Review Article

A narrative review of theophylline: is there still a place for an old friend?

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Background and Objective: Theophylline has been used for decades in human medicine for its psychostimulant, anti-inflammatory, and bronchodilator effects. Historically, in pulmonary medicine, theophylline has been used in the treatment of obstructive pulmonary diseases such as bronchial asthma (BA) or chronic obstructive pulmonary disease (COPD). This review aims to determine whether theophylline still has its place in the therapy of obstructive pulmonary diseases or whether we can even extend its use to other diagnoses such as atropine-resistant cardiac arrests, apnea of prematurity, or others. Moreover, we also aim to determine if there is a rationale for using low-dose theophylline due to its immunomodulatory and anti-inflammatory effect, or if the future of methylxanthines lies in newly synthesized derivates of theophylline such as bamifylline, or doxofylline.

Methods: The narrative review is based on a literature search of the articles indexed in the PubMed database in 2023. We searched the database since the year 2009 using the MeSH terms "theophylline", "aminophylline", and "methylxanthines" and we included original articles in the English language.

Key Content and Findings: Theophylline has a number of adverse drug reactions (ADRs), the most serious of which is its effect on the cardiovascular system. It can cause severe arrhythmias or even cardiac arrest when overdosed. On the other hand, there is still a substantial amount of its applications in current clinical practice.

Conclusions: There is considerable controversy associated with its use in current medicine, which can be attributed both to its narrow therapeutic range and its mentioned cardiotoxic effect. Herein, we summarize the current state-of-art of theophylline and its use in human medicine.

Keywords: Theophylline; aminophylline; methylxanthines; chronic obstructive pulmonary disease (COPD); bronchial asthma (BA)

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Introduction

Theophylline (1,3-dimethylxanthine) as a part of the methylxanthines family is known for its broad spectrum of effects in the human body. This alkaloid, mainly found in tea, coffee, or chocolate, has been used for decades in medicine for its psychostimulant, anti-inflammatory, and bronchodilator effects (1).

On the other hand, theophylline is subject to lots of controversy as it is a drug with many adverse drug reactions (ADRs) and a compromised safety profile. Questions remain about whether there is still a place for its application in current clinical practice. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1781/rc).

Methods

The PubMed database was searched for references with the terms "theophylline", "aminophylline", and "methylxanthines" in the title or abstract. Relevant articles were identified from the reference lists of selected articles. Randomized trials and publications from the last 15 years were prioritized but we also cited other references where historically relevant and necessary. The search strategy is summarized in *Table 1*.

Theophylline

Mechanism of action

Similarly to other methylxanthines, theophylline has a dual mechanism of action: (I) it is a non-selective competitive phosphodiesterase inhibitor, and it is also (II) a non-selective competitive adenosine receptor antagonist.

(I) Theophylline is a competitive non-selective phosphodiesterase inhibitor and thus affects the intracellular concentration of cyclic nucleotides—cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which as second messengers play a pivotal role in signal transmission and regulation of physiological response in the human body. The intracellular levels of these second messengers are controlled by the family of phosphodiesterase enzymes (PDEs) (2). PDE participates in the regulation of the immune system and other organ systems (lungs, heart, smooth muscles, brain, fat tissue, liver, and others). PDE3 and PDE4 are two isoenzymes of the PDE family, which are particularly important targets of theophylline action. PDE3 is present in smooth muscle cells and its inhibition results in smooth muscle relaxation in the airways and thus represents one of the pharmacological routes to bronchodilation (3). PDE4, on the other hand, is apart from lung tissue represented mostly in the cells of the immune system (3,4). Therefore, its inhibition suppresses inflammation as one of the main pathophysiological mechanisms involved in the development and worsening of bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD).

(II) Adenosine is an endogenous extracellular messenger that affects many physiological processes in the human organism. All adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3) are expressed in human lungs (5,6). Adenosine levels are increased in the lungs of both BA and COPD patients, while adenosine receptors are mostly expressed in inflammatory and stromal cells involved in the pathogenesis of both conditions (7). Although adenosine has little effect on normal human airway smooth muscle *in vitro*, inhaled adenosine causes significant constriction of airway smooth muscle cells in patients with BA (8). The mechanism of bronchoconstriction is indirect and involves the release of histamine and leukotrienes from the airway mast cells (9). The bronchoconstriction effect of adenosine can be prevented by therapeutic concentrations of theophylline (8,10). As an adenosine antagonist, theophylline also acts as a psychostimulant. Its effect on the central nervous system (CNS) was mainly studied in children taking theophylline as part of their BA therapy. The results of clinical trials were inconclusive, thus we cannot state whether theophylline has a positive or negative effect on mood or behavior (11,12).

Along with its two main types of anti-inflammatory action, theophylline has an additional anti-inflammatory effect via the mechanism of increased interleukin-10 activity and it also inhibits the translocation of the (pro-inflammatory) transcription nuclear factor-κB (NF-κB) (13).

Above that, even relatively low plasma levels of theophylline (~5 mg/L) can stimulate the activity of histone deacetylase-2 (HDAC2) and thus restore the anti-inflammatory effects of corticosteroids in patients with

Table 1 The search strategy summary

Items	Specification
Date of search	19/9/2023
Databases and other sources searched	PubMed
Search terms used	"Theophylline", "aminophylline", and "methylxanthines"
Timeframe	2009–2023
Inclusion criteria	Observational and retrospective studies, as well as case series and case reports
Exclusion criteria	Articles in other than English language, without full-text available
Selection process	Identification of historically relevant or related articles by agreement between M.S. and K.B.

COPD (14). In this group of patients, HDAC2 activity is often inhibited by phosphatidylinositol 3-kinase-δ (PI3K-δ), which is induced by oxidative stress, frequently present in COPD patients (13).

Pharmacokinetics

Theophylline is mainly metabolized in the liver by the microsomal p450 cytochrome system (CYP1A2, CYP2E1 isoforms). Its increased metabolism by cytochrome p450 occurs in cigarette and marijuana smokers or during the use of concurrent medications (e.g., rifampin). On the contrary, its hepatic elimination can be decreased in patients with liver diseases or with various simultaneous medications (e.g., erythromycin, ciprofloxacin, clarithromycin, fluconazole, acyclovir, or verapamil) (13).

Accordingly, theophylline is most often manufactured in the form of extended-release tablets to overcome rapid hepatic breakdown and maintain more stable plasma levels (15). In this form, theophylline is administered twice daily with doses ranging between 100 and 400 mg, maintaining a relatively stable plasma concentration during the day. It is also possible to administer theophylline as a slow intravenous infusion in its more soluble form (aminophylline). Aminophylline is a compound formed by two molecules of theophylline and one molecule of ethylenediamine.

Pharmacodynamics

Theophylline has many effects on the human organism, that result from non-selective inhibition of PDE and the adenosine receptor. The most important are the bronchodilatation and anti-inflammatory effects. Importantly, obstructive pulmonary diseases (BA and COPD) are characterized by different types of inflammation and airway remodeling, resulting in variable reversibility of airway obstruction. Therefore, the complementary anti-inflammatory and bronchodilatation effects are beneficial.

Bronchodilation

Theophylline improves lung function, represented by both forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) (16). Theophylline improves patients' exercise tolerance (17), probably due to the reduction of "air trapping" (18). This finding may explain the discordance between significant clinical improvement in dyspnea despite minimal improvement in spirometry (19). The bronchodilator action of aminophylline, unlike the anti-inflammatory effect, occurs only at higher plasma concentrations, which are, in turn, associated with a higher probability of ADRs (3). Theophylline also increases the diaphragmatic and intercostal muscle strength (20-24) and stimulates the cerebral respiratory center (25).

Antiinflammatory effect

Both BA and COPD are lung diseases characterized by variable degrees of inflammation in the lung tissue. Low-dose theophylline suppresses inflammation and reduces the number of eosinophils in bronchial biopsies, bronchoalveolar lavage fluid, and induced sputum in BA patients (26). The anti-inflammatory effect of theophylline has been observed even at lower plasma concentrations and occurs more likely if administered in the long term (3). In patients with COPD, theophylline reduces the rate of sputum neutrophils and the degree of neutrophilic inflammation in the airways (27). Interestingly, a withdrawal of xanthines rebounds airway inflammation, even in patients

simultaneously treated by corticosteroids, suggesting that xanthines have additional pharmacological properties not shared by corticosteroids (28,29).

ADRs and toxicity

Theophylline has several ADRs, not only occurring during overdose but also at normal therapeutic plasma concentrations (i.e., serum level 10–20 mg/L) (15). Its narrow therapeutic range is the main limitation of its use as theophylline requires frequent plasma level checks as a precaution in preventing adverse events. If the recommended therapeutic plasma concentrations are exceeded, adverse effects may develop. These include (more frequent) headache, dizziness, anxiety, insomnia, nausea, and/or vomiting; or rarer but more serious cardiac arrhythmias or epileptic seizures (3).

Undoubtedly, the most serious are the effects on the cardiovascular system. Rapid intravenous infusion of aminophylline (30) but also oral overdose of theophylline (31) are associated with ventricular fibrillation or even cardiac arrest. Despite a general decline in the use of theophylline in routine clinical practice, episodes of theophylline overdose are not uncommon (32). Aminophylline use is associated with tachycardia while even therapeutic plasma levels can cause severe arrhythmias (33,34).

Cardiac arrhythmias occur in more than 20% of patients who overdosed on theophylline, and the risk of arrhythmias in overdosed patients is significantly higher in those with a chronic overdose rather than in cases of acute intoxication (35). Theophylline treatment is associated with atrial fibrillation (AF) (31,35,36). AF with a rapid ventricular response can be directly induced by intravenous administration of aminophylline and after its discontinuation and a decrease in serum levels, AF usually terminates (37). The most alarming fact about theophylline treatment in patients treated with theophylline is the higher death rate from cardiovascular causes (38,39).

Theophylline interacts with the metabolism of many drugs. For example, the central antagonism of adenosine reduces the sedative effect of propofol. In a randomized volunteer trial, theophylline prolonged the time to loss of consciousness and shortened the time to regain consciousness upon awakening from general anesthesia (40). Other data suggest that theophylline also reduces the sedative effect of morphine (41), barbiturates (42), or benzodiazepines (43).

The treatment of theophylline overdose depends on the current plasma level and the degree of adverse events. If clinically relevant adverse effects are absent, supportive care and monitoring of vital functions can be sufficient. As any specific antidote for theophylline doesn't exist, activated carbon hemoperfusion with/without hemodialysis can be a life-saving method in the event of life-threatening systemic adverse effects (44).

Theophylline and the current clinical practice

Theophylline has been used in the treatment of obstructive lung diseases for more than 80 years (13). Both BA and COPD are characterized by episodes of acute deterioration (exacerbations) that develop due to lower airway infections, exposure to air pollutants or idiopathic events. Theophylline is widely used in stable disease but also during exacerbations where the intravenous form (aminophylline) is preferred. In the last two decades, theophylline has mostly been replaced by inhaled betamimetics, which are incomparably more effective bronchodilators, as well as inhaled corticosteroids (ICSs) thanks to their more prominent anti-inflammatory effect. On the other hand, theophylline is significantly cheaper than these new molecules. Another advantage is the possibility of oral administration, which can be important in the elderly or patients with poor compliance to inhaled treatments (45). Therefore, theophylline still maintains its position in BA and COPD treatment, particularly in lower-income countries (46,47).

Stable COPD

The latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report doesn't recommend (nor mention) theophylline for the treatment of stable COPD (48). The latest [2020] American Thoracic Society (ATS) guidelines do not comment on the use of methylxanthines in the treatment of stable COPD (49). However, national guidelines vary between countries (50). In Spain and France, theophylline is recommended as a third-line adjunctive treatment in severe COPD with persistent dyspnea despite established dual bronchodilator therapy (50,51). According to the latest [2020] Czech guidelines, theophylline should be considered only as a phenotype-specific therapy for patients with the emphysematous phenotype of COPD (52).

However, the reality of common clinical practice may be completely different. Real-life experience shows that theophylline continues to be prescribed for all stages of COPD by general practitioners but also respiratory

specialists. Lee *et al.* demonstrated that methylxanthines continue to be widely prescribed in patients with mild to moderate COPD even in developed countries (53).

There are several reports on the beneficial effects of theophylline on patients' outcomes. In a meta-analysis by Ram *et al.*, theophylline improved lung function (FEV_1 and FVC) and blood gases [arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$)], and was preferred over a placebo by patients with stable COPD (19). In another study, prehospital use of theophylline in patients with COPD and subsequent nosocomial sepsis was associated with a lower risk of mortality (54). Last, withdrawal of theophylline caused significant clinical deterioration despite complex treatment in patients with severe COPD (28,55).

However, the effect of theophylline on the risk of COPD exacerbations was examined in two studies only, bringing conflicting results (56,57). To date, no randomized trial has directly evaluated the effect of theophylline on the rate of COPD exacerbations.

In contrast, a meta-analysis by Horita *et al.* suggested serious safety concerns as the authors demonstrated an increased risk of all-cause mortality (pooled hazard ratio of 1.07; P=0.003) in COPD patients treated with theophylline (58).

COPD exacerbation

Hospitalization due to COPD exacerbations [acute exacerbations (AEs)] contributes significantly to hospital morbidity and mortality (59). The COPD exacerbation treatment algorithm is standardized and includes high doses of nebulized β-agonists and/or nebulized anticholinergic drugs, systemic corticosteroids, low-flow or high-flow oxygen therapy, mucolytic therapy, antibiotics, or even ventilatory support (48). Theophylline has been part of the treatment algorithm of AEs for decades, e.g., the 2001 GOLD Report listed theophylline as an add-on therapy for patients who do not improve with complex standardized treatment (60).

However, the latest [2024] GOLD Report recommends against the use of intravenous methylxanthines for the treatment of AEs due to the risk of adverse events (48). Similarly, the latest joint ERS/ATS guidelines do not mention methylxanthines as a therapeutic option for the treatment of AEs (61).

A recent meta-analysis didn't demonstrate any benefit of methylxanthines as add-on therapy in the treatment of AEs (62). Similarly, Duffy *et al.* found no benefit of intravenous theophylline as add-on therapy in patients treated for AEs as patients on theophylline didn't improve blood gases, lung functions (FEV_1 and FVC), symptoms, or hospital length of stay (LOS) (63).

Stable BA

The current treatment of stable BA is based on dual inhaled drugs [ICS/long-acting beta2-agonist (LABA)], while the most severe cases of BA require management with the use of biologicals (after fulfillment of indication criteria) (64). Theophylline is no longer recommended for use in the BA treatment algorithms. However, theophylline is still used in daily practice as a rescue therapy for difficult-to-treat BA (65).

Similarly to COPD, the latest 2020 ERS/ATS guidelines on asthma management and also the Global Initiative for Asthma (GINA) 2023 Report don't recommend (nor mention) methylxanthines as the treatment of stable BA (64,66).

Studies examining the effectiveness of theophylline in stable BA brought controversial results. In some studies, the addition of theophylline appeared to be beneficial, while in others, theophylline treatment proved ineffective, particularly in patients treated with ICS/LABA (67-69).

BA flare-ups (exacerbations)

Treatment of AEs of BA [acute AEs (AAEs)] is based on high doses of short-acting betamimetics and systemic oral corticosteroids in combination with low-flow oxygen therapy and, in case of ventilatory failure, also more advanced ventilatory support (64).

The latest 2023 GINA Report recommends against the use of methylxanthines in the treatment of AAEs due to their low efficacy and high risk of adverse events (64).

However, theophylline is still frequently used in hospitals (70), although its use can be justified only in patients with severe asthma refractory to betamimetics and corticosteroids (65).

A systematic review did not reveal any benefit of combined treatment of inhaled betamimetics with theophylline in the treatment of AE of asthma compared to inhaled betamimetics alone in adults (71) or children (72).

Low dose theophylline

Current research interests are drawn to low-dose theophylline

due to its immunomodulatory and anti-inflammatory effect, synergistic with ICS (by increasing HDAC2 activity) (13,14).

A study by Cosio *et al.* suggests a positive effect of low-dose theophylline in COPD patients at plasma concentrations of <10 mg/L (73). On the contrary, a recent study by Jenkins *et al.* showed low-dose theophylline (100 mg 1–2× daily) ineffective in patients with moderate-to-severe COPD (74). At these low doses, however, cardiotoxicity was absent (75).

Other data suggest a reduction in AAEs and an anti-inflammatory effect of low-dose theophylline in patients with BA (76). Patients with BA inadequately controlled by high-dose ICS experienced significant improvement after adding low-dose theophylline (77). Above that, discontinuation of low-dose theophylline treatment can rebounce airway inflammation, and worsen asthma symptoms and lung functions (78). In childhood asthma, low-dose theophylline may improve spirometry and shorten hospital LOS in exacerbated patients, maintaining a reasonable safety profile (79).

Less usual indications for use

Theophylline and aminophylline effects have been tested in the treatment of further unrelated diseases.

The effect of aminophylline in atropine-resistant cardiac arrests has been considered as an accumulation of adenosine in the heart during cardiac arrest followed by cardiac ischemia which may reduce the effectiveness of catecholamines during resuscitation. Despite initial promising results (80), this hypothesis wasn't confirmed in an independent meta-analysis (81).

Theophylline is also used for the treatment of clinically relevant bradycardia during propofol sedation or in cases of atrioventricular blocks after myocardial infarction or after spinal trauma (82-84).

Apnea of prematurity, affecting premature infants, is defined as an apneic pause lasting for at least 20 seconds, which is accompanied by hypoxia, bradycardia, cyanosis, and severe hypotonia. Theophylline is part of a complex therapy of this condition due to its stimulating effect on the CNS and respiratory muscles (85).

Single-dose prophylaxis with theophylline also prevents severe renal dysfunction in mature newborns with severe birth asphyxia (86).

Ventilator-induced diaphragmatic dysfunction (VIDD) is a condition caused by a significant reduction in the contractile strength of the diaphragm and atrophy of its muscle fibers. VIDD is one of the main problems during weaning from the ventilator. Theophylline can increase the contractility of the diaphragm and thus improve lung function, reducing "air trapping" and lung hyperinflation (87).

Other possible uses of theophylline have been proposed and studied, including: (I) reduction of body fat in obese patients (88); (II) prevention of acute mountain sickness (89); or even (III) treatment of chronic lymphocytic leukemia (90). As a non-selective PDE inhibitor, theophylline has also been considered as an alternative treatment for male subfertility (91).

Future perspectives

In the last two decades, new xanthine derivatives have been synthesized, including enprofylline, bamifylline, or doxofylline (92). Some of these molecules demonstrated a potential for greater efficacy and a better safety profile than theophylline.

Doxofylline has demonstrated significant anti-inflammatory activity in both allergic and non-allergic murine lung inflammation models and appeared to reduce steroid consumption (93). Doxofylline has a better pharmacological profile compared to theophylline (94,95), has no significant effect on any known PDE isoforms, and lacks adenosine receptor antagonism (96). There is evidence that doxofylline is a potent bronchodilator that relieves airway obstruction (96-98). Therefore, it appears as an attractive alternative to theophylline and should be considered a completely new bronchodilator and anti-inflammatory drug with a reasonable safety profile rather than a new theophylline analog (65). To date, doxofylline is absent in any guidelines for COPD or BA treatment, probably due to limited evidence on its efficacy (99).

Another future path to the use of theophylline is the above-mentioned low-dose (i.e., 100–200 mg daily) theophylline treatment. This approach would significantly reduce the rate of adverse events while maintaining its anti-inflammatory effect.

Conclusions

Theophylline has been a widely used drug for many decades. Despite its low price and good safety profile with adequate serum levels, the treatment is associated with several (and potentially severe) ADRs, therefore most

guidelines recommend against its use for COPD and BA treatment. Most theophylline ADRs are concentration-related hence there is an imminent need for slow infusion during intravenous administration as rapid administration may cause pulmonary vasodilation in the hypoventilated lung areas and even result in increased hypoxia. Recent research demonstrated the anti-inflammatory effect of low-dose theophylline while maintaining its anti-inflammatory effect.

Alternatively, novel xanthine derivatives with a reasonable pharmacological, safety, and efficacy profile emerged, promising potential for clinical benefits in the future.

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Footnote

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