



REVIEW ARTICLE

Oral theophylline as a preventer and oral salbutamol as a reliever in childhood asthma: An option when resources are scarce

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ABSTRACT

Asthma treatment remains challenging, especially in low-resource settings, as it revolves around inhaler devices. The inhalers are too expensive to buy from a pharmacy and not available from a public health facility. Besides, one-to-one training is required for the correct use of inhalers. Therefore, this therapy is associated with low adherence. Improper training leads to faulty use, inadequate treatment, and drug wastage. Asthma is an inflammatory condition that requires a bronchodilator for relief during acute exacerbation and an anti-inflammatory agent for prevention. The use of oral salbutamol, in place of inhaled beta-agonists, and oral slow-release theophylline in place of inhaled corticosteroids offers a feasible option. This may make the treatment easier to deliver and more affordable in low-resource settings.

Introduction

Asthma is a global disease affecting countries worldwide and populations of all age groups⁽¹⁾. The disease incurs direct costs on pharmaceuticals, indirect costs due to work loss, and unquantifiable costs such as decreased quality of life⁽²⁾. Children from low-mid income countries (LMICs) particularly suffer disproportionately due to the higher burden of asthma morbidity and mortality^(3,4). The Global Alliance Against Respiratory Diseases (GARD), which WHO supports, advocates that the goals and action plans for chronic respiratory disease (CRD) control should suit the country's income level. Therefore, affordable asthma management needs country-specific guidelines⁽⁵⁾, in the absence of which only one in four countries had a national asthma strategy, as revealed by a survey conducted by the Global Asthma Network (GAN) in 120 countries⁽⁶⁾. The present communication proposes the combination of oral salbutamol as a reliever and oral theophylline as a preventer presenting a "non-inhaler/oral option" replacing inhaled beta-agonists and corticosteroids for asthma control in LMICs.

Discussion

Despite advancements in understanding asthma and the development of evidence-based treatment guidelines⁽⁷⁾, locally suitable programs for managing asthma are not in place in LMICs. A systematic review reported low adherence to asthma-preventer inhaler medication in children with a mean adherence of 36.4% for the cohort, and >75% adherence was only 14.6% of patients⁽⁸⁾. As a result, 90% of the global asthma burden is shouldered by LMICs, where underdiagnosis and under-treatment are common⁽⁹⁾. Access to essential asthma medications is also limited in these regions; inhaled bronchodilators are available in half of the public primary healthcare facilities, while steroid inhalers are accessible in just one-third⁽¹⁰⁾. Obtaining out-of-pocket asthma medicines can severely strain household budgets. For instance, a 2011 survey across 12 countries revealed that the

cost of inhaled corticosteroids (ICS) exceeded two days' wages for individuals earning lower salaries, and, in four countries, it surpassed one week's wages⁽¹¹⁾. Therefore, prescribing cost-effective medications is crucial for reducing morbidity and mortality associated with asthma⁽¹²⁾.

Also, proper inhaler usage ensures optimal drug delivery and prevents wastage⁽¹³⁾, for which, one-on-one training is necessary. However, such training is time-consuming, labor-intensive, and challenging in busy clinics in countries like India⁽¹⁴⁾. Asthma management has two components: relief from symptoms and prevention of recurrence. Short-acting beta-agonists (SABAs) like salbutamol provide rapid symptom relief; the World Health Organization (WHO) recognizes salbutamol as one of the most effective and safest medications available⁽¹⁵⁾. However, SABAs do not address underlying inflammation or prevent recurrence. Inhaled corticosteroids are popularly recommended for this purpose.

Oral theophylline was a popular asthma treatment from the 1960s to 1980s. With the introduction of a slow-release version, theophylline was given once or twice daily, and it became a standard of chronic therapy in the late 1970s⁽¹⁶⁾. Later, theophylline has largely been supplanted by inhaled β 2-agonists in asthma relief due to their superior efficacy and fewer side effects. Theophylline is a bronchodilator at a higher plasma concentration, 20 μ g/mL, and anti-inflammatory at 10 μ g/mL, with a reduced risk of dose-related side effects. This understanding led to its renewed relevance in asthma prophylaxis. As a result, GINA asthma guidelines recommended theophylline as an add-on therapy in patients whose disease was uncontrolled with inhaled corticosteroids alone⁽¹⁷⁾. A systematic review, that included 18 studies, determined the efficacy of xanthines such as theophylline, in the prevention of pediatric asthma. The studies compared xanthine versus placebo. The symptom-free days were more, and the rescue medication requirement was lower with xanthine.

The author's comment says that the xanthines are suitable as first-line preventative asthma therapy in children when inhaled corticosteroids are unavailable⁽¹⁸⁾.

A double-blind placebo-controlled study demonstrated attenuation of inflammation, with significant reductions in activated eosinophils, following treatment with oral slow-release theophylline⁽¹⁹⁾. Theophylline compared well in efficacy with inhaled corticosteroids, the gold standard asthma prevention strategy. In a multicenter randomized controlled trial involving 195 children with asthma, oral theophylline was equally effective as beclomethasone aerosol in symptom control while reducing bronchodilator use⁽²⁰⁾. Another study comparing inhaled budesonide, sustained-release theophylline, and montelukast indicated that all three treatments improved asthma control similarly⁽²¹⁾. A before-and-after study involving 40 children, in a LMIC, administered sustained-release theophylline, 10 mg/kg, at night for six months. Theophylline levels were not estimated. In these patients, chronic asthma was severe enough to require regular daily medication for at least a month in the preceding six months. Emergency hospital attendance, which has a good recall value, was taken as an outcome variable of interest. A substantial decline in emergency hospital visits—from 32 to just one—demonstrated its effectiveness in preventing severe asthma exacerbations. The monthly cost of this prevention strategy was approximately Rs. 24 (US \$0.50), making theophylline a viable option where cost and compliance are critical factors⁽²²⁾. The monthly cost of steroid inhalation would have been six times higher, Rs.150 (US \$ 3). Obviating the need for hospital attendance during out-of-hours is immensely important since emergency services are not dependable in developing countries⁽²³⁾. In our “multicentric experience,” after⁽²²⁾, we pursued the policy of using only oral treatment at other institutions including two medical colleges, Pune and Talegaon Dabhade, and a primary health center at Kamshet. The “non-

inhaler” approach is also environmentally friendly; metered-dose inhalers (MDIs), commonly used for asthma treatments, contribute significantly to climate change due to their propellant gases and associated greenhouse gas emissions⁽²⁴⁾. The production and transportation of MDIs also generate greenhouse gas emissions. MDIs account for approximately 13% of the NHS's carbon footprint⁽²⁵⁾.

Conclusion

A combination that integrates oral theophylline as a preventive measure and oral salbutamol as a reliever, presents a pragmatic solution for effectively managing childhood asthma, especially in low-resource environments. This step will avoid the massive efforts required, in the first place, to enhance the use of inhalers for asthma treatment and later, to abandon their use to address environmental concerns.

Conflict of Interest:

None

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