Royal Brompton Grand Rounds

Readers are invited to submit articles in the style of Royal Brompton Grand Rounds and Hammersmith Staff Rounds. Advice on how to do this appeared in the "BMJ" on 16 November, p 1258-9.

Unstable asthma and theophylline

Therapeutic concentrations may not always prevent attacks

Theophylline has a narrow therapeutic index and is associated with extrapulmonary side effects. Its metabolism varies among individuals, which together with the numerous interactions with drugs and food, makes it difficult to prescribe.¹⁻³ A therapeutic range of 10-20 mg/l has been found experimentally to optimise the balance between therapeutic efficiency and toxicity,^{1,2} although the clinical value of theophylline has been questioned.²

Asthmatic symptoms are worse at night,^{4,6} and because of this it has recently become common to give a controlled release preparation of theophylline at night, which decreases symptoms and improves lung action in the early morning.⁷⁻¹³

We present the case of a young woman with life threatening asthma whose symptoms seemed to be controlled by careful surveillance and maintenance of her serum theophylline concentration. Because the initial improvement was convincing, we undertook a trial of domiciliary monitoring of theophylline concentration.

Case history

A 35 year old woman with asthma was referred to this hospital for development of a strategy for preventing her life threatening episodes. Her asthma had been mild until the age of 25, when her symptoms became more frequent and more severe. She had had life threatening exacerbations that required intermittent positive pressure ventilation on four occasions. Between exacerbations, she was virtually free of symptoms during the day unless exposed to known precipitants but was always symptomatic in the early hours of the morning, with an appreciable decrease in peak expiratory flow rate. She was taking slow release theophylline (350 mg twice daily), prednisolone (10 mg/day, intermittently up to 40 mg/day), terbutaline

FIG 1—Diurnal variation in peak expiratory flow in patient taking slow release theophylline 350 mg twice daily

FIG 2—Variation in serum theophylline concentration and peak expiratory flow rate in response to changes in treatment

(5 mg/day), ipratropium bromide (0.5 mg/day), and inhaled beclomethasone 2 mg/day.

On examination she was mildly cushingoid but well. Except for a sputum eosinophilia, all initial investigations gave normal results and her random serum theophylline concentration was within the therapeutic range at 16 mg/l. Figures 1 and 2 show her peak flow measurement before and after changes in treatment. Her condition improved after she was given slow release theophylline (Uniphyllin) but its withdrawal was followed by a severe attack of asthma, which responded rapidly to intravenous aminophylline. On reintroducing slow release theophylline the morning fall in her peak expiratory flow rate was again eliminated, and her serum theophylline concentration was maximal at 4 am and fell gradually through the day with an accompanying fall in peak flow. This fall was corrected by a mid-morning dose of slow release theophylline (fig 2). It seemed, therefore, that her serum theophylline concentration needed to be consistently maintained within the therapeutic range for control of her asthma.

After discharge from hospital her asthma was stable for six weeks while she was taking slow release theophylline (400 mg in the morning, 800 mg at night) but worsened during an attack of gastroenteritis associated with vomiting and diarrhoea. Four weeks later she took one dose of theophylline two hours early and had a further severe exacerbation of asthma. These

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episodes suggested that diligent control of theophylline concentration was essential. We therefore set up a trial of home monitoring of serum theophylline concentration.

We used a monoclonal immunoassay of theophylline (Acculevel, Syntex Medical Diagnostics, Palo Alto, California)¹³⁻¹⁵ for domiciliary monitoring to assess the feasibility of domiciliary monitoring; to assess the effect of environmental changes at home on theophylline concentrations; to compare theophylline concentrations and pulmonary function at home and in hospital; and to assess clinical benefit. The patient was trained to use the immunoassay kit and asked to measure theophylline concentration three times daily for two weeks and then twice daily for a further two weeks. In addition she was asked to record and document her peak expiratory flow rate and to keep a diary.

Her measurements of theophylline concentration were checked by a series of concurrent measurements in the hospital laboratory with a fluorescence polarisation technique (Therapeutic Drug System, Abbot Diagnostic, Berkshire). Guidelines for adjusting the dose of theophylline according to serum concentrations were drawn up, and we decided that changes in dose would be made only after discussions with medical staff at this hospital.

For reasons explained below, the trial lasted only 16 days. Domiciliary monitoring of theophylline concentration with the kit proved feasible and accurate. On four separate occasions theophylline concentrations measured simultaneously by fluorescence polarisation and with the kit were almost identical. Her theophylline concentration tended to fluctuate between the lowest and highest margins of the therapeutic range over short periods, and it became clear that changes in her symptoms and peak flow were not related to changes in serum theophylline concentration (fig 3). The trial was stopped because she had a severe acute exacerbation which required admission to hospital and ventilation at a time when her serum theophylline concentration was well within the therapeutic range. Theophylline concentration and peak expiratory flow rate continued

to be measured while she was in hospital. The steady state theophylline concentration achieved in hospital was not reproduced at home on the same dose regimen.

Comment

The immunoassay kit is accurate and practical and could be used in a selected group of patients—that is, well motivated patients with good insight into their illness. In our patient it proved a useful way of establishing just how important (or unimportant) theophylline was in managing her asthma. Home monitoring had no long term benefit in this patient as despite so called therapeutic concentrations of theophylline she remained prone to unpredictable, catastrophic decompensations. Use of home monitoring in other groups of asthmatic patients requires further investigation.

Whether theophylline ever had or should in the future have a place in our patient's management remains unclear. Withdrawal of theophylline by doctors and as a result of her gastroenteritis were both associated with subtherapeutic serum concentrations and the rapid onset of symptoms with a fall in pulmonary function. On the other hand, therapeutic concentrations did not prevent a serious clinical exacerbation. The accepted therapeutic range on which doses are based may not be as straightforward as previously thought, and certainly the relation between dose of theophylline and the prophylactic effects of the drug remains undelineated.^{2,16} Perhaps, we never gave our patient high enough doses to sustain airway stability. Obviously this was difficult in view of the known risks of toxicity. She did, however, continue taking theophylline, and we have yet to elucidate the precipitant(s) of her crises.

Two further questions emerged from this case. The first relates to the rapidly fluctuating theophylline concentrations found in the trial. How do we explain these variations over short periods while she was taking a drug which is designed to smooth out variability? The second question is whether we can extrapolate data collected in a hospital to real life. Patients eat different foods, keep different hours, take drugs at different times, and are subject to different emotions, and these factors may influence the pharmacokinetics of theophylline. Elimination of these differences in theophylline concentrations may be where home monitoring will prove most useful.

Discussion

DMG: We failed to show any definite cause for the changes in peak flow or any relation between treatment and peak flow in this patient, and I think this is what most people find when they look at morning dipping.

JVC: Did you look at the relation between reflux and changes in airway calibre? Firstly, much data exist relating intraoesophageal pH changes with changes in airway calibre, and reflux in the night is a well documented phenomenon. Secondly, theophylline may itself promote reflux, independent of asthma.

DMG: No. The patient had no such symptoms. But even if intraoesophageal monitoring and pH studies had shown that she was refluxing, could we have taken this to predict changes in airway calibre? Has anyone shown a temporal link between episodes of reflux and episodes of asthma?

TE: The literature seems to suggest that if a patient with asthma has reflux it is worth treating the reflux as in some cases the asthma improves.

MG: I sometimes see patients who convince me, and are convinced themselves, that slow release theophylline helps them at night. Occasionally there is even evidence to show that this is true. In these patients I

FIG 3—Domiciliary monitoring of peak expiratory flow rate and serum theophylline concentration in woman with asthma. Measurements were continued in hospital after her attack on day 16

prescribe theophylline and I don't monitor anything.

DMG: I think the message is that it is much more difficult to attain steady state theophylline concentrations than can be predicted from published reports or from hospital monitoring. Perhaps the actual blood concentration is not the relevant parameter; it may be the rate of change of blood concentration that is important. There is evidence that withdrawal of β agonists is followed by rebound airway hyperresponsiveness.¹⁷ If this occurs with theophylline then a fall in serum concentration from 20 mg/l to 10 mg/l could be the most dangerous occurrence in asthma. If we find evidence for this we might have to reopen the whole issue.

In conclusion, we have shown that home monitoring of serum theophylline concentration is possible, that theophylline concentration varies much more at home than in hospital, and that maintenance of theophylline within the therapeutic range failed to prevent life threatening asthma.

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Medicine in Europe

1992 and all that

Tessa Richards

Although 31 December 1992 is, to quote Lord Cockfield, "more of a milestone than a finishing post," the (incorrect) idea persists that something dramatic will happen as the clock strikes midnight.

In the run up to the Maastricht summit polemic about federalism, foreign policy, defence, a single currency, and the recently agreed pact with the European Free Trade Association (EFTA) countries has focused public attention on the future of Europe. The imminence of the summit has also sharpened awareness of the power of the European Community's institutions and how this is set to increase if revised treaties on political and monetary union are signed next month.

General interest apart, should doctors be concerned? How might these changes and the run up to 31 December 1992, with its Orwellian overtones, affect their working practice?

This article is the first of a series on medicine in Europe, in which the *BMJ* will attempt to answer these questions by looking at existing European Community legislation and speculating on the likely effect of what is proposed. The articles emphasise that despite a scant legal basis many decisions which affect health have been made at community level over the past decade or so (box), and if this legal base broadens with the creation of a formal health competence more and more decisions will be made in Brussels. Topics covered will

Overview of some established and draft EC legislation affecting health

Mutual recognition of diplomas—Doctors' directive established in 1975; nurses' 1977; dentists', vets', midwives' 1980; pharmacists' 1980. Directive on vocational training for GPs (1986); minimum two years' training. Future agenda: harmonising specialist training.

Reciprocal arrangements for acute medical care—E111 form. European Council has adopted a recommendation for a European emergency health card.

Pharmaceuticals—Directives on assessing safety and efficacy of drugs (and medical equipment). Recommendations on clinical trial procedures. Draft directives on distribution, advertising, and packet leaflets. Proposed European Medicines Agency (to be set up by 1993). Some moves to iron out drug price differentials.

Food—Directives on additives, food irradiation, radionuclide limits (post-Chernobyl) and growth promoters in meat. Proposed legislation on standards of food hygiene and labelling foodstuff nutrient values.

Environment—Directives on air pollution and water quality. Draft directives on exposure to chemical products, lead, cadmium, pesticides, etc. The framework

of a European Environmental Agency has been agreed. **Health and safety**—Directives on safety in the workplace; personal protective equipment; manual handling of loads; use of display screens (VDUs); exposure to hazardous chemicals, asbestos, and biological agents. Draft directives on protection of pregnant workers and young people.

Consumer protection—Draft directives on the liability of suppliers of services; safety of children's toys and equipment. Rapid alert system for "dangerous" consumer products.

Tobacco—Directives on tar yield and strengthening the warning labels on tobacco products. Draft directive banning tobacco advertising.

Health promotion—Europe against Cancer, Europe against AIDS. Five million ecus allocated (1991) to combat drug misuse. Pending: Europe against Cardiovascular Disease.

Research—Medical and health research programme BIOMED 1 (1990-4), budget >130m ecu, split between research on: disease prevention, care, and health systems; major diseases (AIDS, cancer, cardiovascular disease, etc); human genome analysis; biomedical ethics.

This is the first of a series of articles looking at medical issues in Europe