



Post-tuberculous lung disease: should we be using Theophylline?

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Abstract: Tuberculosis affects 10 million people and over 320,000 South Africans every year. A significant proportion of patients treated for tuberculosis develop post-tuberculous lung disease (PTBLD), a disease of chronic respiratory impairment for which there is a lack of affordable treatment options. PTBLD a heterogenous disorder that shares phenotypical features with chronic obstructive lung disease, bronchiectasis, lung fibrosis and destruction as well as pulmonary hypertension. There remains a paucity of proven pharmacotherapy for the management of PTBLD. Theophylline, a widely available and affordable medicine that has largely fell out of favour in high-income settings due to its toxicity and narrow therapeutic index, may be repositioned for the treatment of PTBLD. In this review, we unpack the potential role of theophylline in the management of PTBLD by reviewing the evidence for its bronchodilatory, anti-inflammatory and potential pleotrophic effects.

Keywords: Post tuberculous lung disease (PTBLD); theophylline; tuberculosis (TB); chronic obstructive pulmonary disease (COPD); pulmonary hypertension

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Introduction

Tuberculosis affects 10 million people and over 320,000 South African every year. A significant proportion of these patients will develop post-tuberculous lung disease (PTBLD) secondary to a complex interplay between *Mycobacterium tuberculosis*, host genetic factors and the immune response which may result in activation of proteases with ensuing lung damage (1).

PTBLD is a blanket diagnosis loosely applied to patients with residual parenchymal destruction and symptoms after tuberculosis, and there is renewed interest in defining the various clinical presentations. PTBLD represents a spectrum of diseases with varying phenotypes that in

any individual may share features of chronic obstructive pulmonary disease (COPD), bronchiectasis, lung fibrosis and destruction as well as pulmonary hypertension, with potential ongoing inflammation and associated tissue damage.

There remains a lack of evidence on effective pharmacotherapy for the management of PTBLD. Theophylline may have utility in the treatment of PTBLD given its bronchodilatory, anti-inflammatory and potential pleotrophic effects. Theophylline is frequently used in South African and low to middle income countries (LMIC) for COPD, asthma due to its availability and low cost (2). However, theophylline has largely been abandoned in high-

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income countries because of concerns around safety due to its narrow therapeutic index.

Given the lack of alternative, affordable treatment options available for PTBLD in high burden countries, including our own, we review the mechanism of action, and evidence both for and against the use of theophylline in the treatment of COPD, bronchiectasis and pulmonary hypertension, the analogous clinical syndromes of PTBLD. In this review, we discuss the potential role of theophylline in the management of PTBLD, by reviewing the evidence for its bronchodilatory, anti-inflammatory and potential pleiotrophic effects.

History of theophylline & use in SA

Historical uses

Theophylline, a dimethylxanthine has been in clinical use for more than 85 years (3). Theophylline occurs naturally in tea and cocoa beans, and was first extracted and chemically synthesized in 1895. The bronchodilator properties were only later recognized and clinical application for the treatment of asthma began in 1922 (3). Theophylline is prescribed in approximately 35% of patients with COPD worldwide, and is retained in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as a controversial therapy with conflicting data with a number of subsequent trials demonstrating some effect (2,4-6). The role of theophylline in the treatment of asthma and COPD has changed dramatically over the last few decades due in part to the introduction of beta-2 agonists and inhaled corticosteroids, which demonstrated superior bronchodilatation and anti-inflammatory properties respectively (3,7). The place for theophylline in local clinical practice guidelines has waxed and waned due to its narrow therapeutic index, inherent toxicity and a myriad of drug interactions; despite this, the use of theophylline has persisted largely driven by cost and availability compared to alternate therapies.

Mechanism of action

The pharmacodynamic action of theophylline remains speculative. A number of potential molecular mechanisms have been suggested which includes phosphodiesterase (PDE) inhibition, adenosine receptor antagonism, upregulation of IL-10, attenuation of IL-8, effects on cell survival, transcription, histone deacetylase activation and

enhanced protein phosphatase 2A activity (3) (see *Figure 1*).

Bronchodilation & PDE inhibition

Theophylline has demonstrated large and small human airway bronchodilation *in vitro* (3). However, the bronchodilator effect is poor at therapeutic concentrations. Intravenous aminophylline has demonstrated efficacy in acute asthma, with a dilatory effect on airway smooth muscle and a prophylactic effect on exercise-induced bronchospasm (8). Theophylline may prove beneficial in COPD patients by reducing air trapping (3,8,9).

Theophylline non-selectively inhibits PDE isoenzymes, which are responsible for degradation of cyclic nucleotides. The net effect of this process is elevated intracellular concentrations of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) with subsequent smooth muscle relaxation and bronchodilatation (3). Theophylline mediated airway smooth muscle relaxation has been attributed to inhibition of PDE3 activity, an effect only achieved at supra-therapeutic concentrations (10). Theophylline also exerts a modest anti-inflammatory effect by preventing the release of cytokines from alveolar macrophages via inhibition of PDE4 activity (10).

Adenosine receptor antagonism

A further basis for theophylline mediated bronchodilation may be attributed to its antagonistic activity on adenosine receptors, in particular, the A1 and A2 subtypes (3,11). Studies have demonstrated that inhaled adenosine constricts bronchial airways in asthmatics by mediating the release of histamine and leukotrienes, an effect that is inhibited by therapeutic concentrations of theophylline (11).

Anti-inflammatory effects

Theophylline exerts an anti-inflammatory effect in both asthma and COPD, which are achieved at plasma concentrations lower than that required for bronchodilation (3). Low-dose theophylline has been reported to attenuate the hyper-eosinophilic reaction in response to inhaled antigens in mild asthma (12), seen in bronchial biopsies and sputum samples (13). In the context of COPD, theophylline has been associated with a quantitative reduction of neutrophils in sputum supporting an anti-inflammatory effect (4,14,15). A number of mechanisms have been proposed to contribute to these anti-inflammatory effects:

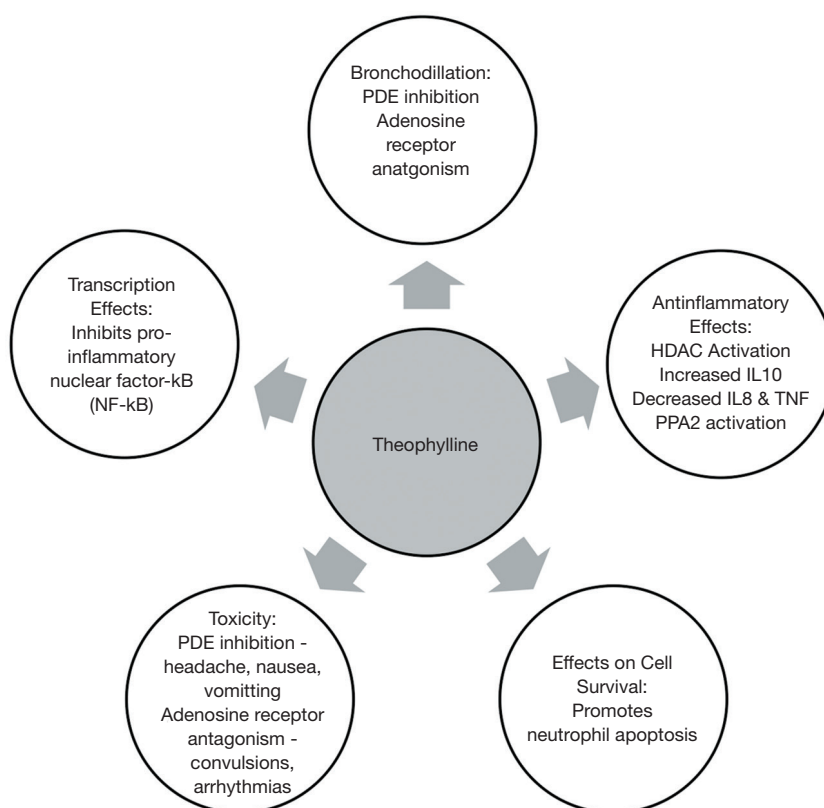


Figure 1 Theophylline: potential mechanisms of action and toxicity.

(I) Increased interleukin-10 (IL-10)

Asthma and COPD patients have diminished secretion of IL-10, an anti-inflammatory cytokine. Theophylline increases IL-10 release via PDE inhibition (16), albeit at relatively high concentrations, in excess of the low doses effective in asthma (17).

(II) Decreases interleukin-8 (IL-8) and tumor necrosis factor

IL-8, previously neutrophil chemotactic factor, functions in the recruitment and stimulation of neutrophils and other granulocytes, and *in vitro* secretion is suppressed by only 10 mM (1,801 µg/mL) of theophylline (18). Notably, this effect is mediated via protein phosphatase 2A (PP2A), and is independent of PDE inhibition and cAMP-dependent MKP-1 up-regulation (5,6).

(III) Protein phosphatase 2A (PP2A)

PP2A is a serine/threonine phosphatase that dephosphorylates several kinases that propagate inflammation, and thus has anti-inflammatory effects (9,18). A study by Patel and Rahman [2016] linked theophylline with PP2A activation *in vitro* (16,19). PP2A is pivotal in the control of respiratory inflammation, infectious

exacerbations, and glucocorticosteroid sensitivity—all conditions that may be improved by theophylline (9).

(IV) Histone deacetylase activation (HDAC)

HDACs are enzymes that remove acetyl groups from histones, resulting in a tightly coiled conformation (5) and inhibiting the transcription of inflammatory mediators. Low plasma concentrations of theophylline (<5 mg/L) activates HDACs in states of high oxidative stress (9,20). Oxidative stress in chronic lung diseases (e.g., COPD) leads to activation of inflammatory genes, mucus secretion, and inactivation of protective anti-proteases. This, in conjunction with an altered histone acetylation/deacetylation balance, leads to increased pro-inflammatory mediators in the lung. Which, in turn, results in the neutralizing of the effectiveness of glucocorticosteroids, as corticosteroids are in part dependent on HDAC2 to turn off pro-inflammatory genes (21,22). Therapeutic and lower concentrations of theophylline activate HDAC and restore its function, thus potentially overcoming this insensitivity to steroids, and reducing inflammation (5,23).

(V) Effects on transcription

Theophylline, at high plasma concentrations, attenuates

the activity of inflammatory genes in asthma and COPD patients (24). This is achieved mechanistically by inhibiting the translocation of the pro-inflammatory transcription factor nuclear factor- κ B (NF- κ B) (24) into the nucleus by preventing the degradation of the inhibitor, I- κ Ba (24).

(VI) Effects on cell survival

Prolonged survival of granulocytes appears to propagate chronic inflammation in COPD. Theophylline promotes apoptosis in neutrophils *in vitro* through a reduction in the anti-apoptotic protein Bcl-2 (25). Theophylline also causes apoptosis of T lymphocytes and decreases their survival, again mediated through PDE inhibition (26).

Use of theophylline in clinical disease

We were unable to find specific data on the use of theophylline in PTBLD when searching published literature or conference abstracts. Therefore, we review the evidence for theophylline in the parallel respiratory diseases of COPD, bronchiectasis and pulmonary hypertension.

Theophylline in COPD

Theophylline is considered an essential medicine to treat COPD in the Standard Treatment Guidelines and Essential Medicines List for South Africa.

Theophylline has been shown to increase exercise tolerance in patients with COPD by improving respiratory muscle performance (27), increased diffusing capacity and a reduction in peak ventilation (8). In doses that achieve a plasma concentration of 10–20 mg/L, theophylline exhibits a bronchodilatory effect in COPD patients, which is further augmented by the addition of a long acting beta2 agonist (LABA) (28).

A 2005 meta-analysis of 20 placebo-controlled studies in patients with COPD, which represents the majority of current published clinical efficacy studies, reported that theophylline statistically improved FEV₁, FVC, PaO₂, and PaCO₂ levels, and VO₂ max (29), while inhibiting cough and improving diaphragmatic function (30,31). Theophylline has also been shown to help improve mucociliary clearance (32).

Reports suggest that monotherapy with low-dose theophylline may reduce COPD exacerbations by approximately 50% over 1 year (6). *In vitro* and *ex vivo* studies suggest that COPD associated inflammation is partially refractory to glucocorticosteroid therapy. It has been proposed that lower plasma concentrations of theophylline (1–5 mg/L) may augment the anti-inflammatory effects

of corticosteroids in COPD by enhancing or restoring HDAC activity in airway macrophages, resulting in suppression of inflammatory genes and enhancement of the anti-inflammatory effects of glucocorticoids (5,29). Although there are laboratory data supporting the steroid sparing effects in COPD, current literature from clinical trials is conflicting. Low-dose theophylline has been shown to enhance the recovery from acute exacerbations of COPD, and is associated with reduced inflammation and increased HDAC activity (33). A small study of 30 patients with moderate COPD in a double-dummy, randomised, double-blind, parallel study, demonstrated that low-dose theophylline elicited a greater anti-inflammatory effect and improvement in FEV₁ when added to an inhaled corticosteroid than either drug alone (34). A more recent randomised control trial in 1,567 patients, failed to demonstrate a reduced number of COPD exacerbations over a 1 year period, when low dose theophylline was added to inhaled corticosteroid (7). However, a post hoc sub-analysis revealed that there were more COPD related hospital admissions in the placebo group compared to the theophylline-treated group (7). Thus, although there appears evidence for synergism of theophylline with glucocorticosteroids in COPD, current literature remains conflicting in this regard.

Bronchiectasis

Bronchiectasis is defined as abnormal, permanent dilation of the airways for which there are many causes. Post-infectious causes remain the most frequent aetiology for bronchiectasis in LMICs, of which tuberculosis is the most important locally (35).

Bronchiectasis predisposes to recurrent infections, inflammation and further damage to the airways, in turn perpetuating the cycle of recurrent infections and damage in the airways. Frequently, bronchiectasis demonstrates airflow obstruction, and theophylline with the proposed therapeutic bronchodilatory and anti-inflammatory mechanisms described above, may have some theoretical utility in this disease. Currently, there is no evidence for or against the use of theophylline in bronchiectasis. A Cochrane review conducted in 2000, investigating the utility of oral methylxanthines in the treatment of bronchiectasis, failed to identify any trials supporting the use of theophylline in bronchiectasis (36). A clinical trial conducted by Zhong *et al.*, 2015, which evaluated the clinical efficacy and safety of theophylline in the treatment

Table 1 Drug interactions and factors affecting theophylline clearance (3)

Increased clearance	Decreased clearance
Enzyme inducers (rifampicin, phenobarbitone, ethanol)	Enzyme inhibition (cimetidine, erythromycin, ciprofloxacin, allopurinol, zileuton)
Smoking (tobacco, cannabis)	Congestive heart failure
High protein, low carbohydrate diet	Liver disease
Barbecued meat	Pneumonia
Childhood	Viral Infection
	Vaccination (immunization)
	High carbohydrate diet
	Old age

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of non-cystic fibrosis bronchiectasis, reached completion in study objective, however, the results of the study have yet to be published (37). Thus, we currently have no evidence to either support or refute the use of theophylline in the management of bronchiectasis.

Theophylline in pulmonary hypertension

Tuberculosis has not been cited as a cause of pulmonary hypertension in major guidelines (38), however local clinical experience suggests otherwise and potentially may be the most important cause of group 3 pulmonary hypertension (due to chronic lung disease) locally (39). Theophylline may be beneficial in treating pulmonary hypertension. Early studies suggested that intravenous aminophylline reduces pulmonary artery pressures and pulmonary vascular resistance with associated increases in right and left ventricular ejection fraction in COPD patients (40). Oral long-acting theophylline is thought to produce a similar and chronic improvement in biventricular performance. Postulated mechanisms by which theophylline augments right and left ventricular systolic function includes a reduction in ventricular afterload and positive inotropy (40). Theophylline has not been studied in isolated pulmonary hypertension, but it is possible that theophylline may demonstrate utility in patients with a combination of COPD, pulmonary artery hypertension, and right or left heart failure. However, patients with right ventricular failure may have decreased clearance of theophylline, warranting careful monitoring of plasma levels (see below) (41).

Relevant pharmacology

“Theophylline in the PTBLD” (Pharmacokinetics)

Theophylline is considered by many clinicians as a “dirty drug”, due perceived toxicity, side-effects, and intra- and interpatient variability. There appears to be a linear relationship between serum theophylline concentrations and improved airway function. Bronchodilator effects are negligible below 10 mg/L, whilst side effects are commonplace above 25 mg/L and therefore, the therapeutic range for theophylline has been reported as 10 to 20 mg/L (3). Notably, non-bronchodilator effects of theophylline are achieved at concentrations of less than 10 mg/L (3). The attainment of therapeutic concentrations is influenced mainly by population and interpatient variances in clearance, which is, in turn, determined primarily by hepatic metabolism. Theophylline is rapidly and completely absorbed and is metabolised in the liver by the cytochrome P450 microsomal enzyme system (CYP1A2 in particular). The hepatic metabolism of theophylline is influenced by several pharmacokinetic factors, concurrent disease states, as well as drug interactions (see *Table 1*) (3). Increased clearance is seen in children and in cigarette and marijuana smokers (3). For example; concomitant administration of CYP450 enzyme inducers phenytoin, or rifampicin, result in low theophylline plasma levels, thus higher doses may be required. Decreased clearance of theophylline may be seen with liver disease, and heart failure, and therefore appropriate dose reduction and monitoring of plasma levels is required (24). There is a paucity of data on the pharmacogenetics of theophylline. However, a Turkish

study conducted in COPD patients found that the T allele of rs35694136 is linked with decreased metabolism of theophylline (42). Furthermore, data from a study conducted in Japanese asthmatic patients (replicated by a study in Korean asthmatic patients), demonstrated that genotypes AA and AG of rs2069514 in the *CYP1A2* gene are associated with decreased metabolism of theophylline (43-45). Various single nucleotide polymorphisms (SNPs) in the *CYP2E1* and *CYP1A2* promoter regions have been linked to altered hepatic metabolism and lower plasma theophylline levels, respectively (45). There are no pharmacogenetic studies on theophylline in sub-Saharan Africa.

Potential pitfalls

Drug interactions (see Table 1)

A reduction in theophylline clearance occurs with the co-administration of the following drugs: erythromycin, quinolone antibiotics (excluding ofloxacin), allopurinol, cimetidine, selective serotonin uptake inhibitors (fluvoxamine), and the 5-lipoxygenase inhibitor zileuton, all of which induce the CYP1A2 isoenzyme. With respect to the macrolide class; similar interactions are seen with clarithromycin, but there is no reported interaction with azithromycin (46). Vaccinations (influenza immunizations) have also been reported to reduce clearance (3).

Due to the wide variations in theophylline hepatic metabolism and clearance, careful therapeutic drug monitoring and dose is required. Plasma concentrations should ideally be measured 4 hours after the last dose with slow-release preparations (3).

Side effects and toxicity

In high-income country settings, toxic exposures to theophylline have decreased significantly since its management for asthma and COPD has declined. From 1985 to 1995 in the United States, theophylline poisoning requiring haemodialysis or haemoperfusion accounted for 49 cases per one million poison centre calls, compared to the 6 cases per one million poison centre calls from 1996 to 2005. According to the American Association of Poison Control Centres, there were 133 exposures to theophylline in 2014 (47). A South African toxicovigilance study conducted by Veale *et al.*, 2013 found that theophylline overdose comprised only 1.5% of the total medicine related exposures (48).

Theophylline has a narrow therapeutic window with toxic effects occurring when serum theophylline levels surpass the levels in the therapeutic range (usually >20 mg/L). This occurs primarily by intentional overdose or unintentionally when metabolism and/or clearance of theophylline is altered due to certain physiological stressors. The main toxic effects may be summarized as follows (3,47):

- ❖ General: Agitation, irritability, restlessness;
- ❖ Cardiovascular: Sinus tachycardia, ventricular tachycardia atrial fibrillation, supraventricular tachycardia, hypotension, cardiac arrest;
- ❖ Respiratory: Tachypnoea, acute lung injury, respiratory alkalosis;
- ❖ Gastrointestinal: Nausea, vomiting, abdominal pain;
- ❖ Neurological: Tremors, hallucinations, seizures.

The inhibition of PDE isoenzymes frequently result in headache, nausea and vomiting, increased acid secretion, and gastroesophageal reflux, whilst diuresis has been attributed to adenosine receptor antagonism. Convulsions and cardiac arrhythmias may occur at high plasma concentrations and are associated with adenosine A1A-receptor antagonism. Side effects may be mitigated by slow dose titration until therapeutic concentrations are achieved. Furthermore, avoiding the toxic effects of theophylline can be achieved by appropriate therapeutic drug monitoring, patient education and prescriber pharmacovigilance. The clinical presentation and management of non-accidental overdose of theophylline is beyond the scope of this review. Given the above side effect profile of theophylline and the potential efficacy of low doses in context of PTBLD, theophylline may prove to be a safe therapeutic and cost-effective agent for the management of this disease entity. Currently no direct comparator or cost-effectiveness studies exist that compare theophylline with other medications used in pulmonary hypertension. However, if found of benefit, the cost saving of theophylline (USD 21.00 for one month at 200 mg) compared to, for example, oral sildenafil (USD 282.00 for one month at 50 mg) could be an important consideration in places where PTBLD is prevalent.

The use of lower doses than that used in chronic obstructive lung disease or asthma limits the need for intensive therapeutic drug monitoring and most of the drug side effects which are dose related. We do however advocate therapeutic drug monitoring for some patients with PTBLD who may have altered drug metabolism (liver disease, renal disease) and may have drug-drug interactions secondary to use of concomitant enzyme inhibiting/inducing drugs.

We advocate comprehensive patient education with respect to side effect awareness, informing prescribers of changes in drug regimens and the use of concomitant over-the-counter medications. A national drug registry may help with monitoring of adverse effects and efficacy of low dose theophylline in TB associated lung disease.

Conclusions

Theophylline for chronic respiratory diseases remains controversial with more effective agents promoted for COPD, while no data exists in bronchiectasis or pulmonary hypertension, yet it remains both affordable, available and prescribed in many low- and middle-income countries, including South Africa. The narrow therapeutic index, side-effect profile and drug-drug interactions, need to be balanced against anti-inflammatory effects at lower-doses and safety facilitated by therapeutic drug monitoring. The anti-inflammatory, bronchodilatory and possible pulmonary-vascular effects make it an attractive potential agent for PTBLD, which has overlapping phenotypes of bronchiectasis, chronic airflow obstruction and pulmonary hypertension. Given the paucity of evidence supporting the use of theophylline in patients with PTBLD, robust clinical trials are needed.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-1298>). The authors have no conflicts of interest to declare.

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