THORAX

Editorials

What role for theophylline?

What role for theophylline today? After two decades of study and experience should we not be able to define the role of theophylline with almost "Hegelian" certainty? One can hear the retorts from the back benches. On a worldwide basis the use of theophylline remains substantial. In recent years, however, its role has been diminished, certainly by the emphasis on early institution of inhaled anti-inflammatory drugs, and now by the advent of inhaled long acting β_2 agonists. Inhaled corticosteroids do not eliminate entirely the need for bronchodilators, however, nor do they fully normalise airway responsiveness.[1] Addition of long acting β_2 agonists reduces residual bronchospasm and improves nocturnal symptoms and sleep quality in most patients.[2] This leaves us the task of redefining the role of theophylline by focusing on those properties of the drug that are still useful in certain clinical and economic circumstances.

Sustained levels that can be tailored to meet the pattern of bronchospasms

The constancy of action inherent in sustained release products remains an advantage of theophylline. As new β_2 agonists are introduced one can assume that market forces will lower the cost of conventional β_2 agonists so that many patients will continue to use them for economic reasons. Addition of theophylline to these agents blunts the recurring distress that signals the need for each new dose, reducing asthma symptoms and histamine reactivity.[3] Nocturnal bronchospasm can be treated by a twice daily preparation of theophylline, if necessary skewing the dose to the night hours, or else using a once daily preparation in the evening. There are no detectable adverse effects on sleep quality[4] even when studied in normal subjects.[5] As generic forms of these older agents appear, it is entirely possible that the cost of such combined treatment will be substantially less than the cost of the new β_2 agonists.

Additive bronchodilation to inhaled agents

We have enough accumulated data, especially from studies in chronic obstructive pulmonary disease (COPD), to show that theophylline adds significantly to both peak and trough pulmonary function at usual doses of inhaled β_2 agonists,[6–9] ipratropium bromide alone,[10] or these two combined.[11] In fact a surprising further reversibility can be shown in the patient with COPD or bronchitis when larger than conventional doses of β_2 agonists are combined with theophylline. In one study Barclay *et al* incrementally increased serum theophylline levels to their maximum response in forced vital capacity, or to a practical cutoff point. When 400 μg salbutamol given by metered dose inhaler was then added, the final response was doubled.[12] For most patients with chronic bronchitis 1400–3000 μg was required to reach this maximum with salbutamol alone.[13] Similar results were shown by Filuk *et al*.[9] The presence of theophylline at adequate levels produces an optimal response to the inhaled agent. This may be simply by additive action, or the systemic agent may improve penetration of the inhaled agent – a view long held by Svedmyr and Svedmyr.[14] The potential for overadditivity, or synergism, also exists, judging from in vitro studies with canine[15] or guinea pig[16] trachea. Proper consideration of the non-linearity of the bronchodilator response as its limits are approached has seldom been considered when comparing additivity with synergy. A strictly additive numerical result may actually indicate overadditivity when applied to a non-linear response curve.

Systemic access

Systemic access of bronchodilators becomes important in the asthmatic patient as small airways become plugged with secretions, necessitating mechanical ventilation in the extreme case. With our inability to judge whether inhaled β_2 agonists are actually penetrating the airways to reach their intended receptors, however, it is amazing that the systemic route is so frequently ignored. This situation would seem made to order for intravenous bronchodilators, whether aminophylline or β_2 agonists, certainly before reaching the point when the patient must be paralysed and sedated in order to reduce mean airway pressure.

There are few studies of methylxanthines in these patients. Fernandez *et al* showed that intravenous aminophylline was equally as effective as two puffs of salbutamol or ipratropium bromide when applied directly by special adaptor into the endotracheal tube,[17] and Poggi *et al* showed a 30–40% reduction in lung resistance with intravenous doxophylline, a theophylline derivative, after correction for the contribution of the endotracheal tube.[18] Most studies focus only on the peak response, but a study with inhaled fenoterol found a duration of action of only two hours,[19] suggesting that application at this interval is necessary to maintain the benefit of inhaled β_2 agonists. Addition of aminophylline should add to and prolong the response. Strict guidelines for its administration must be observed, however, and serum levels monitored daily.[20,21] Patients should be otherwise stable since cardiovascular instability, pneumonia, and sepsis introduce unpredictable changes in theophylline pharmacokinetics.[22]

Increase in respiratory muscle force

This is a controversial area. The body of work, commencing with the studies of Aubier *et al* showing increased diaphragmatic force upon phrenic stimulation in young normal subjects,[23] and ending with their large scale cross-

over study of 60 patients with severe COPD, makes a compelling case.[24] In the latter study they found an improvement in blood gases, tidal volumes, and maximum oesophageal pressure generated against an occluded airway. Other groups working with human subjects either support[25 26] or deny[27-32] a significant effect on diaphragm contractility. It should be noted that this group used a mean theophylline level of 14·8 μg/ml, essentially at the middle of the therapeutic range, to accomplish their results.[24]

An interesting aspect of the dose-response curves for theophylline in COPD is raised by the studies of Chrystyn *et al*[33] and McKay *et al*[34] which showed a progressive reduction of the "trapped gas volume" as theophylline levels moved up through the therapeutic range. The improvement in diaphragmatic position resulting from the decreased functional residual capacity and residual volume is likely to contribute to the increase in diaphragmatic force, tidal volume, exercise capacity, and symptomatic relief. An increase in the electrical activity of the diaphragm, which is a reflection of neural drive, does not seem to be the predominant factor at therapeutic levels.[26 35]

No trials of the effect of aminophylline on weaning success in adults have been reported. A single case study showing considerable improvement of diaphragmatic force in a quadriplegic patient whose diaphragm was electrically paced is very difficult to explain on any other basis than an increase in diaphragmatic force of contraction.[36]

Suppression of inflammation

Several groups have shown significant suppression of the late phase response to antigen at modest serum levels of theophylline, proportionally more than its inhibition of the immediate phase,[37 38] and we are now back full circle into the phosphodiesterase (PDE) family in the search for a mechanism. Inhibition of the PDE III ("cGMP inhibited") and PDE IV ("cAMP specific") enzymes by various specific inhibitors produces smooth muscle relaxation, and specific inhibitors of PDE IV in the particulate fraction of granulocytes, and probably other cells, inhibit their activation and release of mediators.[39] While theophylline is a non-specific PDE inhibitor, it has sufficient inhibitory activity at concentrations in the therapeutic range against extracts of these separated enzymes to be taken seriously when considering mechanisms of both muscle relaxation and suppression of inflammation, particularly in synergy with stimulants of adenylyl cyclase.[40] Another intriguing area is the fact that theophylline, at nominal concentrations, strongly inhibits release of sensory neuropeptides in a guinea pig model.[41] Whether these anti-inflammatory actions are significant in a clinical sense remains to be shown.

Low cost and convenience

"Non-scientific" considerations also figure in the equation. In countries without a universal health care system the cost of medications for asthma or COPD may consume a large part of a patient's pension. The advent of reliable generic preparations of slow release theophylline brings their cost down further (at my corner pharmacy only $8·00 per month), making them the cheapest antiasthmatic medication in the United States. In some less developed countries this low cost and the convenience of the oral route are major advantages. One of our medical residents who had worked in the field in Nigeria stated that she "wouldn't have known how she could have managed without oral aminophylline." Worldwide distribution patterns for this drug can be explained partly by these considerations, as well as by the preference of some cultures for oral compounds.

Negative factors

The variable clearance, narrow therapeutic index, and severity of toxic reactions of theophylline necessitate close attention to dosing routines and subsequent monitoring; these represent the disadvantages of its use. Normal clearance rates of theophylline vary several fold, and this variation is increased by smoking, age, and interfering medications; the mean rate of clearance of theophylline in the elderly is reduced by 25%.[42] If the effects of cardiac instability, liver disease, sepsis, sustained fever, and hypothyroidism are added, one naturally recoils. However, there are guidelines and measures which largely eliminate these disadvantages. The presence of, or a history of, recurring heart failure, overt liver disease, seizures, or cardiac arrhythmias are relative contraindications to the use of theophylline. With this mental checklist, a conservative dosing approach and monitoring of levels, together with education of the patient regarding those side effects which necessitate withdrawal of the drug (nausea, vomiting, headache, nervousness), theophylline can be safely prescribed. One usually begins with one half to two thirds of the initial full dose as an "adaptation phase." The initial full dose should be no more than 600 mg/day in the adult,[43] and serum levels should be monitored, preferably within a few days but possibly longer provided close contact between doctor and patient is maintained. The daily dose is then adjusted, usually with a twice daily preparation. If treatment is primarily to be directed to nocturnal symptoms, the dosing can be skewed or one of the once daily preparations can be administered in the evening.

Potential for serious toxicity

In the USA a lucrative legal practice has grown up around theophylline toxicity, including newspaper advertisements soliciting potential victims, and the exorbitant settlements that characterise the tort system. This is a sobering reality in the USA, and anyone using theophylline should be monitoring its levels and be aware of the major drug and host interactions. It is not surprising that its original popularity has declined. Dangerous scenarios include: (1) the use of prolonged intravenous infusions without daily monitoring of levels, particularly in the otherwise unstable patient; (2) polypharmacy under several physicians with its danger of duplicate prescribing of theophylline and interfering drug reactions; (3) prescription of theophylline in teaching institutions by inexperienced operators; (4) inadequately informed patients who are driven to use more of the "breathing drug;" and (5) unvolunteered over the counter sources of added theophylline. Suicidal attempts with this common and accessible drug have been reported, but a hospital with an organised approach to theophylline intoxication can manage such cases with a high degree of success.[44] Concern for the effect of theophylline on behaviour, mood and cognitive processes in children seems to have settled into one of being on the alert for the occasional vulnerable child already experiencing problems.[45] Early concerns appear to have been exaggerated.

Clear indications

Theophylline is clearly indicated in the following cases. (1) Patients with severe COPD who are dependent on

bronchodilators and oxygen for any benefit. If they are adequately informed and closely followed, a trial of theophylline in the mid to slightly lower therapeutic range (12–15 μg/ml) is important for those in whom dyspnoea gradually assumes total dominion over their lives. (2) Severe asthmatic patients in whom oral corticosteroids are being used or may be otherwise necessary. (3) Asthmatic patients with nocturnal symptoms, despite use of inhaled corticosteroids and the β_2 agonists available. (4) Patients with acute, severe asthma who are progressing into respiratory failure; this would include patients being mechanically ventilated, primarily for airway disorders, but who are otherwise stable. (5) Those socioeconomic systems where, through cost or non-availability, theophylline becomes the most feasible means of controlling airway obstruction.

Contested areas

At what point in the escalation of the severity of acute asthma is the addition of intravenous aminophylline warranted? There is still no agreement. National and international bodies agree that it should not be routinely used in the initial treatment of acute asthma since many studies have failed to show an advantage in the first three hours. Large doses of inhaled β_2 agonists and intravenous corticosteroids should be used first; those patients not responding, and those with life threatening features, are candidates for theophylline.[2] Two recent studies in children in hospital were unable to show a significant advantage to the addition of aminophylline,[46 47] but Weinberger pointed out that both studies excluded from their protocol those patients with impending respiratory failure, not wishing to risk the use of placebo in these cases.[48] Most would recommend its use in such patients.[49 50] In adults the results are conflicting. Self *et al* found no advantage to using aminophylline in 39 patients randomised to receive active drug or placebo,[51] but Huang *et al* did find an advantage in the first few hours and point out a similar suggestive effect during the first eight hours in the study by Self *et al* as acknowledged by those authors.[52] They suggest that aminophylline provides a "headstart" early in the course of treatment in the hospitalised patient. If so, the next question is how long it should be continued, since the risks of toxicity mount if the drug is not carefully monitored initially and daily. This entire issue thus remains unresolved.

A confounding study was published by Wrenn *et al* and prompted considerable interest.[53] A total of 123 subjects with acute asthma were randomised to receive aminophylline or placebo, all receiving maximum treatment with the other agents. Despite any lack of difference whatsoever in the spirometric response (usually the basis used to compare regimens in the "negative" studies), only one third as many patients were deemed by independent observers to require admission in the group receiving aminophylline. McFadden speculated that aminophylline may have useful properties in this situation other than measurable bronchodilatation.[54] A confirming study of this important issue is needed, since spirometry still fails to reflect this.[55]

Theophylline has recently been studied in sleep apnoea with the finding that the number of apnoeic and hypopnoeic episodes is reduced.[56] The authors recommend its use in those patients in whom continuous positive airway pressure or surgery is either unacceptable to the patient or not indicated. This may become another indication.

In lesser grades of COPD and asthma the use of theophylline is in a "grey zone," subject to the preference of physician and patient, but certainly acceptable. Asthmatic children are often treated with theophylline for obvious practical reasons, and the current concerns about the effects of inhaled corticosteroids on growth rate may broaden its use.

Let me end with a musical analogy. Theophylline has been moved out of the first violin section into the viola or cello section where it selectively adds its own rich tones to the whole. It is definitely not playing second fiddle.

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