Theophylline in the management of airflow obstruction

1 *Much evidence suggests that theophylline is valuable*
George J Addis

As theophylline is still controversial after 60 years it must have some value; otherwise it would have disappeared without trace like theobromine. The problem is to define what that value is. Published work is for the most part confusing and contradictory. A solution to the problem however, is now available with the application of power analysis to the published evidence.^{1,2} By this means it is possible to consider only those papers with findings robust enough to be likely to be generally applicable. Although it eliminates a large number of papers on both sides of the argument, it reduces the burden of the reviewer considerably, and I will discuss only such papers here.

A further major problem exists—there is no good measure of the real value of such treatments to patients. We have no index incorporating all its gains and losses, and indices of expiratory flow tend to dominate the measurement of effect. More direct measures such as the ability to exercise or even the degree of wellbeing are proving much more difficult to validate. Even the absolute measure of death or survival in critical circumstances scarcely emerges from published data.

The evidence

Four reliable studies show between them that in acute asthma intravenous theophylline improves the peak flow³ and the forced expiratory volume in one second⁴ within 15 minutes after starting the infusion, adds enormously to the effect of inhaled or parenteral β adrenergic agents,⁵ and shows a dose related effect in improving expiratory flow and shortening the time for which intensive treatment is required.⁶

Two papers are concerned with nocturnal asthma. Barnes *et al* showed that slow release oral doses affect the peak flow on waking⁷ and Zwillich *et al* that theophylline is better than a β adrenergic agent in doing this.⁸

In conditions in which airflow limitation is less reversible, ranging from stable asthma to emphysema, much sound evidence suggests that theophylline's effects are probably valuable. In 1981 Greening *et al* showed that air flow was improved with steady state concentrations in the therapeutic range without im-

pairing the response to salbutamol,⁹ and Leitch *et al* soon followed with evidence that this dose regimen and salbutamol were equally effective in increasing the distance patients could walk.¹⁰ Mahler *et al* showed that it also improved patients' assessment of their functional impairment by nearly a fifth, even though the patients did not really respond at all to isoprenaline.¹¹ Guyatt *et al* also used a structured questionnaire to detect 98% power that the combination of steady state oral theophylline in the therapeutic range with regular inhaled salbutamol produced a 31% benefit to patients' perception of their physical ability.^{11a} Their study had the power to detect any change greater than 17% in their patients' emotional state but neither theophylline nor salbutamol, nor their combination, produced any detectable change. Meanwhile, Dull *et al* had shown that patients whose air flow responded to isoprenaline had an equal response to steady state oral theophylline,¹² confirming the flow response to theophylline in a study which was otherwise of inadequate power. Barclay *et al* had already shown that even when the maximum possible response had been obtained to theophylline salbutamol produced still more response in 10 out of 12 such patients¹³; they subsequently showed that four of these patients could achieve a further response to a short term infusion of theophylline at the height of their response to salbutamol.¹⁴

Clearly, either salbutamol or theophylline could improve the lung function of some subjects to the maximum set by their damaged lungs, which was well below predicted normal values. Further support for the value of the combination comes from Taylor *et al*, who showed that patients prefer, and flow indices improve with, the combined treatment, theophylline alone being the next best.¹⁵ Whiting *et al* subsequently showed that given one steady state plasma concentration and its matching forced vital capacity measurement it was possible to predict with uncanny accuracy the forced vital capacity for any specified concentration (figure).¹⁶ They also established that the relation between plasma concentration and response is linear over the usable range. Most recently Chrystyn *et al* showed that with time regular theophylline treatment reduces the volume of trapped gas,¹⁷ a new concept suggesting that gas exchange is improved so that parts

EDITORIAL COMMENT

Patients either love them or hate them. Theophyllines can cause nausea and vomiting (a problem I have found to be particularly troublesome in pregnant women²) but, more worrying, can produce serious illness or even death if toxic concentrations are achieved through injudicious dosing or drug interaction. On the other hand, there are undoubtedly some patients in whom a theophylline preparation substantially improves their clinical condition when other drugs have failed. The con-

venience and efficacy of β agonists and other inhaled drugs must make these the first line approach to airflow obstruction. I have no doubt, however, that theophyllines have a continuing important role in certain groups of patients either when the initial treatment regimen has produced an inadequate response or when theophyllines are particularly suited, such as in nocturnal asthma or in children who find inhalers difficult to use. When a decision to use theophylline has been made then monitoring of drug concentrations is important to avoid underdosing or overdosing. —PETER C RUBIN, professor of therapeutics, University of Nottingham

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Absolute ventilatory response to increasing steady state theophylline concentrations in 56 patients with chronic bronchitis.¹⁶ Heavily shaded area represents 1 SD around mean baseline value of 1.58 litres. Lighter shaded area extends to 2 SD. Clear line shows mean response with slope of 0.04 l μg^{-1} ml. Reproduced with permission of Blackwell Scientific

of the lungs that cannot equilibrate with helium in the ordinary measurement of total lung capacity become accessible with the opening up of small airways.

Conclusions

All the evidence quoted above has passed a test of truth. This does not mean it is true, for we cannot rule out chance or honest error, but it does support my clinical conviction in prescribing theophylline. For the first 20 years of my career in respiratory medicine I

considered theophylline to be a nuisance with no obvious effect except to make people feel sick. Ten years ago it became possible to use recent developments in clinical pharmacology to work out why some patients swore by the drug and to apply these advances to the benefit of some of the most severely handicapped and disadvantaged people in the population.

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2 Difficult drugs to use, few clinical indications

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Theophyllines have been used for treating airflow obstruction for over 100 years.¹ In the United Kingdom alone 29 theophylline containing preparations are available, 16 of them being slow release. So why is their use still controversial?

Difficulties in using theophyllines

Theophyllines are undoubtedly difficult drugs to use properly. Firstly, effective bronchodilation without excessive side effects is achieved only within a narrow range of plasma concentrations. This therapeutic range is 10-20 mg/l, though some bronchodilation occurs from 5 mg/l upwards.¹² Patients in general practice, however, tend to be given low doses, often with little or no therapeutic effect.¹

Secondly, theophyllines often cause adverse effects. Minor or moderate effects such as nausea, headache, and jitteriness occur even at concentrations <10 mg/l and are common in the therapeutic range. Such effects may be reduced by introducing the drug slowly,²³ but they are severe enough to preclude maintenance

treatment in a quarter of patients.⁴ Toxicity, however, may be serious at concentrations >20 mg/l, when fits, arrhythmias, and death may occur.⁵ These reactions are difficult to predict as they are not necessarily preceded by minor warning side effects and are not closely related to plasma concentrations.³

Thirdly, the dose of theophylline necessary to obtain therapeutic concentrations varies tremendously among patients—for example, from 450 to 2250 mg/day—because of wide individual variations in pharmacokinetics.²⁴ The clearance of theophylline is increased (concentrations will be lower) in children and smokers and decreased (concentrations will be higher) in older and obese patients and in heart failure, liver disease, and viral infections.²³ Many commonly prescribed drugs interact either to reduce plasma concentrations—for example, phenytoin, phenobarbitone—or, more seriously, to increase plasma concentrations, with potential toxicity—for example, cimetidine, erythromycin, oral contraceptives, ciprofloxacin, and allopurinol.²³ Therefore, to avoid toxicity and ensure drug effectiveness management must be guided by

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