International Journal of Basic & Clinical Pharmacology
*Malamatari M. Int J Basic Clin Pharmacol. 2024 Jan;13(1):174-180*
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20233912

**Review Article**

# Inhaled theophylline: old drug new tricks?

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**Received:** 17 November 2023
**Accepted:** 07 December 2023

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## ABSTRACT

Theophylline and aminophylline (i.e., the soluble complex of theophylline with ethylenediamine) have been used in the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease for more than 90 years. Theophylline's narrow therapeutic index and side effects, as well as the discovery of more potent and safer bronchodilators, made it to fall out of favour with healthcare professionals and patients. New scientific knowledge on the molecular mechanism of action of theophylline, along with increasing clinical evidence suggest that theophylline should be exploited as an anti-inflammatory agent rather than a bronchodilator. This review covers the journey of theophylline from rise to fall and back to its potential re-emergence as a combination formulation with inhaled corticosteroids in the management of chronic inflammatory lung diseases. Several approaches to formulate theophylline either as a monotherapy or as a combination therapy for delivery to the lungs are presented.

**Keywords:** Theophylline, Respiratory disease, Pulmonary drug delivery

## INTRODUCTION

In 1922, the first study was published reporting that theophylline should be considered clinically for both acute and prophylactic treatment of asthma.[1] However, it was not until 1940 that theophylline was approved by the Food and Drug Administration for the treatment of asthma. Theophylline became the mainstay of management of acute asthma exacerbations when it came into general use, as it was more effective (i.e., rapid onset of action, reasonable half-life) and safer than the available medications at the time (i.e., adrenaline, ephedrine, benzyl benzoate and asthma powders composed of potassium nitrate and stramonium leaves).[2] Improved understanding of its pharmacodynamics and pharmacokinetics together with the development of modified-release drug delivery systems extended its use in the prophylaxis of chronic asthma.[3] Currently, due to the development of more effective therapies as the β2-agonists and the inhaled corticosteroids (ICS) and the rising concerns related to the potential side effects of theophylline, the use of theophylline has decreased markedly. For example, a 20-year Danish drug utilization study on the nationwide use of theophylline among adults reported that the number of theophylline users in treatment per year decreased from 401 per 100,000 individuals in 1997 to only 26 per 100,000 individuals in 2016.[4] The several drug-drug interactions and the fact that it frequently requires therapeutic drug monitoring (i.e., measurement of drug's concentration in the plasma) also led to theophylline being considered either an 'obsolete agent' or 'as last-choice treatment in uncontrolled asthmatics with severe disease'.[5,6] At this point, it should be stated that due to their affordability, generic formulations of oral theophylline are available and more likely to be used compared to inhaled medications in developing countries.[7]

## PHARMACOKINETICS OF THEOPHYLLINE

Theophylline exhibits rapid and complete absorption, achieving peak levels at 2 h after oral administration. Protein binding is 40-60%, the average volume of distribution is 0.45 l/kg.[8] In adults and children, theophylline is mainly metabolised in the liver (CYP1A2

enzyme) by oxidation and N-demethylation. In neonates, minimal biotransformation occurs and ~50% of theophylline is excreted unchanged in the urine because of their immature hepatic function. Large inter-subject variability in the clearance of theophylline is observed, that is attributed to differences in hepatic metabolism. Several factors have been reported to influence the metabolism of theophylline, such as the concurrent administration of drugs (e.g., rifampicin, ciprofloxacin, phenytoin), age and smoking. A review of the population pharmacokinetics of theophylline in patients of different age summarised the most important covariates to which the large variability in the pharmacokinetics of theophylline may be attributed.[9] The optimal doses of theophylline for each population should be determined based on these covariates (Figure 1).

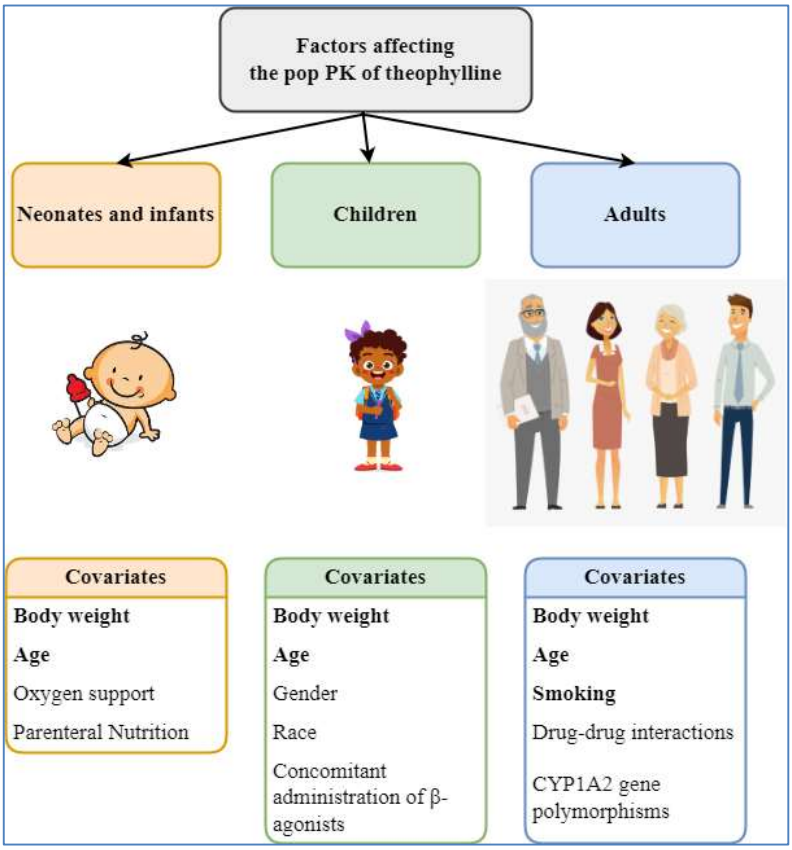


**Figure 1: Factors affecting population PK of theophylline.[9]**

***Current use of theophylline for the treatment of asthma and COPD***

According to the Global Initiative for Asthma stepwise approach to control symptoms and minimise risks in asthma, theophylline is classified as an alternative, add-on treatment to low- or high-dose ICS (Steps 3 to 5).[10] Add-on theophylline is not recommended for children due to lack of efficacy and safety data. According to the Global Initiative for Chronic Obstructive Lung Disease, theophylline exerts a modest bronchodilator effect compared with placebo in stable COPD.[11] Theophylline and aminophylline are indicated for the treatment of chronic asthma and reversible airway obstruction.[12] The indications and posology of theophylline and aminophylline in adults and children are presented in Table 1.

Theophylline due to its narrow therapeutic index (plasma concentration 10-20 mg/l) is an ideal candidate for controlled-release preparations. In this way, maintenance of optimal drug concentration and increased duration of therapeutic effect is achieved with reduced side effects. Moreover, less frequent administration (once or twice daily) facilitates patient adherence to medication.[13] Recently, innovative technologies such as extrusion-based 3D-printing of pharmaceuticals have been used to prepare flexible theophylline formulations with extended-release characteristics.[14] However, controlled-release preparations of theophylline should not be generically prescribed, and patients should be maintained on the brand on which they have been stabilised.[12] This may be explained by the clinically significant differences in the extent and the rate of absorption observed among different commercially available controlled-release formulations of theophylline.[15]

## PHARMACOLOGY OF THEOPHYLLINE

Theophylline exerts a double action in the treatment of respiratory diseases: at high plasma concentrations, it acts

as a bronchodilator while at lower plasma concentrations it exhibits bronchoprotective action.[16] The bronchodilation of airway smooth muscles caused by theophylline is mediated by two molecular mechanisms: phosphodiesterase (PDE) inhibition and adenosine receptor antagonism.

**Table 1: Indications and posology of theophylline and aminophylline medicinal products.[12]**

| Indications | Theophylline | Aminophylline |
|---|---|---|
| **Chronic asthma** | By mouth using modified-release formulations, Adults and children 12-17 years: 200 mg every 12 hours, adjusted according to response to 400 mg every 12 hours, Children 2-11 years: 9 mg/kg every 12 hours (max per dose 200 mg) | By mouth using modified-release formulations, Children (body weight ≥40 kg): initially 225 mg twice daily for one week, then increased, if necessary, to 450 mg twice daily[#] |
| **Reversible airways obstruction** | Yes | Adults (body weight ≥40 kg): initially 225 mg twice daily for one week, then increased if necessary, to 450 mg twice daily[#] |
| **Severe acute asthma** | Yes | By intravenous infusion; Adults and children 12-17 years: 500-700 micrograms/kg/hour [#], Elderly: 300 micrograms/kg/hour[#] Children 1 month to 1 years: 1 mg/kg/hour[#] |
| **Severe acute asthma in patients not previously treated with theophylline** | N/A | By slow intravenous injection; Adults and children: 5 mg/kg (max per dose 500 mg) |
| **Severe acute exacerbation of COPD** | N/A | By intravenous infusion; Adults: 500-700 micrograms/kg/hour[#], Elderly: 300 micrograms/kg/hour[#] |
| **Severe acute exacerbation of COPD in patient not previously treated with theophylline** | N/A | By slow intravenous injection; Adults: 250-500 mg (max per dose 5 mg/kg). |

# Adjusted according to theophylline plasma concentration; N/A: not applied.

Theophylline is a weak bronchodilator, and a plasma concentration of 10-20 mg/l needs to be achieved for bronchodilation to occur. At these high plasma concentrations and above, theophylline may also cause side effects. The side effects caused by theophylline are mediated by the same molecular mechanisms which are involved in bronchodilation. Specifically, PDE inhibition accounts for nausea, vomiting, headaches and diuresis. Adenosine receptor antagonism accounts for cardiac arrhythmias and seizures when very high plasma concentrations are reached.[17] Another concern with theophylline is that it interacts with various medications as it is metabolized in the liver by cytochrome P450 isoenzyme. Several drugs interact with theophylline by inhibiting or inducing its metabolism by CYP1A2 leading to toxic or sub-therapeutical plasma theophylline levels, respectively. As theophylline non-selective PDE inhibition results in bronchodilation, but also adverse effects, research has focused on the discovery of highly selective PDE inhibitors for the treatment of respiratory diseases that will have greater efficacy but fewer side effects.[18] In 2010, roflumilast (Daxas®; Nycomed), a PDE4 inhibitor with anti-inflammatory properties was approved in Europe as an add-on therapy to bronchodilators for the maintenance treatment of severe COPD associated with chronic bronchitis and a history of frequent exacerbations.[19] In contrast to theophylline, PDE4 inhibitors do not require plasma monitoring and exhibit far less interactions with other drugs.[20] Airway inflammation plays a critical role for both asthma and COPD. In the last decades, studies have suggested that theophylline has clinically-relevant anti-inflammatory properties in patients with asthma at plasma concentrations (≈ 5 mg/l) which do not pose toxicity problems.[21,22] The immunomodulatory effects of theophylline were also observed even in patients already in treatment with ICS, indicating that ICS and theophylline mitigate inflammation through different molecular mechanisms, and thus combination therapy may lead to synergistic effects.[23] Combining oral theophylline (250-375 mg per day) with a low dose of inhaled budesonide (400 micrograms per day) was found to be equally effective as a high dose of budesonide (800 micrograms per day) for asthma control.[24] As a result, it was suggested that addition of low-dose theophylline to ICS may be a preferable low-cost option than increasing the dose of ICS.[25] The two molecular mechanisms involved behind the immunomodulatory effects of theophylline are: adenosine receptor antagonism and

histone deacetylase activity (HDAC). By directly increasing the histone deacetylase enzymatic activity in epithelial cells and macrophages, theophylline inhibits the acetylation of core histones promoting repackaging of chromatin. In this way, it suppresses the expression of pro-inflammatory genes.[26]

***Low-dose theophylline restores corticosteroid resistance in chronic inflammatory diseases of the lungs***

COPD is characterised by chronic inflammation of the lungs that results in progressive and poorly reversible airflow limitation with periodic exacerbations. Macrophages play a pivotal role in the pathophysiology of COPD. A significant increase in their numbers in the lungs of COPD patients.[27] High levels of inflammatory mediators such as interleukin-8 (IL-8) and tumour necrosis factor alpha (TNF-α) are also increased in the sputum of COPD patients.[28] The anti-inflammatory response of inhaled or oral corticosteroids is reduced in alveolar macrophages from COPD patients. This may be explained by a reduction in HDAC2 activity because of oxidative and nitrate stress in the macrophages of the patients. The reduced HDAC2 activity results in increased acetylation of the glycorticosteroid receptor which prevents it from inhibiting inflammation.[29] Theophylline was found to induce a six-fold increase in HDAC activity in macrophages of COPD patients and to enhance dexamethasone suppression of induced IL-8.[30] The synergistic effect of theophylline with corticosteroids has also been reported in patients who suffer from asthma and smoke.[31] A combination of low-dose theophylline (400 mg per day) and inhaled beclometasone (200 micrograms per day) significantly improved both lung function and asthma control in these patients compared with monotherapy.[32] Reversal of corticosteroid resistance is recognised as a highly promising approach for emerging pharmacotherapies in COPD.[29] Therefore, co-administration of low-dose theophylline with ICS has the potential to evolve as a future treatment for chronic inflammatory lung diseases. At this point, it should be noted that a clinical trial demonstrated that among adults with COPD at high risk of exacerbation treated with ICS, the addition of low-dose oral theophylline (200 mg theophylline modified-release tablets once or twice daily depending on the participant's ideal body weight), compared to the placebo did not reduce the number of COPD exacerbations over a one-year period.[33] The results of this study did not support the preclinical finding that low plasma concentrations (1-5 mg/l) of theophylline enhance the anti-inflammatory effects of ICS in COPD. However, the limitations of this study included a high rate of patients ceasing taking medication, the study was based on participant-reported exacerbations rather than documented by healthcare professionals and the study did not measure the effect on mild exacerbations. Recently, a systematic review and meta-analysis evaluated the efficacy and safety of low-dose theophylline in addition to ICS therapy in COPD. It was found that low-dose theophylline as an add-on therapy to ICS did not reduce the exacerbation rate of COPD while it increased the hospitalisation rate. However, it was also observed that theophylline improved lung function compared to the non-theophylline group.[34]

## FORMULATIONS OF THEOPHYLLINE FOR PULMONARY DELIVERY

Developing inhalable formulations of theophylline for targeted administration to the lungs is a key step towards translating the aforementioned scientific and clinical evidence to a drug product. This review presents studies on the development of formulations of theophylline to the lungs either as monotherapy or as a combination therapy with ICS. Zhu et al developed a low-dose pressurized metered dose inhaler (pMDI) inhalable formulation of theophylline to eliminate the adverse effects related to oral delivery.[35] To enhance the solubility of the drug in the propellant, HFA134a, and deliver 50 μg of drug per actuation, ethanol was incorporated as a co-solvent in the formulation. The pMDI formulation exhibited a fine particle fraction (FPF) of 38.0%±1.1% and a mass median aerodynamic diameter (MMAD) of 1.2±0.01 μm. Cell studies (using a modified Andersen cascade impactor and Calu-3 model) showed that 97.9±1.2% of the deposited theophylline was transported across the epithelial cells to reach its site of action on the smooth muscle cells, while less than 2% was retained in the cells. Transport of the drug resulted in theophylline concentration of 1.7 mg/l which is below the plasma concentration related to side effects (i.e., >10 mg/l). A significant reduction in IL-8 concentration released from Calu-3 cells following stimulation with TNF-α was observed when the cells were pre-treated with theophylline, indicating the anti-inflammatory potential of theophylline pMDI formulation. In a follow-up study, Zhu et al developed a DPI formulation of theophylline.[36] The formulation was produced by spray drying a hydroalcoholic solution of theophylline containing 1.0% w/w sodium stearate as a lipophilic adjunct. The formulation showed suitable physicochemical and aerodynamic properties for lung delivery (i.e. FPF%: 29.7±2.5%, MMAD: 3.3±0.3 μm). Cell studies demonstrated that 56.1±7.62% of the total theophylline deposited, was transported across the Calu-3 monolayer over 180 min following deposition, while 37.1±16.2% was retained in the cells. The high amount of theophylline retained in the cells was attributed to the lipophilic nature of sodium stearate. However, the transport rate over the first 30 min was found to be significantly higher for theophylline as DPI compared to the pMDI formulation. The higher transport rate could potentially result in faster onset of action. Solidification of nanosuspensions to respirable nanoparticle agglomerates (i.e. with aerodynamic diameter in the range of 1-5 μm) has been characterised as 'an approach to harmonise the advantages of nanoparticles with the aerodynamics of small microparticles to achieve an improved bioavailability and aerosolation behaviour of the drug'.[37] Following this approach, Salem et al. prepared theophylline nanosized rod agglomerates by using anti-solvent precipitation to prepare theophylline

nanosuspensions, which were further agglomerated by ionic interaction of a diluted solution of the strong electrolyte, sodium chloride.[38] The nanosized rod agglomerates exhibited a FPF of 79.4±4.6% and a MMAD of 2.3±0.9 μm.

Using a scalable manufacturing method, Malamatari et al. prepared nanoparticle agglomerates of theophylline by wet milling in isopropanol followed by spray drying.[39] Nanoparticle agglomerates with various ratios of theophylline to mannitol were prepared. The addition of mannitol was found to facilitate the size reduction of the needle-like crystals of theophylline and their assembly in microcomposite structures. Microcomposite particles containing theophylline and mannitol in a ratio of 25:75 w/w exhibited a FPF of 56.8±8.7% and a MMAD of 2.9± 0.1 μm. Their enhanced in-vitro aerosolisation performance was attributed to their smaller size, spherical shape and enhanced porosity compared to engineered particles containing lower amounts or no mannitol. Recently, Leng et al used spray drying to formulate budesonide (ICS) with theophylline into inhalable dry powders for pulmonary combination therapy.[40] In this study two types of spray nozzles were used, namely a two-fluid and a three-fluid nozzle. For the conventional spray dryer equipped with a two-fluid nozzle, both drugs should be dissolved/dispersed in a single liquid feed. In contrast, the use of three-fluid nozzle allows particle engineering of drug combinations, where the different drugs are dissolved/dispersed in different feed samples.[41,42] Hence, using two types of spray nozzles and liquid feeds where the drugs were either dissolved or suspended, four types of inhalable formulations were obtained and characterized for their micromeritic and solid-state properties, dissolution and aerosolisation performance. The formulation prepared by spray drying an aqueous feed containing a nanosuspension of budesonide and dissolved theophylline using the two-fluid nozzle was found to exhibit the most advantageous properties for pulmonary drug delivery. Specifically, in this formulation the crystalline state of both drugs was retained ensuring the long-term physical stability of the spray-dried particles upon storage, rapid dissolution of budesonide was attained, and co-deposition of both drugs was achieved in the in-vitro aerodynamic assessment using the next generation impactor (NGI). Co-deposition of both drugs in the stages of the impactor is a key attribute as it indicates improved co-location to targeted parts of the lung which may lead to pronounced synergistic or additive efficacy between budesonide and theophylline on respiratory inflammation.[43] Spray drying with a three-fluid nozzle was also used for the preparation of particles composed of theophylline and salbutamol sulfate.[44] It was reported that the two drugs had different in-vitro deposition. This was attributed to the mixing time being insufficient to generate a homogeneous mixture of the two drugs at the tip of the three-fluid nozzle. Instead, it was indicated that salbutamol sulfate may acts a carrier for the delivery of theophylline crystals. Salama et al developed a new approach to concurrently deliver oral theophylline and inhaled budesonide and terbutaline as a single formulation. In this formulation, theophylline was acting as a carrier while the other two drugs were targeted to the lungs.[45] This multicomponent drug delivery technology shows potential as a combination therapy by reducing the need for multiple formulations and thus increasing patient adherence. Co-micronising theophylline using an air-jet mill with inhaled corticosteroids such as fluticasone propionate in the presence of magnesium stearate was patented as a way to produce inhalable particles where the aerodynamic particle size distribution of the two active substances relative to their delivered doses were substantially the same (i.e., ±25% on each impactor stage).[46]

## CONCLUSION

Theophylline is an old drug which has been used for the treatment of respiratory diseases for more than 90 years. Its use as a bronchodilator has fallen out of favor mainly due to its narrow therapeutic index, adverse events and need for therapeutic monitoring. Current evidence suggests that at low doses theophylline may exhibit a synergistic effect in reducing inflammation when administered with ICS. The two mechanisms involved behind the immunomodulatory effects of theophylline are adenosine receptor antagonism and histone deacetylase activity. Several studies have been conducted on the efficacy and safety of theophylline as an add-on therapy to corticosteroids for the treatment of COPD. However, controversial results have been reported on the effect of theophylline on lung function, exacerbation rates and hospitalization rates. Administration of theophylline to the lungs has been suggested to enhance local efficacy while reducing side effects. Low-dose inhaled theophylline as an add-on treatment to ICS had attracted interest from the pharmaceutical industry. Several particle engineering approaches have been used to produce inhalable particles of theophylline either as monotherapy or as a combination therapy with ICS. The various engineering approaches indicate the feasibility in administering theophylline to the lungs. This review covers the journey of theophylline from rise to fall and back to its potential re-emergence as a combination formulation with inhaled corticosteroids in the management of chronic inflammatory lung diseases.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Malamatari M. Inhaled theophylline: old drug new tricks?. Int J Basic Clin Pharmacol 2024;13:174-80.