Application for the Inclusion of Aminophylline in the WHO Model List of Essential Medicines

SUBMITTED BY:

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Chronic Respiratory Disease And Arthritis
Management of Noncommunicable Disease  World Health Organization
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1. Summary statement of the proposal for inclusion, change or deletion

Intravenous methylxanthines including aminophylline have equivalent bronchodilator effect to inhaled $\beta_2$ agonists and recommended to treat acute exacerbation of asthma and also COPD. (Global Initiative for Asthma GINA2002, Global Initiative for Chronic Obstructive Pulmonary Disease GOLD, and Japanese Asthma Prevention and Management Guidelines 2003, see Section 7)

Since theophylline is hardly soluble, aminophylline, an ethylenediamine compound, which is soluble, is used for injection in most cases. Aminophylline is formed by a union of theophylline molecules and ethylenediamine molecules at a ratio of 2 to 1 (with theophylline accounting for about 80% in weight). In the body, ethylenediamine dissociates and theophylline exists by itself.

Intravenous aminophylline is used to treat moderate to severe asthmatic attacks with following backgrounds; aminophylline has rapid bronchodilating effects as compared to corticosteroids, aminophylline has effects on asthma patients who visited emergency department symptomatic in spite of repeated inhalation of $\beta_2$ agonists. Price of intravenous aminophylline is low in both developed and developing countries. Due to recent progress of measurement of blood level of theophylline and understanding pharmacodynamics of theophylline use of intravenous aminophylline is easier and safer. With this background intravenous aminophylline can be maintained in the list of WHO Essential Drugs.

In Japan Asthma Prevention and Management Guidelines 1989 and 2003 (1) specifies aminophylline as a remedy against acute attacks of asthma in both adults and children. Aminophylline is recommended for treatment of a moderate to severer attacks with/without inhaled $\beta_2$-adrenergic agonist. In particular, in case of severe attacks where inhalation medication does not give enough bronchodilating effect, aminophylline plays a significant role as it can be given by means of injection and also it takes effect rapidly. Moreover, few problematic cases of adverse effects have been reported when the blood concentration is controlled. Thus, in Japan, aminophylline has been long used as a remedy of acute asthma exacerbation.

On the other hand, GINA(1), representative international guidelines, recommend that the use of aminophylline should be considered when asthmatic attacks cannot be controlled with inhaled $\beta_2$-adrenergic agonist and a systematic corticosteroid, or in case a severe asthmatic attacks symptoms cannot be controlled sufficiently and hospitalization is required. The underlying reasoning for this recommendation seems that add-on effects of aminophylline were examined in cases where combination therapy of $\beta_2$-adrenergic agonist and systematic corticosteroid has already given. Therefore, it does not seem right methodologically to negate the usefulness of aminophylline.

Against this background, we explored latest literature (as of June 2004) concerning evidences of the efficacy of aminophylline against acute exacerbations of asthma (attacks), and closely reviewed references of higher quality among them. As a result, it has been ascertained that aminophylline is not only obviously effective against acute exacerbation of asthma (attacks) when used independently but also has add-on effects for patients using inhaled $\beta_2$-adrenergic agonist and corticosteroid together. Moreover, adverse effects can be safely avoided by controlling the dosage shown in the guidelines. At least a prospective survey on the safety conducted in Japan showed no serious side effects and only 0.29% for the frequency of not serious adverse effects. In addition to such efficacy, the affordability of aminophylline preparations in developing countries enhances its clinical significance. For the ground described above, again, its state as a designated essential drug should be maintained.
2. Name of the focal point in WHO submitting or supporting the application
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   Management of Noncommunicable Diseases
   World Health Organization

3. Name of the organization(s) consulted and/or supporting the application
   GINA (Global Initiative for Asthma)
   JSA (Japanese Society of Allergology)
   JSPA (Japanese Society of Pediatric Allergy and Clinical Immunology)

4. International Nonproprietary Name (INN, generic name) of the medicine
   aminophylline (WHO recommended INN)

5. Whether listing is requested as an individual medicine or as an example of a therapeutic group?
   as an individual medicine

6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)
   6.1 epidemiological information on disease burden
   GINA (Global Initiative for Asthma)
     • Asthma is one of most common chronic disease worldwide, imposing a substantial social burden on both children and adults.
     • Asthma occurs in all countries regardless of the level of development but varies greatly between populations, even within countries. There is evidence that over the last 20 years its prevalence has considerably increased, especially among children.
     • Strategies to improve asthma control can lead to socioeconomic gains in terms of improved school attendance, fewer absences from work, and, by implication, a smaller burden on families.
     • Data on asthma incidence, severity, hospitalization, and mortality are needed for all countries to assist in more effective health planning.
     • Developed economies might expect 1 to 2 percent of total health care expenditures to be spent on asthma. Developing economies are likely to face an increased demand for health care expenditures related to asthma.
     • Poorly controlled asthma is expensive to manage. Investment in preventive medication is likely to yield cost saving in emergency care for acute exacerbations.
Prevalence of Asthma

CHILDREN

The prevalence of asthma symptoms in children varies from 0 to 30 percent in different populations. Figure 2-1 shows illustrative (not comprehensive) data on the prevalence of current asthma, diagnosed asthma, recent wheeze (symptoms in the last 12 months), airway hyperresponsiveness, and atopy in children. There are many data available for Australia and England, but fewer data for other countries other than those derived from questions on wheeze in the ISAAC study.

There are large differences in asthma prevalence among different populations, with the highest prevalence found in Australia, New Zealand, and England. Data are insufficient to determine whether the differences between populations are the consequence of responses to the environment, to industrialization, or to different allergen loads. Although there is some evidence that asthma is less prevalent in children with high levels of parasitic infections, there have been no systematic studies relating parasitic infections to asthma where there has been adjustment for other environmental factors.

Figure 2-1. Prevalence of Asthma in Children

<table>
<thead>
<tr>
<th>Country</th>
<th>Study year</th>
<th>Number</th>
<th>Age</th>
<th>Current asthma</th>
<th>Diagnosed asthma</th>
<th>Recent wheeze</th>
<th>AHR</th>
<th>Atopy (SPT)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>69-72</td>
<td>2,757</td>
<td>6 to 9</td>
<td>11.1</td>
<td>7.8</td>
<td>8.6</td>
<td>6.4</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>79-86</td>
<td>2,751</td>
<td>6 to 9</td>
<td>11.1</td>
<td>7.8</td>
<td>8.6</td>
<td>6.4</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td>Australia</td>
<td>86-93</td>
<td>2,751</td>
<td>6 to 9</td>
<td>11.1</td>
<td>7.8</td>
<td>8.6</td>
<td>6.4</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>90-92</td>
<td>2,751</td>
<td>6 to 9</td>
<td>11.1</td>
<td>7.8</td>
<td>8.6</td>
<td>6.4</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td>New Zealand</td>
<td>90-92</td>
<td>2,751</td>
<td>6 to 9</td>
<td>11.1</td>
<td>7.8</td>
<td>8.6</td>
<td>6.4</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td>England</td>
<td>90-92</td>
<td>2,751</td>
<td>6 to 9</td>
<td>11.1</td>
<td>7.8</td>
<td>8.6</td>
<td>6.4</td>
<td>2.5</td>
<td>15</td>
</tr>
<tr>
<td>Summary</td>
<td>90-92</td>
<td>2,751</td>
<td>6 to 9</td>
<td>11.1</td>
<td>7.8</td>
<td>8.6</td>
<td>6.4</td>
<td>2.5</td>
<td>15</td>
</tr>
</tbody>
</table>

*Data are illustrative of the variation of childhood asthma prevalence and not a comprehensive list. Current asthma is defined as wheeze in the last 12 months, which is consistent with the data in Figure 2-1, but few conclusions can be drawn about the risk factors for wheeze in children from these data. Figure 2-3 shows changes in the prevalence of asthma symptoms in children, young adults, and adults over time. Populations were studied with the same methods on two occasions at least 9 years apart. In all cases an increase in prevalence was documented.

This trend reflects a true increase in asthma prevalence, but is also affected by a recent tendency to label all episodes of wheezing as asthma. Thus, questionnaire estimates may not be regarded as reliable measures of the true change in the prevalence of asthma over time. The reasons for the increase in the prevalence of asthma in children are poorly understood, but are discussed in the chapter on the risk factors.

Figure 2-2, from the ISAAC study, shows the prevalence of wheezing in the last 12 months—documented by written questionnaires among children 13 to 14 years old in a number of populations. The data show a wide range in the prevalence of wheezing in different populations (consistent with the data in Figure 2-1), but few conclusions can be drawn about the risk factors for wheeze in children from these data.

Figure 2-3 shows changes in the prevalence of asthma symptoms in children, young adults, and adults over time. Populations were studied with the same methods on two occasions at least 9 years apart. In all cases an increase in prevalence was documented.

This trend reflects a true increase in asthma prevalence, but is also affected by a recent tendency to label all episodes of wheezing as asthma. Thus, questionnaire estimates may not be regarded as reliable measures of the true change in the prevalence of asthma over time. The reasons for the increase in the prevalence of asthma in children are poorly understood, but are discussed in the chapter on the risk factors.
Adults

Data on prevalence of asthma in adults are more controversial. As can be seen in Figure 2-3, there has been some increase in asthma in adults, but the increase is not as striking as that in children. Figure 2-4 shows data from the adult population in the ECRHS in which airway hyperresponsiveness was measured. However, in many of these studies, the relationship between symptoms and airway hyperresponsiveness has not been reported so it is difficult to define clinically relevant asthma, especially as there was no video questionnaire to document the prevalence of wheezing in the last year that was likely to be due to asthma.

There are few data on asthma in older adults. Although some studies have demonstrated that asthma prevalence among the elderly is equal to that asthma in the elderly in underdiagnosed. Diagnosis of asthma in older adults is often confounded by similar symptoms from cardiac failure and chronic obstructive pulmonary disease, and normal age-related changes in respiratory function. It is also more difficult because lung function testing is limited in this age group and elderly group are less likely to complain about asthma symptoms and have poorer perceptions of shortness of breath than younger patients.
7. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

WHO Formulation

Theophylline and Aminophylline

Aminophylline is a representative xanthine bronchodilator. Various drugs including theophylline can serve as alternatives

Tablets, theophylline 100 mg
Modified-release tablets, theophylline 200 mg, 300 mg
Injection (Solution for injection), aminophylline 25 mg/ml, 10-ml ampoule

Uses:
chronic asthma including nocturnal asthma; acute severe asthma

Contraindications:
porphyria; known hypersensitivity to ethylenediamine (for aminophylline)

Precautions:
cardiac disease, hypertension, hyperthyroidism, peptic ulcer, epilepsy, hepatic impairment (Appendix 5), pregnancy (Appendix 2), breastfeeding (Appendix 3), elderly, fever; smokers may require larger or more frequent doses; interactions: Appendix 1

Dosage:
Chronic asthma, by mouth (as tablets), ADULT and CHILD over 12 years, 100–200 mg 3–4 times daily after food; by mouth (as modified-release tablets) ADULT 300–450 mg every 12 hours
Nocturnal asthma, by mouth (as modified-release tablets), ADULT total daily requirement as single evening dose

Note. Plasma theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose; see notes above; a range of 5–15 mg/litre (27.5–82.5 micromol/litre) may be effective and associated with fewer adverse effects

Acute severe asthma (not previously treated with theophylline), by slow intravenous injection (over at least 20 minutes), ADULT and CHILD 5 mg/kg; maintenance, by intravenous infusion, ADULT 500 micrograms/kg/hour; CHILD 6 months–9 years, 1 mg/kg/hour, 10–16 years, 800 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

Note. Patients taking oral theophylline (or aminophylline) should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage

Adverse effects:
nausea and other gastrointestinal disturbances, restlessness, anxiety, tremor, palpitations, headache, insomnia, dizziness; convulsions, arrhythmias and hypotension—especially if given by rapid injection; urticaria, erythema and exfoliative dermatitis—resulting from hypersensitivity to ethylenediamine component of aminophylline

US Pharmacopoeia

Usual adult dose
Bronchodilator
Loading dose—

For patients not currently receiving theophylline preparations—Intravenous, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight as a single dose, infused over twenty to thirty minutes, to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per ml (27.5 to 82.5 micromoles per L).

For patients currently receiving theophylline preparations—Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration.

Maintenance—

Young adult smokers—Intravenous infusion, the equivalent of anhydrous theophylline, 700 mcg (0.7mg) per kg of body weight per hour.

Otherwise healthy nonsmoking adults—Intravenous infusion, the equivalent of anhydrous theophylline, 400 mcg (0.4 mg) per kg of body weight per hour.

Older patients and patients with cardiac decompensation, cor pulmonale, or hepatic function impairment—Intravenous infusion, the equivalent of anhydrous theophylline, 200 mcg (0.2 mg) per kg of body weight per hour.
mg) per kg of body weight per hour.
Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.

Antidote (to dipyridamole toxicity)1
Intravenous, the equivalent of 50 to 100 mg (range, 50 mg up to a maximum dose of 250 mg) administered over thirty to sixty seconds.

Usual pediatric dose
Bronchodilator
Loading dose
For patients not currently receiving theophylline preparations—Children up to 16 years of age:
Intravenous, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight as a single dose over twenty to thirty minutes to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L).

For patients currently receiving theophylline preparations—Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration.

Maintenance

Note: May also be administered to infants less than 1 year as an intravenous infusion, the equivalent of anhydrous theophylline, dose in mg per kg of body weight per hour = (0.008)(age in weeks) + 0.21.
Children 1 to 9 years of age—Intravenous infusion, the equivalent of anhydrous theophylline, 800 mcg (0.8mg) per kg of body weight per hour.
Children 9 to 16 years—Intravenous infusion, the equivalent of anhydrous theophylline, 700 mcg (0.7 mg) per kg of body weight per hour.
Note: If the above maintenance dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic aminophylline dosage and minimize the risk of toxicity.
GINA 2002 recommends to consider the use of intravenous aminophylline with other regimens in case of severe episode, for patients who admitted to hospital with incomplete response to treatment within 1-2 hours, and patients who admitted to intensive care unite with poor response to the treatment within 1 hour.
In JGL 1998 intravenous aminophylline drip is recommended to be administered in case of moderate to severe asthmatic attacks with repeated inhalation of β2 agonist by nebulizer, with/without intravenous corticosteroids, and oxygen if needed. In the guidelines infusion of aminophylline (6mg/Kg) and isotonic solution (200-250ml) is recommended to be given with half dose administered in 15 minutes, and the remainder over 45 minutes. Treatment should be discontinued at appearance of any of toxic symptoms, including headache, nausea, palpitation, premature beats. In patients who are receiving regular treatment with theophylline, serum theophylline level should be monitored.

### Table 4. Management and treatment of asthma exacerbation (acute attack)

<table>
<thead>
<tr>
<th>Severity of attack</th>
<th>Dry cough</th>
<th>Shortness of breath</th>
<th>Type of treatment</th>
<th>Where performed</th>
<th>Test values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Can be down</td>
<td>Somewhat difficult</td>
<td>Inhaled β2 agonist as needed</td>
<td>At home</td>
<td>PEF 70-80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral theophylline as needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Cannot lie down (orthopnea)</td>
<td>Quicker difficult</td>
<td>Repeated inhalation of β2 agonist by nebulizer</td>
<td>Emergency medical facility of clinic or hospital, discharge from emergency facility to home if patient remains asymptomatic for 1 h</td>
<td>PEF 50-70% PaO2 &gt; 60 torr PaCO2 &lt; 45 torr SPO2 &gt; 96%</td>
</tr>
</tbody>
</table>
|                     |           |                     | Subcutaneous β2 agonist (Bromine) 
IV aminophylline drip 
IV corticosteroid 
Oxygen | |            |
|                     |           |                     | Consider inhaled anticholinergics | |            |
| Severe             | Cannot move | Cannot walk | Difficulty in speaking | Emergency room | PEF < 50% PaO2 > 60 torr PaCO2 < 45 torr SPO2 < 96% |
|                     |           |                     | Subcutaneous β2 agonist (Bromine) 
IV aminophylline drip 
IV corticosteroid 
Oxygen | |            |
|                     |           |                     | Consider inhaled anticholinergics | |            |

* Values as measured after bronchodilatation, to be used for reference.
* β2 agonist inhalation using MDI, 2 puffs every 30 min, repeated no more than twice. If symptoms do not respond to treatment, or appear to be aggravated, 1 tablet of oral β2 agonist and chlorine thalidoxilene or aminophylline (300 mg) should be given as needed.
* β2 agonist inhalation by nebulizer, repeated every 20-30 min. The patient should be monitored to ensure that pulse rate remains below 130/min.
* Bromine (epinephrine 0.1%) 0.1-0.5 ml injected subcutaneously, may be repeated at intervals of 20-30 min. Pulse rate should be maintained at below 130/min. Contraindicated in patients with ischemic heart disease, glaucoma (except open-angle simple glaucoma), or hyperthyroidism. Blood pressure and ECG should be monitored during treatment in hyopertensive patients.
* IV infusion of aminophylline (6 mg/kg) and isotonic IV solution (200-250 ml), with (1/2 dose administered over 15 min and the remainder over 45 min.
* Treatment must be discontinued at the appearance of any toxic symptoms, including headache, nausea, palpitations, or premature beats. In patients who are receiving regular treatment with theophylline, serum theophylline levels should be monitored if possible.
* IV injection of hydrocortisone (200-300 mg) or methylprednisolone (40-60 mg) every 4-6 h as required.
* Oxygen 1-2 l/min via nasal cannula.
* Continuous infusion of aminophylline, after initial infusion, same conditions apply as for footnote 9 above. Aminophylline (250 mg, 1 ampoule) is continuously infused for 5-7 h (approximately 0.6-0.8 mg/kg). Serum theophylline level should be monitored and maintained at 10-20 µg/ml (up to 15-20 µg/ml for maximum effect), with treatment discontinued immediately if toxic symptoms develop.
* Oxygen to increase and maintain PaO2 at approximately 80 torr.
* Endotracheal intubation and mechanical ventilation: intubation and mechanical ventilation of a patient in severe respiratory failure can be a high-risk procedure, and should be performed by two or more experienced specialists except in an emergency.
* ICU intensive care unit or equivalent facility where endotracheal intubation, assisted respiration, bronchial lavage, and continual monitoring of blood pressure, ECG, and oxygen saturation are available.
CHILDREN (Table 6)

Treatment of Moderate Attacks

Symptoms and Signs

Patients with moderate attacks of asthma have wheezing, suprasternal retractions, and obvious dyspnea. They appear uncomfortable, and speaking may be interrupted because of difficulty in breathing. Infants may cry feebly and show poor appetite for milk. School age and older children may report some difficulties with eating, sleeping, and other normal daily activities.

Poor response to treatment: Patients who have no obvious clinical improvement within 30 min of inhaled therapy or who have a poor response to treatment for a mild asthma attack should be advanced to step 2 treatment.

<Step 2> <for moderate attacks>

Secure an appropriate blood vessel, add 4 to 5 mg/kg of aminophylline to 20 ml of a 20% glucose or maintenance solution, then administer by IV or drip infusion over at least 20 min.

The above dose of intravenous aminophylline should be reduced by one-half if the patient has received oral sustained release theophylline or IV aminophylline within the previous 4 h. Subsequent doses should preferably be adjusted on the basis of serum theophylline levels.

The patient should be monitored for at least 60 min, after which symptoms should be reevaluated.

Inadequate response to treatment: If symptoms show no obvious improvement, the patient should again be treated with an inhaled $\beta_2$ agonist by nebulizer, and then be switched to treatment with continuous drip infusion of aminophylline. Ideally, the aminophylline dose should be adjusted by measuring and maintaining serum theophylline levels in the range of 5 to 15 µg/ml.

The patient’s condition should be reevaluated each hour. Patients who experience obvious improvement or relief of symptoms may be discharged to home with proper instructions for daily activities and a plan of treatment for periods when they are asymptomatic.

Treatment of Severe Attacks

Symptoms and Signs

Patients with severe attacks of asthma present with panting, nasal alar breathing, and severe dyspnea. They often appear anguished with pale lips, cannot walk upright, break out in cold sweats, and have interrupted speech because of difficulty in breathing. Infants may make grunting sounds. More pronounced dyspnea and confused behavior indicates a very severe asthma attack.

<Step 2> <for severe attacks>

Begin a drip infusion of aminophylline using the doses listed in table 8 as a guideline. Intravenous fluid replacement should also be started as shown in table 9. Because aminophylline metabolism is affected by many factors, including the presence of viral infections, the dose should preferably be adjusted on the basis of measured serum drug concentrations. Serum theophylline levels in excess of 15 µg/ml are associated with the development of various concentration-dependent adverse effects. Therefore, the dose of aminophylline should be adjusted to maintain theophylline levels below 15 µg/ml.
8. Summary of comparative effectiveness in a variety of clinical setting

1. Study method
At the National Library of Medicine, Advanced Medline Search (Advanced Pub Med), I searched scientific theses on allergies and respiratory organs for studies on treatment using theophylline or aminophylline in acute stages of asthma. We also referenced results of prospective safety tests conducted in Japan.

2. Clinical efficacy of aminophylline

2-1. A bronchodilating effect of aminophylline (effective blood concentrations)
Mitenko\(^2\) studied the relationship between the lung function and blood concentration in nine hospitalized asthmatic patients when intravenous aminophylline was dosed. In a range from 5 to 20µg/mL of blood concentration of theophylline, significant improvements were observed with the lung capacity and the FEV1.0 (the forced expiratory volume in 1.0 second) value in a dose-dependent manner. Side effects of tachycardia (100 - 120/min) appeared on three patients, and one of them also experienced nausea, according to the report.

Koup\(^3\) studied 72 severe respiratory cases, and reports that intravenous drips of aminophylline enable control of no less than 70% of cases with respiratory symptoms in a range from 8 to 20µg/mL of blood concentration of theophylline.

Hendekes\(^4\) used intravenous drips of aminophylline to 48 hospitalized patients with bronchial asthma and chronic obstructive pulmonary disease (or COPD), and reports that respiratory symptoms were controlled without adverse effects in a range from 10 to 20µg/mL of blood concentration of theophylline.

Carrier\(^5\) reports that intravenous infusion of theophylline took effect in adult asthmatic...
patients having minor to medium seizures, with improvements of %FEV, FEV1.0, and %PEF one hour after starting dosage, and that the effect still continued 24 hours later. The blood concentration of theophylline was 15µg/mL two hours after the start of dosage.

As described above, it has been ascertained that independent use of aminophylline improves the respiratory function without any serious adverse effects in a range of 5 to 20µg/mL of blood concentration of theophylline.

2-2. Effect to reduce the hospitalization rate and hours

Wrenn⁶ undertook a randomized placebo-controlled intervention study to assess the role of aminophylline in the treatment of acute exacerbation of asthma or COPD when used in addition to the inhaled β₂-adrenergic receptor agonist and intravenous methylprednisolone in combination. As a result, he found that the hospital admission rate of the aminophylline-treated group was 6% while that of the placebo-treated group was 21%, showing a significant difference. He reports that there was no difference between the frequency of adverse effects except for a trend toward a higher frequency of nausea.

Roberts⁷ conducted randomized double-blind tests on cases where intravenous salbutamol (15µg/kg) or instilled aminophylline (initially 5mg/kg, 0.9mg/kg/h) were dosed for children with asthma having severe acute seizures. Eventually, tests were allocated to 18 cases in the salbutamol-treated group and 26 cases in the aminophylline-treated group. As a result, it was found that the oxygen dosage time for the aminophylline-treated group was significantly shorter, that is, 7 hours against 17.8 hours for the salbutamol-treated group. Furthermore, the hospitalization period for the aminophylline-treated group was significantly shorter 57.3 hours against 85.4 hours for the salbutamol-treated group. He reports that there was no difference between the two groups in terms of adverse effects.

On the other hand, Wendel⁸ and Strauss⁹ concludes that additional dosage of aminophylline has no effect on the hospital admission rate. However, it should be noted that the paper by Wrenn⁶ referenced above was based on randomized double-blind tests on 133 patients, while Wendel⁸ conducted open tests on 65 pregnant patients and Strauss⁹ conducted tests on children aged 5 to 18, with high-dosage steroid use - intravenous methylprednisolone dosed four times a day, 1 mg/kg each time in addition to inhaled β₂-adrenergic receptor agonist. Considering the above, the report by Wrenn⁶ should be more reliable as scientific argument.

2-3. Add-on effects of aminophylline to inhaled β₂-adrenergic receptor agonist and intravenous steroid

Montserrat¹⁰ examined the add-on effects of intravenous aminophylline in hospitalized patients with seizures of asthma added to standard therapies using inhaled β₂-adrenergic receptor agonist and intravenous corticosteroids by conducting randomized placebo-controlled tests. As a result, significant increases of the lung function were observed in the aminophylline-treated group. There were no adverse effects observed in the aminophylline-treated group.

Huang¹¹ conducted randomized placebo-controlled tests to examine add-on effects of aminophylline in hospitalized adult patients with acute seizures of asthma added to inhaled albuterol and intravenous methylprednisolone in combination. Aminophylline and placebo were dosed for 48 hours. When compared 3 hours and 48 hours after the start, FEV1.0
improved significantly in the aminophylline-treated group against the placebo-treated group. Furthermore, the aminophylline-treated group needed a fewer number of albuterol inhalations. No differences were observed concerning adverse effects between the two groups.

Ohta\textsuperscript{12} conducted tests on patients with acute seizures of asthma, treating with intravenous aminophylline or inhaled salbutamol for the initial one hour, and then, if it had no effect, switching the treatment. In the aminophylline-treated group, only 6 out of 34 patients needed additional treatment with albuterol while 17 patients out of 19 in the salbutamol-treated group needed additional dosage of aminophylline. No serious adverse effects were identified in either group.

Yung\textsuperscript{13} conducted randomized placebo-controlled tests on 163 cases to examine add-on effects of aminophylline in children with severe acute seizures of asthma after using high-level inhaled salbutamol, inhaled ipratropium, and intravenous steroid. Among patients taking aminophylline, 48 cases showed remarkable improvements of spirometry after 6 hours and PaO2 (partial pressure, oxygen) for the initial 30 minutes. In the placebo-treated group, 5 patients required tracheal intubation, while none in the aminophylline-treated group needed it.

Mitra\textsuperscript{14} conducted meta-analysis of 57 randomized tests on the effects of aminophylline in children aged 2 or older with severe acute seizures that were using inhaled bronchodilator and oral steroid. From the tests, it was learned that aminophylline significantly improved expected FV1.0 6 to 8 hours after the start of dosage with the effect lasting for the subsequent 24 hours although the length of hospitalization and the number of use instances of β\textsubscript{2}--agonist nebulizer remained the same. Similarly, it significantly improved the symptom score 6 to 8 hours after the start of dosage. Based on these results, Mitra concludes that aminophylline should be considered as an additional initial remedy against severe acute seizures when seizures cannot be adequately controlled with inhaled bronchodilator and hospitalization is required.

However, Rodrigo\textsuperscript{15} conducted randomized placebo-controlled tests on 94 patients with mild to severe acute seizures of asthma who were treated with 500 mg of hydrocortisone and high-level salbutamol dosage against a placebo-treated group to examine the effects of aminophylline used in combination with salbutamol. Since there was no difference in effectiveness and adverse effects occurred at a significant rate in the aminophylline-treated group, Rodrigo does not support combined use of aminophylline. Similarly, Siegel\textsuperscript{16} conducted open tests to examine the effect of aminophylline used in combination with metaproteranol and made comparison with a group receiving metaproteranol alone. As no obvious effect was observed and the frequency of adverse effect occurrences including headache was high, Siegel does not support use of aminophylline. Strauss\textsuperscript{9} studied the efficacy of combined use of aminophylline in child patients aged 5 to 18 taking 4 dosages of 1 mg/kg methylprednisolone per day in combination with salbutamol dosage against a placebo-treated group. He reports that there was no difference between the two groups and the frequency of adverse effects was higher with the aminophylline-treated group. It should be noted, however, that those reports are based on cases using higher-level steroid dosage or inhaled β\textsubscript{2}-adrenergic receptor agonist use compared to typical cases in Japan.

The reports referenced above indicate that intravenous injection of aminophylline has add-on effects on acute exacerbations subject to use of inhaled β\textsubscript{2}-adrenergic receptor agonist and intravenous steroid. They also indicate that aminophylline has an efficacy when used independently as much as inhaled or intravenous β\textsubscript{2}-adrenergic receptor agonist use or even more. Against acute exacerbations, the GINA and many other guidelines recommend that
inhaled β2-adrenergic receptor agonist be used at home first, and if it has no effect, a clinic's assistance be sought. Those guidelines suggest addition of systematic steroid after similar treatment was repeated on outpatients only to deliver an inadequate result. However, since it takes time for steroid to demonstrate its efficacy, it is reasonable to use aminophylline that has an instant bronchodilating effect working in an action mechanism different from that of steroid.

2-4 Conclusion

From a viewpoint of an immediate efficacy of aminophylline, it can be effectively and safely used for both adults and children at acute stages of asthma in independent dosage, and also it obviously works in combination with other therapies at least in a certain groups of asthmatic patients, demonstrating its add-on effects. Besides such instant effectiveness delivered immediately after treatment, it demonstrates an aspect of its effectiveness through long-time observation including a lower hospital admission rate even in cases where no obvious add-on effects appearing after repeated use of inhaled β2-adrenergic receptor agonist and steroid use. In other words, use of aminophylline against attacks of asthma can be considered as its appropriate usage. Additionally, considering the fact that aminophylline preparations are priced low, its usefulness is even greater in developing countries. Therefore, the designation as an essential drug should be maintained.

9. Summary of comparative evidence on safety

It is said that adverse effects of aminophylline depend upon the blood concentration of theophylline.

In a report on the relationship between the blood concentration and adverse effects in 50 patients, 32 of them did not show any adverse effects and the blood concentration was in a range from 10 to 20 µg/mL with each of them (averaged at 14.6). Among them, 6 patients having minor nausea, vomiting, headache, jittery nerve, or insomnia had an average blood concentration of 27.6 µg/mL. The blood concentration of 6 patients having mild tachycardia or PVC was an average of 40.5 µg/mL. The blood concentration of 6 patients with severe multiple PVCs or ventricular tachycardia, or grand mal seizures was an average of 46.5 µg/mL.

In babies and infants, minor adverse effects may occur at a blood concentration no higher than 10µg/mL. However, serious and fatal adverse effects would be rare at a blood concentration of 20µg/mL or lower. Out of the entire population, 88% resulted from overdosage. In those cases, the blood concentration reached 30 µg/mL or higher, and 94% were subject to adverse effects. A result of meta-analysis of 57 randomized tests on infants aged 2 or older indicates that a risk of vomiting occurrences increases.

In the studies referenced in Section 3 on the efficacy of aminophylline, only minor foreseen adverse effects appeared and no serious ones were observed.

A prospective survey on the safety lately conducted in Japan among adult asthmatic patients aged 15 to 64 delivered the following result; only 2 cases out of 682 patients receiving theophylline or aminophylline experienced adverse effects (one patient with palpitation, nausea, vomiting, and tachycardia and the other with hot flush, headache, tinnitus, and perspiration), and no serious adverse effects were observed.

Based on the above, we can conclude that aminophylline is a medicine that can be used safely,
avoiding serious adverse effects by carefully controlling the dosage and the blood concentration of theophylline at 20 µg/mL or lower.

For the issue of safety, serious adverse effects can be avoided by controlling the dosage according to the guidelines. However, in cases of infants in particular, the theophylline clearance varies greatly between individuals, and infant patients are more easily affected by fever, virus infection, contents of diets, and drugs used in combination. Additionally, it should be noted that when administering aminophylline to babies, it is particularly important to measure the blood concentration and handle the dosage in a most meticulous manner.

### 10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Defined Daily Dose</th>
<th>Price</th>
<th>Price per Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophylline</td>
<td>500mg</td>
<td>0.0108–0.0184 (250mg/10ml)</td>
<td>0.0216–0.0368</td>
</tr>
<tr>
<td>Theophylline</td>
<td>400mg</td>
<td>0.0059 (200mg)</td>
<td>0.0118</td>
</tr>
<tr>
<td>Ipratropium Bromide</td>
<td>0.12mg</td>
<td>0.005–0.1810 (250mcg/1ml)</td>
<td>0.025–0.905</td>
</tr>
<tr>
<td>Salbutamol (Respol)</td>
<td>10mg</td>
<td>0.0028–0.1310 (5mg/ml)</td>
<td>0.0056–0.2620</td>
</tr>
<tr>
<td>Salbutamol (Inhaler)</td>
<td>0.8mg</td>
<td>0.0095–0.0135 (0.1mg/Dose)</td>
<td>0.0760–0.1040</td>
</tr>
<tr>
<td>Beclometasone (Inhaler)</td>
<td>0.8mg</td>
<td>0.0100–0.0191 (50mcg/Dose)</td>
<td>0.1600–0.3056</td>
</tr>
</tbody>
</table>

Table 1: Cost of daily dose (Data from the International Drug Price Indicator Guide)

### 11. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

In many countries of the world aminophylline is available commercially.

### 12. Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

British Pharmacopoeia: Available
International Pharmacopoeia: no
United States Pharmacopoeia: Available
(For reference: Japanese Pharmacopoeia: Available)

### 13. Proposed (new/adapted) text for the WHO Model Formulary

**Theophylline and Aminophylline**

Aminophylline is a representative xanthine bronchodilator. Various drugs including theophylline can serve as alternatives
Tablets, theophylline 100 mg
Modified-release tablets, theophylline 200 mg, 300 mg
Injection (Solution for injection), aminophylline 25 mg/ml, 10-ml ampoule

Uses:
chronic asthma including nocturnal asthma; acute severe asthma

Contraindications:
porphyria; known hypersensitivity to ethylenediamine (for aminophylline)

Precautions:
cardiac disease, hypertension, hyperthyroidism, peptic ulcer, epilepsy, hepatic impairment (Appendix 5), pregnancy (Appendix 2), breastfeeding (Appendix 3), elderly, fever; smokers may require larger or more frequent doses; interactions: Appendix 1

Dosage:
Chronic asthma, by mouth (as tablets), ADULT and CHILD over 12 years, 100–200 mg 3–4 times daily after food; by mouth (as modified-release tablets) ADULT 300–450 mg every 12 hours
Nocturnal asthma, by mouth (as modified-release tablets), ADULT total daily requirement as single evening dose

Note. Plasma theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose; see notes above; a range of 5–15 mg/litre (27.5–82.5 micromol/litre) may be effective and associated with fewer adverse effects

Acute severe asthma (not previously treated with theophylline), by slow intravenous injection (over at least 20 minutes), ADULT and CHILD 5 mg/kg; maintenance, by intravenous infusion, ADULT 500 micrograms/kg/hour; CHILD 6 months–9 years, 1 mg/kg/hour, 10–16 years, 800 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

Note. Patients taking oral theophylline (or aminophylline) should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage

Adverse effects:
nausea and other gastrointestinal disturbances, restlessness, anxiety, tremor, palpitations, headache, insomnia, dizziness; convulsions, arrhythmias and hypotension—especially if given by rapid injection; urticaria, erythema and exfoliative dermatitis—resulting from hypersensitivity to ethylenediamine component of aminophylline

14. References

16) Rodrigo C, Rodrigo G. Treatment of acute asthma. Lack of therapeutic benefit and increase of the toxicity from aminophylline given in addition to high doses of salbutamol delivered by metered-dose inhaler with a spacer [see comments]. Chest. 1994;106(4):1071-1076.