THEOPHYLLINE

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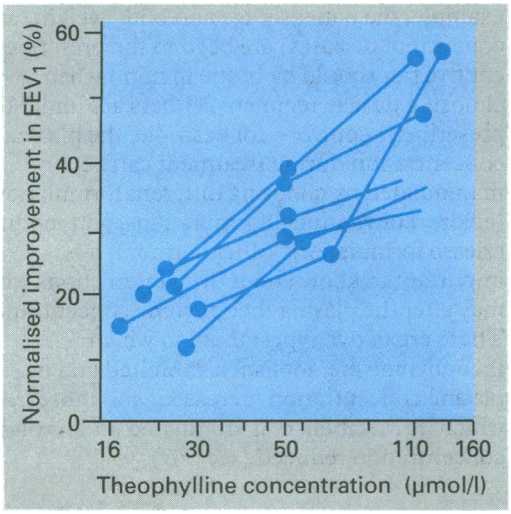
Theophylline is a xanthine that is used in the treatment of asthma, both for long term prophylaxis and for acute severe attacks

It is not possible to establish a single dosage regimen for theophylline or its derivatives (for example, aminophylline) that will suit all patients because the metabolism of theophylline varies greatly from person to person. This variation is reflected in its elimination half life, which varies from four hours in healthy adult smokers to about 25 hours in patients with hepatic cirrhosis.

Several of the factors responsible for the variation (age, smoking habits, body weight, diet, concomitant illness, and drug interactions) can be considered when estimating the most appropriate dosage regimen. But the therapeutic:toxic ratio for theophylline is very small, and only by measuring the plasma theophylline concentration can the dosage be tailored for individual patients.

In this article we apply to theophylline the criteria that must be fulfilled in part or in full before the measurement of its plasma concentration can be considered worth while.

Criteria for measurement



The therapeutic effect of theophylline (shown as the change in FEV_1) increased with increasing plasma concentration in six patients with asthma.

The plasma theophylline concentration range for an optimum effect in the absence of complicating factors is 55-110 μmol/l

Is there difficulty in interpreting clinical evidence of the therapeutic or toxic effects?

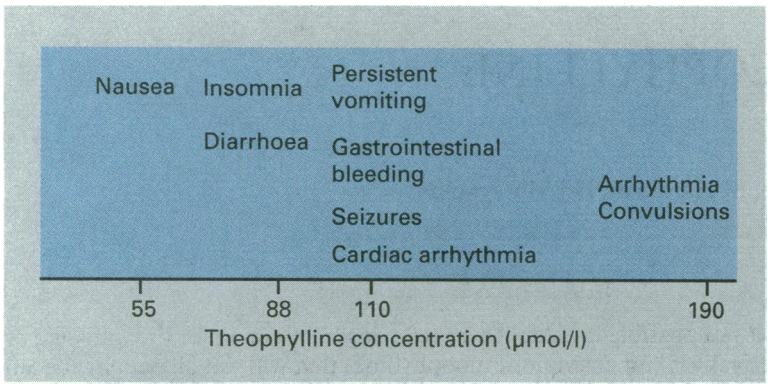
There is a relation between the dose of theophylline and the reduction in airways resistance achieved. The drug's chief therapeutic effect, however, is the relief of bronchoconstriction, which is only one of the three factors that cause airways obstruction in asthma, the other two being mucosal oedema and mucus plugging of the airways. Thus in asthmatic patients a change in FEV_1, which reflects all three factors, is an unreliable guide to theophylline dosing, and monitoring of plasma concentrations is essential in order to optimise treatment.

Many patients experience gastrointestinal symptoms when their plasma concentration is within the therapeutic range, but minor adverse effects do not always precede major ones. Several of the adverse effects (nervousness, tachycardia, arrhythmias, and cardiorespiratory arrest) can be features of an acute attack of asthma, and it may be impossible to distinguish between features of the underlying disease and those attributable to theophylline toxicity without measuring the plasma theophylline concentration.

Is there a good relation between the plasma concentration and its therapeutic or toxic effects?

In experimental studies there is a linear relation between changes in forced expiratory volume in the first second (FEV_1) and the logarithm of the plasma theophylline concentration over the range 17-110 μmol/l. Improvement in FEV_1 is often only slight with concentrations less than 55 μmol/l, and clinical evidence suggests that 55 μmol/l may be considered as the lower limit of the therapeutic range. The upper limit is generally accepted as 110 μmol/l, which is the concentration at which agitation and tachycardia usually become apparent.

Minor adverse effects, such as nausea, insomnia, nervousness, and headache, are common if the plasma theophylline concentration is rapidly increased above 55 μmol/l. Most patients will tolerate the drug better if the dose is gradually increased to attain maintenance plasma concentrations in the middle or upper part of the therapeutic range. About 5% of patients



Adverse effects of theophylline.

develop unacceptable nausea and diarrhoea at plasma concentrations below 80 μmol/l. Serious adverse effects—persistent vomiting, gastrointestinal bleeding, seizures, cardiac arrhythmias, and cardiorespiratory arrest—often occur at concentrations above 110 μmol/l. Plasma concentrations above 190 μmol/l are invariably associated with a high risk of dangerous cardiac arrhythmias.

Is theophylline metabolised to active metabolites?

Theophylline is metabolised in the liver to 1,3-dimethyluric acid and, by N-methylation of both theophylline and 1,3-dimethyluric acid, to 1-methyluric acid and 3-methylxanthine. The metabolites are excreted through the kidney, along with about 10% of the unchanged drug. The 3-methylxanthine metabolite is not as active as theophylline, so the presence of active metabolites does not create a problem in interpreting the plasma theophylline concentration.

Measurement techniques

Theophylline can be detected rapidly by immunoassay

Most laboratories use an enzyme linked or fluorescent immunoassay. A paper test strip (Acculevel, Syva, Maidenhead), to which a capillary blood sample is applied, provides a theophylline assay within 30 minutes, but this method is expensive and is not widely used in the United Kingdom.

Factors affecting concentration

Factors that affect the plasma theophylline concentration

Factors that increase concentration

Formulation: Elixirs *v* modified release formulations

Age: Premature babies; neonates; elderly people

Weight: Obesity

Diet: High carbohydrate; low protein; dietary methylxanthines

Diseases: Chronic obstructive airways disease; pneumonia; hepatic cirrhosis; heart failure

Drugs: Allopurinol; cimetidine; macrolide antibiotics (such as erythromycin); oral contraceptives; viloxazine

Factors that reduce concentration

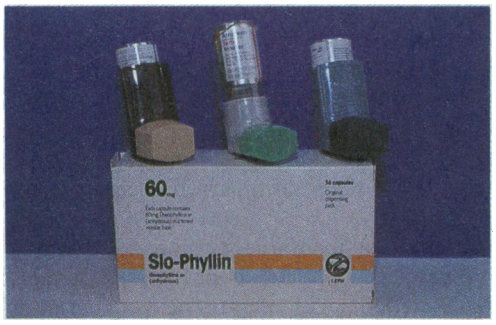
Age: Children

Diet: Low carbohydrate; high protein; charcoal cooked meats

Drugs: Carbamazepine; phenobarbitone; phenytoin; rifampicin; sulphinpyrazone

Certain factors can increase or decrease the plasma theophylline concentration. Some (for example, the patient's age and body weight, and concurrent diseases) are beyond the prescriber's control but should be borne in mind when choosing dosage regimens. Others are under the prescriber's control—for example, the plasma concentration during treatment can be manipulated by choosing different formulations (elixirs, conventional formulations, and modified release formulations). Furthermore, it is important to know about drug interactions which may alter the plasma theophylline concentration. These are of two types: those in which theophylline metabolism is inhibited and its plasma concentration increased, and those in which its metabolism is stimulated and its plasma concentration reduced (see box).

Use of plasma measurements



Inhaled drugs used in the treatment of asthma.

Prophylaxis

In patients with recurrent severe attacks of asthma theophylline is often added to the regimen if combinations of inhaled β_2 adrenoceptor agonists (such as salbutamol), ipratropium, and a corticosteroid are inadequate. It is important to ensure that the patient is receiving an adequate dosage of theophylline to provide optimum protection against further acute attacks of asthma. The patient's respiratory function test results during an episode of remission cannot, however, be used to assess the therapeutic response to theophylline. This can be achieved only by measuring the plasma theophylline concentration and by adjusting the dosage so that the concentration is within the therapeutic range. This assumes that the patient does not experience any adverse effects of theophylline.

Case history: drug interaction

A 72 year old man with longstanding obstructive airways disease treated with modified release aminophylline had an acute infective exacerbation of his symptoms. He was given erythromycin by his general practitioner and after a week his breathing was much improved. However, two days later he developed severe nausea and vomiting and was admitted to hospital after suffering a small haematemesis. The plasma theophylline concentration on admission was 120 μmol/l. Aminophylline and erythromycin were withdrawn and his condition improved. A few days later his breathing had worsened, with an associated fall in FEV_1, and aminophylline was restarted in his usual maintenance dosage. The plasma theophylline concentration two weeks later was 90 μmol/l.

Conclusion

There was an interaction between erythromycin and theophylline in this patient. A reduction in the maintenance dosage of theophylline of the order of 25% is required if macrolide antibiotics are continued for more than five days.

Case history: problems caused by previous theophylline

A 19 year old woman was admitted to hospital with a severe attack of acute asthma. No information was available on her current drug therapy, and she was too unwell to volunteer the information. Her condition worsened despite nebulised salbutamol and ipratropium, so an intravenous infusion of aminophylline 500 mg was given over 30 minutes. Towards the end of the infusion she had a cardiac arrest, was successfully resuscitated, and was transferred to the intensive therapy unit. The plasma theophylline concentration three hours after the end of the infusion was 245 μmol/l. It subsequently transpired that she had been taking oral theophylline daily for some years and indeed had increased the dose during the two days before admission because of worsening asthma.

Conclusion

This case illustrates the danger of giving intravenous theophylline to patients who are already taking oral theophylline.

Routine therapy

Patients taking theophylline for chronic reversible airways obstruction whose condition is not adequately controlled may require an increased dosage. Measuring the plasma concentration allows the clinician to adjust the dosage without risking the toxic effects, which in most cases can be predicted from the plasma concentration. For example, if the patient has a plasma theophylline concentration below 55 μmol/l the dosage can be safely increased, whereas if the concentration is above 110 μmol/l the risk of toxicity with an increase in dosage is much greater. Knowing the plasma concentration would allow the most appropriate change in dosage to be made.

The plasma concentration is linearly related to dosage, and increases in dosage can be calculated on that basis. For example, in a patient taking 500 mg of aminophylline a day with a steady state plasma theophylline concentration of 60 μmol/l, increasing the total daily dose of aminophylline to 750 mg would be expected to increase the steady state theophylline concentration to 90 μmol/l.

In acute asthma a knowledge of the plasma theophylline concentration is useful for two reasons. Firstly, if it is measured before theophylline is given it reduces the risk of theophylline toxicity, which can arise if a patient already taking the drug is given an intravenous loading dose. It is therefore important to ask patients whether they have been taking theophylline before coming into hospital. Remember that certain over the counter remedies (for example, Dodo tablets) contain theophylline. Secondly, if the patient has not responded to intravenous theophylline the rate of infusion can be increased to ensure that the optimal dosage is being administered without unnecessarily risking severe toxicity.

Toxicity

Measuring the plasma theophylline concentration will help to confirm a diagnosis of theophylline toxicity. In a case of theophylline overdose measuring the plasma concentration will help to assess the prognosis, plan the treatment, and assess the response to treatment.

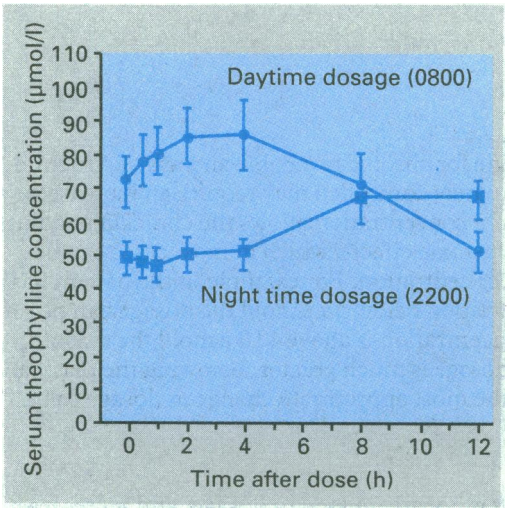
Timing of measurements

Intravenous infusion—Take the sample after 4-6 hours of infusion, having stopped the infusion for 15 minutes

Oral administration—Take the sample 8-12 hours after the last dose. For sequential monitoring take samples at the same time each day

Intravenous infusion

During intravenous infusion a sample for measurement of plasma theophylline concentration may be taken at any time if theophylline toxicity is suspected. If there are no adverse effects a sample should be taken four to six hours after the start of the infusion, and the infusion should be stopped for 15 minutes before a sample is taken so that the plasma concentration reflects the total body concentration; otherwise the plasma theophylline concentration may be significantly higher because of the diffusion gradient from the plasma to the tissues.



The plasma concentration profile during the 12 hours after a dose of theophylline depends on the time of day the drug was taken. Plasma concentrations are higher after daytime administration. (Data from 13 asthmatic children who took a modified release formulation.)

Oral theophylline

In patients taking oral theophylline ideally a "trough" (minimum steady state) plasma concentration should be measured. The time at which the "peak" plasma concentration occurs varies from 15 minutes after the dose (for elixirs) to two hours (for ordinary formulations) and four to six hours (for modified release formulations). This strictly limits the period during which the sample should be taken. As there is a circadian rhythm of theophylline metabolism, resulting in higher trough concentrations in the morning than later in the day, repeat samples for measurement of the trough concentration should be taken at the same time of day as previous samples to allow direct comparison of the results.

Given all these considerations the most practical strategy for routine monitoring is to tell the patient to take the morning dose on wakening and to measure the plasma theophylline concentration during the afternoon. Modified release formulations may be taken at night, with measurement of the plasma concentration the next morning.

The sources of the data presented in the graphs are: Mitenko and Ogilvie, *N Engl J Med* 1973;**289**:600-3 for the therapeutic effect of theophylline; and Smolensky *et al*, *J Asthma* 1987;**24**: 90-134 for theophylline concentration *v* time after dose. The data are reproduced with permission of the journals.

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OBITUARY

A M Adelstein

Obituaries must be submitted exclusively to the BMJ and should be under 250 words; we give preference to those submitted within three months of the person's death. We welcome self written obituaries and good quality, recent photographs, and, as a medical journal, we encourage authors to include the cause of death.

A M ADELSTEIN

MD, FRCP, FFPHM

> How the people of England live is one of the most important questions that can be considered; and how—of what causes, and at what ages—they die is scarcely of less account; for it is the complement of the primary question teaching men how to live a longer, healthier and happier life. (W Farr, 1875)

Abe Adelstein, the eighth chief medical statistician for England and Wales, was to the twentieth century what William Farr was to the nineteenth. Both believed that, by promoting understanding of the variations in health and sickness, society could develop strategies for overcoming many of the causes of human misery. Farr, the first chief medical statistician in 1837, set about building a basis for recording systematically what was happening around him. The statistics based on routine records such as death certificates enabled him and other public health reformers to facilitate major changes to the social infrastructure and bring about substantial improvements to the nation's health.

In the period immediately after the second world war there existed a sense of social justice and a determination for mankind to control social and environmental factors that affected the health and quality of life. Abe Adelstein was a leading figure in the social medicine movement for over 40 years. He achieved this standing through his own research, through lasting changes in national vital statistics systems, and by enabling other researchers to address issues of import. His own research, including work on accident proneness and the incidence of mental illness in the community, as well as his studies of migrants and of social and economic differences in health, show his commitment to environmental explanations for patterns that he recorded.

His main contribution to the statistical infrastructure came through the use of record linkage—as in the national cancer registration scheme, the Office of Population Censuses and Surveys' longitudinal study, and the support that the OPCS provided to over 500 researchers wishing to follow up people in cohort studies. He also played a leading part in the development of the ninth revision of the International Classification of Diseases. The Medical Research Council's Epidemiological Monitoring Unit and Environmental Epidemiology Unit and the National Perinatal Epidemiology Unit were all established as a consequence of Abe's recognition of the value of subjecting routinely collected information to systematic in depth analysis.

Abe Adelstein was a private man; he achieved through collaboration, not conflict. His writing was simple and to the point. He was a wonderful mentor and genuinely wise. He prompted and questioned, without needing to demonstrate his knowledge and understanding. He recognised and overcame prejudices and barriers that had limited many of his medical contemporaries and predecessors. He was able to transcend class, disciplinary, and ethnic boundaries and enabled those with whom he had dealings to achieve their potential.

Above all, Abe Adelstein was a man of courage and determination with a remarkable will to live; despite all the health problems that affected him from the early 1950s he never complained. He is survived by his wife, Cynthia, and a son and a daughter.—JOHN FOX

Abraham Manie Adelstein, the chief medical statistician 1967-81, died 18 October aged 76. Born 29 March 1916; educated Marist Brothers College, Johannesburg, and Witwatersrand University (MB, BCh 1940). Health officer to South African Railways 1947-61. Senior lecturer at Manchester University 1961-7. Visiting professor of epidemiology at London School of Hygiene and Tropical Medicine 1981-4. At various times was chairman of Society for Social Medicine, medical section of Royal Statistical Society, and section of epidemiology of Royal Society of Medicine. Awarded Donald Reid medal of London School of Hygiene and Tropical Medicine 1979, Bisset Hawkins medal of Royal College of Physicians 1982.