

THEOPHYLLINE IN CHILDHOOD ASTHMA

Niranjan Shendurnikar

The advent of highly effective drug therapy for childhood asthma and the availability of appropriate delivery systems has improved the management of this disease). Theophylline, a naturally occurring methyl xanthine has been used to treat childhood asthma for more than three decades(2,3). The drug is an important adjunct in the management of chronic asthma along with the inhaled beta agonists and corticosteroids(4). The drug's narrow therapeutic window and the potential for serious toxicity have led to concern regarding its safety and usage in childhood asthma(2,5).

The mechanism of action of theophylline is not due to a single effect but rather multiple pathways(6,7). The drug serves as

From the Department of Pediatrics, Medical College, Baroda 390 001.

Reprint requests: Dr. Niranjan Shendurnikar, B/142, Jagannath Puram, Near Lalbaug Crossing, Baroda 390 011.

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a mild to moderate bronchodilator depending upon the serum concentrations, blocks the immediate and late pulmonary response to allergens and exercise and the consequent airway hyper-reactivity. This may be due to its mild anti-inflammatory properties, as it reduces microvascular leakage(6).

Therapeutic Benefits

Recent reports in hospitalized patients with acute severe asthma have shown that theophylline does not provide additional benefit over the use of beta-agonists and systemic steroids(8-10). A meta-analysis of thirteen controlled trials in acutely ill asthmatics failed to demonstrate that the theophylline therapy was better than various non-xanthine regimens(10). Despite these limitations, intravenous theophylline (aminophylline) can be used in the treatment, if acute attack of asthma in those children who do not respond to combined beta agonists and corticosteroids(11-13). In addition, theophylline reduces respiratory muscle fatigue, increases mucociliary clearance and possesses some degree of antiinflammatory activity(14).

The place of theophylline in the management of chronic asthma is better defined. Continuous use of theophylline in children with chronic asthma increases their symptom free interval, decreases the use of inhaled bronchodilators and provides an important steroid sparing effect(15,16). In addition to bronchodilator effect, theophylline has a very mild antiinflammatory action(5). Sustained release oral preparations of theophylline ensure its long duration of action and are thus particularly useful in the control of nocturnal asthma(17).

Theophylline remains a useful adjunct

in, the long term prophylaxis of the asthma in children and is particularly useful when more than one drug is required for prolonged maintenance therapy(2,5,6,17). Theophylline is not recommended for the use in chronic mild asthma. In chronic moderate asthma, a good anti-inflammatory agent like cromolyn sodium is recommended for use. However, if the cost is a limiting factor, theophylline remains a useful alternative drug in these cases.

Risks of Toxicity

Theophylline has the potential for significant toxic effects but these can be frequently avoided by appropriate dosage and monitoring. The serum concentration of theophylline must be maintained within a relatively narrow range to obtain an optimal therapeutic response while avoiding toxic side effects(18). Minor caffeine like side effects are well tolerated if the serum levels remain in the therapeutic range(5,6).

Transient caffeine like side effects can be avoided mostly by starting with a sufficiently low dose and slowly increasing the dose if required at the interval of 3 days or longer(5). Undesirable side effects like headache, loss of appetite, nausea, vomiting, dizziness and epigastric pain have been associated with theophylline levels beyond recommended therapeutic range. However, lack of availability of monitoring of theophylline levels stresses the need for optimal dosing, patient and parent education, early recognition of these side effects and withdrawal of theophylline and substitution with another drug.

Peak serum concentrations between 10 to 20 mg/L usually provide an optimal balance between the bronchodilatation and safety(18). However, dosage required to maintain these levels vary substantially due

to individual differences in theophylline metabolism(19). Monitoring of serum levels is recommended at the beginning of theophylline therapy, when the child does not show expected effect on appropriate dose and/or develops an adverse effect on the usual dose(17).

Serious adverse effects like cardiac arrhythmias, hypokalemia and convulsions occur more frequently at theophylline levels above 30 mg/L. Seizures may be refractory to anticonvulsants with a high incidence of neurologic sequelae and even death(18). The effect of theophylline on learning and behavior problems is controversial and has led to the reassessment of its role in asthma therapy(3,5).

Theophylline clearance is reduced by several factors such as febrile illness, liver disease, heart failure and certain drugs(17,18). The dosage of theophylline should be reduced by one half for the duration of illness in the children on chronic theophylline therapy, who have sustained febrile illness beyond 24 hours. The common drugs that inhibit theophylline metabolism include erythromycin, cimetidine, propranolol, frusemide and thiabendazole(18). The concurrent use of these drugs should be avoided or the dosage of the theophylline be decreased by one half(18).

In view of the above information and absence of drug monitoring facilities, it is recommended that either the theophylline dose should be reduced or the drug totally removed and other therapeutic agents should be substituted.

Dosage(5)

The optimal dosage of theophylline in children is 12-16 mg/kg/day, upto a maximum of 400 mg/day. In infants below one

year, who have a slower rate of metabolism, the dosage can be calculated as:

$$\text{Dose (mg/kg/day)} = (0.2) \text{ Age in weeks} + 5.0$$

Careful selection of patients for theophylline therapy provides the benefit of good compliance, convenient twice daily dosage, and low cost. It is essential to supervise the therapy and educate the parents and the patient to minimize the adverse effects of theophylline therapy.

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