## Review – Aminophylline

### Background

The current 13th edition of the WHO Model Essential Medicines List (dated April 2003) includes aminophylline on the “Complementary” List. The listing is as shown below (together with the other respiratory tract medicines listed).

<table>
<thead>
<tr>
<th>25. Medicines Acting on the Respiratory Tract</th>
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<tbody>
<tr>
<td><strong>Antiasthmatic and medicines for chronic obstructive pulmonary disease</strong></td>
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</table>
| Bucal 
beclometasone | Inhalation (aerosol); 50 micrograms per dose (dipropionate); 250 micrograms (dipropionate) per dose |
| Epinephrine (adrenaline) | Injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule |
| Ipratropium bromide | Inhalation (aerosol); 20 micrograms/ metered dose |
| **Salbutamol** | Tablet, 2 mg, 4 mg (as sulfate); inhalation (aerosol); 100 micrograms (as sulfate) per dose; syrup, 2 mg/5 ml; injection, 50 micrograms (as sulfate)/ml in 5-ml ampoule; respirator solution for use in nebulizers, 5 mg (as sulfate)/ml |
| Theophylline * | Tablet, 100 mg, 200 mg, 300 mg |
| * the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee |

### Complementary List

| **Aminophylline** * | Injection, 25 mg/ml in 10-ml ampoule |
| * the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee |
| **Cromoglicate acetate** * | Inhalation (aerosol); 20 mg (sodium salt) per dose |
| * the public health relevance and/or efficacy and/or safety of this item has been questioned and its continued inclusion on the list will be reviewed at the next meeting of the Expert Committee |

Box 1: 13th Model EML listing of medicines acting on the respiratory tract

The entry in the WHO Model Formulary is more extensive, as shown in the box on the next page. Two important safety messages relevant to the use of methylxanthines are made:

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

Box 2. WHO Model Formulary 2004 entry for theophylline and aminophylline
This review therefore considers the evidence for the possible deletion of aminophylline as a specific parenteral methylxanthine in relation to the listed indications (predominantly “acute severe asthma”).

**Submissions**

An application has been lodged by the WHO Chronic Respiratory Disease and Arthritis (CRA) division of the Department of Management of Noncommunicable Diseases. Citing the support of GINA (Global Initiative for Asthma), JSA (Japanese Society of Allergology) and JSPA (Japanese Society of Pediatric Allergy), the DRA submission argues as follows:

“...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 β2-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”.

A second submission was made on behalf of the International Society of Drug Bulletins. This review concluded as follows:

“It should be retained in the WHO Model List of Essential Medicines, listed in the Formulary as a complementary agent. The Formulary entry should include a note about the need for special caution in patients who present having already taken slow release theophylline or a beta2 agonist”

A third submission, from MSF, while not supported by any literature, states: “Still useful in severe case of asthma resistant to salbutamol and hydrocortisone. MSF suggest at least to keep aminophylline injectable in the list”.

**External review**

**Current positioning of the agent in international guidelines**

The most widely quoted asthma guideline is that provided by the Global Initiative for Asthma (GINA), which was updated in 2004. Aminophylline is included as an option in the management of acute attacks of asthma, but with a considerable caveat: “The role of theophylline/aminophylline in treating exacerbations remains controversial”.

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The level of uncertainty about the mechanism of action of the methylxanthines and their place in therapy is well described in the GINA Workshop Report, as updated. Below is the section on the use as a "reliever".

"Methylxanthines"

- **Mode of administration**– Oral (ingested) or parenteral.
- **Mechanisms of action**– Theophylline is a bronchodilator that is, in general, less effective than an inhaled β2-agonist.
- **Role in therapy**– Short-acting theophylline may be considered for relief of symptoms (although its onset of action is considerably longer than that of a rapid-acting β2-agonist) **(Evidence A)**. The role of theophylline/aminophylline in treating exacerbations remains controversial. Short-acting theophylline may provide no additive bronchodilator effect over adequate doses of rapid-acting β2-agonists, but it may benefit respiratory drive or respiratory muscle function and prolong or sustain the response to rapid-acting β2-agonist between doses.
- **Side effects**– As already noted, theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. Short-acting theophylline should not be administered to patients already on long-term treatment with sustained-release theophylline unless the serum concentration of theophylline is known.

The place in therapy is further explained in a figure entitled “Hospital-Based Management of Asthma Exacerbations”. This is duplicated overleaf. It is clear from this algorithm that parenteral use of a xanthine is only to be considered when (a) the response to inhaled β2-agonist plus systemic corticosteroids has been inadequate, or (b) when inhaled β2-agonists are not available.

The British Guidelines, updated in April 2004 take a similarly cautious approach. 2 It states: “In acute asthma, the use of IV aminophylline is not likely to result in any additional bronchodilation compared to standard care with inhaled bronchodilators and steroid tablets. Side-effects such as palpitations, arrhythmias and vomiting are increased if IV aminophylline is used”. It reserves aminophylline use only for rare individuals, under the guidance of senior consultants, and after the measurement of baseline theophylline concentrations. The same advice is given in relation to children – it should be used only under intensive care conditions for life-threatening cases unresponsive to multiple doses of the first-line agents.

Please see page 137, Figure 7-11, Hospital-Based Management of Asthma Exacerbations from the GINA Workshop Report 2004.  
Evidence from systematic reviews

A number of Cochrane Reviews have considered pertinent aspects of the use of theophylline in both asthma and COPD. These are summarised below, with mention of other reviews covering the same issues.

1. Use in adults as an adjunct to inhaled β2-agonists

A Cochrane Review published in 2000 considered the following: “To determine the magnitude of effect of the addition of intravenous aminophylline to beta2-agonists in adult patients with acute asthma treated in the emergency setting.” A total of 15 studies, with 739 participants, were included. Only 3 trials included more than 30 participants per group. Overall, the authors considered the quality of the studies included only to be “moderate”. The results were as follows: “There was no statistically significant effect of aminophylline on airflow outcomes at any time period. The aminophylline treated group had higher values of PEFR at 12 (PEFR 8 L/min or 2.3%) and 24 hours (PEFR 22 L/min or 6.4%), but these were not significant (p>0.05). Two subgroup analyses were performed by grouping studies according to mean baseline airflow limitation (n = 11 studies) and the use of any steroids (n = 9 studies). There was no relationship between baseline airflow limitation nor the use of steroids on the effect of aminophylline. Aminophylline treated patients reported more palpitations/arrhythmias (OR: 2.9; 95% CI: 1.5 to 5.7) and vomiting (OR: 4.2; 95% CI 2.4 to 7.4), but no difference was found in tremor or hospital admissions”.

Notably, only 2 of the 15 included studies were from developing country settings (one each from Uruguay and Malaysia). This is reflected in the use of accurate accounts of prior theophylline use or theophylline serum concentrations as exclusion criteria. In 1 study, patients who had received 500mg or more of theophylline in the previous 24 hours were excluded. In another, patients who had used any theophylline in the same period were excluded. A third excluded patients with baseline theophylline concentrations >8mg/l, whereas a fourth excluded any who had used any bronchodilator in the preceding 3 hours. Dosing of aminophylline was also careful. In one study, a baseline theophylline concentration was first measured and then an individualized loading dose determined. In another 2 studies, the maintenance dose was adjusted to reach a target serum concentration. In 3 more studies, the size of the loading dose was reduced if theophylline had been used in the preceding 6, 12 or 24 hours. In the remaining 4 studies, including both conducted in developing countries, the method of dosing in relation to prior theophylline use was not clear. Given these careful dosing strategies, it would be appropriate to view the safety data with some caution. In addition, there were insufficient data to produce any meta-analytic results for the more serious events of hypokalaemia or convulsions.

The final conclusion is worth repeating: “There is insufficient evidence to support the routine use of aminophylline in the management of acute asthma when adequate beta-agonist treatment is provided. The development of side effects is significantly higher with aminophylline treatment than beta2-agonist therapy alone. Treatments of proven benefit should be encouraged before consideration is given to intravenous aminophylline therapy”. 
These results should also be contrasted with those for a competing intervention – systemic corticosteroids. Rowe et al. set out to “To determine the benefit of treating patients with acute asthma with systemic corticosteroids within an hour of presenting to the emergency department (ED)”.

This review included 12 studies, involving 863 patients randomised to receive either corticosteroids or placebo. The results were impressive: “Twelve studies involving 863 patients (435 corticosteroids; 428 placebo) were included. Early use of CS for acute asthma in the ED significantly reduced admission rates (N = 11; pooled OR: 0.40, 95% CI: 0.21 to 0.78). This would correspond with a number needed to treat of 8 (95% CI: 5 to 21). This benefit was more pronounced for those not receiving systemic CS prior to ED presentation (N = 7; OR: 0.37, 95% CI: 0.19 to 0.70) and those with more severe asthma (N = 7; OR: 0.35, 95% CI: 0.21 to 0.59). Oral CS therapy in children was particularly effective (N = 3; OR: 0.24, 95% CI: 0.11 to 0.53); no trials in adults used the oral route. Side effects were not significantly different between corticosteroid treatments and placebo”.

Of the 6 studies included, 5 specifically dealt with adults and 5 only with children. All were rated as Jadad score 3 or above. A subsequent follow-up in 2002 failed to reveal any new data to be included. As could be seen in the British Guidelines, this evidence is considered to be sufficient to direct emergency room treatment of severe asthmatic to be based on the addition of oral steroids, rather than any parenteral addition to the first-line treatment with inhaled bronchodilators.

2. Use in children

A Cochrane Review published in 2000 (updated in 2001) has considered the role of aminophylline in children. It set out “To determine whether addition of intravenous aminophylline produces a beneficial effect in children with acute severe asthma receiving oxygen, maximised inhaled bronchodilators and oral/intravenous glucocorticoids”. While 7 trials involving a total of 335 children were included, the results were dominated by one of these trials (with n=163). Only 1 trial was from a country with some developing aspects (Turkey). In all cases, the participants were hospitalised after failing to respond to nebulised β2-agonists, but none had received theophylline beforehand or were shown to have baseline theophylline levels below a predetermined cut-off. The safety results should therefore be interpreted with this in mind. All studies were of good quality, with a mean Jadad score of 4.7/5.

The main results were as follows: “Aminophylline significantly improved percentage predicted FEV1 by 6 - 8 hours (WMD8.4%; 95% CI: 0.82, 15.92%). The effect was maintained for 24 hours. Improvements were also seen in symptom scores at 6-8 hours (WMD = -0.71; 95% CI: -0.82,-0.60). There was no reduction in hospital stay or in number of nebulisers required. Vomiting was more likely with aminophylline therapy (Relative Risk = 3.69; 95% CI: 2.15, 6.33)”. However the authors reported that “There were insufficient data to pool results for change in PEF and in symptom score in the initial 4 hours and 6-8 hours, level of oxygenation, need for supplemental
A relationship between serum concentrations and the risk of vomiting was demonstrated: in the largest trial, which maintained serum aminophylline level greater or equal to 15 mg/L the RR was 4.43 (95% CI: 2.19, 8.96) compared to the 4 trials maintaining levels lower than 15 mg/L with an RR of 2.73 (95% CI: 1.17, 6.39). However, it was reported that “[t]here were no significant group differences in the incidence of headache (RR 1.28;95%CI: 0.70, 2.33; 3 trials), tremor (RR 1.35;95% CI: 0.88, 2.07; 2 trials), seizures (RR 1.01; 95% CI: 0.06,15.91; 4 trials) and arrhythmias (RR 0.40; 95% CI: 0.02, 9.12;2 trials). There were no deaths reported in the included studies. Critically, as there were insufficient trials reporting on these outcomes, data for tachycardia, hypertension, diuresis and hypokalaemia could not be aggregated. The authors concluded that “The careful monitoring of serum theophylline in these critically ill children seemed to have prevented the occurrence of seizures associated with overdose”. The same cannot therefore be said about settings where this careful management is not possible, nor about settings where aminophylline use is combined with widespread use of oral theophyllines, whether of immediate or sustained release types. This must be borne in mind when considering the stated conclusion of the review: that “Aminophylline should be considered for the management of children admitted to hospital with acute severe exacerbations of asthma with a baseline FEV1 of 35 to 40% predicted, baseline Pulmonary Index of 5-6 or Pulmonary Index greater than 3 after intensive bronchodilator therapy. Addition of aminophylline as a loading dose of 6 -10 mg/Kg followed by a maintenance infusion to systemic corticosteroids and maximised nebulised beta agonists and anticholinergics will improve FEV1 by a further9% predicted FEV1 over standard therapy, with no apparent reduction in length of hospital stay or number of inhaled beta2-agonists nebulisations. This improvement is achieved at the cost of a 4-fold increase in the risk of vomiting, particularly when serum theophylline level are maintained at or above 15 mg/ml”.

Exhortations to maintain levels below 15mg/l are also of little use if the means to measure such concentrations or to predict concentrations from pharmacokinetic data are not available.

The Cochrane Review can be contrasted with a previous review that was the subject of a DARE consideration. This considered trials using IV aminophylline or IV theophylline as an addition to the standard bronchodilators and steroids, transforming the outcomes into effect sizes. Although a greater improvement in spirometry measures (FEV1 or PEFR) was shown in the theophylline group, this was not significant. In contrast, the theophylline group appeared to require more albuterol treatments and also demonstrated a longer hospital stay. The DARE reviewers found the original authors’ conclusions (that there was not a significant beneficial effect of theophylline in hospitalised children with acute asthma) to be broadly true. Adverse effects were not the focus of the review, although the authors did conclude that there was “evidence for a weak detrimental effect”, a conclusion the DARE reviewers considered “speculative”.

oxygen therapy, admission to the intensive care unit, intubation rate, and readmission rates”.
Considerations of suitability and cost
While the evidence referred to above is able to answer questions related to efficacy and, to some extent, questions of safety, it does not provide data on suitability and cost.

The most worrying aspect of the use of IV aminophylline, particularly in resource-constrained settings, is the obvious need for (a) an accurate history or prior theophylline use, particularly in the early stages of an acute exacerbation in which there may be a temptation to take additional doses of oral medication available at home, and (b) the ability to use theophylline serum concentration measures to guide loading and/or maintenance dosing. At best these consideration would justify the current listing as “Complementary”.

Cost data are less important in this analysis, as the alternatives have to be used first and not instead of the IV aminophylline. The International Drug Price Indicator Guide (MSH, WHO; 2003) includes the price of the 25mg/ml ampoules, quoting a median price per ml of only US$0.0122.

Overall assessment and recommendations
The available evidence supports the views expressed in the most recent global guidelines, that aminophylline should be a last resort choice, considered only when the first-line treatments (inhaled bronchodilators and systemic steroids) have proven to be ineffective in the individual patient. Only in exceptional circumstances should inhaled β2-agonist bronchodilators not be available, in which case aminophylline would be considered instead. The modest efficacy of aminophylline, its more prevalent adverse effects, its potential for life-threatening adverse effects (particularly in over-dose) and the need for therapeutic drug monitoring all argue for its deletion from the list, or at the very least its retention as a “complementary” agent. Judging from the British Guidelines, provided the first-line options are available, the need for aminophylline would be rare indeed. If IV aminophylline is removed from use, the dangers of allowing continued use of theophylline preparations (only as a step 3 alternative in moderate to severe persistent asthma) will be lessened.

It is recommended that:
1. Aminophylline be removed from the WHO Model List.
2. Consideration be given to reviewing the inclusion of other parenteral medicines used in acute asthma, such as intravenous salbutamol.
3. The necessary amendments be made in relation to the rational use of oral theophylline preparations.

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References


