTS

Patient characteristics

FROM 2009 to 2011, we identified 1,380 patients with acute asthma who presented to one of the 23 participating EDs. The ED characteristics are shown in Table S2. The median number of annual ED visits was 29,000 (IQR, 20,000–38,000) and the number of annual ED patients with acute asthma was 107 (IQR, 59–123). Approximately 90% of EDs were residency affiliated and located in urban areas.

The patient characteristics are shown in Table 1. Overall, the median age was 35 years (IQR, 26–43 years) and 42% were men. Methylxanthines were used for 79 patients (5.7%; 95% CI, 4.6–7.0%) in the ED. Patients who were treated with methylxanthines in the ED were older, more likely to have used oral methylxanthines prior to the ED visit, more likely to have lower initial oxygen saturation (94% versus 96%; $P < 0.001$), and more likely to be hospitalized (all $P < 0.05$) compared to those who did not receive methylxanthines in the ED. Figure 1 shows the rate of methylxanthine use among the 23 participating EDs. Methylxanthines were used for acute asthma in 15 EDs, with a wide variation in the rate, ranging from 0% to 26.1%.

Table 1. Characteristics of adult patients who visited 23 Japanese emergency departments (ED) with acute asthma, grouped according to methylxanthine treatment in the ED

Variable	Treated with Methylxanthine (*n* = 79)	Not treated with methylxanthine (*n* = 1,301)	*P*-value
Age, years; median (IQR)	41 (28–46)	34 (26–42)	0.020
Male sex	31 (39)	542 (41)	0.720
History of hospital admission for asthma	7 (8)	71 (5)	0.20
Current use of oral methylxanthine	20 (25)	132 (10)	<0.001
Duration of symptoms			
≤3 h prior to ED arrival	10 (12)	216 (16)	0.520
>3 h	64 (81)	1,043 (80)	
Initial oxygen saturation, %; median (IQR)	94 (91–97)	96 (94–98)	<0.001
Concurrent infection	30 (37)	506 (38)	0.900
Systemic corticosteroid use in ED	67 (84)	515 (39)	<0.001
Hospital admission	18 (22)	140 (10)	0.003

Data are expressed as *n* (%) unless otherwise specified.
IQR, interquartile range.

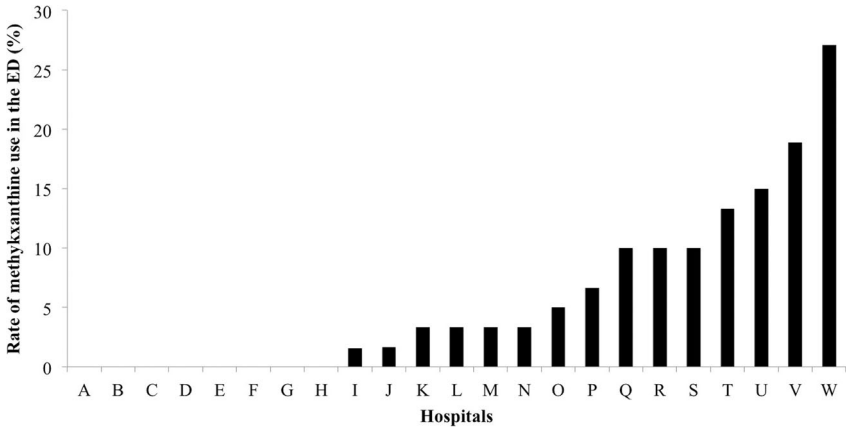

Fig. 1. Rate of methylxanthine use for acute asthma in 23 Japanese emergency departments (ED) by hospital (identified as A–W). The rate of methylxanthine differed greatly across the 23 participating hospitals, ranging from 0% to 26.1%. Eight hospitals (34.7%) did not use methylxanthines for acute asthma in the ED whereas seven hospitals (30.4%) used methylxanthines in >10% of patients with acute asthma.

Emergency department- and patient-level factors associated to methylxanthine use in the ED

Table 2 shows the factors associated with methylxanthine treatment in the ED. In terms of ED-level factors, the number of annual ED patients with acute asthma was associated with a lower likelihood of methylxanthine treatment in the ED (OR per 100 increase in annual asthma patients in the ED, 0.12; 95% CI, 0.04–0.34; $P < 0.001$) whereas having a protocol for ED asthma treatment was associated with a higher likelihood of methylxanthine treatment in the ED (OR 2.91; 95% CI, 1.06–8.00; $P = 0.04$). In terms of patient-level factors, systemic corticosteroid use in the ED was significantly associated with a higher likelihood (OR 6.39; 95% CI, 3.34–12.22; $P < 0.001$), whereas current use of oral methylxanthine was not significantly associated ($P > 0.05$). In the sensitivity analysis, that is, the complete case analysis with a limited statistical power, the results did not materially change except for the non-significant association of having a protocol for ED asthma treatment with methylxanthine treatment.

DISCUSSION

IN THIS ANALYSIS of 1,380 randomly sampled patients with acute asthma in 23 Japanese EDs, we found that 6% of acute asthma was treated with methylxanthines in Japanese EDs, with a wide variation in their use across EDs (from 0% to 26.1%). In the multivariable analysis, the number of annual ED patients with acute asthma was significantly associated with a lower likelihood of methylxanthine use in the ED, whereas having a protocol for asthma treatment and systemic corticosteroid use in the ED were associated with a higher likelihood. To the best of our knowledge, this is the first study to report the current practice of methylxanthine use for patients with acute asthma in the Japanese ED.

Methylxanthine is a bronchodilator agent that might also improve respiratory muscle function through increases in mucociliary clearance and actions to stimulate respiration.[27–29] Methylxanthines could also show anti-inflammatory and immunomodulatory actions that are associated with apoptosis of granulocytes.[28,29] These potential mechanisms had supported methylxanthine treatment for patients with acute asthma over decades. However, the current international guidelines no longer recommend methylxanthines for acute asthma treatment because of the narrow therapeutic concentration window that can result in adverse effects including vomiting, arrhythmias, and seizure.[8] In addition, the 2012 and 2018 meta-analyses of >40 randomized controlled trials have indicated that methylxanthine use did not improve lung function or hospital admission rate in ED patients with acute asthma but increased the risk of adverse events.[8,30] With the dissemination of the current international guidelines, methylxanthine use has decreased in other industrialized nations. For example, in Australia, only 4 of 421 adult patients with acute asthma (<1%) were treated with methylxanthines.[9] In a single-center study in Brazil, the rate of patients treated with methylxanthines had decreased from 11.1% in 2001 to 1.0% in 2005.[10] By contrast, in our multicenter analysis of Japanese EDs, the rate of

Table 2. Factors associated with treatment with methylxanthine in patients with acute asthma who visited Japanese emergency departments (ED)

Variables	Primary analysis using multiple imputation		Sensitivity analysis using complete cases	
	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
ED-level characteristics				
Number of annual ED patients with acute asthma (per 100 patients)	0.12 (0.04–0.34)	<0.001	0.03 (0.01–0.13)	<0.001
Having bundle for asthma treatment	2.09 (0.87–5.02)	0.100	1.73 (0.68–4.41)	0.250
Having protocol for asthma treatment	2.91 (1.06–8.00)	0.040	3.05 (0.86–10.79)	0.080
Patient-level characteristics				
Age, years				
18–29	Reference		Reference	
30–39	0.45 (0.22–0.93)	0.030	1.13 (0.36–3.52)	0.840
40–54	1.20 (0.68–2.13)	0.530	1.39 (0.51–3.77)	0.520
History of hospital admission for asthma	2.30 (0.99–5.39)	0.054	2.63 (0.88–7.84)	0.080
Current use of oral methylxanthine	1.82 (0.96–3.44)	0.070	1.60 (0.58–4.44)	0.360
Duration of symptoms				
≤3 h prior to ED arrival	Reference		Reference	
>3 h	0.99 (0.47–2.07)	0.980	0.61 (0.22–1.69)	0.340
Initial oxygen saturation				
≥94%	Reference		Reference	
<94%	1.35 (0.77–2.34)	0.290	1.62 (0.70–3.74)	0.260
Concurrent infection	0.99 (0.58–1.71)	0.980	1.69 (0.66–4.33)	0.280
Systemic corticosteroid use in ED	6.39 (3.34–12.22)	<0.001	22.33 (4.76–104.69)	<0.001

CI, confidence interval; OR, odds ratio.

methylxanthine use was relatively higher than these prior studies from other nations.

The current study also showed a wide interhospital variation in the rate of methylxanthine use: one-third of EDs did not use methylxanthines, whereas another one-third used methylxanthines in more than 10% of patients with acute asthma. The reasons for the observed variation are likely multifactorial. First, some EDs could have had capacity to measure the serum concentration of methylxanthines in 24/7. Emergency physicians in such EDs might have preferred methylxanthines for acute asthma. Second, the observed high prevalence of oral methylxanthine use (25% in the methylxanthine group) suggests the potential role of patients' preference (and their health beliefs) and chronic asthma medications in the choice of acute asthma management options in the ED. Third, the current Japanese guidelines still list methylxanthine use for moderate to severe acute asthma as a therapeutic option,[31] which provides some support to their use against the recommendations based on the international guidelines. Additionally, the Japanese guidelines created by pulmonologists and allergists might have also affected the ED protocol for asthma management. As inpatient care is generally managed by these specialists, ED protocols might have included methylxanthines for treatment according to their preference. Indeed, in the current study, having a protocol for asthma treatment was associated with a higher likelihood of methylxanthine use. Finally, these potential mechanisms are not mutually exclusive.

The discrepancies in the recommendations of methylxanthine use for acute asthma between the Japanese and international guidelines should be addressed based on high-quality evidence. The current Japanese guidelines recommend methylxanthines for moderate to severe acute asthma by citing a small trial of 53 Japanese patients with acute asthma in 1996.[5] This study only examined physiologic measures (e.g., pulmonary function) but did not examine the clinically important outcomes, such as ED length of stay or hospital admission rate. In contrast, for example, the current Global Initiative for Asthma guidelines do not recommend methylxanthine use. The recommendation is based on the 2012 meta-analysis included 17 studies involving 739 patients (353 methylxanthines versus 386 non-

methylxanthines).[8] The currently available evidence (i.e., the lack of additive effects of methylxanthines to β2-agonists and the higher adverse event rates), in conjunction with the complexity of monitoring the serum concentration in the ED, lends support to the avoidance of methylxanthine use in ED patients with acute asthma.

Potential limitations

The current study has several potential limitations. First, this study relied on chart review for data collection, which is a potential source of bias.[32] However, a previous study of ED patients with acute asthma reported that the data accuracy by chart review was similar to that by direct observation, specifically on ED treatments (κ-statistic, 0.55–0.82).[33] Additionally, in this multicenter study, the interobserver agreement was also moderate to perfect (κ-statistic, 0.56–1.00).[12] Second, this study did not examine the relationships between methylxanthine treatment in the ED with patient outcomes (e.g., adverse events and in-hospital mortality). Although the methylxanthine group had a higher hospital admission rate compared to the non-methylxanthine group, the results might have been confounded by severity (e.g., acute severity of asthma exacerbation and chronic asthma severity). Nevertheless, the goal of the current study was to investigate inappropriate methylxanthine use in the ED, which is no longer recommended by international asthma guidelines.[7] Third, the imputation of missing data is another potential source of bias. However, the results did not differ materially between the analysis using imputed data and complete case analysis. Fourth, the data did not include information on the reasons why ED physicians used methylxanthines. Fifth, we do not have information on annual changes in methylxanthine use in Japanese EDs. Therefore, this study was unable to report whether the rate of methylxanthine use had increased or not over years. Finally, as our study sample consisted of 23 EDs (i.e., only a portion of Japanese EDs), and predominantly EDs affiliated with a residency program in urban areas, these results might not be generalizable to asthma management practice in non-academic or rural EDs. Regardless, as the participating EDs train future emergency physicians, these hospitals have disproportionate effects on the quality of current and future ED care of acute asthma.

CONCLUSIONS

BY USING MULTICENTER data of patients with asthma exacerbation from 23 EDs across Japan, we found that approximately 6% of patients were treated with methylxanthines with a wide interhospital variation in their use. The number of annual ED patients with acute asthma was significantly associated with a lower likelihood of methylxanthine use, whereas having a protocol for asthma treatment and systemic corticosteroid use in the ED were associated with a higher likelihood. Our multicenter data indicated that most ED physicians avoid methylxanthine use for acute asthma. However, the existing discrepancies between the asthma guidelines complicate the current practice on acute asthma management in the ED. Our findings underscore the importance of developing consistent evidence-based guideline recommendations, which will, in turn, advance excellence in patient care and improve outcomes of patients with acute asthma.

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DISCLOSURE

Approval of the research protocol: The Institutional Review Board of each participating center and Massachusetts General Hospital approved the study with a waiver of written informed consent before data collection.
Informed consent: N/A.
Registry and the registration no. of the study: N/A.
Animal studies: N/A.
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APPENDIX I

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Details of missing data

Table S2. Characteristics of 23 participating emergency departments (EDs)