REVIEW – THEOPHYLLINE

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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Type and Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>beclometasone</td>
<td>inhalation (aerosol), 50 micrograms per dose (dipropionate); 250 micrograms/dose</td>
</tr>
<tr>
<td>epinephrine (adrenaline)</td>
<td>injection, 1 mg (as hydrochloride or hydrogen tartrate) in 1-ml ampoule</td>
</tr>
<tr>
<td>ipratropium bromide</td>
<td>inhalation (aerosol), 20 micrograms/metered dose</td>
</tr>
<tr>
<td>salbutamol</td>
<td>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</td>
</tr>
<tr>
<td>theophylline *</td>
<td>tablet, 100 mg, 200 mg, 300 mg</td>
</tr>
<tr>
<td>aminophylline *</td>
<td>injection, 25 mg/ml in 10 ml ampoule</td>
</tr>
<tr>
<td>cromoglicate acti *</td>
<td>inhalation (aerosol), 20 mg (sodium salt) per dose</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
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<tr>
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<td>inhalation (aerosol), 20 mg (sodium salt) per dose</td>
</tr>
</tbody>
</table>

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

No indication is given as to whether the tablet formulations listed are immediate-release or of a sustained release form.

The entry in the WHO Model Formulary is more extensive, as shown in the box on the next page. It is made clear that the 100mg tablets listed are of the immediate release type, whereas the 200mg and 300mg variants are of a sustained release type. 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 theophylline as a specific oral methylxanthine in relation to the listed indications (“chronic asthma including nocturnal asthma; acute severe asthma”), as well as in the management of chronic obstructive pulmonary disease (COPD).

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), GOLD (Global Initiative for Chronic Obstructive Lung Disease), JSA (Japanese Society of Allergology) and JSPA (Japanese Society of Pediatric Allergy), the DRA submission argues as follows:

“Theophylline is proposed to be retained in the WHO Model list of essential medicines for “25. Medicines Action on the respiratory tract” “antiasthmatic and medicines for chronic obstructive pulmonary disease.” Following summary of reports on theophylline shows theophylline is an effective drug with bronchodilating and anti-inflammatory effects and can be used alone or in combination in asthma and COPD. Its safety has been verified. Theophylline is the only oral agent among the essential drugs in asthma and COPD. Current international and national guidelines for asthma and COPD have recommended sustained release theophylline for long-term control of these diseases.”

Further, the CRA submission makes it clear that the submission calls for the retention of theophylline as an individual medicine (as listed in the EML). However, it does not include COPD as a listed indication in the suggested Model Formulary text. Nonetheless, this review will include consideration of that possibility.

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

“Theophylline has modest effects in asthma and its unwanted effects are troublesome, however it should remain on the WHO Model List of Essential Medicines, to be used as a second-line drug for the treatment of asthma in patients who do not respond to a beta 2 agonist plus an inhaled corticosteroid, and, where appropriate, an anticholinergic drug. The importance of therapeutic monitoring should be stressed, but even so, the product should continue to be available even where routine measurement of plasma concentration cannot be provided.”
**Current positioning of the agent in international guidelines**

1. **Asthma - adults**

The most widely quoted asthma guideline is that provided by the Global Initiative for Asthma (GINA), which was updated in 2004.1 Theophylline is included as an option, but not first-line choice in mild, moderate and severe persistent asthma. The operative statements are as follows:

- "For intermittent asthma, no daily medication is recommended for the vast majority of patients. Treatment of exacerbations should depend on the severity of the exacerbation. A rapid-acting inhaled β2-agonist may be taken as needed to relieve asthma symptoms. The occasional patient with intermittent asthma, but severe exacerbations, should be treated as having moderate persistent asthma.

- Patients with mild persistent asthma require controller medication every day to achieve and maintain control of their asthma. Treatment with an inhaled glucocorticosteroid is preferred. Sustained-release theophylline, cromones, or a leukotriene modifier are other options.

- The preferred therapy for moderate persistent asthma is regular treatment with a combination of inhaled glucocorticosteroid and a long-acting inhaled β2-agonist twice daily. Sustained-release theophylline or a leukotriene modifier are alternatives to the β2-agonist in this combination therapy. An alternative to combination therapy is a higher dose of inhaled glucocorticosteroid.

- The primary therapy for severe persistent asthma includes inhaled glucocorticosteroid at higher doses plus a long-acting inhaled β2-agonist twice daily. Alternatives to the long-acting inhaled β2-agonist for add-on treatment are an oral sustained-release theophylline, leukotriene modifier, or oral β2-agonist. These drugs may also be added to the combination of high-dose inhaled glucocorticosteroid and long-acting inhaled β2-agonist if necessary."

It is also very clear from these statements that immediate release theophylline is not a preferred option, nor is oral theophylline in any form an alternative to inhaled rapid-acting inhaled β2-agonists in patients with intermittent asthma. The level of uncertainty about the mechanism of action of the methylxanthines and their place in therapy is also well described in the GINA Workshop Report, as updated. These are quoted verbatim, as they encapsulate all the issues of contention. The first section deals with their use as “controllers”, the next as “relievers”.

**Methylxanthines.**

- Mode of administration–Oral (ingested).

- Mechanisms of action–Theophylline is a bronchodilators that may have extrapulmonary effects, including anti-inflammatory effects. The
bronchodilator effect of theophylline may be related to phosphodiesterase inhibition and is seen at high concentrations (>10 mg/l), whereas the anti-inflammatory effect is due to an unknown mechanism and may occur at lower concentrations (5-10 mg/l). At low doses theophylline has some minor influence on chronic airway inflammation in asthma. Most studies show little or no effect on airway hyperresponsiveness.

- Role in therapy–Sustained-release theophylline and aminophylline can be used as controller medications in asthma. Many clinical studies have shown that long-term treatment with sustained-release theophylline is effective in controlling asthma symptoms and improving lung function. When given as a sustained-release preparation, it has a long duration of action and is thus useful in the control of nocturnal symptoms that persist despite the regular treatment with anti-inflammatory therapy. Theophylline is also useful as an additional bronchodilator in patients with severe asthma. Now that theophylline at low doses has been shown to be effective in asthma control in both adults and children, it may be used in patients with milder disease and as an add-on therapy to low or high doses of inhaled glucocorticosteroids when further asthma control is needed (Evidence B). As add-on therapy, theophylline is less effective than long-acting inhaled β2-agonists (Evidence A). It is, however, a less expensive option. Due to the risk of adverse effects, and the difficulty of monitoring therapy (see discussion of side effects below), theophylline is regarded in some countries as a therapy that should be reserved for use after inhaled glucocorticosteroids and inhaled β2-agonists fail to achieve therapeutic goals. In other countries, theophylline is recommended earlier in the course of daily long-term therapy because it is a bronchodilator useful for the control of asthma, especially of nocturnal asthma symptoms, and it is inexpensive.

- Side effects – At higher doses (10 mg/kg body weight/day or more), theophylline has the potential for significant adverse effects, although these can generally be avoided by appropriate dosing and monitoring. The signs and symptoms of theophylline intoxication involve many different organ systems. Gastrointestinal symptoms, nausea, and vomiting are the most common early events. However, theophylline intoxication in children and adults can result in seizures and even death, and these events may not be preceded by evidence of central nervous system stimulation. Cardiopulmonary effects include tachycardia, arrhythmias, and, occasionally, stimulation of the respiratory center. Generally, serious toxic effects do not occur at serum concentrations below 15 µg per ml. Individual patient needs will vary, but a general approach to dosing and monitoring is to aim for a steady-state serum concentration for theophylline of between 5 and 15 µg per ml (28 to 85 µM) during long-term theophylline treatment. Monitoring of serum concentrations is advised when high-dose theophylline therapy (10 mg/kg body weight/day or more) is started and at occasional intervals thereafter. Monitoring is also advised when a patient develops an adverse effect on the usual dose, when expected therapeutic aims are not achieved, and when conditions or concomitant medications known to alter theophylline metabolism exist. For example, febrile illness, pregnancy, and anti-tuberculosis medications
reduce blood levels while liver disease, congestive heart failure and use of certain drugs including cimetidine, certain quinolones and certain macrolides increase the risk of toxicity. Lower doses of theophylline are associated with less frequent side effects, and there is less need for measurement of plasma levels in patients on low-dose therapy (unless there are problems of side effects or lack of therapeutic effect).

**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.

2. Asthma – children
The GINA guidelines also provide extensive comment on the use of methylxanthines in this group. As above, the relevant section is quoted verbatim, in relation to their use as “controllers”. Methylxanthines are not listed as “relievers” in children.

“**Methylxanthines.**

The role of theophylline in the long-term treatment of children with asthma is limited, but the low cost of this treatment may justify more frequent use in some countries.

- **Mode of administration**—Oral.
- **Pharmacokinetics**—Because children metabolize theophylline very rapidly, frequent dosing (4 to 6 times a day) is required when plain tablets are used for long-term treatment. Therefore, sustained-release products are preferable for maintenance therapy, and they enable twice-daily dosing in most children. It is important to note that concomitant intake of food may change the absorption characteristics of many sustained release theophylline products in an unpredictable way. Reduced absorption, dose dumping, and marked variations in absorption profiles may be seen, complicating the task of ensuring safe, effective treatment. Because the effect of concomitant food intake is quite unpredictable, only sustained-
release products that have been shown to be well absorbed in combination with food should be used for maintenance treatment. In this respect, it is important to evaluate both mean and individual absorption profiles; the variation in absorption with food seems to be more pronounced in children than in adults. Sustained-release theophylline products with reliable absorption profiles and complete bioavailability with food have been developed. Dose-response studies with theophylline in a limited number of children with asthma have mainly assessed bronchodilation and protection against exercise induced asthma. Dose recommendations have been based on lean body weight and aim at plasma theophylline levels between 55 and 110 µmol/l, which may be required to achieve maximum bronchodilatory effect in children with acute wheeze. However, there is still considerable difference in opinion regarding the optimum plasma levels that should be obtained. Studies in adults and some studies in children suggest that lower levels may be sufficient to achieve a measurable effect on other outcomes in day-to-day management. For example, theophylline’s anti-inflammatory effects may be seen at about one-half of the plasma levels required for maximum bronchodilatory effect. Therefore, it seems rational to individualize the dose on the basis of the clinical effect rather than aiming at specific plasma levels, which are more useful in preventing intoxication. At present, good studies of therapy with low-dose theophylline in children are lacking. Within each age group in children, interindividual variations in theophylline half-life may be up to 10-fold. Other drugs may affect theophylline metabolism, such as β2-agonists (which increase clearance so that higher doses are required), as may viral infections (which reduce clearance). Therefore, the theophylline dose must always be individualized, and if high doses are used plasma theophylline levels must be measured two hours before administration of the next dose. When dose adjustments are made on the basis of serum theophylline concentrations, theophylline often shows dose-dependent kinetics so that, on average, the percent change in serum concentration is about 50 percent greater than the percent change in dose.

- **Role in therapy**—Sustained-release theophylline may be used as an alternative to inhaled glucocorticosteroids for maintenance therapy in mild persistent asthma and as add-on therapy with a low dose of inhaled glucocorticosteroids. School children. Theophylline is significantly more effective than placebo at controlling symptoms and improving lung function, even at doses below the normally recommended therapeutic range (Evidence A). Furthermore, a single dose of 15 mg/kg of sustained release theophylline taken before bedtime is effective at preventing nocturnal asthma symptoms. Long-term maintenance treatment offers a marginal protective effect against exercise-induced asthma. Theophylline and oral β2-agonists seem to have an additive effect on control of asthma, although it remains unclear whether the combination has any clear clinical advantage compared to either drug used alone. Preschool children. There are indications that theophylline treatment has some beneficial clinical effects, such as bronchodilation, in this age group (Evidence C). However, further double-blind studies are needed to assess the optimal dose and preference of theophylline relative to other treatments in young
children. Infants. The effect of long-term theophylline treatment has not been assessed in double-blind controlled studies in infants with wheeze.

- **Side effects**—Theophylline has a narrow therapeutic window and potentially lethal side effects when overdosed. The most common side effects are anorexia, nausea, vomiting, and headache. Mild central nervous stimulation, palpitations, tachycardia, arrhythmias, abdominal pain, diarrhea, and, rarely, gastric bleeding may also occur. When maintenance therapy with theophylline is begun, the initial dosage should be low because side effects seem to occur much more frequently if the initial dose is high. Some patients do not tolerate theophylline, regardless of what precautions are taken. Theophylline has been reported to induce changes in mood and personality and to impair school performance in children, although these findings were not reproduced in another study.”

The two GINA management approaches are summarised in the following figures, taken from the Pocket Guide as updated in 2004. Note that Figure 9 does mention theophylline as an alternative reliever in children under the age of 5 years. While theophylline is always listed as a second-line choice, there is an acknowledgment in these guidelines that its relatively low cost in some countries may be a factor influencing selection. In other tables, the issue of therapeutic drug monitoring is also touched upon: the glossary of “controllers” states that "Theophylline level monitoring is often required". The “reliever” equivalent is more prescriptive: “Theophylline level monitoring is required. Obtain serum levels 12 and 24 hours into infusion. Maintain between 10-15 mcg/mL”. A key question is therefore whether settings that choose theophylline before the preferred first-line options will be able to afford to use this agent safely, including by monitoring serum concentrations. This is particularly important in the management of acute attacks – the Pocket Guide advice is as follows: “Methylxanthines are not recommended if used in addition to high doses of inhaled β2-agonist. However, theophylline can be used if inhaled β2-agonists are not available. If the patient is already taking theophylline on a daily basis, serum concentration should be measured before adding short-acting theophylline”. The concern would be that resource-constrained settings may opt for immediate release formulations of theophylline as a cost-saving measure, but will then try to use the same agent in acute treatment settings without having access to serum concentration measurements.

The GINA approach in both adults and children is echoed in the British Guidelines, updated in April 2004. Theophylline is listed as an alternative “reliever” in intermittent asthma, but not as a preferred choice, because of the low onset of action and higher prevalence of adverse effects. The use of theophylline is a “controller” is adjudged to be of “some beneficial effect”, but it is stated that “side effects are more common and monitoring of plasma levels is required. Theophylline is listed as an alternative “add-on” when a fourth medicine is required in cases of poor control. It is stated that there is limited evidence for the use of theophylline as a steroid-sparing tactic. Critically, all mention is of sustained release theophylline, not of immediate release formulations. Earlier guidelines, such as the US Agency for Healthcare
Research and Quality Evidence Report/technology Assessment “Management of Chronic Asthma”, dating from 2001, are also of the same mind.4

Please see


3. Chronic obstructive pulmonary disease
The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were also updated in 2004.5 The key statement is: “Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms. The principal bronchodilator treatments are β2-agonists, anticholinergics, theophylline, and a combination of these drugs (Evidence A)”. In stable COPD, the advice on selection is as follows: “The choice between β2-agonist, anticholinergic, theophylline, or combination therapy depends on availability and individual response in terms of symptom relief and side effects”. Again, a case is made for sustained-release formulations: “Long-acting inhaled bronchodilators are more effective and convenient, but more expensive”, and later: “Theophylline is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations”.

The full text of the advice on the methylxanthines is as follows:

“Methylxanthines. Controversy remains about the exact effects of xanthine derivatives. They may act as nonselective phosphodiesterase inhibitors, but have also been reported to have a range of non-bronchodilator actions, the significance of which is disputed. Data on duration of action for conventional, or even slow-release, xanthine preparations are lacking in COPD. Changes in inspiratory muscle function have been reported in patients treated with theophylline, but whether this reflects changes in dynamic lung volumes or a primary effect on the muscle is not clear (Evidence B). All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations. Theophylline is effective in COPD but, due to its potential toxicity, inhaled bronchodilators are preferred when available. Adverse effects. Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given (Evidence A).
Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental). Theophylline, the most commonly used methylxanthine, is metabolized by cytochrome P450 mixed function oxidases. Clearance of the drug declines with age. Many other physiological variables and drugs modify theophylline metabolism; some of the potentially important interactions are listed in Figure 5-3-7."

Again, the relevance seems greatest for resource-constrained settings where use of immediate release theophylline preparations may be common.

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 maintenance treatment of asthma
A Cochrane Review published in 2003 considered the following: “To assess the comparative efficacy, safety and side-effects of long-acting beta-2 agonists and theophylline in the maintenance treatment of adults and adolescents with asthma”. A total of 12 studies, with 1329 participants, were included. The quality of the included studies was considered to be variable. An update in April 2004 did not reveal any new data that could be included. The overall results stated were: “Salmeterol improved forced expiratory volume in one second (FEV1) significantly more than theophylline in five studies and salmeterol use was associated with significantly more symptom free nights in all the studies comparing these agents. Formoterol, used in two studies was reported to be as effective as theophylline. Bitolterol, used in only one study, was reported to be less effective than theophylline. Participants taking salmeterol experienced fewer adverse events than those using theophylline (Parallel studies: Relative Risk 0.44; 95% confidence interval (CI) 0.30 to 0.63), Risk Difference -0.11; 95% CI -0.16 to -0.07), Numbers Needed to Treat (NNT) 9; 95% CI 6 to 14. Significant reductions were reported for central nervous system adverse events (Relative Risk 0.50; 95% CI 0.29 to 0.86), Risk Difference -0.07; 95% CI -0.12 to -0.02), NNT 14; 95% CI 8 to 50) and gastrointestinal adverse events (Relative Risk 0.30; 95% CI 0.17 to 0.55), Risk Difference -0.11; 95% CI -0.16 to -0.06), NNT 9; 95% CI 6 to 16)."

The study population in those studies included was predominantly adults, with no children under 12 years included. Most studies were short, with only one exceeding 12 weeks. Thus, while physiological variables (e.g. FEV1) may have been adequately measured, harder outcomes measures and adverse events may not have been as accurately captured. Variations in the way FEV1 was reported precluded meta-analysis. The conclusion reached was therefore
cautious: “in twelve studies. This review found that whilst salmeterol and theophylline were both effective in increasing lung function, salmeterol was more effective in treating nocturnal symptoms such as night waking and need for rescue medication. The pooled difference in the beneficial effects of salmeterol over theophylline did not reach statistical significance, but this may relate to the fact that many of the studies did not present data suitable for meta-analysis and all of the individual studies reported significantly less symptom-free nights with salmeterol over theophylline. This review also reported significantly fewer adverse events with salmeterol as compared to theophylline. With regards to formoterol, another long-acting beta-2 agonist, the two studies found reported it to be as efficacious as theophylline in improving lung function, treating nocturnal asthma symptoms and use of rescue medication, but the number of participants was small. In this review, the efficacy of bitolterol, another long-acting beta-2 agonist was found to be less than theophylline.”

In relation to the safety profile of theophylline, it must be noted that most of the studies reviewed used dose-adjusted theophylline. Despite this, a significant increased risk of all common side effects was seen with theophylline compared to the long-acting beta-2 agonists (LABAs).

Three other recent reviews have addressed the question of how to choose which agents to add to the “controller” regimen when the response to inhaled corticosteroids is inadequate. Green et al. noted the decline in the use of theophylline after many years of widespread use. It noted that the possible anti-inflammatory activity of low-dose theophylline may point to a possible role in some patients. Kallstrom has reviewed the evidence and provided similar tables to those in the GINA guidelines, but does make a more strongly worded statement about the need for serum concentration monitoring: “Because of wide interpatient variability of theophylline metabolic clearance, routine serum theophylline level monitoring is important”. Kankaanranta et al. have specifically addressed the so-called “step 3 dilemma”. Although limited only to studies in English, extensive data are provided to argue that doubling the inhaled corticosteroid (ICS) dose is “not sufficient to significantly improve lung function or reduce symptoms” in these patients. Their conclusions on the role of theophylline deserve closer attention. The authors noted that “the results from two relatively small studies suggest that addition of low-dose theophylline may be equal to doubling the dose of ICS in the treatment of asthma not adequately controlled by low dose of ICS. However, one needs to remember that the effect of doubling the dose of ICS on asthma control is generally small or negligible … Furthermore, a placebo group should be included in these studies to see whether an improvement in asthma control is obtained by doubling the dose of ICS. Thus, more data is needed to confirm the present results”. Later, having considered trials that have compared LABAs, antileukotrienes and theophylline, the authors conclude as follows: “Use of theophylline at concentrations at the lower limit or slightly below the recommended therapeautic range may help to limit the adverse effects. (salmeterol). There is evidence that addition of low-dose theophylline to the treatment regimen may be equal to doubling of the dose of ICS. However, more studies are needed to better clarify the role of leukotriene antagonists
and theophylline as "add on"-therapies. However, one final comment is made which points to ongoing concerns about the ability of patients to effectively use inhaled medicines: "For patients with inappropriate inhalation technique the value of LTRA or theophylline are especially worth considering. More studies are now needed to compare between different add-on therapies and to explore the effect of more than one add-on therapy in patients with more severe asthma as well as in those having symptoms but not significant bronchodilators response".

One more meta-analysis has been reported, but a DARE review has criticized it as only using data held by one pharmaceutical company (GlaxoWellcome). The original review found that salmeterol had a superior safety and efficacy profile than theophylline.

Overall, therefore, there is no strong evidence to support the preferential selection of theophyllines as add-on agents of choice. However, issues of suitability and/or cost may preclude the selection of more effective and better tolerated agents, especially the LABAs, in resource-constrained settings.

2. Use in maintenance treatment of COPD

A Cochrane Review last updated in April 2002 has considered the role of theophylline in COPD management. In this case the comparator was placebo in each case. A total of 20 randomised controlled trials met the inclusion criteria, all of which were of a crossover design and enrolled between 10 and 60 patients each. Duration of the studies varied from 7 to 90 days. Theophylline demonstrated a "modest effect", as follows: "Forced expiratory volume in one second (FEV1) improved with treatment: Weighted Mean Difference (WMD) 100 ml; 95% Confidence Interval (CI) 40 to 160 ml. Similarly for forced vital capacity (FVC): WMD 210 ml 95%CI 100 to 320. Two studies reported an improvement in maximum oxygen consumption (VO2 max); WMD 195 ml/min, 95%CI 113 to 278. At rest, arterial oxygen tension at rest (PaO2) and arterial carbon dioxide tension at rest (PaCO2) both improved with treatment (WMD 3.2 mm Hg; 95%CI 1.2 to 5.1, and WMD -2.4 mm Hg; 95%CI -3.5 to -1.2, respectively). Walking distance tests did not improve (four studies, Standardised Mean Difference 0.30, 95%CI 0.01 to 0.62), neither did Visual Analogue Score for breathlessness in two small studies (WMD 3.6, 95%CI -4.6 to 11.8). The Relative Risk (RR) of nausea was greater with theophylline (RR 7.7; 95%CI 1.5 to 39.9). However, patients' preference for theophylline was greater than that for placebo (RR 2.27; 95%CI 1.26 to 4.11). Very few participants withdrew from these studies for any reason".

The low withdrawal rate was found to be unusual by the reviewers, who wondered whether this suggested a prior selection of theophylline tolerant patients. Although the magnitude of the lung function changes seen was modest, it was noted that this was similar to that achieved with inhaled β2-agonists. The final conclusion was cautiously worded and raised the spectre against of the need for theophylline serum concentration monitoring: "We conclude that, with close monitoring of individual patients and their serum theophylline levels, it appears that beneficial effects may be obtained in those
who remain symptomatic from COPD despite first-line bronchodilators therapy”.

Provided first-line bronchodilators are available, there seems little evidence therefore to support the selection of theophylline. However, it must be noted that COPD patients are difficult to manage and that a wide range of options may be needed in some cases.

A recent attempt at a meta-analysis of all contemporary management approaches in COPD has been published. However, insufficient data on longer-term outcomes (e.g. mortality or exacerbations) from trials involving theophylline were available, precluding meta-analysis. The authors therefore noted the results of the Cochrane Review by Ram et al., agreeing that “some beneficial effects on FEV1 as well as on the arterial contents of oxygen and carbon dioxide of patients with moderate to severe COPD” had been demonstrated. Equally, they noted that this effect was mitigated by an approximately 7-fold increase in the risk of nausea.

3. Use in exacerbations of COPD
A Cochrane Review first published in 2003 considered the use of methylxanthines (by any route, so including theophylline) in exacerbations of COPD. The same data were published in the BMJ in the same year (BMJ 2003; 327: 643). Only 4 placebo-controlled studies were included, with 169 participants. However, the quality of the studies was high, with 2 scoring 5/5 and 2 scoring 4/5 on the Jadad criteria. However, while data on FEV1, adverse events and symptoms scores were available, little information was found on clinical outcomes (e.g. hospitalisation, length of stay). The results were not promising: “Mean change in forced expiratory volume in one second (FEV1) at 2 hours was similar in methylxanthine and placebo groups but transiently increased with methylxanthines at 3 days (WMD: 101 ml; 95% CI: 26 to 177). Data on clinical outcomes were sparse. Trends toward improvements in hospitalisation and length-of-stay were offset by a trend toward more relapses at one week. Changes in symptom scores were not significant. Methylxanthines caused more nausea and vomiting than placebo (OR: 4.6; 95% CI: 1.7 to 12.6) and trended toward more frequent tremor, palpitations, and arrhythmias”. Accordingly, the authors concluded that, based on current evidence, methylxanthines should not be used for COPD exacerbations. Demonstrable risks clearly outweighed possible benefits.

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.

There are repeated references in both the guidelines and reviews mentioned that theophylline is best administered in a sustained release formulation, or even that what evidence of efficacy exists has only been demonstrated with such formulations. In addition, more frequent administration would be expected to be associated with poor adherence in the indications listed – each
of which refers to the use of theophylline as a “controller” or maintenance
treatment in a chronic condition not responding to other medication. The need
for immediate release formulations should be carefully considered. Sustained
release paediatric formulations are available, but are expensive. It has to be
acknowledged that there are many theophylline-containing combination
preparations, including oral liquid formulations, still in use in developing
countries. Any amendments to the WHO Model List should therefore make it
quite clear that the use of such products is not supported.

The suitability of even the sustained release preparations is however reduced
by the wide interpatient variability in metabolic clearance, considerable food-
drug and drug-drug interactions noted, and by the need (in most guidelines
and in most circumstances) for therapeutic drug monitoring.

An additional suitability issue to consider is that of the route of administration.
The GINA guidelines do mention the possibility of short-acting theophylline
being used as an alternative “ reliever”. However, that choice should not be
based on cost alone, as generic inhaled β2-agonists are available. The real
challenge is to ensure adequate inhaler technique in all patients, whether
when using a “ reliever” or an inhaled first-line “controller” (i.e. an ICS). In this
regard the availability of suitable spacers or advice on how to fashion home-
made spacers from available materials needs to be considered. NThere is
good evidence for the equivalence of various delivery systems for inhaled
therapy, and a cost-minimization approach can be used to guide selection. 8,14
All settings should be able to select at least a pressurized metered dose
inhaler formulation of both a short-acting β2-agonist and a corticosteroid (both
of which are listed as “Essential”).

Cost data are difficult to assess. The International Drug Price Indicator Guide
(MSH, WHO; 2003) only includes the price of the 100mg immediate release
tablet. The median price per tablet is low (US$0.0044), compared to a single
100mg dose of inhaled beclometasone (US$0.0246). However, the real cost
comparison that needs to be made is between meaningful adult doses of
sustained release theophylline and LABAs, and not the Defined Daily Doses.
For example, the South African private sector price of a 300mg twice a day
dose of a generic sustained release theophylline is currently approximately
ZAR43 for a month’s supply, whereas the same course of salmeterol
inhalations (at 50µg twice a day) would cost approximately ZAR230 – a 5-fold
difference. Formoterol costs are similar.

Overall assessment and recommendations
The available evidence supports the views expressed in the most recent
global guidelines for both asthma and COPD. However, what the evidence
also points to is that theophylline should be a second-line choice in each case,
used only if a more efficacious and/or better tolerated alternative is not
available, not suitable, or has proven to be ineffective in the individual patient.

The modest efficacy of theophylline, its more prevalent adverse effects, its
potential for life-threatening adverse effects (particularly in over-dose) and the
need for both sustained release formulations (in the main) and therapeutic
drug monitoring all argue for its relegation to the status of a “complementary” agent. However, the availability of the first-line options for the various indications must be assured before theophylline is withdrawn from a country’s EML and STGs. Were considerations of cost of no consequence, LABAs could possibly be considered for inclusion on the Model EML, with the appropriate caveats about the need for access to short-acting agents as “relievers”. However, as it appears that a sizeable number of patients would need some additional treatment when moderate doses of ICS failed to control their asthma, and the evidence points to a lack of benefit from very high doses of the already listed ICS, the inclusion of a suitable “step 3” option seems essential.

It is recommended that:

1. Theophylline be retained, but as a “complementary” not an “essential” medicine.
2. The entry indicate that theophylline should not ordinarily be available as an immediate release formulation (as is noted in the WHO Formulary dosing table, but not in the list of presentations).
3. The entry further indicate that it should be reserved for “step 3” use in asthma, in cases where access to a LABA is not possible, but that it should only be considered in patients who have failed to be controlled with adequately doses ICS.
4. The entry include mention of its use as a maintenance therapy in COPD, but not as an option in the management of acute exacerbations.
5. The WHO Formulary contain mention of the problem of continued use of irrational combination preparations containing methylxanthines, particularly oral liquid preparations.

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