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 β₂ agonists. Inhaled corticosteroids do not eliminate entirely the need for bronchodilators, however, nor do they fully normalise airway responsiveness. Addition of long acting β₂ agonists reduces residual bronchospasm and improves nocturnal symptoms and sleep quality in most patients. 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 β₂ agonists are introduced one can assume that market forces will lower the cost of conventional β₂ 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. 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 even when studied in normal subjects. 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 β₂ 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 β₂ agonists, ipratropium bromide alone, or these two combined. In a surprising further reversibility can be shown in the patient with COPD or bronchitis when larger than conventional doses of β₂ 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. For most patients with chronic bronchitis 1400–3000 μg was required to reach this maximum with salbutamol alone. Similar results were shown by Filuk et al. 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. The potential for overadditivity, or synergism, also exists, judging from in vitro studies with canine or guinea pig trachea. Proper consideration of the non-linearity of the bronchodilator response as its limits are approached has seldom been considered when comparing additive 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 β₂ 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 β₂ 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 methyloxanthines 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, 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. Most studies focus only on the peak response, but a study with inhaled fenoterol found a duration of action of only two hours, suggesting that application at this interval is necessary to maintain the benefit of inhaled β₂ 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. Patients should be otherwise stable since cardiovascular instability, pneumonia, and sepsis introduce unpredictable changes in theophylline pharmacokinetics.

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, and ending with their large scale cross-
over study of 60 patients with severe COPD, makes a
compelling case. In the latter study they found an im-
provement in blood gases, tidal volumes, and maximum
oesophageal pressure generated against an occluded air-
way. Other groups working with human subjects either
support26 or deny27-32 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 al25 and McKay et al24 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 dia-
phragm, which is a reflection of neural drive, does not seem
to be the predominant factor at therapeutic levels.26 25
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 contrac-
tion.46

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 inhib-
ited”) 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 activa-
tion and release of mediators.9 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 adenyl cyclase.40 Another intriguing
area is the fact that theophylline, at nominal concentra-
tions, 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 equa-
tion. 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 antiallergic
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 pat-
terns 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 clear-
ance 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. How-
ever, there are guidelines and measures which largely
eliminate these disadvantages. The presence of, or a his-
tory of, recurring heart failure, overt liver disease, seiz-
ures, or cardiac arrhythmias are relative contraindica-
tions 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
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 be-
haviour, mood and cognitive processes in children seems
to have settled into one of being on the alert for the
occasional vulnerable child already experiencing prob-
lems.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 mild 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 cortico-
steroids and the β₂ agonists. (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 β² agonists and intravenous cortico-
steroids should be used first; those patients not responding, and those with life threatening features, are candidates for theophylline. Two recent studies in children in hospital were unable to show a significant advantage to the addition of aminophylline, 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. Most would recommend its use in such patients. 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, 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. 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. 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 bronchodi-
latation. A confirming study of this important issue is needed, since spirometry still fails to reflect this.

Theophylline has recently been studied in sleep apnoea with the finding that the number of apnoeic and hypo-
poic episodes is reduced. 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 order.

In lesser grades of COPD and asthma the use of theophylline is in a “gray zone,” subject to the preference of physician and patient, but certainly acceptable. Asth-
matic 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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