

REVIEW

Theophylline in the management of asthma: time for reappraisal?

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Theophylline in the management of asthma: time for reappraisal? P.J. Barnes, R.A. Pauwels. ©ERS Journals Ltd 1994.

ABSTRACT: Theophylline has been used for several decades in the treatment of asthma and remains the most widely prescribed anti-asthma drug worldwide, although the development of newer anti-asthma medications, especially inhaled steroids, has resulted in declining use of theophylline in industrialized countries.

Theophylline is now considered to be a bronchodilator, but it is increasingly recognized that theophylline has other anti-asthma activities, which may be more important. Theophylline, even at low plasma concentrations, inhibits the late asthmatic reaction following allergen challenge. These clinical pharmacological observations are substantiated by experimental animal and *in vitro* data showing that theophylline has several anti-inflammatory activities relevant to asthma. These include the inhibition of cytokine synthesis and release, the inhibition of inflammatory cell activation and microvascular leakage, and the prevention of airway hyperresponsiveness induced by airway inflammation. Theophylline appears to have immunomodulatory effects, even at relatively low plasma concentrations.

Based on these considerations, theophylline can be regarded as a useful alternative to other anti-inflammatory drugs for the chronic treatment of mild to moderate asthma. Theophylline should be used at lower doses to achieve plasma concentrations of 5–10 mg·l⁻¹, which will avoid the risk of side-effects.

Further studies are required to evaluate the role of low-dose theophylline as an adjunct to low-dose inhaled steroids in the management of chronic asthma. It may now be appropriate to re-evaluate the role of theophylline in asthma management. *Eur Respir J., 1994, 7, 579–591.*

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Theophylline has been used for over 50 yrs in the treatment of asthma and remains the most widely prescribed anti-asthma treatment worldwide. The development of reliable slow-release preparations has greatly enhanced its therapeutic use. The development of newer anti-asthma medications, especially inhaled steroids, has resulted in a decline in its use in the treatment of asthma in many industrialized countries. Theophylline is now relegated to the position of third-line treatment as an additional bronchodilator, indicated only for patients with relatively severe asthma who are not controlled on high dose inhaled steroids [1–4]. Some have even suggested that theophylline may be obsolete [5–7], although others have emphasized its special beneficial effects, which still give it an important place in asthma management [8–10]. The growing recognition that theophylline has other anti-asthma activities than bronchodilatation and that these activities may indeed be the most important contribution of theophylline in asthma, means that its role in asthma management should be reassessed, particularly with the demonstration that nonbronchodilator actions of theophylline may be achieved at lower plasma concentrations, thereby reducing the risk of adverse effects which have been the main

reason for the decline in its use. We review the evidence that theophylline is more than a bronchodilator and discuss the future place of theophylline in the management of asthma.

Molecular mechanism of action

Despite its long history and widespread use, the molecular mechanisms responsible for the therapeutic activity of theophylline remain unclear [11, 12]. Several mechanisms (table 1) have been proposed, but each of these hypotheses lacks sufficiently strong evidence. It is possible that several mechanisms may be operative.

Table 1. – Mode of action of theophylline

Phosphodiesterase inhibition
Adenosine receptor antagonist
Increase in circulating adrenaline
Mediator antagonism (prostaglandins, TNF- α)
Inhibition of calcium ion flux
Unknown mechanism

TNF- α : tumour necrosis factor- α .

Phosphodiesterase inhibition

It is widely held that the bronchodilator effect of theophylline is due to inhibition of phosphodiesterase (PDE), which breaks down cyclic nucleotides in the cell, thereby leading to an increase in intracellular cyclic 3',5' adenosine monophosphate (cAMP) and cyclic 3',5' guanosine monophosphate (cGMP) concentrations (fig 1). Several families of PDE are now recognized, based on enzyme characteristics, the development of selective inhibitory and, more recently, molecular cloning [13]. Theophylline is a nonselective PDE inhibitor, but the degree of inhibition is small at concentrations of theophylline which are therapeutically relevant. Thus, total PDE activity in human lung extracts is inhibited by only 5–20% at therapeutic concentrations of theophylline [14, 15]. However, this modest inhibition may, in the presence of endogenous activators of adenylyl cyclase, be sufficient to cause a substantial increase in intracellular cyclic nucleotide levels [16]. There is no evidence that airway smooth muscle or inflammatory cells concentrate theophylline to achieve higher intracellular than circulating concentrations. Furthermore, inhibition of PDE could lead to synergistic interaction with

β -agonists, but this has not been convincingly demonstrated *in vivo*, although this might be explained by the recent observations that relaxation of airway smooth muscle by low concentrations of β -agonists may involve direct coupling of β -receptors *via* a stimulatory G-protein to the opening of potassium channels, without the involvement of cAMP [17–20].

Isoenzymes of PDE may be differentially expressed in different cells, and it is now becoming clear that some isoenzymes may play an important role in the regulation of cells relevant to asthma. Thus, PDE III is predominant in airway smooth muscle relaxation; whereas PDE IV is important in inflammatory cells, such as mast cells, eosinophils and T-lymphocytes [13, 21–23]. Theophylline appears to be a nonselective PDE inhibitor, and there is no convincing evidence that it has a greater inhibitory effect on PDE III or PDE IV isoenzymes. There is some evidence for increased expression of PDE isoenzymes, and particularly PDE IV in atopic dermatitis [24–26]. It is, therefore, possible that PDE isoenzymes may have an increased expression in asthmatic airways, either as a result of the chronic inflammatory process, or as a result of therapy. Elevation of cAMP by β -agonists may result in increased

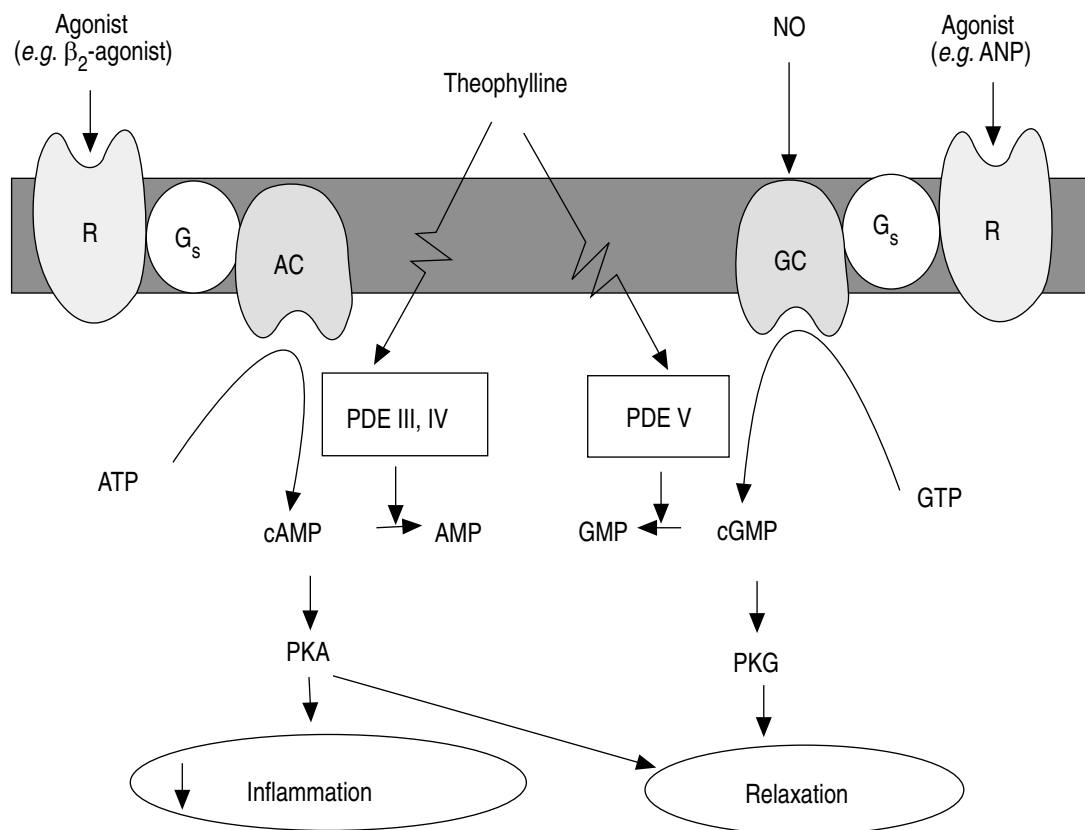


Fig. 1. — Action of theophylline as a phosphodiesterase (PDE) inhibitor. PDE III and PDE IV break down cyclic adenosine 3',5' monophosphate (cAMP), whereas PDE V breaks down cyclic guanosine 3',5' monophosphate (cGMP). Theophylline is a nonselective PDE inhibitor and, therefore, increases cAMP and cGMP levels, resulting in bronchodilatation and inhibition of inflammatory cells. AC: adenylyl cyclase; ATP: adenosine triphosphate; GTP: guanosine triphosphate; R: receptor; GC: guanylyl cyclase; G_s : stimulatory G-protein; PKA: protein kinase A; PKG: protein kinase G; ANP: atrial natriuretic peptide.

PDE activity, thus limiting their effect. Indeed, there is evidence that alveolar macrophages from asthmatic patients have increased PDE activity [27, 28]. This may mean that theophylline may have a greater than expected inhibitory effect on PDE in asthmatic airways than in normal airways. Support for this is possibly provided by the lack of bronchodilator effect of theophylline in normal subjects, compared to a bronchodilator effect in asthmatic patients [29]. Further studies on the effect of theophylline and selective PDE inhibitors in asthmatic tissues are required.

Adenosine receptor antagonism

Theophylline is a potent inhibitor of adenosine receptors (both A₁- and A₂-receptors) at therapeutic concentrations, suggesting that this could be the basis for its bronchodilator effects [30]. Although adenosine has little effect on normal human airway smooth muscle *in vitro*, it causes constriction of asthmatic airways *in vitro* and bronchoconstriction in asthmatic subjects when given by inhalation [31, 32]. The mechanism of bronchoconstriction is indirect, and involves release of histamine and leukotrienes from airway mast cells [32, 33]. The bronchoconstrictor effect of adenosine is prevented by therapeutic concentrations of theophylline [34]. This confirms the fact that theophylline is capable of antagonizing the effects of adenosine at therapeutic concentrations, but does not necessarily indicate that this is important for its anti-asthma effect. The observation that the concentration of adenosine is elevated in the epithelial lining fluid of asthmatic patients, would favour the hypothesis [35]. Enprofylline, which is more potent than theophylline as a bronchodilator, has no significant inhibitory effect on adenosine receptors at therapeutic concentrations, suggesting that adenosine antagonism is an unlikely explanation for the bronchodilator effect of theophylline [36]. Similarly doxofylline, which also has anti-asthma effects, apparently has no effect on adenosine receptors [37]. However, the identification of different adenosine receptor types and subtypes makes it clear that data on adenosine antagonism cannot be extrapolated from one tissue to another [38, 39]. Further characterisation of the adenosine receptor(s) in the human airways and the development of potent and selective antagonists active at this receptor, will be necessary before the adenosine receptor hypothesis can be completely evaluated.

Adenosine antagonism may account for some of the side-effects of theophylline, such as central nervous system stimulation, cardiac arrhythmias, gastric hypersecretion, gastro-oesophageal reflux and diuresis.

Increased catecholamine release

Theophylline increases the secretion of adrenaline from the adrenal medulla [40, 41], although the increase in plasma concentration is small and insufficient to ac-

count for any significant bronchodilator effect [42]. The release of catecholamines may only be relevant when aminophylline is given intravenously.

Mediator inhibition

Theophylline antagonizes the effect of some prostaglandins on vascular smooth muscle *in vitro* [43], but there is no evidence that these effects are seen at therapeutic concentrations or are relevant to its airway effects. Theophylline may also interfere with the action of the inflammatory cytokine tumour necrosis factor- α (TNF- α), which may be involved in severe asthmatic inflammation. Theophylline inhibits TNF- α induced airway hyperresponsiveness in an *in vivo* animal model of airway inflammation [44]. A related compound, pentoxifylline, prevents TNF- α -induced lung injury and enhanced hypoxic pulmonary vasoconstriction, but its mechanism of action is not yet understood [45, 46].

Inhibition of calcium ion flux

There is some evidence that theophylline may interfere with calcium mobilization in airway smooth muscle. Theophylline has no effect on entry of calcium ions (Ca²⁺) *via* voltage-dependent channels, but it has been suggested that it may influence calcium entry *via* receptor-operated channels, release from intracellular stores, or may have some effect on phosphatidylinositol turnover (which is linked to release of Ca²⁺ from intracellular stores). There is no direct evidence in favour of this, other than an effect on intracellular cAMP concentration due to its PDE inhibitory action. An early study suggesting that theophylline may increase Ca²⁺ uptake into intracellular stores has not been followed up [47].

Pharmacological activities relevant to asthma

Airway smooth muscle effects

The primary effect of theophylline is assumed to be relaxation of airway smooth muscle, and *in vitro* studies have shown that it is equally effective in large and small airways [48, 49]. In airways obtained at lung surgery, approximately 25% of preparations fail to relax with a β -agonist, but all relax with theophylline [49]. The molecular mechanism of bronchodilation is almost certainly related to PDE inhibition, resulting in an increase in cAMP. The bronchodilator effect of theophylline is reduced in guinea-pig and human airways by the toxin charybdotoxin, which inhibits large conductance Ca²⁺-activated K⁺ channels (maxi-K channels), suggesting that theophylline opens maxi-K channels *via* an increase in cAMP [18, 19]. Theophylline acts as a functional antagonist and inhibits the contractile response of several spasmogens. In airways

obtained at postmortem from patients who have died from asthma, the relaxant response to β -agonists is reduced, whereas the bronchodilator response to theophylline is no different from that seen in normal airways [50]. There is now evidence that β -adrenoceptors in airway smooth muscle of patients with fatal asthma become uncoupled [51], and theophylline may, therefore, have a theoretical advantage over β -agonists in severe asthma exacerbations. However, theophylline is a weak bronchodilator at therapeutically relevant concentrations (5–20 mg·l⁻¹), suggesting that some other target cell may be more relevant for its anti-asthma effect. In human airways the median effective concentration (EC₅₀) for theophylline is approximately 1.5×10⁻⁴M, which is equivalent to 67 mg·l⁻¹ assuming 60% protein binding [49]. However, as discussed above, it is important to consider the possibility that PDE activity may be increased in asthmatic airways, so that theophylline may have a greater than expected effect.

In vivo intravenous aminophylline, the ethylene diamine salt of theophylline, has an acute bronchodilator effect in asthmatic patients, which is probably due to a relaxant effect on airway smooth muscle [52]. However, the bronchodilator effect of theophylline in chronic asthma is small in comparison with β -agonists. Several studies have demonstrated a small protective effect of theophylline on histamine, methacholine, distilled water or exercise challenge [34, 53–57]. This protective effect does not correlate well with any bronchodilator effect, and it is interesting that in some studies the protective effect of theophylline is observed at plasma concentrations of < 10 mg·l⁻¹ [54, 55]. These clinical studies suggest that theophylline may have anti-asthma effects which are unrelated to any bronchodilator action (that may only occur at very high plasma concentrations and may only be relevant in the management of acute severe asthma). Not all studies have confirmed the protective effect of theophylline. A study by DUTOIT *et al.* [58] failed to show any significant effect of chronic treatment with theophylline on histamine airway responsiveness in a group of patients with relatively severe asthma. A more recent study in children with mild to moderate asthma observed a significant reduction in methacholine responsiveness during a year long treatment with theophylline [59]. In general, the protective effect of theophylline against the bronchoconstriction caused by directly acting agents is rather weak.

The weak bronchodilator action of theophylline at therapeutically relevant concentrations raises the question of whether bronchodilatation is important for its anti-asthma effects. Indeed, the rather high therapeutic range currently recommended stems from studies of the bronchodilator response to infusions of aminophylline [52], rather than from studies of the anti-asthma effects of the drug.

Effect in allergen challenge studies

Theophylline protects rather poorly against the immediate asthmatic reaction following allergen challenge.

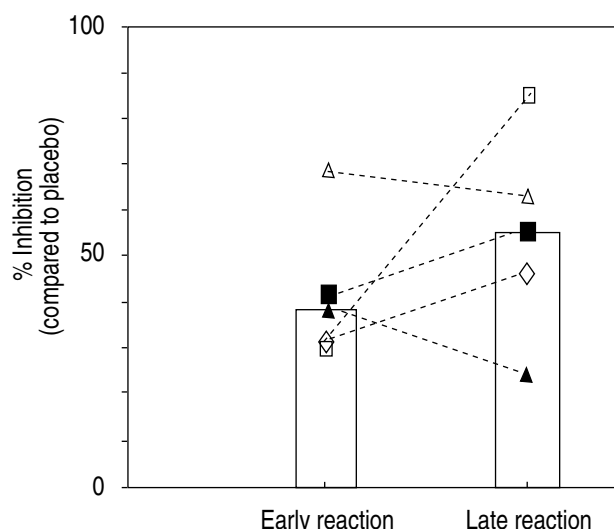


Fig. 2. — Protective effect of theophylline on the early and late asthmatic reaction to allergen. Each symbol represents a study, and the mean effect has been calculated from the individual data in all published studies.

Several studies have been performed, and have observed either no or only partial protection against the early response [60–69]. However, all studies except one observed, a marked protective effect against the late asthmatic reaction following allergen challenge (fig 2). The early asthmatic reaction is essentially a bronchoconstrictor response to mediators, such as histamine, leukotriene D₄ and prostaglandin D₂ released from mast cells. The late asthmatic reaction is associated with the presence of airway inflammation, and the observation that theophylline is more protective against the late asthmatic reaction suggests that pharmacological activities other than smooth muscle relaxation play a role in the therapeutic activity of theophylline in asthma.

The increase in airway responsiveness following allergen challenge is regarded as an expression of the ongoing airway inflammation induced by the inhaled allergen. Four studies have looked at the effect of theophylline on the allergen-induced increase in airway responsiveness. In two studies on six patients each, theophylline had no significant effect on the increase in methacholine responsiveness following the late asthmatic reaction [65, 67]. CRESCIOLI *et al.* [66] observed that in five out of six subjects theophylline significantly inhibited the increase of airway responsiveness to methacholine compared to placebo and control day. HENDELES *et al.* [69] reported a study involving 15 patients and found a significant inhibition by theophylline of the increase in airway responsiveness to histamine, measured 4.5 h after allergen challenge.

Anti-inflammatory effects

There is increasing evidence that theophylline has several anti-inflammatory effects at concentrations which are therapeutically relevant (table 2).

Table 2. – Anti-inflammatory effects of theophylline

<i>In vitro</i>	
Mast cells	Decreased mediator release
Macrophages	Decreased release of reactive oxygen species
Monocytes	Decreased cytokine release
Eosinophils	Decreased basic protein release
	Increased/decreased release of reactive oxygen species
T-lymphocytes	Decreased proliferation
	Decreased cytokine release
Neutrophils	Decreased release of reactive oxygen species
<i>In vivo</i>	
Experimental animals	Decreased late response to allergen (guinea-pigs)
	Decreased airway responsiveness to allergen and PAF (guinea-pigs, sheep)
	Decreased airway inflammation after endotoxin and allergen (guinea-pigs, rats)
	Decreased plasma exudation (guinea-pigs)
Asthmatic patients	Inhibition of late response to allergen
	Increased CD8 ⁺ cells in peripheral blood
	Decreased T-lymphocytes in airways

PAF: platelet-activating factor.

Animal models

In a guinea-pig model of the allergen-induced bronchial reactions, ANDERSSON *et al.* [70] demonstrated that the intravenous injection of a low dose of theophylline immediately before the antigen challenge significantly inhibited both the immediate bronchoconstriction and the late reaction. The late reaction in the guinea-pig is characterized by the influx of neutrophils, eosinophils and lymphocytes. Pretreatment with theophylline significantly reduced the neutrophilic airway inflammation. The intravenous injection of theophylline 90 min after the antigen-induced immediate bronchoconstriction also had an inhibitory effect on the late reaction. Similar findings were obtained in an allergic sheep model [71]. Theophylline at a serum concentration of 10 mg·l⁻¹ inhibited the late reaction after allergen challenge, both when given prior to and following the allergen challenge.

Theophylline has an inhibitory effect on eosinophil influx into the lung following allergen exposure in sensitized guinea-pigs [72]. TARAYRE and co-workers [73–75] investigated, both in rats and in guinea-pigs, the effect of theophylline on the influx of inflammatory cells in the airways of sensitized animals 24 h after exposure to an aerosolized antigen. In guinea-pigs, treatment with theophylline 5 min and 5 h after the aerosol exposure significantly inhibited the eosinophilic infiltration of the airways. In rats, a similar treatment with theophylline inhibited the influx of both eosinophils and neutrophils.

In a rat model of nonallergic airway inflammation and hyperresponsiveness, PAUWELS and co-workers [76–78] investigated the effect of theophylline on endotoxin-induced airway inflammation and responsiveness. Pretreatment with theophylline significantly inhibited the endotoxin-induced increase in bronchial responsiveness and did so at theophylline serum concentrations

considered to be therapeutic. Theophylline treatment also significantly inhibited the influx of neutrophils in the airways, even at rather low serum concentrations. At least part of this endotoxin-induced airway inflammation and airway hyperresponsiveness in this animal model is due to the secretion of TNF- α [79]. Theophylline did not modify the endotoxin-induced secretion of TNF in this *in vivo* model, but inhibited the increase in airway responsiveness induced by exposure to an aerosol of human recombinant TNF- α [44]. Theophylline, therefore, seems to inhibit the effect, rather than the release of TNF- α , in this animal model.

A short-term infusion of platelet-activating factor (PAF) induces a long-lasting and non-selective increase in airway responsiveness in guinea-pigs which is inhibited by theophylline [80].

Effects on inflammatory cells in vitro

The anti-inflammatory effect of theophylline has been demonstrated *in vitro* using several inflammatory cell types.

Mast cells. Theophylline inhibits histamine release from mast cells and basophils [81]. However, the concentration required to obtain this inhibitory effect is one to two orders of magnitude above the therapeutic theophylline concentrations, and is, therefore, of little relevance to the *in vivo* situation. At therapeutic concentrations, theophylline inhibits the adenosine-induced enhancement of mediator release from mast cells and for this reason, adenosine-receptor antagonism has been put forward as a possible mode of action of theophylline [82].

Theophylline has also been shown to stabilize or inactivate a variety of inflammatory cells, including macrophages, neutrophils platelets and may do so at therapeutically relevant concentrations.

Neutrophils. NIELSON and co-workers [83–85] reported on the effect of theophylline on the generation of oxygen metabolites by human polymorphonuclear leucocytes. Theophylline, at therapeutic concentrations, significantly inhibits neutrophil activation and potentiates the inhibitory activity of isoprenaline. By contrast, others report an enhancing effect of therapeutic concentrations of theophylline on human neutrophil superoxide production [86, 87]. The reasons for these discrepancies are not clear, but might be related to the cell preparation and the strength of the stimulus.

Monocytes/macrophages. Theophylline also has an inhibitory effect on release of reactive oxygen species in peripheral blood monocytes and alveolar macrophages [88, 89]. Alveolar macrophages recovered from patients receiving theophylline have a reduced level of activation, indicating that this inhibitory effect is achieved at therapeutically relevant concentrations [90]. For alveolar macrophages, the inhibitory effect of theophylline is related to phosphodiesterase inhibition and is blocked by a cAMP inhibitor [89]. Theophylline, at a concentration of 10^{-5} M, inhibits the induction of interleukin- 1β (IL- 1β) in human peripheral blood monocytes by interleukin- 1α (IL- 1α) [91]. Theophylline similarly inhibits the synthesis and release of TNF- α by human peripheral blood monocytes [92].

Eosinophils. The effect of theophylline on eosinophil cell function *in vitro* is not clear, in view of the somewhat contradictory findings that have been published. Theophylline, at therapeutic concentrations, inhibited eosinophil degranulation and the release of basic proteins, such as eosinophil derived neurotoxin [93]. The cells were stimulated by immunoglobulin G (IgG)- or serum immunoglobulin A (sIgA)-coated sepharose-beads. In contrast, therapeutic concentrations of theophylline enhanced (by 36%) the release of superoxide anion from human eosinophils obtained by differential centrifugation of blood from patients with peripheral eosinophilia and stimulated *in vitro* with opsonized zymosan [94]. The enhanced release of superoxide anion is due to adenosine receptor antagonism, and is mimicked by other adenosine antagonists. At high concentrations, theophylline has an inhibitory effect due to PDE inhibition. Selective PDE IV inhibitors are very effective in inhibition of superoxide anion release from activated eosinophils [95, 96].

T-lymphocytes. T-lymphocytes may play a critical role in orchestrating the characteristic eosinophilic inflammation of asthma. Theophylline diminishes E rosette formation and decreases the proliferative responses to mitogens [97, 98], and has an inhibitory effect on release of interleukin-2 (IL-2) [99]. Theophylline also inhibits interferon-gamma induced expression of IL-2-receptors on a cultured lymphocyte line [100]. An inhibitory effect on T-lymphocyte induced cytokine release may account for the inhibitory effect of theophylline on the influx of inflammatory cells after inhaled allergen in animal models [72–78].

Inhibition of plasma exudation

A consistent sign of airway inflammation is plasma exudation [101]. The extravasated plasma distributes not only in the submucosa and mucosa, but also enters the airway lumen. In patients with allergic rhinitis, theophylline has been shown to reduce nasal plasma exudation following local allergen challenge [102]. Data on the effect of theophylline on plasma exudation in asthmatic airways are lacking, but the observations on some of the effects of theophylline on the late asthmatic reaction could be explained in this way. Data obtained in guinea-pig tracheobronchial mucosa demonstrate that theophylline reduces the local airways inflammatory stimulus-induced plasma exudation, although this effect may be dependent on the strength of the stimulus [103–106].

Immunomodulatory effects in vivo

The inhibitory effects of theophylline on T-lymphocytes *in vitro* suggest that theophylline may have immunomodulatory effects. Chronic administration of theophylline increases the number of suppressor T-cells (CD8⁺ cells) in peripheral blood of asthmatics and impairs the graft vs host reaction of these lymphocytes [107–109]. By contrast, acute administration of theophylline appears to decrease circulating CD8⁺ cells [110]. WARD *et al.* [111] recently observed that theophylline, at a mean trough serum concentration of 7.8 mg·l⁻¹, inhibits the late asthmatic reaction following allergen challenge and the allergen-induced increase in CD4⁺ and CD8⁺ lymphocytes observed in peripheral blood 48 h after the allergen challenge.

KIDNEY *et al.* [112] studied clinical, functional and immunological parameters following the controlled withdrawal of theophylline in a group of asthmatic patients chronically treated with this medication, who were also treated with high dose inhaled steroids. There was a clinical deterioration and fall in lung function in parallel with a fall in both activated CD4⁺ and CD8⁺ lymphocytes in peripheral blood, suggesting that theophylline increases the proportion of activated T-lymphocytes in peripheral blood. In a subset of patients, bronchial biopsies were also performed and showed a mirror image of the peripheral blood changes, with an increase in both CD4⁺ and CD8⁺ T-cells during theophylline withdrawal [113]. This suggests that theophylline may inhibit the trafficking of T-lymphocytes from the circulation into the airways and, thus, plays an immunomodulatory role. In this study, the mean plasma theophylline concentration was <10 mg·l⁻¹, indicating that this modulatory effect may be observed at low plasma concentrations, in agreement with the study with allergen challenge [111].

Extrapulmonary effects

For a long time it has been suggested that theophylline may exert its effects in asthma *via* some action outside

the airways. Hyde Salter believed that one of the major effects of caffeine was its action as a cerebral stimulant. It may be relevant that theophylline is ineffective when given by inhalation until therapeutic plasma concentrations are achieved [114]. This could indicate that theophylline has effects on cells other than those in the airway. One possible target cell is the platelet, and theophylline has been demonstrated to inhibit platelet activation *in vitro* [115]. The effect of theophylline on peripheral blood T-lymphocytes may indicate an effect in the circulation, although this could be a reflection of an effect on airway inflammation, in the same way that inhaled corticosteroids may affect circulating eosinophils [116]. The fact that theophylline appears to increase activated T-lymphocytes in the blood, whilst decreasing their presence in the airway, may reflect an effect on trafficking of activated T-lymphocytes, possibly *via* an effect on endothelial cells [112, 113].

An effect of theophylline which remains controversial is its action on respiratory muscles. Aminophylline increases diaphragmatic contractility and reverses diaphragm fatigue [117]. This effect has not been observed by all investigators, and there are now doubts about the relevance of these observations to the clinical benefit provided by theophylline [118].

Clinical use

Acute severe asthma

Intravenous aminophylline has been used in the management of acute severe asthma for over 50 yrs, but this use has been questioned in view of the risk of adverse effects compared with nebulized β -agonists. In patients with acute asthma, intravenous aminophylline is less effective than nebulized β_2 -agonists [119], and should, therefore, be reserved for those patients who fail to respond to β -agonists. There is some evidence that the use of aminophylline in the emergency room reduces subsequent admissions to hospital with acute asthma [120]. In a meta-analysis of 13 acceptably designed clinical trials to compare nebulized β -agonists with or without intravenous aminophylline there was no overall additional benefit from adding aminophylline [121]. This indicates that aminophylline should not be added routinely to nebulized β -agonists. Indeed, addition of aminophylline may only increase side-effects [122, 123]. Several deaths have been reported after intravenous aminophylline. In one study of 43 asthma deaths in southern England, there was a significantly greater frequency of toxic theophylline concentrations (21%) compared with matched controls (7%) [124]. These concerns have led to the view that intravenous aminophylline should be reserved for the few patients with acute severe asthma who fail to show a satisfactory response to nebulized β -agonists. When intravenous aminophylline is used, it should be given as a slow intravenous infusion with careful monitoring, and a plasma theophylline concentration should be measured prior to infusion.

Chronic asthma

Theophylline has little or no effect on bronchomotor tone in normal airways, but reverses bronchoconstriction in asthmatic patients, although it is less effective than inhaled β -agonists and is more likely to have unwanted effects. Indeed, the role of theophylline in the routine management of chronic asthma has been questioned [5–7], and in the various guidelines for asthma treatment theophylline is used as an additional bronchodilator if asthma remains difficult to control after moderate to high dose inhaled steroids [1–4, 125]. The recent introduction of long-acting inhaled β_2 -agonists, such as salmeterol and formoterol, has further threatened the position of theophylline, since the side-effects of these agents may be less frequent than those associated with theophylline.

Whether theophylline has some additional benefit over its bronchodilator action is now an important consideration. In chronic studies, oral theophylline appears to be at least as effective as sodium cromoglycate in controlling young allergic asthmatics, and provides additional control of asthma symptoms even in patients taking regular inhaled steroids [126–128]. A comparative study with inhaled beclomethasone in children concluded that both treatments were active in children with mild to moderate asthma. Beclomethasone dipropionate (320 μ g daily for 1 yr) resulted in a comparable symptom control with less bronchodilator use and fewer courses of systemic steroids than did theophylline [59]. In one study of a group of difficult adolescent asthmatic patients who were controlled with oral and inhaled steroids, nebulized β_2 -agonists, inhaled anticholinergics and inhaled cromoglycate in addition to regular oral theophylline, withdrawal of the oral theophylline resulted in a marked deterioration of asthma control, which could not be controlled by further increase in steroids, and only responded to reintroduction of theophylline [129]. This suggests that there may be a group of severe asthmatics who particularly benefit from theophylline. It is important to investigate these patients in more detail and to determine why theophylline, but apparently not corticosteroids, is able to benefit such patients. Deterioration in symptom control and lung function was also seen in patients with severe chronic asthma after placebo-controlled theophylline withdrawal, despite the fact that these patients were also receiving high dose inhaled steroids [112, 113].

Theophylline may be a useful treatment for nocturnal asthma and a single dose of a slow-release theophylline preparation given at night may provide effective control of nocturnal asthma symptoms [130–133]. There is evidence that slow-release theophyllin preparations are more effective than slow-release oral β_2 -agonists and short-acting inhaled β_2 -agonists in controlling nocturnal asthma, although long-acting inhaled β_2 -agonists are also effective in controlling nocturnal asthma symptoms and provide a better sleep quality than theophylline [134]. The mechanism of action of theophylline in nocturnal asthma may involve more than long-lasting bronchodilatation, and could involve inhibition of some

components of the inflammatory response which may increase at night [135].

Therapeutic range

The therapeutic range of theophylline was based on measurement of acute bronchodilatation in response to the acute administration of theophylline [52]. However, it is possible that the nonbronchodilator effects of theophylline, whether they are related to protection against bronchoconstriction or some anti-inflammatory or immunomodulatory effect, may be exerted at lower plasma concentrations. Since side-effects are also related to plasma concentration, these may be markedly reduced by aiming for plasma concentrations of 5–15 mg·l⁻¹ (28–55 µM), rather than the previously recommended doses of 10–20 mg·l⁻¹ (55–110 µM). Improvement in slow-release preparations, including the introduction of once daily products, means that fluctuations in plasma concentration are no longer a problem.

Interaction with β-agonists

If theophylline exerts its effects by PDE inhibition then a synergistic interaction with β-agonists would be expected. Many studies have investigated this possibility, but whilst there is good evidence that theophylline and β-agonists have additive effects, true synergy is not seen [136, 137]. This can now be understood in terms of the molecular mechanisms of action of β-agonists and theophylline. β-agonists may cause relaxation of airway smooth muscle *via* several mechanisms. Classically, they increase intracellular cAMP concentrations, which were believed to be an essential event in the relaxation response. It has recently become clear that β-agonists may cause bronchodilatation, at least in part, *via* maxi-K channels in airway smooth muscle cells which are directly linked to relaxation [17–20]. Maxi-K channels are opened by low concentrations of β-agonists which are likely to be therapeutically relevant. There is now evidence that β-receptors may be coupled directly to maxi-K channels *via* the α-subunit of G_s [17], and therefore may induce relaxation without any increase in cAMP, thus accounting for a lack of synergy. Another reason for the lack of synergy may be that cells other than airway smooth muscle may be the main target for the anti-asthma effect of theophylline.

Side-effects

There is no doubt that theophylline provides clinical benefit in asthma, but the main limitation to its use is the frequency of adverse effects. Unwanted effects of theophylline are usually related to plasma concentration and tend to occur when plasma levels exceed 20 mg·l⁻¹. However, some patients develop side-effects even at lower plasma concentrations. To some extent, side-effects

may be reduced by gradually increasing the dose until therapeutic concentrations are achieved [128, 138–141].

The commonest side-effects are headache, nausea and vomiting, abdominal discomfort and restlessness. There may also be increased acid secretion, gastro-oesophageal reflux and diuresis. There has recently been concern that theophylline, even at therapeutic concentrations, may lead to behavioural disturbance and learning difficulties in school children [142–144], although a carefully designed study could not confirm this [145]. At high concentrations, convulsions and cardiac arrhythmias may occur, and there is concern that intravenous aminophylline administered in the emergency room may be a contributory factor to the deaths of some patients with severe asthma [124].

Some of the side-effects of theophylline (central stimulation, gastric secretion, diuresis and arrhythmias) may be due to adenosine receptor antagonism and may, therefore, be avoided by drugs such as enprofylline, which has no significant adenosine antagonism at bronchodilator doses [146]. The commonest side-effects of theophylline are nausea and headache, which are also seen with enprofylline [147].

The side-effects of theophylline can be markedly reduced by aiming for lower plasma concentrations. It now appears that theophylline exerts most of its anti-asthma effects (as opposed to bronchodilator effects) at relatively low plasma concentrations (5–10 mg·l⁻¹), when side-effects are almost nonexistent. For the treatment of chronic asthma in adults and children it would, therefore, seem sensible to use lower doses than currently recommended. The pharmacokinetics of theophylline are complex, and this has led to development of complex nomograms to predict dose and to the recommendation that plasma concentrations should be monitored. This has discouraged the use of theophylline, particularly when such facilities are not readily available. If lower doses of theophylline are now to be recommended, it may be less important to monitor plasma concentrations. Thus, plasma monitoring could be used as a device to monitor compliance, rather than to avoid adverse effects.

Future directions

Although theophylline is an old drug, we still have much to learn about its mechanism of action in asthma and its most effective use in the management of chronic asthma. There is increasing evidence that theophylline has anti-asthma properties other than bronchodilation, and these nonbronchodilator effects include anti-inflammatory and immunomodulatory actions. These nonbronchodilator, anti-asthma effects may be manifest at plasma concentrations lower than those required for bronchodilatation, so that the therapeutic range should perhaps be reset to 5–10 mg·l⁻¹, rather than the widely recommended 10–20 mg·l⁻¹. This would also largely avoid the side-effects which limit the use of theophylline. If theophylline is now to be regarded as an immunomodulator, then its place in the hierarchy of

asthma therapy needs to be re-evaluated. It may be that theophylline should be introduced at an earlier stage in treatment as an oral baseline therapy in combination with low dose inhaled steroids. Studies exploring the interaction between theophylline and steroids are now needed. For example, it is important to know whether theophylline should be added once the dose of inhaled steroid reaches 800 µg daily, rather than increasing the dose of inhaled steroid to 1,500–2,000 µg daily before its introduction. Careful comparative studies, including the measurement of adverse effects, should now be made.

It is still not clear how much of the anti-asthma effect of theophylline is due to inhibition of PDE activity, but there have been considerable advances in the development of more potent and selective PDE inhibitors, several of which are now in clinical development [22, 23, 148]. PDE IV inhibitors are of particular interest, since they have inhibitory effects on the inflammatory cells activated in asthmatic inflammation, including mast cells, macrophages, eosinophils and T-lymphocytes. However, whether these agents will be effective in the control of clinical asthma remains to be determined. In the meantime, it is sensible to reassess the role of theophylline and to design clinical studies to explore its potential as a disease-modifying agent. An important advantage of theophylline is its relative cheapness, and this is a significant consideration since asthma is a worldwide clinical problem.

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