Significance of the Therapeutic Range of Serum Theophylline Concentration in the Treatment of an Attack of Bronchial Asthma

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The purpose of this study was to evaluate the accuracy of the recommended theophylline therapeutic range in the treatment of acute airway obstruction. Twenty seven patients (20 to 64 years) with acute asthma attack were given aminophylline intravenously to obtain a theophylline concentration between 10 and 20 $\mu\text{g/ml}$. Peak expiratory flow rates (PEFR) and serum theophylline concentrations were measured before and after aminophylline injection. When a marked improvement was not seen after aminophylline injection, the treatment was followed by inhalation of a β -agonist and intravenously administered hydrocortisone. In order to clarify the relationship between theophylline efficacy at a therapeutic level and PEFR, as measured before aminophylline administration, the patients were classified into four groups. Group A ($n=7$): asthma attack persisted regardless of treatment with aminophylline, β -agonist and hydrocortisone, group B ($n=7$): asthma attack improved by aminophylline, β -agonist and hydrocortisone, group C ($n=6$): asthma attack improved by both aminophylline and β -agonist, group D ($n=7$): asthma attack improved by intravenous aminophylline alone. The means ($\pm$ S.E.) PEFR before aminophylline administration were $94.3 \pm 11.31/\text{min}$ in group A, $114.3 \pm 10.01/\text{min}$ in group B, $196.7 \pm 22.21/\text{min}$ in group C, and $220.0 \pm 12.51/\text{min}$ in group D, respectively. There were significant differences in PEFR between the A and C, A and D, B and C, and B and D groups. These findings suggest that theophylline efficacy is not expected in patients with low PEFR (less than 200 l/min) at the time of treatment of an attack, even if a therapeutic theophylline concentration was obtained.

Key words theophylline; therapeutic range; peak flow; bronchial asthma; serum concentration

Since theophylline, a xanthine derivative, possesses a relaxing action on the smooth muscle of the bronchi, it is used as one of the first choice drugs in the treatment of bronchial asthma.^{1,2)}

In recent years, the relation between the dose and therapeutic effect of drugs has been investigated using serum concentrations. The therapeutic range of serum drug concentration is determined by pharmacokinetic theories.³⁾

The therapeutic range of serum theophylline concentration is known to be 10 to 20 $\mu\text{g/ml}$.^{4,5)} The method by which the therapeutic range of serum concentration is clinically applied is called therapeutic drug monitoring (TDM), and the application of TDM has improved the therapeutic results of theophylline in the treatment of bronchial asthma.^{6–8)}

Many methods of analysis, which are capable of easily measuring serum drug concentration in clinical practice, have been developed and installed in a number of medical institutions. When proceeding with theophylline treatment while measuring serum drug concentration in patients with bronchial asthma, we have encountered some patients in whom no effect was observed, despite practical achievement of the therapeutic range of theophylline concentration. Therefore, the clinical significance of the therapeutic range of the drug must be investigated in more detail.

MATERIALS AND METHODS

Subjects (Table 1) Twenty-seven patients with bronchial asthma who visited the outpatient service of the Department of Internal Medicine at Nippon Medical

School, Tama Nagayama Hospital, because of an attack of bronchial asthma despite being treated with oral sustained-release theophylline preparations, were studied. They showed serum theophylline concentrations below 10 $\mu\text{g/ml}$ at the time of visit; (12 patients are males and 15 females; age: ranged from 20 to 64 years, mean $\pm$ S.E. 40.3 ± 2.6).

Study Design (1) Measurement of the Peak Expiratory Flow Rate (PEFR): Prior to treatment, a Mini Wright Peak Flow Meter (Clement Clarke Co., Ltd.) was used to measure the peak expiratory flow rate (PEFR) in all patients while in the sitting position. The presence or absence of experience in using the Mini Wright Peak Flow Meter was determined in all the patients. An explanation of the method of measurement was given, and a demonstration of the measurement was conducted for those patients who had no experience with its use. Subsequently, five measurements were performed, and the maximum measurement on three occasions, after excluding the values obtained on the first and second occasions, was considered as the PEFR at the time of visit. Measurements were conducted on three occasions in those patients experienced at using the meter, and the maximum value obtained on these occasions was considered the PEFR. Furthermore, those patients whose measured values were below 60 l/min on all three occasions, the lowest detection limit of this PEFR meter, were excluded from this study.

(2) Measurement of Serum Theophylline Concentration: Blood (1 ml) was collected to measure serum theophylline concentration immediately after the measurement of PEFR. Vision® (Dynabott Co., Ltd.), a biochemical autoanalyzer, was used to measure the concen-

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Table 1. Subjects Data

Pt No.	Age (y.o.)	Sex	Ht (cm)	B.W. (kg)	Age of disease development	Frequency of visits to hospital in emergency outpatient service (Times/year)	Treatment period ^{b)}	Status of chronic stage ^{c)}	Combination drug ^{d)}			
									β	S	M	A
A1	31	M	173	60	30	3	A	Step 2	○		○	
A2	22	F	159	49	P	7	D	Step 3	○	○	○	○
A3	57	M	172	60	P	2	D	Step 1			○	
A4	33	F	152	42	28	5	B	Step 3	○	○	○	
A5	50	M	160	54	40 ^{a)}	2	D	Step 1				
A6	40	F	172	58	P	3	D	Step 2	○		○	
A7	64	M	164	61	45	1	D	Step 1				
B1	27	F	150	38	23	6	B	Step 3	○	○	○	
B2	22	F	159	52	P	2	D	Step 1	○			
B3	59	F	156	59	40 ^{a)}	4	D	Step 3	○	○	○	
B4	28	M	176	70	P	2	D	Step 1	○			
B5	45	M	160	62	45	1	B	Step 1				
B6	29	M	160	55	P	3	D	Step 2	○		○	
B7	50	F	149	49	48	3	B	Step 2	○		○	
C1	24	F	155	45	P	2	D	Step 2				
C2	35	F	156	53	P	7	D	Step 4	○	○	○	○
C3	51	F	150	55	40 ^{a)}	4	D	Step 3	○		○	○
C4	58	M	172	60	30 ^{a)}	1	D	Step 1	○			
C5	35	M	170	75	35	1	A	Step 1			○	
C6	48	M	160	55	20 ^{a)}	3	D	Step 2	○			
D1	24	F	162	48	P	2	D	Step 2	○			
D2	31	F	157	42	P	3	D	Step 2	○		○	
D3	54	F	158	55	30 ^{a)}	6	D	Step 3	○	○	○	○
D4	20	F	155	45	17	5	B	Step 3	○	○	○	○
D5	46	M	170	59	46	1	A	Step 1	○			
D6	57	M	172	70	30 ^{a)}	1	D	Step 1				
D7	48	F	155	47	35	2	A	Step 1	○			

All the patients have been prescribed β -stimulant aerosols. All the patients have received theophylline RTC regimen. All the patients are non-smokers or have no history of smoking within the last year. P, since their childhood (before the age 15), a) Approximate age, b) A, within 1 year; B, 1–5 years; C, 6–10 years; D, more than 10 years. c) Classification according to the management of asthma (Japanese Guidelines), d) Combination drug, β , β -stimulants; S, steroids; M, mast cell stabilizers; A, anticholinergics.

tration. This system is called a two-dimensional centrifugation-based simple biochemical autoanalyzing system, and has been developed with an aim to be installed in the consultation room to rapidly conduct required tests. Serum theophylline concentration is one of the items which can be measured by the device. This system measures serum theophylline concentration according to a homogeneous enzyme immunoassay which uses acetylcholinesterase inhibitor-labeled theophylline. Setting of the sample-added specified reagent pack to a Vision® analyzer will automatically conduct in the reagent pack a series of procedures for measurement, e.g., blood cell separation, serum uptake, reagent separation, mixing, and absorbance determination.⁹⁾

Method Assuming that the distribution volume of theophylline is 0.451/kg and aminophylline contains 80 percent theophylline, the dose of aminophylline (Neophyllin® injection) was calculated in each patient using Eq. 1, which is designed to allow the serum concentration of theophylline to reach 17.5 $\mu\text{g}/\text{ml}$ at the time of termination of the drip infusion of aminophylline. The dose of aminophylline calculated using this formula was mixed in 100 ml of physiological saline and infused in a 30-min period.

$$\text{dose (mg) of aminophylline} = (17.5 - c) \times 0.45 / 0.8 \times B.W. \quad (1)$$

Where, C: Serum theophylline concentration at the time of visit to hospital ($\mu\text{g}/\text{ml}$)

B.W.: Actual body weight and standard body weight, whichever is smaller (kg).

Blood was re-collected 5 min after the termination of aminophylline administration to measure serum theophylline concentration, and the concentration was thus confirmed to have reached a level over the therapeutic range of 10 $\mu\text{g}/\text{ml}$. Simultaneously, clinical features, e.g., status of improvement of rale in the chest and subjective symptoms, were based to judge the actions of theophylline. The PEFR was re-measured at the same time. The patients were allowed to go home when symptoms were improved by aminophylline administration and such improvement lasted for 1 h. Inhalatory administration of 50 μg of procaterol hydrochloride (Meptin® inhalation solution) was used for 20 min in those patients who failed to improve, despite achievement of the therapeutic range of theophylline. These patients were allowed to go home when the attack was improved and such improvement lasted for 1 h.

Hydrocortisone sodium phosphate (Hydrocorton Phosphate®) was subsequently administered to those patients whose bronchial asthma attacks failed to improve, even after nebulization using 300 to 500 mg of hydrocorton Phosphate®, mixed in 500 ml of Solita T3®, was given by 2-h intravenous drip infusion. Effects were similarly judged after the termination of administration of hydro-

cortisone sodium phosphate. The patients who finally failed to show improvement were admitted to the hospital for treatment.

Statistical Analysis Statistical analysis was performed using Student's *t*-test.

RESULTS

Therapeutic Effect of Theophylline on Bronchial Asthma Attack Using the Therapeutic Range Intravenous drip infusion of aminophylline was used to attain a serum theophylline concentration in a therapeutic range. However, there was a considerable number of patients whose asthma attacks failed to improve. The patients were classified into the following four groups according to the therapeutic course after intravenous drip infusion of aminophylline;

Group A: Seven patients who failed to attain the disappearance of the attack, despite the inhalation of a β -agonist in a nebulized solution and intravenous drip infusion of hydrocortisone sodium phosphate after intravenous drip infusion of aminophylline, finally requiring hospitalization. The mean ($\pm$ S.E.) age was 42.4 ± 5.8 years, height 164.4 ± 3.1 cm, and body weight 54.7 ± 8.9 kg.

Group B: Seven patients who failed to attain the disappearance of the attack following the intravenous drip infusion of aminophylline and the inhalation of a β -agonist of nebulized solution, but attained it by intravenous drip infusion of hydrocortisone sodium phosphate. The mean ($\pm$ S.E.) age was 37.1 ± 5.3 years, height 158.6 ± 3.0 cm, and body weight 55.0 ± 3.9 kg.

Group C: Six patients who attained the disappearance of the attack by intravenous administration of aminophylline and the inhalation of a β -agonist of nebulized solution. The mean age ($\pm$ S.E.) was 41.8 ± 5.2 years, height 169.5 ± 3.6 cm, and body weight 57.2 ± 4.1 kg.

Group D: Seven patients who attained the disappearance of the attack by intravenous administration of aminophylline alone. The mean ($\pm$ S.E.) age was 40.0 ± 5.6 years, height 161.3 ± 2.7 cm, and body weight 52.3 ± 3.7 kg.

No statistically significant difference was noted among the groups in terms of the mean age, mean height, and mean body weight.

Aminophylline Dose and Changes in Serum Theophylline Concentration (Fig. 1) (Fig. 2) Serum theophylline concentrations at the time of visit to the hospital were between $4.4 \mu\text{g/ml}$ and $9.6 \mu\text{g/ml}$, with a mean ($\pm$ S.E.) concentration of $7.47 \pm 1.59 \mu\text{g/ml}$. The mean serum theophylline concentration in each group was as follows: $7.21 \pm 0.44 \mu\text{g/ml}$ in group A; $7.40 \pm 0.62 \mu\text{g/ml}$ in group B; $7.70 \pm 0.76 \mu\text{g/ml}$ in group C; and $7.61 \pm 0.74 \mu\text{g/ml}$ in group D, respectively. No statistically significant difference was noted among the groups.

The mean ($\pm$ S.E.) dose of aminophylline in all patients was 294.4 ± 60.2 mg. The mean ($\pm$ S.E.) dose of aminophylline in each group was as follows: 307.1 ± 24.8 mg in group A; 292.9 ± 18.7 mg in group B; 291.7 ± 31.4 mg in group C; and 285.7 ± 23.1 mg in group D. No statistically significant difference was noted among the groups.

Fig. 1. Comparison of Theophylline Serum Concentrations among Four Groups before and after Intravenous Administration of Aminophylline

Differences among each group were not statistically significant.

Fig. 2. Average Intravenous Dose of Aminophylline

Differences among each group were not statistically significant.

The mean ($\pm$ S.E.) serum theophylline concentration in all patients after the administration of aminophylline was $16.6 \pm 2.59 \mu\text{g/ml}$. The mean ($\pm$ S.E.) serum theophylline concentration in each group was as follows: $16.5 \pm 1.01 \mu\text{g/ml}$ in group A; $16.5 \pm 1.19 \mu\text{g/ml}$ in group B; $17.9 \pm 0.54 \mu\text{g/ml}$ in group C; and $15.4 \pm 1.03 \mu\text{g/ml}$ in group D. No statistically significant difference was noted among the groups in terms of the serum theophylline concentration after administration of aminophylline.

PEFR at the Time of Visit to the Hospital and after Aminophylline Injection (Fig. 3) (Fig. 4) The PEFRs of the patients at the time of their visits to the hospital were between 60 to 280 l/min, with a mean ($\pm$ S.E.) of 154.8 ± 64.51 l/min. The mean ($\pm$ S.E.) PEFR in each group was as follows: 94.3 ± 11.31 l/min in group A; 114.3 ± 9.97 l/min in group B; 196.7 ± 22.21 l/min in group C; and 220.0 ± 12.5 l/min in group D. A statistically significant difference was noted: between groups A and C ($p < 0.01$); between groups A and D ($p < 0.001$); between groups B and C ($p < 0.01$); and between groups B and D ($p < 0.001$). The PEFR after the administration of aminophylline was between 70 and

Fig. 3. PEFR before Intravenous Administration of Aminophylline
Data connected with horizontal lines were significantly different between 2 groups (* $p < 0.01$, ** $p < 0.001$).

Fig. 4. PEFR after Intravenous Administration of Aminophylline
Statistically significant difference in the PEFR was seen after aminophylline administration. (** $p < 0.001$). The PEFR after aminophylline administration had a tendency to increase. (* $p < 0.1$).

380l/min, with a mean ($\pm$ S.E.) of 214.1 ± 12.5 l/min. The mean ($\pm$ S.E.) PEFR in each group was as follows: 102.9 ± 23.6 l/min in group A; 122.9 ± 29.3 l/min in group B; 291.2 ± 39.2 l/min in group C; and 350.5 ± 20.0 l/min in group D. The time-course of the changes in the mean PEFR observed before and after the administration of aminophylline revealed no statistically significant difference in groups A and B. However, group C showed a tendency to increase ($p < 0.1$), and group D showed a statistically significant increase ($p < 0.001$).

DISCUSSION

Improvement in the measurement of serum drug concentration has now enabled us to easily measure about 30 classes of drugs in daily clinical practice, and there is an increasing number of patients in whom TDM is applied clinically.³⁾ This fact has improved not only the thera-

peutic results but also the prevention of adverse reactions.¹⁰⁾ Theophylline is one of the drugs which has been investigated, especially from the pharmacokinetic viewpoint. Concrete methods of the use of theophylline have been proposed, including the invention of RTC (Round The Clock) therapy⁸⁾; dose-finding methods which consider the patient's status; and countermeasures for drug interactions in the case of combination use of the drugs.³⁾ In these circumstances, special attention has been paid to the drug therapeutic range as a parameter to examine the appropriate method of administration for individual patients.

Vision® was used to measure serum theophylline concentration in this study. Comparison of this system with the currently widely used method for serum drug concentration, FPIA (Fluorescence Polarization Immunoassay), has demonstrated that this system is highly reliable.¹¹⁾

PEFR is one of the important factors used to determine the severity of bronchial asthma. The primary parameter used to measure the severity of airway obstruction, is generally PEFR. The air speed at the time of forced expiration can be expressed using Eq. 2. Namely, the flow speed at the time of forced expiration is proportional to the airway cross-section and lung elastic pressure, and is inversely proportional to air density.

$$\text{flow speed} = \frac{\text{airway cross-section at the point where the pressure inside and outside the airway is equal} \times [2 \times \text{gravitational acceleration} \times \text{lung elastic pressure} / \text{constant} \times \text{air density}]^{1/2}}{\quad} \quad (2)$$

Apart from the factors shown in the above formula, an extrapulmonary factor, *i.e.*, the activity of the respiratory muscles, is involved in PEFR. Since the PEFR is usually determined under an ordinary atmosphere, the effect of air density is negligible. Therefore, PEFR can be determined by the airway cross-section, lung elastic pressure, and extrapulmonary factors. Concretely, the contraction speed of the respiratory muscles is involved as an extrapulmonary factor. Since the airway cross-section and pulmonary elastic pressure are reduced and the activity of respiratory muscles is decreased in obstructive pulmonary disease, PEFR will show a low value. Therefore, the usefulness of determining PEFR to diagnose and manage bronchial asthma and other disorders has been recognized in daily clinical practice, and the development of a simple and highly precise peak flow meter has progressed. The Mini Wright Peak Flow Meter, which was used in this study, is a device that is widely accepted and used at present and has gained high appreciation in terms of precision and reproducibility through a number of studies.¹²⁾ The use of a drug therapeutic range in clinical practice as represented by TDM will allow the exhibition of many opinions for the drug therapeutic range, which is broadly indicated in general. The therapeutic range indicated for each drug is an important parameter in determining the required dose which would allow the maximal exertion of the efficacy and safety inherent to the drug for an individual patient. However, we consider that the administration of a drug in a therapeutic range does not necessarily guarantee that the desired therapeutic effect of

the drug will be exerted in all patients. When a drug is used in an attempt to clinically allow the maximal exertion of the efficacy inherent to the drug, the desired clinical effects occasionally cannot be attained due to the pathological status of the patient. Therefore, it is considered that the clinical usefulness of the drug therapeutic range would be further improved if it could be possible to quantitatively demonstrate at what magnitude the drug therapeutic range exerts its clinical effects. Aminophylline tablets, sustained-release theophylline tablets, and aminophylline injections are the theophylline preparations mainly used. These preparations are used not only for alleviation at the time of attack, but also for the prevention of attack. Aminophylline injection is very frequently used as the drug of first choice at the time of an attack of bronchial asthma. In the treatment of an asthma attack, it is necessary to remove airway obstruction in a short period of time, to alleviate dyspnea of the patient, and to avoid the risk of provoking asphyxia. Therefore, the β -stimulants and theophylline preparations are used first, and steroids are then used in those patients who failed to attain improvement with the former medication. Hence, the application of steroids is determined by the result of the administration of aminophylline. Steroids were finally administered the patients who failed to attain clinical effects, even within the therapeutic range of theophylline. The retrospective analysis of such patients would lead us to consider that the use of steroids from the beginning of the treatment of asthma attack could have achieved their purpose. From the aspect of appropriate use of a drug, however, the use of steroids in all patients from the beginning of treatment involves problems. All of the patients who were subject to this study had been given the oral theophylline preparations since before the time of their visit to the hospital. However, the serum theophylline concentration measured at the time of each patients visit to the hospital was below $10\text{ }\mu\text{g/ml}$ and did not reach the therapeutic range. Furthermore, no difference was noted among the groups in terms of serum theophylline concentration. Therefore, none of the groups appeared in a condition in which the effects of theophylline were sufficiently exerted. Therefore, the intravenous drip infusion of aminophylline was conducted in each patient on the assumption that the distribution volume (V_d) of theophylline is 0.45 l/kg . Serum theophylline concentration was thus adjusted to reach the level of $10\text{ }\mu\text{g/ml}$ or higher in all patients. Consequently, seven of 27 patients showed improvement and were allowed to go home without any other treatments (group D). Another six patients failed to attain improvement with aminophylline drip infusion alone, but improved with nebulization of a β -stimulant and were allowed to go home (group C). However, the remaining 14 patients (groups A and B), in whom serum theophylline concentrations of $10\text{ }\mu\text{g/ml}$ or higher were attained, did not experience the disappearance of the attack with aminophylline; they also failed to show improvement despite nebulization of a β -stimulant, and required the injection of the steroids.

No direct review of the factors which prohibited the efficacy of aminophylline administration was noted in groups A and B of this trial. However, the following is

conjectured: attention is being paid to the correlation between inflammation-induced edema of the airways and the severity of bronchial asthma in recent studies on the physiopathology of the disease.¹³⁾

Microvascular leakage is an essential component of inflammation, and there is considerable evidence that it may be involved in asthma.¹⁴⁾ Many chemical mediators, which interact in a complex way to provide pathologic features of airway inflammation, are able to cause microvascular leakage in the airways which may result in mucosal edema, leading to airway narrowing.¹⁵⁾ The recent observation that theophylline prevents the late response to an allergen may be particularly relevant, since it implies that theophylline may provide some protection against the development of airway edema.¹⁶⁾

It is considered that the more severe the bronchial asthma is, the more markedly airway edema develops. Therefore, it is interpreted that the responsiveness to theophylline is lowered in patients with severe bronchial asthma, despite the maintenance of serum drug concentrations within the optimal effective concentrations, which hampered the manifestation of the effects of theophylline.

In this study, the mean ($\pm$ S.E.) PEFR at the time of visit to the hospital was $209.2 \pm 43.9\text{ l/min}$ in groups C and D, in which the therapeutic range of theophylline showed clinical usefulness. Therefore, these findings suggest that the patient in whom the therapeutic range of theophylline would be effected in treating an attack of bronchial asthma is that patient whose approximate PEFR is 200 l/min or higher. It was not deemed inconvenient to consider the administration of a steroid from the beginning of the treatment of an attack of bronchial asthma in the patient showing a PEFR below that level. In the treatment of an attack of bronchial asthma, the usefulness of the therapeutic range of theophylline was considered high in the patient whose PEFR was 200 l/min or higher.

CONCLUSIONS

1. To investigate the clinical usefulness of the therapeutic range of theophylline, the relationship between the PEFR at the time of asthma attack and the effect of theophylline given in a therapeutic range was examined.
2. The mean ($\pm$ S.E.) PEFR was $209 \pm 43.9\text{ l/min}$ in the patients in whom serum theophylline concentration reached the therapeutic range during an attack of bronchial asthma. Most of the patients whose PEFR at the time of visit to hospital was below 200 l/min failed to attain the effect of theophylline, even when it was administered in a manner to reach its therapeutic range. These patients required the administration of a steroid.
3. Maintained at its therapeutic range, theophylline is expected to exert a positive effect in patients whose PEFR was 200 l/min or higher, and it is necessary to consider the administration of a steroid from the beginning of the treatment in the patient whose PEFR is below that level.
4. We suggest that the broadly indicated therapeutic range (10 to $20\text{ }\mu\text{g/ml}$) of theophylline shows high clinical usefulness in patients whose PEFR at the time of an attack of bronchial asthma is 200 l/min or higher.

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