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Theophylline

A Review of its Potential Steroid Sparing Effects in Asthma

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Data Selection

Sources: Medical literature published in any language since 1966 on theophylline, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'theophylline', and 'asthma'. Medline and EMBASE search terms were 'theophylline' and 'asthma'. Searches were last updated 23 Nov 1998.

Selection: Studies in patients with asthma who received low dose theophylline plus low dose inhaled corticosteroids. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: theophylline, asthma, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Abstract

Theophylline is generally considered to be a bronchodilatory drug. However, recent pharmacodynamic studies indicate that it has anti-inflammatory effects. It reduced eosinophil survival rates *in vitro*, and reduced eosinophil accumulation in bronchial tissue in patients with atopic asthma. Theophylline has also been shown to reduce T cell proliferation and accumulation. These changes were mirrored by improved pulmonary function in patients with asthma in studies that evaluated this parameter.

Three randomised double-blind studies have evaluated the potential role of theophylline as an anti-inflammatory treatment in patients with asthma not controlled by low doses of inhaled corticosteroids. Patients were randomised to receive low dose theophylline (400 to 750mg daily) plus low dose inhaled corticosteroids, or an increased dose of inhaled corticosteroids. Clinical pulmonary function improved to the same or a greater extent in patients who received low dose inhaled corticosteroids plus theophylline than in those treated with high dose inhaled corticosteroids plus placebo. Where reported, the dosages of theophylline used in these studies resulted in serum theophylline concentrations of ≈9 to 10 mg/L. Approximate monthly costs were provided in one study: these were $60 (year and currency not specified) for theophylline plus budesonide 800 μg/day, compared with $100 for budesonide 1600 μg/day, and $155 for a regimen of budesonide 800 μg/day and salmeterol 100 μg/day.

Conclusions: Low dose theophylline has been shown to reduce requirements for inhaled corticosteroid therapy in patients with asthma and may reduce overall treatment costs.

1. Introduction

It is now widely acknowledged that inflammation is the main abnormality in the lungs of patients with asthma. Within a few minutes of inhaling an antigen to which they are sensitive, patients experience a reduction in forced airflow; this phenomenon is termed the early asthmatic response (EAR) and is thought to result from the release of preformed mediators, such as histamine, leukotriene D_4 and prostaglandin D_2 from mast cells (reviewed by Barnes & Pauwels[1]). The EAR is transient and may be followed 2 to 5 hours later by a reduction in pulmonary function in response to recruitment and activation of inflammatory cells (T cells, macrophages and, importantly, eosinophils) and further release of preformed and newly synthesised inflammatory mediators; this is termed the late asthmatic airways response (LAR).

Although theophylline has been traditionally classified as a bronchodilator, its mechanism of action in patients with asthma has not been precisely determined. The drug has a clear effect on the LAR, but its effects on the EAR are less obvious.[2-5] Interestingly, recent studies indicate that theophylline may have anti-inflammatory and immunomodulatory properties. This review evaluates the role of sustained release theophylline in the management of asthma, with emphasis on these anti-inflammatory and immunomodulatory properties and their potential corticosteroid sparing effects.

2. Pharmacodynamic Properties

2.1 Immunomodulatory and Anti-Inflammatory Effects

2.1.1 Effects on Eosinophils

Accumulation and survival of eosinophils during the LAR is mediated by the actions of several cytokines, particularly interleukin (IL)-5; theophylline has been shown to inhibit IL-5–mediated prolongation of eosinophil survival *in vitro*. Eosinophils isolated from peripheral blood taken from patients with various disorders (including asthma) were cultured in the presence or absence of human recombinant IL-5 and/or theophylline [at a concentration of 10^{-4} mol/L (≈18 mg/L)]. At day 4 the survival rate of eosinophils cultured with IL-5 alone was 100% relative to a 32.2% survival rate in cells cultured in medium only. Survival rates of 63.1% and 34.3% were observed in cells cultured with IL-5 plus theophylline ($p < 0.005$ *vs* IL-5 alone) and theophylline alone, respectively.[6] Further analysis indicated that theophylline moderates eosinophil survival via apoptosis.[6,7] The drug has also been shown to attenuate eosinophil activation *in vitro*.[8] In this study human venous blood was preincubated with theophylline 10^{-3} mol/L at 37°C for 15 minutes. Subsequent stimulation with platelet activating factor (PAF) significantly reduced generation of low-density (characteristic of activation) eosinophils relative to control samples. Stimulation with PAF also modulated expression of the adhesion molecules CD11b and L-selectin, in a manner characteristic of eosinophil activation, in theophylline-incubated (at a more clinically relevant concentration of 10^{-4} mol/L) versus control samples.

In a clinical setting, 6 weeks' double-blind treatment with low dose theophylline (200mg twice daily; producing a median serum concentration of 36.6 μmol/L at end-point) decreased antigen (*Dermatophagoides pteronyssinus* allergen)-induced accumulation of eosinophils in the bronchial tissue of patients with mild atopic asthma.[9] A significant reduction in activated eosinophil count was evident at end-point in bronchial biopsies taken from patients (n = 9) randomised to theophylline (median 5.9 cells/mm of basement membrane at baseline *vs* 2.1 at week 6; $p < 0.05$) but not those randomised to placebo (n = 6) [5.9 *vs* 3.9; $p < 0.05$ between treatments]. In a further study in patients with asthma (n = 6) slow release theophylline, titrated to maintain serum levels between 10 and 20 mg/L, was associated with a significant reduction in sputum eosinophil cationic protein levels (from 227 mg/L at baseline to 74 mg/L after 6 weeks; $p < 0.01$). Sputum IL-5 levels increased during the study but the difference was not significant.[10]

2.1.2 Effects on Lymphocytes, Monocytes and Various Cytokines

Theophylline has demonstrated multiple effects on T lymphocytes and cytokine production. *In vitro* studies have shown that the drug reduces both antigen and mitogen stimulated T cell proliferation (reviewed by Vassallo & Lipsky[11]), and prolonged administration of theophylline decreased accumulation of T cells in peripheral blood, an event associated with LAR.[12]

In a randomised placebo-controlled study in 25 patients with asthma who had received theophylline at conventional dosages plus high dose inhaled corticosteroids for ≥6 months, withdrawal of theophylline therapy was associated with a significant decrease in peripheral blood monocyte count (CD14+). A significant reduction in peripheral blood activated CD8+/HLA-DR+ and CD4+/CD25+ T cells was observed during the placebo phase in patients who had plasma theophylline concentrations ≥5 mg/L during active treatment (n = 20). This was mirrored by a significantly increased activated CD8+ T cell count in bronchial mucosa (n = 8). CD3+, CD4+, CD25+ and CD14+ cell counts were also increased in this tissue, but the differences were not statistically significant. The total leucocyte count or lymphocyte count was not significantly different between the 2 groups[13]

A subsequent similarly designed study also found no difference in total peripheral blood lymphocyte count; however, in contrast to the results of Kidney et al.,[13] no significant changes in lymphocyte subpopulations were observed.[14]

Reduced IL-4 ($p < 0.05$) and IL-5 (not significant) expression was observed in bronchial biopsies taken from patients with mild to moderately severe atopic asthma treated with theophylline (at dosages producing a mean serum concentration of 10.9 mg/L) in a randomised double-blind placebo-controlled study. The T cell (CD3+) count in bronchial epithelium and submucosa biopsy was similar in both groups; the helper T cell (CD4+) count was reduced in theophylline recipients but the difference relative to placebo was not statistically significant. The suppressor T cell (CD8+) count was, however, significantly lower in the theophylline group ($p < 0.01$).[15]

A 2.8-fold increase ($p < 0.01$) in production of IL-10 by peripheral blood monocytes was seen after exposure to theophylline 150 μg/L *ex vivo*. Increased IL-10 levels might reasonably be expected to contribute to decreased production of pro-inflammatory cytokines such as IL-1β, tumour necrosis factor-α (TNFα), IL-6, IL-12 and interferon-γ (IFNγ). Indeed, reductions in IFNγ and TNFα production were noted in this study.[16]

2.2 Relationship Between Immunomodulatory/Anti-Inflammatory Effects and Pulmonary Function in Patients with Asthma

The reduced bronchial infiltration of cells associated with LAR during theophylline therapy in patients with asthma was associated with improvement in pulmonary function tests in studies that conducted these.[9,13,15] Sullivan et al.[9] reported a slight increase from baseline in forced expiratory volume in 1 second (FEV_1) [from 3.34 to 3.58L] during low dose theophylline therapy compared with a significant decrease (from 3.67L at baseline to 3.46L after 6 weeks; $p < 0.05$) in placebo recipients ($p < 0.05$ between treatments). In the study of Finnerty et al.[15] low dose theophylline recipients experienced a modest, albeit significant, improvement in peak expiratory flow (PEF) [from 530 L/min at baseline to 559 L/min after 6 weeks; $p < 0.05$] relative to a slight decrease in placebo recipients (from 532 to 523 L/min).

Withdrawal of theophylline therapy in small ($n = 17$ to 25) groups of patients with asthma who were also receiving moderate to high dose inhaled corticosteroids was associated with a significant increase in asthma symptoms after 6 or 8 weeks in 2 studies.[13,14] In both trials analysis of diary card data revealed reduced morning PEF when placebo was substituted for theophylline. In one study[13] clinic-measured PEF was 356.4 L/min during continued theophylline therapy but dropped to 328.1 L/min when theophylline therapy was replaced with placebo ($p < 0.05$ between treatment groups). Clinic-measured FEV_1 decreased significantly during placebo therapy relative to theophylline in both studies. Kidney et al.[13] found that this difference was more pronounced in patients with plasma theophylline levels >5 mg/L than in those with plasma theophylline levels <5 mg/L but the difference between the 2 subgroups was not statistically significant (fig. 1).

The results of several other studies also indicate that the anti-inflammatory/immunomodulatory effects of theophylline are associated with improvements in pulmonary function in patients with asthma.[16-19]

Importantly, Crescioli et al.[18] reported that 1 week's treatment with slow release theophylline significantly inhibited allergen (*D. pteronyssinus* or grass pollen)-induced increases in bronchial responsiveness to methacholine in patients with asthma. Relative to baseline, theophylline treatment did not attenuate methacholine-induced airway hyperresponsiveness 8 hours after allergen challenge; however, relative to placebo, the drug was associated with a significant reduction in airway responsiveness in 5 of 6 patients. In a subsequent 6-week placebo-controlled study, also in patients with asthma ($n = 18$), theophylline (median dose 250mg twice daily; mean serum concentration 11.3 mg/L) significantly reduced methacholine sensitivity versus baseline whereas placebo did not. However, there was no significant difference between the 2 treatment groups.[20]

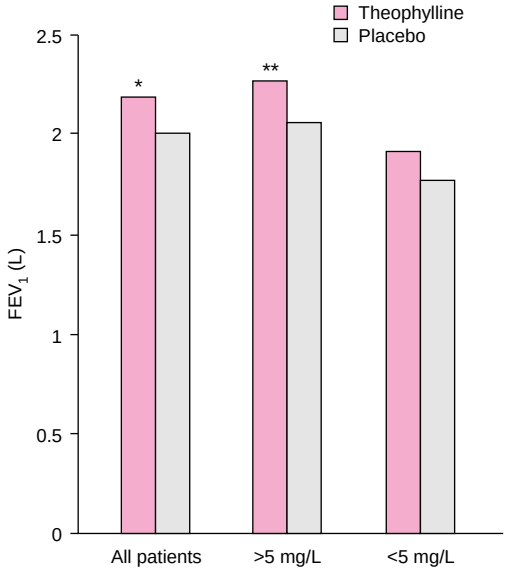

Fig. 1. Mean end-point forced expiratory volume in 1 second (FEV_1) values in patients (n = 25) who either continued regular theophylline therapy or were switched to placebo for 6 weeks in a randomised crossover study. Subgroup analysis was performed according to plasma theophylline levels (during the theophylline treatment phase; <5 *vs* >5 mg/L). All patients were receiving inhaled bronchodilatory and anti-inflammatory (corticosteroid) therapy; a small number (3) were receiving oral prednisolone.[13] * $p < 0.05$, ** $p < 0.02$ versus placebo.

3. Pharmacokinetic Properties

Theophylline has a narrow therapeutic window which necessitates individualised dosing to attain serum concentrations between 5 and 15 mg/L. On this basis pharmacokinetic studies of sustained release theophylline formulations tend to focus on steady-state plasma levels and factors likely to affect them.

3.1 Absorption and Distribution

Theophylline has an absolute bioavailability approaching 100%, although the rate of absorption differs between various sustained-release formulations. In one study the mean protein binding of theophylline was 70%. The mean volume of distribution of the drug is approximately 0.45 to 0.50 L/kg (reviewed by Taburet & Schmit[21]).

Fully published studies evaluating the steroid sparing effects of theophylline used a relatively new pellet formulation designed to allow a once daily evening dose in normal and slow metabolisers (of theophylline) and unequally divided twice daily administration in fast metabolisers. Pharmacokinetic studies of this formulation have assessed its bioavailability, food effects and peak-trough fluctuation between subjects and from day to day. Seven single and 4 multiple dose randomised crossover trials were conducted in a total of 168 male volunteers (n = 12 or 18 per study) [reviewed by Steinijans et al.[22]].

A single 10.8 mg/kg dose of this formulation administered in the evening (before a cold meal) was absorbed over a 14-hour period; absorption was linear (zero order) for ≈70% of the dose but changed gradually to first order thereafter. The absolute bioavailability of a single dose of the formulation (equivalent to 750mg anhydrous theophylline) administered 30 minutes after a hot evening meal was 100% when referenced to an 8-hour intravenous infusion of theophylline (total dose 506mg). Bioavailability remained high (88%) when referenced to a 2-step 14-hour infusion (69 mg/h for 8 hours and 33 mg/h thereafter; total dose 749mg) [reviewed by Steinijans et al.[22]].

On the basis that serum concentrations of certain sustained release theophylline preparations have been shown to vary considerably in response to concomitant food intake, the effects of food intake on the serum concentrations of the once daily pellet formulation have been extensively investigated. Extent of absorption was similar when the preparation was administered 30 minutes before or 30 minutes after a cold evening meal, or 30 minutes after an equicaloric hot or cold meal. In the latter study maximum plasma theophylline concentrations were 18% higher after the hot meal than after the cold meal, although this difference was considered clinically unimportant (reviewed by Steinijans et al.[22]).

Compared with another sustained release theophylline preparation, the once daily pellet formulation had similar bioavailability, but reduced peak-trough serum theophylline fluctuations by 66% ($p < 0.001$)[23] [table I].

Table I. Individual serum theophylline concentrations after repeated evening administration of a 10.8 mg/kg/day dose. Results of a randomised crossover trial comparing sustained release formulations in male volunteers[23]

Subject	24-hour average (range) steady-state serum theophylline concentration (mg/L)	
	pellet formulation	reference formulation
1	8.7 (4.3-12.6)	10.0 (3.9-17.1)
2	11.1 (6.4-13.5)	13.1 (5.9-21.0)
3	10.1 (5.9-12.9)	9.9 (3.7-17.4)
4	13.3 (7.1-17.5)	12.1 (4.8-19.8)
5	12.0 (6.8-16.5)	14.3 (7.1-20.9)
6	6.3 (2.5-10.1)	5.8 (1.5-11.7)
7	14.0 (8.8-18.9)	19.6 (10.0-27.2)
8	7.4 (3.1-10.6)	7.8 (2.2-13.2)
9	7.8 (3.8-10.9)	6.0 (1.7-15.1)
10	7.2 (3.1-10.8)	9.0 (2.8-16.2)
11	10.3 (6.2-13.5)	12.5 (5.8-20.2)
12	9.1 (4.5-13.0)	9.1 (4.7-13.9)

3.2 Elimination

Theophylline is predominantly (≈90% of a given dose) metabolised by the liver. However, the extraction ratio is low and thus clearance is susceptible to alteration by factors that influence the activity of the hepatic enzymes that metabolise the drug; the effects of various drugs on theophylline clearance are detailed in table II. The clearance rate of theophylline is ≈0.4 L/kg · h in otherwise healthy nonsmoking patients with asthma. Correcting factors for various patient populations are listed in table III. Metabolism is mediated by ≥2 cytochromes P450 (CYP); CYP1A2, which is inducible by polycyclic hydrocarbons, is known to be involved (reviewed by Taburet & Schmit[21]).

4. Therapeutic Potential as a Steroid Sparing Agent

Current UK asthma guidelines recommend the use of high dose inhaled corticosteroids in patients with asthma not adequately controlled by low doses of inhaled corticosteroids. However, there is provision for the use of long acting inhaled β_2-agonists in conjunction with low dose inhaled corticosteroids in patients who experience adverse events when treated with high dose corticosteroids or in those with persistent night-time symptoms but otherwise well controlled asthma. It is at this point in the management algorithm that the use of low dose, sustained release, once daily theophylline as an anti-inflammatory has been evaluated. Patients with asthma not controlled by low doses of inhaled corticosteroids were treated with either low dose theophylline (in addition to low dose inhaled cor-

Table II. Influence of concomitant medication on theophylline clearance (from Taburet & Schmit[21])

Concomitant drug	Change in CL or CL/F (%)
Antimicrobials	
Macrolides	
Erythromycin	↓ 5-35
Rroxithromycin	↓ 14
Troleandomycin	↓ 50
Fluoroquinolones/quinolones	
Ciprofloxacin	↔ to ↓ 20-55
Enoxacin	↓ 42-74
Norfloxacin	↔ to ↓ 12
Oofloxacin	↔ to ↓ 12
Pefloxacin	↓ 30
Pipemidic acid	↓ 45-49
Rifampicin (rifampin)	↑ 20-82 to ↓ 50
Isoniazid	↑ 20 to ↓ 8-24
Antiepileptic and sedative drugs	
Phenytoin	↑ 35-75
Phenobarbital (phenobarbitone)	↔ to ↑ 33
Histamine H_2 receptor antagonists	
Cimetidine	↔ to ↑ 8-39
Ranitidine	↔
Sympathomimetic drugs	
Isoprenaline (isoproterenol)	↑ 21-45
Salbutamol (albuterol)	↓ plasma concentration
Terbutaline	↑ 12-23
β-Adrenoceptor blockers	
Propranolol	↓ 30-52
Calcium channel antagonists	
Diltiazem	↔ to ↓ 12-21
Nifedipine	↔ to ↓ 9
Verapamil	↔ to ↓ 14-23
Others	
Oral contraceptives	↔ to ↓ 25-34
Thiabendazole	↓ 66
Disulfiram	↓ 12-33

CL = total plasma clearance; **CL/F** = apparent oral clearance; ↑ indicates increase; ↓ indicates decrease; ↔ indicates no change.

Table III. Correcting factors for theophylline clearance in various patient populations (from Taburet & Schmit[21]). Average clearance in otherwise healthy nonsmoking patients with asthma is 0.04 L/kg • h

Patient population	Correction factor
Smoking adults	1.6
Children	
1-4y	2.4
5-17y	1.6
Diseases	
cirrhosis	0.5
cor pulmonale	0.7
pulmonary oedema	0.5
congestive cardiac failure	0.4

ticosteroids) or an increased dose of inhaled corticosteroid.

Two multicentre randomised double-blind placebo-controlled studies have been published in full.[24,25] Sustained improvements in clinic-measured pulmonary function were seen in both studies. Improvements in mean morning PEF were evident within the first week of treatment in both treatment groups in both studies and were maintained until endpoint. Representative data from the study of Evans et al.[25] are presented in figure 2. Overall improvements from baseline in morning PEF and PEV variability were statistically significant in all treatment groups (table IV).

FEV_1 improved significantly versus baseline with all but the high dose budesonide plus placebo treatment regimen. Indeed, low dose budesonide plus theophylline increased FEV_1 to a significantly ($p = 0.03$) greater extent than high dose budesonide plus placebo.[25] In the second study, however, there was no significant between-treatment difference in this parameter at endpoint.[24]

The dosages of theophylline (250 to 375mg twice daily) used in these studies resulted in respective mean or median serum theophylline concentrations of 10.1[24] or 8.7[25] mg/L.

Summary data are available from a third double-blind placebo-controlled study that compared the efficacy of theophylline 400 mg/day plus beclomethasone 400 μg/day with that of low (400 μg/day) or high (1000 μg/day) dose beclomethasone monotherapy in patients with mild to moderate asthma. 128 patients were treated for an unspecified duration. A significant increase in morning PEF (from 416.2 L/min at baseline to 438.4 L/min at endpoint; $p < 0.002$) was seen in patients treated with theophylline plus beclomethasone. PEF values were not reported for beclomethasone monotherapy but it was stated that there was no significant change.[26]

5. Tolerability

5.1 General Profile

At theophylline dosages producing serum concentrations <20 mg/L, adverse reactions are generally mild and mainly comprise nausea, vomiting, headache and insomnia. However, peak serum concentrations >20 mg/L can be associated with potentially fatal adverse events including persistent vomiting, cardiac arrhythmias and intractable seizures. Other adverse events associated with theophylline at dosages resulting in serum concentrations between 10 and 20 mg/L include diarrhoea, irritability, restlessness, fine tremors and transient diuresis.[27]

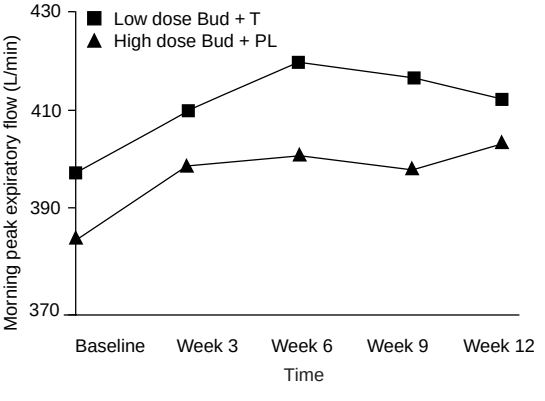

Fig. 2. Patient-assessed morning peak expiratory flow during treatment with low dose budesonide (Bud) plus theophylline (T) [n = 31] or high dose budesonide plus placebo (PL) [n = 31]. Results of a randomised double-blind study in patients with moderate asthma (forced expiratory volume in 1 second 50% of that predicted). There was no significant difference between the 2 treatments.[25]

Table IV. Multicentre randomised double-blind parallel placebo (PL)-controlled studies evaluating the steroid sparing potential of sustained release theophylline (T) in patients with asthma (FEV_1 percentage predicted ≥50%) not fully controlled by inhaled corticosteroid therapy

Reference	Regimen (duration of treatment) [no. of pts]	Clinic[24] or home[23] am PEF (L/min)		Clinic PEV variability (%)		Clinic FEV_1 (L)		Clinic FVC (L/min)	
		baseline	end-point	baseline	end-point	baseline	endpoint	baseline	end-point
Evans et al.[25]	T[a] + Bud 400μg bid (12wk) [n = 31]	430	453**	9.7	8.8***	2.48	2.69**	3.52	3.78**
	PL + Bud 800μg bid (12wk) [n = 31]	411	436*	8.4	6.0*	2.50	2.61	3.49	3.67
Ukena et al.[24]	T[b] + Bec 200μg bid (6wk) [n = 69]	345	458[c]***	10.1	6.9***	2.30	2.56**		
	PL + Bec 400μg bid (6wk) [n = 64]	344	420[c]***	10.1	7.1**	2.40	2.59**		

a Theophylline 250mg bid (in patients weighing <80kg) or 375mg bid (in patients weighing ≥80kg).[24]

b Theophylline 250mg bid for 1 week and 375mg bid thereafter.

c Estimated from graphically presented percentage value.

am = morning; **Bec** = beclomethasone; **bid** = twice daily; **Bud** = budesonide; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **PEF** = peak expiratory flow; **pts** = patients; * $p < 0.03$, ** $p < 0.01$, *** $p < 0.004$ *vs* baseline.

5.2 Low Dose Theophylline Combined with Inhaled Corticosteroids

The low dosages of theophylline used in studies evaluating its efficacy as an adjunct to corticosteroid therapy have obvious implications in terms of tolerability relative to higher dosages of theophylline. Fully published studies investigating the potential steroid sparing effects of theophylline reported that treatment was well tolerated. Low dose inhaled budesonide plus low dose oral theophylline (n = 31) was associated with gastrointestinal upset (in 5 patients), palpitations (2), sore throat (1) and headache (1), whereas high dose budesonide (n = 31) was associated with sore throat (in 3 patients), gastrointestinal upset (2), rosacea (1) and palpitations (1).[25] In the other trial the rate of pharmacologically predictable or potentially asthma-related adverse events (gastrointestinal symptoms, palpitations and respiratory symptoms) was higher in theophylline plus beclomethasone 400 μg/day recipients (27 events in 69 patients) than in patients treated with beclomethasone 800 μg/day (17 events in 64 patients). Other adverse events (comprising myalgia, nonrespiratory bacterial infections and weakness) were also more frequent in theophylline plus beclomethasone recipients than in those receiving beclomethasone 800 μg/day (23 *vs* 12 events).[24]

5.3 Overdosage

Theophylline overdosage has 2 common forms: acute overdosage [such as ingestion of a single large dose (>10 mg/kg)] and chronic overdosage i.e. ingestion of repeated dosages that exceed the patients' theophylline clearance rate. Guidelines for the management of theophylline overdose are extensive and are beyond the scope of this review; readers are referred to manufacturer's prescribing information.[27]

6. Dosage and Administration

In its traditional role as a bronchodilator, theophylline must be administered in individualised dosages to achieve a peak serum concentration within the defined therapeutic range (for further details refer to manufacturer's prescribing information [27]). Until recently this range was defined as 10 to 20 mg/L; however, it has recently been suggested that this be revised downward to 5 to 15 mg/L.[1]

Since studies evaluating the steroid sparing effects of theophylline used dosages of the drug that would be considered subtherapeutic in the traditional context, dosages were not individualised. In 1 of the 3 available studies theophylline was started at a dosage of 250mg twice daily, and after 1 week this was increased to 375mg twice daily.[24] In the

second study the drug was administered at a dosage of 250 or 375mg twice daily in patients weighing <80 or ≥80kg, respectively.[25] These dosages resulted in median/mean theophylline serum concentrations of about 9 to 10 mg/L. The third study used a 400mg daily dose of theophylline but serum level data were not presented.[26]

7. Place of Theophylline in the Management of Asthma

Historically, bronchodilatory therapy formed the mainstay of pharmacological asthma management. Patients not controlled by as-required inhaled β-agonists were usually given long term bronchodilatory therapy; only when this proved unsatisfactory was anti-inflammatory treatment (usually an inhaled corticosteroid) introduced.[28] However, it became apparent during the 1980s that an unacceptably high rate of asthma deaths was partly attributable to underuse of anti-inflammatory medication. This awareness was a motivating factor for the preparation and publication of formal asthma management guidelines in the UK in 1990.[29] These guidelines have been regularly updated, most recently in 1995,[30] and have been joined by US-developed guidelines.[31] Both UK and US guidelines for the management of chronic asthma in adults and school children suggest a 5-step pharmacological treatment plan in response to asthma of increasing severity. Importantly, anti-inflammatory therapy has now supplanted bronchodilatory therapy as the mainstay of pharmacological therapy for asthma.

Although theophylline has been available for more than 80 years, its mechanism of action has not yet been precisely determined.[11] The drug was traditionally classed as a bronchodilator and gives way to newer, more effective and better tolerated bronchodilator drugs in current asthma management guidelines. However, over the past decade, evidence of anti-inflammatory and immunomodulatory properties has appeared. Indeed, the potential role of theophylline as an anti-inflammatory treatment is acknowledged in both US and UK asthma management guidelines, although neither defines a clear place for the drug as an anti-inflammatory treatment.

Results from several recent pharmacodynamic studies indicate that low dose theophylline has anti-inflammatory and immunomodulatory properties at a cellular level in patients with asthma and that these effects manifest as improved asthma control. Importantly, the drug has now been shown to have a steroid sparing effect in clinical trials. Although these studies were of insufficient duration to fully assess the effects of theophylline in this indication, their results do add considerable weight to the contention that the drug has a role as preventive medication.

The fact that its efficacy in these studies was achieved at lower dosages than traditionally used has important tolerability implications. The narrow therapeutic window of theophylline is a serious consideration for clinicians contemplating prescribing the drug as a bronchodilator; since the apparent steroid sparing effects of the drug occurred at lower dosages, tolerability/toxicity concerns, while still relevant, should have a lower overall influence on the decision to prescribe the drug in a preventive role. It is important to note, though, that the potential remains for unexpected increases in theophylline serum levels to occur as a consequence of external factors such as dosage errors or inadvertent prescription of an interacting drug.

In clinical trials, the rate of adverse events was similar with low dose budesonide plus low dose theophylline and high dose budesonide,[25] but was higher with theophylline plus low dose beclomethasone than with high dose beclomethasone.[24]

Compliance with prescribed therapy is an important aspect of asthma management, as poor compliance has been linked to increased morbidity and mortality. Compliance problems with inhaled anti-asthma medications, particularly corticosteroids, are not uncommon; several reasons for this have been suggested, including:

- patient discomfort with the concept of 'steroid' therapy

- lack of a direct relationship between inhalation of corticosteroids and symptom control (in contrast to β-agonist therapy)
- the lag between discontinuation of inhaled corticosteroid therapy and symptom recurrence.[32]

It has been clearly established that inhaled medications are more troublesome to self-administer than oral medications, which may affect relative compliance rates. In one study of medical records data, patients were shown to be significantly more compliant with oral theophylline than with inhaled corticosteroid and/or sodium cromoglycate therapy. Interestingly, dosing frequency (≤2 *vs* ≥3 daily doses) had no significant effect on compliance with either oral or inhaled therapy.[32]

An analysis of the costs of asthma indicated that drug costs account for ≈37% of the total direct costs of the disease.[33] Theophylline is inexpensive compared with traditional anti-inflammatory therapies for asthma and its use as steroid sparing therapy is likely to reduce overall treatment costs. According to Evans et al.[25] the approximate monthly cost of theophylline plus budesonide 800 μg/day is $60 (year and currency not specified) compared with $100 for budesonide 1600 μg/day and $155 for a regimen of budesonide 800 μg/day and salmeterol 100 μg/day. In addition, use of low doses may reduce the requirement for regular monitoring of theophylline serum levels,[9] further reducing costs associated with treatment.

Thus, low dose theophylline has been shown to reduce requirements for inhaled corticosteroid therapy in patients with asthma. Addition of the drug to low dose inhaled corticosteroid therapy instead of increasing the dosage of the latter also has the potential to improve compliance and decrease treatment costs.

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