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# Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L?
## A Randomised Concentration-Controlled Trial

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***Summary*** The optimal serum concentration of theophylline for the management of acute airways obstruction was evaluated by comparing the response to target concentrations at the extremes of the usual therapeutic range. 174 patients requiring intravenous theophylline were randomly assigned to a target concentration of 10 or 20 mg/L. Control of theophylline dosage using measured theophylline concentrations and evaluation of efficacy and toxicity was performed under double-blind conditions. 87 patients (50%) required hospital admission. Of these, 54 patients (62%) were followed throughout their hospital admission and reviewed at an outpatient clinic approximately 1 week after discharge. The duration of hospital stay, and rate and extent of improvement in peak expiratory flow rate were not different between the groups. There was significantly more toxicity in the 20 mg/L group. The initial target concentration for theophylline in the management of acute airway obstruction should be 10 mg/L under circumstances where concentration is used to control theophylline dosages.

The use of intravenous theophylline is a standard part of the management of acute, severe airways obstruction. Access to rapid analytical techniques has changed the therapeutic emphasis from the size of the dose to the serum concentration. The target concentration for theophylline is loosely defined by a therapeutic range of 10 to 20 mg/L and common initial dosage guidelines usually aim for the lower of these values.

Vožeh et al. (1982) compared outcomes in 20 patients with severe, acute airways obstruction assigned to receive a target concentration of either 10 or 20 mg/L. The results were surprising. There was no detectable benefit 28 hours after starting treatment with a target of 10 mg/L, but substantial improvement was observed in those treated with a target of 20 mg/L. On the other hand, pharmacodynamic analysis of the study of Mitenko and Ogilvie (1973) by Holford and Sheiner (1981) suggested that 50% of the maximum bronchodilator effect of theophylline is achieved at 10 mg/L and only 17% more is obtained at 20 mg/L. This prediction would suggest that there is little benefit to be expected from target concentrations at the upper compared with the lower end of the therapeutic range.

In order to resolve the differing predictions of these studies, a trial was undertaken in patients with severe, acute airways obstruction presenting to the Accident & Emergency (A&E) Department of a large general hospital. Both the therapeutic and

undesirable effects of treatment with theophylline at target concentrations of 10 mg/L and 20 mg/L were compared.

## *Methods*

All adult patients with severe, acute airways obstruction presenting at the A&E Department of Auckland Hospital were considered for the trial. They were eligible for entry to the trial if they required treatment with intravenous theophylline. All intravenous theophylline was given as the ethylene diamine salt, aminophylline. This usually occurred after they failed to respond within 20 to 30 minutes to initial treatment with nebulised salbutamol (albuterol) or fenoterol. The only patients excluded were those so severely ill that they warranted admission to the Department of Critical Care. An abbreviated explanation of the trial was given to each patient and oral consent obtained. A more detailed explanation was given subsequently if the patient was admitted to the hospital wards. The study was approved by the Auckland Hospital Ethical Committee.

Patients were treated in the A&E Department until they were well enough to leave or a decision was made to admit them to a hospital ward. If they were admitted to a ward, intravenous theophylline was administered until they were judged well enough to take theophylline orally. All patients discharged from the wards were asked to continue with oral theophylline and to attend an outpatient follow-up clinic approximately 1 week after discharge.

### Study Design

Patients were assigned to treatment aimed at a target serum theophylline concentration of 10 mg/L (Low group) or 20 mg/L (High group) using a previously allocated random sequence. This design is known as a randomised concentration-controlled trial (Sanathanan & Peck 1991).

A loading dose of theophylline (10 mg/ml or 20 mg/ml) 0.5 ml/kg was given over 60 minutes then followed by a maintenance infusion at 0.04 ml/h/kg. These doses were modified as necessary for previous theophylline use, obesity, heart failure and history of cigarette smoking (Powell et al. 1978). An additional loading dose was given if necessary based on theophylline measurement. The maintenance dose was adjusted using the formula proposed by Chiou et al. (1978).

Oral theophylline was started when the patient was well enough. A slow release preparation ('Theo-Dur', Astra) was given every 12 hours at the same rate as an intravenous infusion expected to maintain the target concentration. Based on measurements of serum theophylline concentration, adjustments to the oral dosage were made if necessary prior to discharge. Oral theophylline was continued until the outpatient visit, when a decision to continue was made based on the patient's condition. The trial ended at the outpatient visit.

Blood samples for theophylline concentration were taken before starting treatment with intravenous theophylline, 15 minutes after the end of the initial loading dose infusion, 5 hours after commencement of intravenous theophylline, and each morning between 0800h and 0900h throughout the hospital stay. Additional samples were taken immediately before stopping the intravenous infusion, at the outpatient clinic visit, and at the discretion of the clinical team.

Serum theophylline concentrations were measured by fluorescence polarisation immunoassay using an Abbott 'TDX' analyser or by enzyme multiplied immuno technique (EMIT) using an Abbott VP Bichromatic analyser.

All decisions relating to the care of the patient, including measurement of peak expiratory flow rate (PEFR), assessment of adverse effects, determination of duration of intravenous treatment, interpretation of reported theophylline concentrations, adjustment of theophylline dosage, other bronchodilator treatment, and time of discharge were made by people who were unaware of the patient's trial treatment group.

To maintain the double-blind nature of the trial, it was necessary to conceal the actual theophylline concentration from the clinical team. The nominal target concentration for all patients was 15 mg/L.

**Table I.** Characteristics of patient groups

| Characteristics | High (20 mg/L) | Low (10 mg/L) |
|---|---|---|
| Total in group | 87 | 87 |
| A&E alone | 47% | 45% |
| Hospital admission | 49% | 50% |
| OP follow-up | 41% | 41% |
| Female | 59% | 59% |
| Male | 39% | 39% |
| European | 52% | 62% |
| Polynesian | 26% | 24% |
| Asian | 0% | 1% |
| Unknown | 20% | 12% |
| Average age | 39 years (51% < 40 years) | 37 years (59% < 40 years) |
| Average bodyweight | 66.6kg (recorded in 97%) | 66.6kg (recorded in 97%) |
| Smokers | 22% (average of 21 cigarettes/day) | 18% (average of 27 cigarettes/day) |
| Heart failure | 5% | 5% |
| Asthma | 74% | 80% |
| COPD | 13% | 14% |
| Asthma/COPD | 3% | 1% |
| Pulsus paradoxus | 75% | 71% |
| Mean pulsus | 18mm Hg | 18mm Hg |
| Previous admission | 40% | 50% |
| Time from discharge until follow-up | 9.3 days | 9.5 days |

*Abbreviations:* A&E = Accident and Emergency Department; COPD = chronic obstructive pulmonary disease; OP = outpatient.

The actual target concentration for each patient was known by the laboratory performing the theophylline assays. This was used to scale the theophylline concentration reported to the clinical team. The trial protocol provided the clinical team with the option of choosing a new target concentration if response was inadequate or adverse effects were unacceptable. The double-blind nature of the trial was to be maintained by aiming for a new (nominal) target of 22.5 mg/L if a higher target was sought, or 7.5 mg/L for a lower target.

Theophylline for each patient was obtained from prefilled polypropylene syringes containing either 10 mg/ml or 20 mg/ml theophylline. For the purposes of the trial all intravenous theophylline doses were prescribed in terms of ml of theophylline solution from the prefilled syringes. Dosage calculations were based on a nominal theophylline solution concentration of 15 mg/ml.

At the time of each blood sample for theophylline measurement, the patient's PEFR was determined using an Airmed mini-Wright peak flowmeter. Theophylline was only part of the treatment for severe, acute airways obstruction. The standard treatment suggested for all patients in the trial was (a) initial pretrial treatment with a nebulised β-agonist (usually salbutamol 10mg, sometimes fenoterol 10mg) and intravenous hydrocortisone 400mg; (b) nebulised salbutamol 5mg every 4 hours until 24 hours after oral theophylline was started, then inhaled salbutamol 200μg every 6 hours; (c) intravenous hydrocortisone 200mg every 6 hours until oral theophylline was started then oral prednisone 40 mg/day, reducing by 5 mg/day on alternate days.

The statistical significance of differences between treatment means of continuous variables was assessed using Student's t-test and differences in proportions using Fisher's exact test.

To compare observations at specific times after entry to the trial it was necessary to pool data from a specific time period because observations were not made at exactly the same time in all individuals. The nominal times referred to below reflect the periods preintravenous (from presentation at Auckland Hospital to the start of intravenous theophylline), 1 hour (from 0 to 3 hours after the start of intravenous theophylline), 5 hours (from 3 to 12 hours after the start of intravenous theophylline), 24 hours (from 12 to 36 hours after the start of intravenous theophylline), 48 hours (from 36 to 60 hours after the start of intravenous theophylline), end intravenous (from 12 hours before to 12 hours after the end of intravenous and start of oral theophylline), and discharge (from 24 hours before to 24 hours after discharge from Auckland Hospital).

The significance of differences between groups was assessed by Student's t-test. Statistical power was calculated using the methods provided in Cohen (1988).

## *Results*

### Treatment Group Comparison

174 adult patients were admitted to the trial. The characteristics of each group are shown in table I. 'Unknown' data were those not recorded on the A&E record sheet before record review by the researchers. There were no significant differences between the 2 groups. The theophylline concentration before intravenous treatment was somewhat higher in the High group (7.0 mg/L) than in the Low group (4.3 mg/L). This difference existed before randomisation and must be attributed to chance.

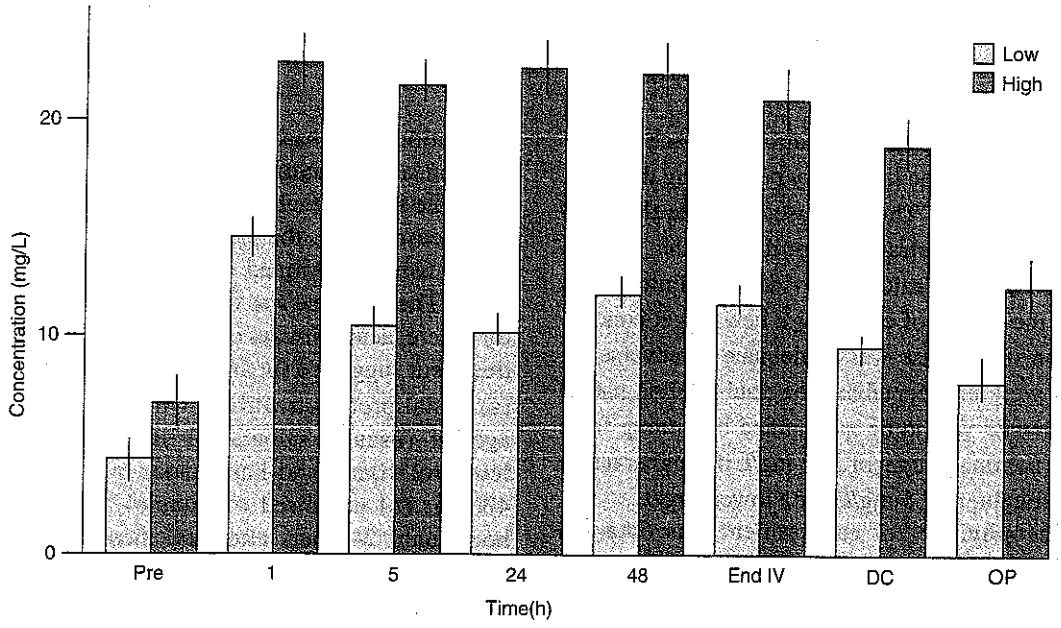


**Fig. 1.** Time course of theophylline concentrations. Low = 10 mg/L target concentration group; High = 20 mg/L target concentration group; Pre = before theophylline administration in the trial; 1, 5, 24, 48 = 1, 5, 24 and 48 hours after entry to the trial, respectively; End IV = at end of intravenous theophylline infusion; DC = at the time of discharge from hospital ward; OP = at the outpatient clinic.

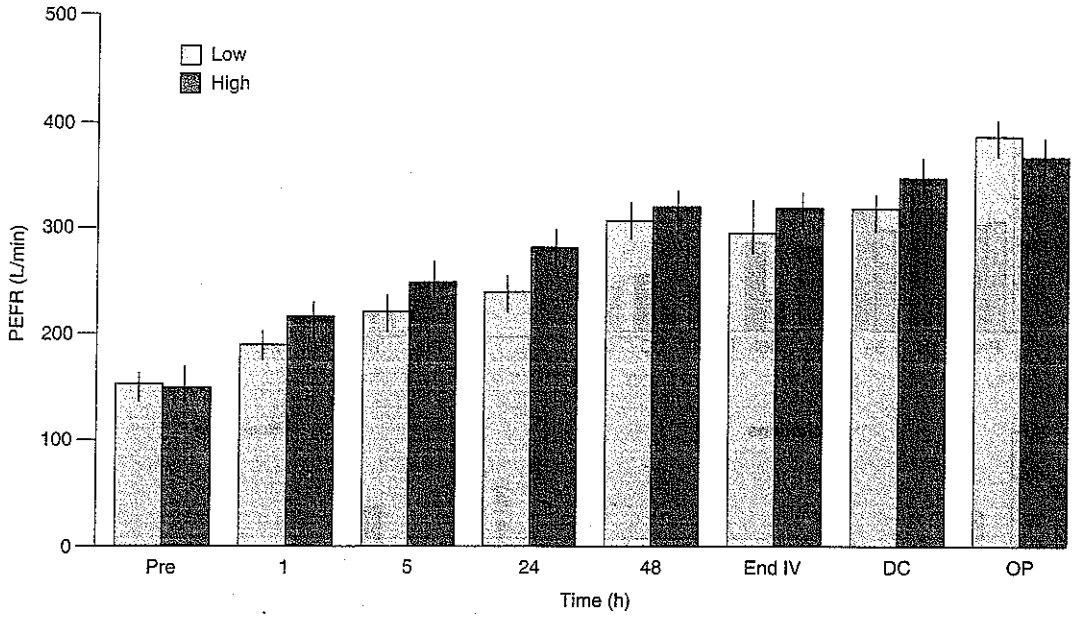


**Fig. 2.** Time course of peak expiratory flow rate (PEFR). Low = 10 mg/L target concentration group; High = 20 mg/L target concentration group; Pre = before theophylline administration in the trial; 1, 5, 24, 48 = 1, 5, 24 and 48 hours after entry to the trial, respectively; End IV = at end of intravenous theophylline infusion; DC = at the time of discharge from hospital ward; OP = at the outpatient clinic.

### Admission Rate to a Hospital Ward

There was no difference between the 2 treatment groups in the proportion who had to be admitted to a hospital ward (High 49%, Low 50%).

### Achievement of Target Concentrations

Figure 1 illustrates the mean (± SE) serum theophylline concentration at different points during the course of treatment of those admitted to hospital who completed all stages of the trial and were eventually followed up at the outpatient clinic. There were 30 such patients in the Low group and 32 in the High group.

### Influence of Theophylline Concentrations on Time Course of Treatment Response in Patients Admitted to Hospital

The time course of increase in PEFR from the start of intravenous theophylline treatment in the same patients shown in figure 1 is shown in figure 2. The greatest between-group difference in PEFR occurred 24 hours after starting intravenous theophylline. There was no significant difference in PEFR at any time. A difference of 67 L/min (25% of the mean PEFR) could have been detected with a power of 80% at $p = 0.05$ (Cohen 1988). This magnitude of difference is not thought to be of clinical significance. The time course of the incidence of 4 adverse effects from all patients in the trial is shown in figure 3.

### Duration of Intravenous Treatment in Patients Admitted to Hospital

The mean (± SEM) total time that intravenous infusion of theophylline was maintained was shorter in the High group ($1.6 \pm 0.02$ *vs* $2.1 \pm 0.04$ days in the Low group). The time from entry to the trial to the end of the final intravenous infusion was also shorter ($1.8 \pm 0.02$ days in the High group *vs* $2.3 \pm 0.04$ days in the Low; note that this excludes periods before the ultimate end of intravenous treatment when the infusion was interrupted for a

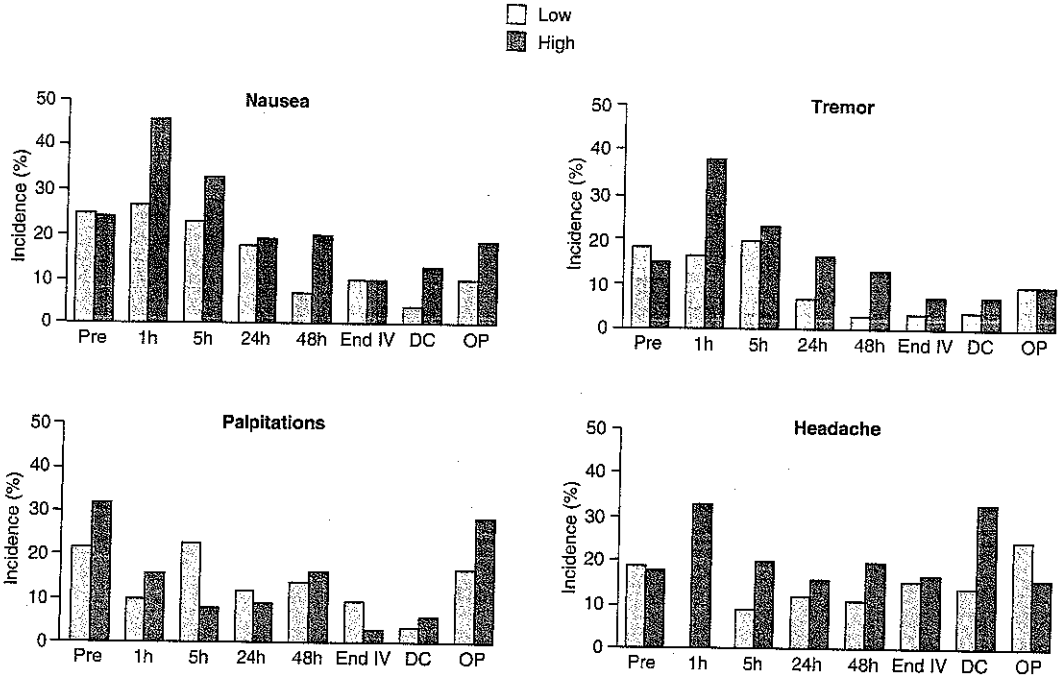


**Fig. 3.** Time course of the incidence of selected adverse effects. Low = 10 mg/L target concentration group; High = 20 mg/L target concentration group; Pre = before theophylline administration in the trial; 1h, 5h, 24h, 48h = 1, 5, 24 and 48 hours after entry to the trial, respectively; End IV = at end of intravenous theophylline infusion; DC = at the time of discharge from hospital ward; OP = at the outpatient clinic.

variety of reasons). These differences are statistically significant ($p < 0.05$).

### Duration of Hospital Admission

The time spent in hospital was determined from the onset of intravenous theophylline treatment until the time of discharge. There was no significant difference between the High and Low groups (5.9 ± 0.54 *vs* 6.1 ± 0.46 hours, respectively) for those discharged from the A&E Department. A difference of 1.8 hours would have led to rejection of the null hypothesis with a power of 80% at $p = 0.05$. For those patients admitted to a hospital ward there was no significant difference in duration of hospitalisation between the High and Low groups (4.5 ± 0.22 *vs* 4.7 ± 0.27 days, respectively). A difference of 0.9 days would have led to rejection of the null hypothesis with a power of 80% at $p = 0.05$.

### Patients' Assessment of Health at Hospital Discharge versus Outpatient Follow-Up

Most patients claimed they felt better at the time of outpatient review than when they left hospital (High 67%, Low 74%). Some felt they were unchanged (High 20%, Low 12%) and a small number felt worse (High 2%, Low 9%).

### Serious Adverse Effects and Withdrawals

Brief details of each of the patients withdrawn from the trial are presented in table II. In the High group, 21 of 87 patients (24%) withdrew. In the Low group, 29 of 87 patients (33%) withdrew. Figure 4 illustrates the phase of the trial at which withdrawals were made.

There was a significantly higher incidence of vomiting in patients in the High target group (12%, or 11 out of 87) than in the Low group (3%, or 2 of 87 patients) [$p < 0.05$]. Vomiting led to withdrawal

from the trial for 5 of the 11 patients in the High group but for neither patient in the Low group. The mean theophylline concentration at the time of vomiting was 23.4 mg/L (High) and 22.9 mg/L (Low). The concentrations for these 2 patients in the Low group were more than twice the target for this group. This reflects the occasional difficulties in predicting the required dose.

Assignment to a New Target Concentration

Because the trial was blinded, the clinicians aimed for an initial target concentration of 15 mg/L. They could move up or down to a new target as they chose, independent of the actual treatment group. No patient was assigned to a higher target concentration. One patient in the Low group with symptoms of anxiety and nausea was assigned to a lower target concentration. Five patients in the High group experiencing vomiting (2), nausea (2) and insomnia (1) were assigned to a lower target of 7.5 mg/L.

## *Discussion*

The relationship between theophylline concentration and its acute bronchodilator action has been frequently discussed but less often studied. The issue was reviewed by Fairshter and Busse (1986), who concluded that concentrations <10 mg/L may produce substantial effects. Like Holford and Sheiner (1981) they rely upon the work of Mitenko and Ogilvie (1973) to describe the pharmacodynamics of theophylline in patients with asthma. However, the scaling of results to the greatest observed value, rather than to the potentially greater maximum if higher concentrations had been studied, led them to conclude that 50% of the bronchodilator effect of theophylline can be expected at 5 mg/L in contrast to the value of 10 mg/L or greater estimated by Holford and Sheiner (1981) and Holford et al. (1992).

The higher target concentration in our study was associated with a 12 hours shorter duration of intravenous treatment with theophylline. This is much less than the 54 hours shorter treatment in patients treated with similar high and low target concentrations reported by Vožeh et al. (1982). It should be noted that the duration of intravenous treatment was similar in Vožeh's high target group (62 hours) to that in the low target group in our study (58 hours). No explicit criteria for stopping intravenous treatment were defined in our study. This was simply left to the clinical team to decide on whatever grounds they felt were appropriate.

Perhaps the most important measures of outcome in this trial are the need for hospital admission and the duration of hospital stay. The lack of any effect on these variables would argue against any tangible benefit from the higher target concentration of 20 mg/L.

Treatment with theophylline using a target concentration of 20 mg/L was associated with a higher incidence of nausea, vomiting and headache. These are well recognised adverse effects of theophylline and were concentration-dependent. The mean theophylline concentration at the time of vomiting was 23 mg/L irrespective of assignment to the high or low target concentration.

The occurrence of supraventricular arrhythmias during treatment with theophylline has been studied by Levine et al. (1985). They were able to correlate the frequency of atrial ectopic beats with theophylline concentrations in older patients who had sustained an episode of multifocal atrial tachycardia during theophylline treatment. Two patients in our study developed a supraventricular tachycardia (at 7.6 and 18.2 mg/L).

Another patient had atrial flutter at 5 mg/L. In this case, electrical cardioversion was unsuccessfully attempted after theophylline was stopped, suggesting the arrhythmia was not caused by theophylline. Four other patients were withdrawn from the study because of palpitations when they had a mean concentration of 21 mg/L. In contrast to those with electrocardiographic (ECG) evidence of an arrhythmia (mean age 69 years) these patients were younger (mean age 30 years).

The findings of no clinical benefit and a higher incidence of severe adverse effects in patients treated with a theophylline target concentration of 20 mg/L are in marked contrast to those reported

**Table II.** Characteristics of patients withdrawing from the trial

| Sex | Race | Age | Study phase | Reason for withdrawal |
|---|---|---|---|---|
| **High target group** | | | | |
| F | E | 18 | A&E | Vomiting |
| M | E | 34 | A&E | Transferred to ICU |
| F | E | 77 | A&E | Study protocol not followed |
| F | E | 18 | A&E | Not airways obstruction |
| F | E | 32 | A&E | Tachycardia, palpitations |
| M | P | 52 | A&E | Unable to understand English properly |
| ? | ? | ? | A&E | Not recorded |
| F | E | 68 | IP | Vomiting |
| F | E | 86 | IP | Vomiting |
| M | E | 63 | IP | Given wrong intravenous theophylline solution |
| F | E | 81 | IP | Not recorded |
| M | E | 76 | IP | Supraventricular tachycardia |
| F | E | 75 | IP | Right-sided focal convulsion |
| F | E | 22 | OP | Palpitations, tremor, insomnia |
| F | E | 18 | OP | Not given tablets for outpatient use |
| M | P | 52 | OP | Failed to attend outpatient clinic |
| M | E | 75 | OP | Unable to attend outpatient clinic |
| F | P | 35 | OP | Palpitations, dizzy, headache |
| M | E | 21 | FU | Did not take tablets as outpatient |
| M | E | 43 | FU | Not given tablets for outpatient use |
| F | E | 65 | FU | Not given tablets for outpatient use |
| **Low target group** | | | | |
| M | E | 30 | A&E | Nausea, tremor, palpitations |
| F | P | 25 | A&E | Transferred to ICU |
| F | P | 23 | A&E | Inadequate response to treatment |
| M | A | 35 | A&E | Transferred to ICU |
| M | E | 35 | A&E | Transferred to ICU |
| F | E | 32 | A&E | Transferred to another hospital |
| M | P | 56 | A&E | Unable to understand English properly |
| F | ? | ? | A&E | Inadequate response to treatment |
| ? | ? | 12 | A&E | Too young |
| M | P | 56 | A&E | Study protocol not followed |
| F | E | 8 | IP | Given wrong intravenous theophylline solution |
| M | E | 73 | IP | Developed pulmonary oedema |
| M | E | 68 | IP | Atrial flutter |
| F | P | 46 | IP | Transferred to another hospital |
| F | E | 26 | IP | Did not wish to stay in the trial |
| M | P | 55 | IP | Inadequate response to treatment |
| M | E | 63 | IP | Supraventricular tachycardia |

**Table II.** Contd

| Sex | Race | Age | Study phase | Reason for withdrawal |
|---|---|---|---|---|
| F | E | 50 | IP | Did not need theophylline |
| F | E | 19 | OP | Failed to attend outpatient clinic |
| M | E | 19 | OP | Failed to attend outpatient clinic |
| F | E | ? | OP | Unable to attend outpatient clinic |
| M | E | 21 | OP | Stopped because of adverse effects |
| M | E | 72 | OP | Unable to attend outpatient clinic |
| F | P | 46 | OP | Unable to attend outpatient clinic |
| M | E | 69 | OP | Failed to attend outpatient clinic |
| F | E | 21 | FU | Stopped because of adverse effects |
| F | E | 76 | FU | Would not wait to see doctor at clinic |
| F | E | 16 | FU | Not given tablets for outpatient use |
| F | E | 30 | FU | Insomnia, anxiety, tremor |

*Abbreviations and symbol:* A = Asians; A&E = Accident and Emergency Department; E = European/Caucasian; F = female; FU = follow-upat outpatient clinic; ICU = intensive care unit; IP = inpatient; M = male; OP = outpatient before clinic visit; P = Maori/Polynesian; ? = not recorded.

by Vožeh et al. (1982). Their population was older than that in our study (mean age 68 years *vs* 38 years, respectively), predominantly male (90% *vs* 37%, respectively) and only 25% had extrinsic asthma, whereas 77% of our patients were diagnosed as having asthma. Furthermore, Vožeh's low target group was unusual in that no measurable improvement in pulmonary function was detectable even 28 hours after the start of treatment. Apart from the differences in population characteristics, the treatment for airways obstruction, other than theophylline, involved lower doses of β-agonist bronchodilators and intravenous steroids (Follath F, personal communication). It should also be noted that control of theophylline concentration was more rigorous, which could account for the apparent benefit of 20 mg/L (Holford et al. 1993).

The basic treatment regimen used in Auckland was determined by consensus of the physicians participating in the trial. At the time, we believed the doses of β-agonist and steroids were at the higher end of those commonly used to treat asthma. Littenberg and Gluck (1986) reported that hospital admission rates were halved in patients with asthma given intravenous methylprednisolone 125mg. This is approximately equivalent to a 3-fold higher dose of hydrocortisone than was given in our trial prior to intravenous theophylline. Our hospital admission rate (49%) was very similar to that of Littenberg's and Gluck's patients who did not receive intravenous methylprednisolone (47%).

This trial was deliberately designed without a placebo group because the use of intravenous theophylline in patients with severe airways obstruction was considered standard treatment. The lack of any convincing clinical benefit when a target concentration of 20 mg/L was compared with 10 mg/L raises the question of how much benefit can be attributed to theophylline at 10 to 20 mg/L compared with no theophylline at all. After a 3-hour follow-up in patients receiving standard bronchodilator therapy, Siegel et al. (1985) detected no difference in improvement in forced expiratory volume in 1 second ($FEV_1$) in patients also receiving intravenous theophylline.

A longer term placebo-controlled comparison of theophylline has been reported by Coleridge et al. (1993). Although the authors claim no benefit from theophylline, the peak flow in their patients was consistently higher in the theophylline-treated group, with diminishing benefit as time passed.

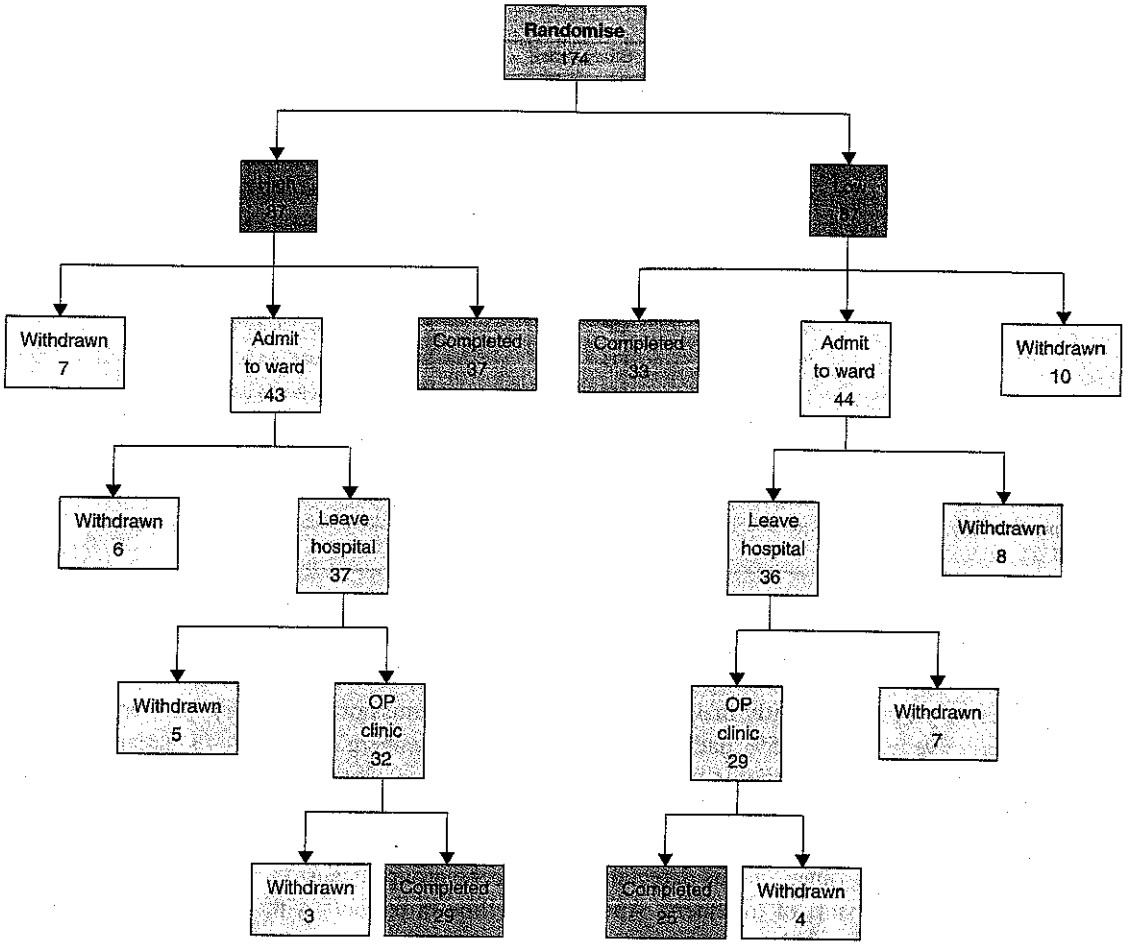


**Fig. 4.** Flow diagram showing the fate of patients who entered the trial. OP = outpatient clinic follow-up.

This is compatible with the observations in our trial and the predictions of a model based on measured theophylline concentrations (Holford et al. 1993).

Rice et al. (1987) compared the effect of theophylline with placebo over a 3-day period after admission for acute chronic obstructive pulmonary disease. Patients with asthma were deliberately excluded. No therapeutic benefit of theophylline was detected with mean concentrations over the 3 days ranging from 8 to 14 mg/L. However, when the observations in the Auckland trial were analysed on the basis of theophylline concentrations that were actually achieved rather than the intended target concentration, a clear concentration-related effect on PEFR was demonstrable (Holford et al. 1993).

Because some of the beneficial effects associated with treatment of acute airways obstruction may be delayed (Holford et al. 1993; Vožeh et al. 1982) it is not possible to conclude from the short term study of Siegel et al. (1985) that theophylline is of no value in the management of severe, acute asthma. It may be particularly important to pay attention to end-points that are valuable to the patient (e.g. prevention of admission or shorter hospital stay) rather than convenient measures of pulmo-

nary function. Wrenn et al. (1991) claimed a 3-fold reduction in hospital admission rate in patients achieving an average theophylline concentration of 9.7 mg/L compared with placebo. The value of oral theophylline for the treatment of asthma between exacerbations and chronic obstructive pulmonary disease is somewhat less controversial, although the demonstration of benefits apart from improved expiratory flow rates are few (Murciano et al. 1989; Tinkelman et al. 1985).

We have been able to detect small differences in clinical benefit in patients treated prospectively under double-blind conditions with target theophylline concentrations of 20 or 10 mg/L. These benefits are outweighed by the higher incidence of minor adverse effects, especially nausea and headache, and more severe adverse effects, such as vomiting. We conclude that the initial target concentration for theophylline in the management of acute airways obstruction is 10 mg/L, but that additional benefit may be obtained with carefully controlled higher concentrations.

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