

Theophylline in chronic asthma: A “before and after” study

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Abstract

Objective : To study effectiveness of theophylline in chronic asthma.

Design : Before and after study.

Methods : Sustained-release theophylline was administered orally, 10mg/kg as a single dose at night to 40 consecutive subjects. The subjects were categorized as follows: Those with persistent cough only (PC) – 14, those with cough & wheeze (CW) - 12, and those who required hospitalization for an acute severe asthma.(HOSP) – 32, including 8 infants with a history of more than 3 episodes of LRTI with wheeze . Hospitalization for an acute episode of asthma six months before and six months after theophylline prophylaxis was taken as an indicator of effectiveness.

Findings : None of the subjects from PC and CW category required hospitalization either before or after theophylline. Most importantly, only one of the patients required hospitalization from HOSP category, after theophylline compared to 32 before theophylline prophylaxis.

Conclusions : Theophylline is an effective drug for chronic asthma. This finding may be particularly important where cost & ease of treatment matter more.

INTRODUCTION

Increasing urbanization in developing countries is, quite predictably, leading to increase in prevalence of childhood asthma. This is also accompanied by an increase in hospital admission for asthma (1). Thus, burden to the society due to asthma is increasing. This affects resource-limited societies to a great extent. Mortality, morbidity and associated cost of care can be substantially reduced in asthmatics. Suppression and reversal of inflammation is the cornerstone for managing acute symptoms and preventing relapse. Current strategies emphasize inhaled glucocorticoids as first line preventing therapy (2). However, cost considerations and difficulties in correctly using the inhalers among our patient-population made us explore the next option; theophylline (3,4).

MATERIAL AND METHODS

This before and after study was conducted on 40 consecutive children attending out-patient department at the Cama Hospital, Mumbai during the year 2003. In them, chronic asthma was severe enough to warrant regular daily administration of medication for at least a month to prevent symptoms. The patients were followed-up bi-monthly. Prior

history of 6 months was recorded for symptoms, mutually exclusive, like persistent cough (PC), cough & wheeze (CW) for at least one week per month and breathlessness requiring emergency care or hospitalization (HOSP). The patients received sustained-release theophylline at night (8.00 pm) in a single oral dose, 10mg/kg, for six months. The parents were alerted about the possible side-effects like nausea, vomiting and insomnia. The patients with persistent cough with no other signs & symptoms received theophylline as a therapeutic trial. The infants were diagnosed to have asthma when they had more than 3 episodes of LRTI with wheeze. Some patients had cough and wheeze after completion of theophylline prophylaxis after a symptom-free period of 3-6 months. They were studied separately. Follow-up rate on theophylline prophylaxis was also studied.

RESULTS

The number of subjects requiring hospitalization declined from 32 to one after theophylline prophylaxis. The subjects with persistent cough or cough and wheeze responded well and none required emergency attendance or hospitalization either before or after theophylline prophylaxis (table). Only

one patient was lost for follow up. Five of the 58 subjects belonging to PC, CW and HOSP categories, had recurrence of cough and wheeze after completion of theophylline. After re-starting theophylline, the symptoms disappeared. None of them required emergency treatment or hospitalization.

Figure 1

Table – Profile of the subjects before and after theophylline

Parameters		Persistent cough (PC) No = 14	Cough + wheeze (CW) No = 12	Required hospitalization (HOSP) No = 23
Age	1-5 years	10	8	20
	6 years and more	4	4	3
Sex	Male	9	4	15
	Female	5	8	8
Hospitalization (No)	BP	0	0	32
	AP	0	0	1
Follow up	Responded	8	10	31
	No response	3	2	1
	LFU	3	0	0

BP – Before prophylaxis, AP – After prophylaxis, LFU – Lost for follow up.

DISCUSSION

Persistent inflammation is a feature of chronic asthma and there are inflammatory infiltrates in the airway wall even in mild asthma (5). The changes like broncho-constriction, bronchial hyperresponsiveness and oedema are mediated through the eosinophilic reaction induced by the allergens. Theophylline attenuates the asthmatic reaction to inhaled allergen (6). Secondly, the anti-inflammatory effect of theophylline occurs at serum concentration below the accepted therapeutic range. Hence, the possibility of dose related side-effects is also reduced. Anti-inflammatory drugs have become mainstay for asthma prophylaxis. However, in selecting an agent from the available range, an application of which agent gives the best results in a given situation is important. The inhaled steroids are recommended as the first line therapy. In resource-scarce settings there are two limitations. One is the cost of inhalers and the second, doubts regarding correct use of the inhalers. Potential of theophylline in asthma prevention needs to be fully explored in such a situation. Once-a-day dosing and oral administration is best suited for our patient population. Although glucocorticoids form first line maintenance / preventive therapy, theophylline is positioned as first alternative (7) or third line medication (8) even in places where other options are inconsequential.

The single most important evidence of effectiveness of theophylline in our study comes from virtual absence of need for hospitalization or emergency attendance after treatment. This is important because emergency services are not up-to-the mark in developing countries (9). Secondly, low drop-out rate, although an imprecise index of effectiveness and acceptance of treatment, is also noteworthy. The relationship between chronic cough and wheeze is unclear, however some cases of chronic cough do respond to bronchodilators. In a study conducted on 15 children presenting with cough and no wheeze who demonstrated changes after exercise in pulmonary function similar to children with asthma, all responded to bronchodilators (10). A therapeutic trial of bronchodilator, preferably a non-steroidal one, is worthwhile in a case of persistent cough before elaborate set of investigations is undertaken. Eight out of eleven cases of persistent cough responded to theophylline in our study. Relief from cough and wheeze in children minimizes self-imposed restriction on playing and enhances their self-esteem. It also improves family functioning. Ten of the twelve patients belonging to group CW responded well to theophylline. None of them required hospitalization. Many infants have wheeze associated with viral respiratory illness. However, an infant with more than three dyspneic episodes with wheeze, is considered to be suffering from early childhood asthma (11). Respiratory syncytial virus (RSV) is likely to trigger asthmatic process in vulnerable children. It is proposed that persistent uncontrolled airway inflammation leads to disruption of airway architecture leading to irreversible narrowing. Therefore, early diagnosis and prophylaxis becomes all the more important. In our study, infants required repeated hospitalization or emergency attendance before theophylline prophylaxis and none required hospitalization on prophylaxis. Our study has some limitations, splitting a sustained-release tablet is not advisable. However, we had to split the tablet for children weighing less than 20 kg. Since tablet with strength less than 200 mg was not available. Before-and-after studies have recall bias. Therefore we have chosen a more definite event like hospitalization to study the effectiveness.

Asthma management now finds place in guidelines meant for primary care at global level (12). Cost of asthma prevention with steroid inhalation is Rs.150 (US \$ 3) per month as against Rs.24/- (US \$ 0.5) with theophylline. Thus, theophylline is an available option where cost and compliance matter most for an effective prevention of chronic asthma in children.

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