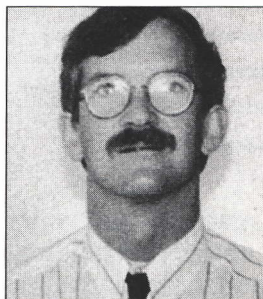


The emerging anti-inflammatory role of theophylline in the treatment of asthma



Curriculum Vitae

Adrian graduated from the UCT Medical School in 1983. After his housemanship at Groote Schuur Hospital, his SHO posts included paediatrics at Red Cross Children's Hospital and Emergency Medicine at Groote Schuur Hospital. He then completed GP vocational training in Surrey, England, before returning to Cape Town in 1988 to join a group family practice in Newlands. He obtained the DCH(SA) in 1989 and the MFGP(SA) in 1990. Allergy and clinical immunology are his special interests. He is a member of the British Society for Allergy and Clinical Immunology, and was a delegate at their last three annual conferences. Whilst in England, he attended the BSACI GP training course in allergy. He has served on the Executive Committee of the Allergy Society of South Africa since 1991, running the Patient Education portfolio. He also works as a part-time allergologist at the Allergy Clinic at Red Cross Children's Hospital in Cape Town.

13 Colinton Road,
Newlands
7700

Summary

Theophylline has been widely used as a bronchodilator in asthma for many years. More recently its role as first line asthma medication has declined as the toxic side-effects and difficulty maintaining therapeutic serum levels have been highlighted.^{1,2} At best, theophylline has been shown to be only a moderately effective bronchodilator. Of greater interest are theophyllines' recently recognised anti-inflammatory properties that have been noted at much lower therapeutic levels than previously used.^{3,4} In this article the anti-inflammatory property of theophylline will be explored further.

Historical perspective

The methyl-xanthines which include caffeine and theophylline have been used in the form of coffee and extracts from the tea plant for the treatment of bronchial asthma for almost 700 years. Theophylline is a naturally occurring xanthine alkaloid found in the leaves of *Carmellia sinensis* which was widely used for making tea. The beneficial effects of coffee in asthmatic patients were first attributed to caffeine by Dr Henry Hyde Salter in 1859. During the past 50 years, theophylline has been a first line treatment in both acute and chronic asthma and was the most common anti-asthma drug prescribed in the USA in the 1970s and 1980s⁵. In recent years there has been a dramatic decline in its use, mainly due to adverse publicity which has highlighted the narrow therapeutic window, adverse side-effects and poor bronchodilatory effect of this once popular drug². So much so that the SA Childhood Asthma Working Group recommended in their

Adrian Morris
MBChB DCH(SA) MFGP(SA)

S Afr Fam Pract
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Theophylline in the treatment of asthma

1994 guidelines that it only be used as a third-line agent when neither B-agonists nor inhaled corticosteroids are available. The recent recognition that airway inflammation plays a considerable role in the aetiology of asthma has also contributed to a decline in the routine use of bronchodilators and more particularly theophylline¹.

Pharmacokinetics uncertain

Although theophylline has been around and used for many years, its exact pharmacological mechanisms of action have remained uncertain⁵. Theophylline is known to be a non-selective phosphodiesterase (PDE) inhibitor and its mechanism of action was always assumed to be due to this enzyme inhibition. Bronchial smooth muscle relaxation was thought to occur when PDE inhibition caused the accumulation of cyclic AMP and cyclic GMP within the muscular contractile machinery⁶. However, the concentration of theophylline required to fully inhibit phosphodiesterase is very high and well above the normal therapeutic range of the drug. At the usual therapeutic range of theophylline, only 10% inhibition of phosphodiesterase

occurs, therefore the therapeutic effect has to involve another mechanism. No one seems to be able to explain the true mechanism of the bronchodilatory effects of theophylline adequately, but it may play a role by inhibiting the adenosine receptor or depleting intracellular calcium. One study has suggested that theophylline may act by increasing calcium uptake into intracellular mitochondrial stores⁷. Theophylline readily distributes to all body compartments and is 60% plasma protein bound, it also crosses the placenta and into breast

milk. The narrow therapeutic index due to its steep dose response curve and wide interpatient variability in hepatic clearance make theophylline plasma concentration monitoring necessary so as to achieve both symptom control and avoid toxicity⁶. Higher doses of theophylline can be tolerated at night because of the circadian increase in clearance.

Previously recognised uses

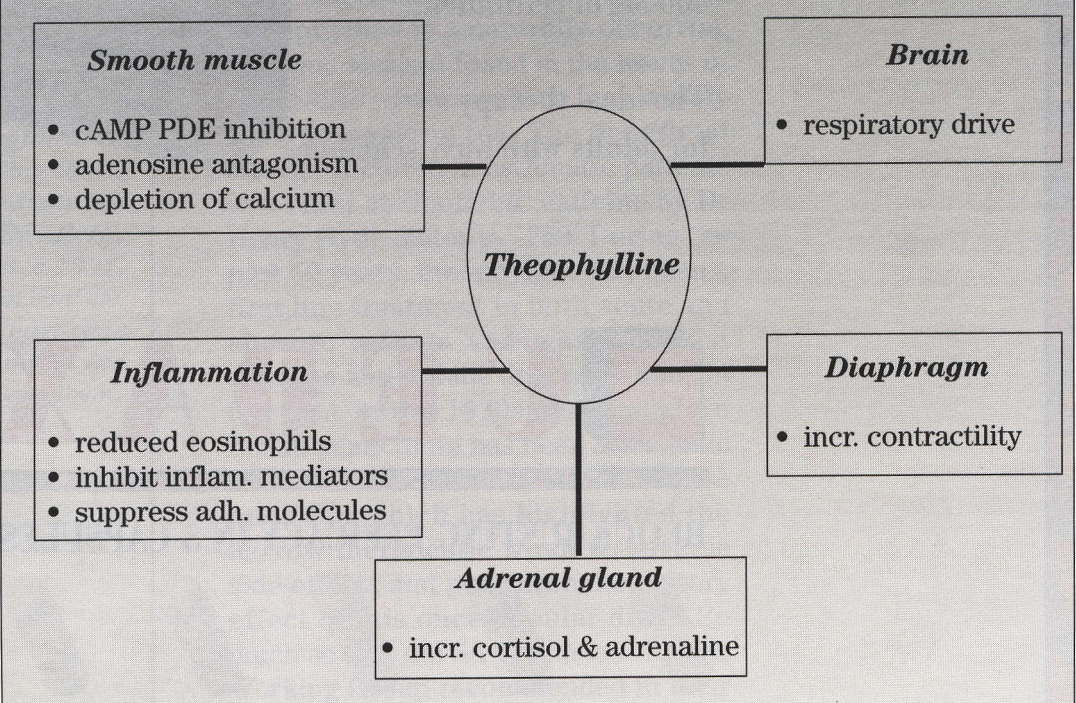
Theophylline as the free agent or as its salts *aminophylline*-the ethylenediamine salt of theophylline and choline *theophyllinate* (64% anhydrous theophylline) have for many years been administered orally or intravenously to relieve smooth muscle contraction of asthmatic bronchoconstriction. However, theophylline appears to have a modest inhibitory activity against the immediate asthmatic reaction following allergen challenge when compared to B-agonists. Other previously recognised pharmacologic properties include stimulation of the medullary respiratory centre and control of apnoea in prematurity, improved contractility of the fatigued diaphragm and increased cardiac output with diuresis⁵.

Only recently recognised that it has anti-inflammatory properties.

Theophylline is only a moderately effective bronchodilator.

Airway inflammation does play a major role in asthma.

Figure 1: Proposed mechanisms of action of theophylline



Theophylline in the treatment of asthma

A rather quaint use mentioned in a pharmacology textbook was that in the dying patient where intravenous aminophylline "may cause brief and unrepeatable but socially useful recovery of consciousness and coherence".

Recently discovered properties

Even in mild asthma, inflammatory infiltrates are noted in the bronchial mucosa and persistent inflammation is a feature of chronic asthma. Therefore treatment with anti-inflammatory drugs is recommended in all but the most trivial cases of asthma^{1,2}. The inflammatory cells normally infiltrate the airways during the so called "late phase asthmatic response" which occurs six to 24 hours after allergen exposure.

Recent evidence^{3,4,8} points to theophylline having significant anti-inflammatory properties and being able to block the late phase asthma response. In addition it also appears to play a role in reducing respiratory muscle fatigue during the acute phase response. This anti-inflammatory or immunomodulatory nature of sustained-release theophylline was demonstrated in 1994 by Barnes and Pauwels at modest plasma levels of 11µg/ml³. Sullivan et al also noted a significant fall in EG-2 positive eosinophils recruited to the bronchial mucosa in asthmatics treated with similar low doses (5-10µg/ml) of theophylline over a 6 week period⁴. In chronic studies, sustained-release oral theophylline appears to be at least as effective as sodium chromoglycate in controlling young allergic asthmatics and provides additional symptom control in asthmatics taking regular inhaled steroids³. At plasma concentrations between 5 and 10µg/ml theophylline also appeared to inhibit exercise induced bronchoconstriction. Other recently recognised beneficial

properties of theophylline included: pulmonary vasodilatation, stimulation of muco-ciliary clearance and inhibition of mast cell mediator release. Theophylline also seems to interfere with the action of the pro-inflammatory cytokine, tumour necrosis factor -α(TNF-α) and increases the endogenous secretion of adrenaline from the adrenal medulla. Evidence now indicates that theophylline may down regulate airway inflammation by reducing eosinophil survival rates and by suppressing the expression of adhesion molecules found on eosinophils⁹.

Lower therapeutic range

The anti-inflammatory properties of theophylline are unrelated to the bronchodilatory properties. Indeed, the high therapeutic range currently recommended for theophylline stem from studies of bronchodilatory response to infusions of aminophylline rather than from studies of the anti-asthma effects of the drug. Theophylline is recognised to be a rather poor bronchodilator even at these high therapeutic ranges⁷. The consequent high side-effect profile at these ranges (10-20 µg/ml) has resulted in theophylline's decline in use generally^{1, 2}. For anti-inflammatory activity, much lower dosages are necessary and consequently toxic side-effects are most unlikely to occur. The dosage of long acting theophylline in this case is 200mg 12 hourly for adults or 5mg/kg body mass 12 hourly for children. This will achieve an anti-inflammatory therapeutic range with serum levels as low as 5-10µg/ml.

Low-dose sustained-release oral theophylline may be a very cost-effective option.

Inhaler devices often unacceptable by rural patients and therefore dogged with non-compliance.

Figure 2: Therapeutic and toxic effects of theophylline

<u>Serum Theophylline level</u>	<u>Clinical effect</u>
40 – 50 µg/ml	death, seizure, brain damage
30 – 40 µg/ml	arrythmia, hypotension
20 – 30 µg/ml	vomiting, diarrhoea, headache irritability, insomnia
10 – 20 µg/ml	<i>bronchodillatory effect</i>
5 – 10 µg/ml	<i>anti-inflamatory effect</i>

Theophylline may take a new role as an anti-inflammatory asthma preventer.

Theophylline in the treatment of asthma

Toxicity

Theophylline is extensively metabolised by the cytochrome P450 system in the liver. Only about 10% of theophylline is excreted unchanged in the urine. Unwanted effects of theophylline are usually related to plasma concentrations exceeding 20µg/ml and occur in up to 20% of patients treated with xanthines. Common side-effects include: headache, nausea, vomiting, abdominal discomfort and restlessness. School children may experience learning difficulties and behavioural disturbances. The half-life of theophylline is *increased* variably, dependent on severity, in conditions such as heart failure, cor pulmonale, cirrhosis, viral infections and by drugs such as allopurinol, cimetidine, erythromycin, verapamil, oral contraceptives and ciprofloxacin. The half-life is *decreased* between 10 and 80% in smokers, heavy drinkers and by drugs such as anti-convulsants and rifampicin. At the previously recommended bronchodilatory dosages as a result of the above factors, if concomitant use of the above drugs with theophylline is essential, the theophylline dose should be adjusted by monitoring plasma concentrations⁵. Fortunately at the far lower anti-inflammatory plasma levels now recommended for theophylline, drug interactions and toxic effects are most unlikely to occur and plasma level monitoring is unnecessary.

Cost-effectiveness

When evaluating the therapeutic choices available, cost is becoming an increasingly important factor. Especially in the South African context where health care resources are limited and sodium chromoglycate and inhaled steroids are mostly unavailable in rural medical practice, low dose sustained-release oral theophylline may be a very cost effective option¹⁰. It could be used for preventing asthma and acting as an alternative anti-inflammatory medication even though we recognise that it is not as effective as low dose inhaled or

oral corticosteroids. An additional point to note is that in rural medical practice the inhaler devices are often found to be unacceptable by patients and falsely perceived to cause damage to the heart (personal communication). Usage of the inhaled route for medication is therefore dogged with non-compliance. Theophylline does not seem to be surrounded by similar misconceptions to limit its acceptability. A comparative study has suggested better patient compliance with theophylline, than inhaled steroids⁹. The oral route is much more popular with patients in general and consequently compliance to medication regimes may be much better in less "medically" educated patients. It has been suggested that the ideal asthma therapy should be a "...tablet that can be administered once-daily to improve compliance..." and specifically targeted at the underlying disease process. Theophylline fulfils many aspects of this role by providing a dual effect on both the underlying disease process and bronchial smooth muscle.⁹

The future

We expect to see a number of clinical studies in the near future that will hopefully confirm that theophylline has a more valuable role to play as first-line anti-inflammatory agent than as a third-line bronchodilator. Another recent advantage is the low side effect profile noted at the lower "anti-inflammatory" therapeutic ranges suggested. It will be exciting to see if, due to its new role, there is a resurgence in use of this once popular bronchodilator, whose mode of action *still* remains obscure. Theophylline may become a cost-effective alternative anti-inflammatory asthma preventer to the inhaled steroids and sodium chromoglycate or be used in addition to these agents to control brittle asthma¹⁰. Newer highly selective PDE inhibitors are being researched at present by a number of pharmaceutical companies. Great interest is being shown particularly in the development of PDE IV inhibitors which restrict the

Inhaler devices are falsely perceived to damage the heart

"...whose mode of action still remains obscure."

Theophylline in the treatment of asthma

release of pro-inflammatory mediators from mast cells, eosinophils, T-lymphocytes, macrophages and epithelial cells³. PDE IV inhibitors will play a significant anti-inflammatory role in asthma if and when they become commercially available.

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