

Effect of oral theophylline on resting energy expenditure in normal volunteers

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Abstract

Background - The aim of this study was to investigate the contribution of regular treatment with oral theophylline to the increase in resting oxygen consumption observed in patients with chronic airflow limitation who are receiving bronchodilator therapy.

Methods - Resting oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured in 10 normal subjects (six men, age 21-48 years, weight 50-85 kg) before and after 11 days of treatment with either placebo or theophylline in a double blind manner, in twice daily oral doses ensuring trough serum concentrations between 8.4 and 13.5 mg/l. An open canopy method was used to measure $\dot{V}O_2$ and $\dot{V}CO_2$ and in all test conditions this was extended for 60 minutes after an inhalation of 800 μ g of salbutamol superimposed on the background placebo or theophylline treatment.

Results - Resting $\dot{V}O_2$ and heart rate were increased during theophylline treatment compared with placebo by 6.5% and 8.4% respectively. Salbutamol inhalation transiently increased $\dot{V}O_2$, $\dot{V}CO_2$, and heart rate in all tests but this was not modified by background theophylline treatment.

Conclusion - Oral theophylline treatment causes a sustained increase in resting oxygen consumption and heart rate but does not modify the metabolic response to acutely inhaled salbutamol.

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There is evidence that resting oxygen consumption in normally nourished patients with chronic airflow limitation is raised by about 10% above normal.¹ This increase may be attributed to the features of the disease, including an increase in respiratory muscle work, the bronchodilator treatment, or a combination of the two.

A recent study on normal volunteers in our laboratory has shown that oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) are increased by acute therapeutic doses of inhaled salbutamol.² This acute metabolic effect of salbutamol was, however, abolished by regular administration,³ suggesting that chronic salbutamol treatment may not contribute to the increased $\dot{V}O_2$ and $\dot{V}CO_2$ observed in patients with chronic airflow limitation.

The effects of therapeutic doses of theophylline, another commonly prescribed bronchodilator, on resting energy expenditure have

not been studied in adult humans. We therefore studied the effects of theophylline on resting $\dot{V}O_2$ and $\dot{V}CO_2$ in normal volunteers. The response to a superimposed acute inhalation of salbutamol was also tested.

Methods

Ten healthy, non-smoking volunteers (six men, aged 21-48 years and weighing 50-85 kg) were studied. The body mass index ranged between 18.2 and 32.2 and these two extreme values were observed in two of the female subjects; in the remaining eight subjects body mass index was between 21.5 and 26.7. Each volunteer was fasted for at least eight hours before each test and abstained from caffeine and chocolate throughout the study. Prior to the study all subjects were regular but moderate coffee and tea drinkers (2-5 cups per day). Informed consent and local ethics committee approval was obtained.

Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured by indirect calorimetry using an open canopy technique with a mass spectrometer, described in detail elsewhere.² Briefly, a plastic hood was placed over the subject's head providing a constant flow of air by a fan distal to a mixing box at a flow rate of 95-110 l/min. The apparatus was calibrated daily at two points using 100% nitrogen and a precisely known gas mixture (argon 2.12%, oxygen 15.45%, carbon dioxide 1.05%, and nitrogen 81.38%). Throughout the study room temperature ranged between 17.9°C and 24°C (median 20.3°C), barometric pressure between 749 and 775 mm Hg (median 763 mm Hg), and ambient humidity between 23% and 54% (median 36.5%). All measurements were made at room temperature and pressure. Corrections of gas volumes to standard temperature and barometric pressure dry were not carried out because the maximum changes obtained with the corrections were well below the 3% resolution of the method to determine $\dot{V}O_2$ and $\dot{V}CO_2$.

The whole system was tested by burning methanol at a known rate through a specially designed burner ensuring complete combustion. Measured values for $\dot{V}O_2$ and $\dot{V}CO_2$ were compared with predicted values calculated from the combustion equation for methanol and a correction factor derived daily. This factor was applied to the results of the day if they exceeded 2% of the predicted values. Although the system was capable of measuring $\dot{V}O_2$ and $\dot{V}CO_2$ every five seconds, all records in this study consisted of averages of 10 consecutive values printed every two minutes.

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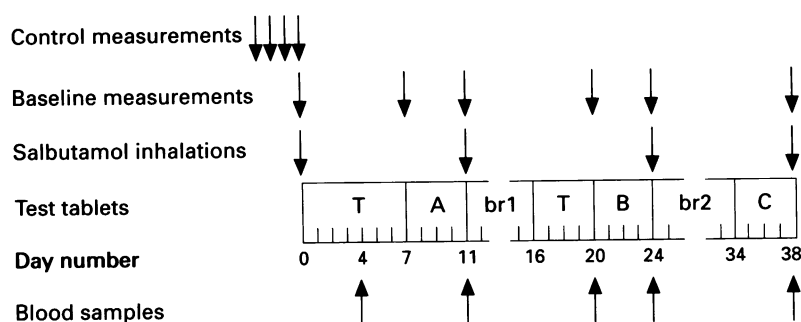


Figure 1 Experimental design for the administration of theophylline or placebo tablets and for the timing of salbutamol inhalations and calorimetric measurements (control and baseline, as defined in text) in 10 subjects. The numbering of the days after the tablet-free periods has been standardised as if all the first breaks (br1) were five days and the second breaks (br2) were 10 days, for simplicity of the diagram. T = known theophylline tablets; A = test tablet A (placebo or theophylline); B = test tablet B (reverse of A in the same subject); C = test tablet C (always placebo, only known to experimenter). There were two tablet-free periods, the first 5–10 days and the second 10–20 days.

All subjects were studied following a 30 minute period of rest with the subject reclining on a comfortable couch listening to light, instrumental music. Subjects were lightly dressed and, depending on the room temperature, made use of a cotton blanket covering part or the whole body (except the head) in order to achieve thermal comfort. $\dot{V}O_2$ and $\dot{V}CO_2$ were measured on at least four occasions before the start of the trial (whilst abstaining from caffeine) to establish control values and the within subject variability. In the last of these measurements a control acute response to 800 μ g salbutamol was also recorded. Throughout the study the term “control” applies to all measurements including responses to salbutamol taken during a tablet-free period. The term “baseline” refers to measurements taken immediately before an inhalation of salbutamol or at the transition between test tablets (fig 1). Following the initial control measurements subjects were knowingly given theophylline before each test period for three reasons: firstly, to allow acclimatisation to the side effects of theophylline; secondly, to establish the dose of theophylline required in each subject to achieve therapeutic plasma levels; and thirdly, to blunt the ability of subjects to distinguish placebo from drug, a method successfully used in previous volunteer studies using theophylline.⁴ Because of the side effects of theophylline, subjects are usually able to distinguish between placebo and drug unless they are exposed to an acclimatisation period in advance of the test. This initial theophylline period lasted seven days taking 200 mg or 300 mg tablets, twice daily, starting with a dose based on height, weight and sex to give therapeutic serum levels of 8–20 mg/l. Venous blood samples were taken on day 4 to ascertain whether trough serum levels were within the required therapeutic range, thus providing a guide to adjust further doses (if necessary) to attain the desired level by day 7 when serum levels were again measured. On day 8 subjects started taking test tablet A (theophylline or placebo 1) for a further four days. A tablet-free period of 5–10 days was then intercalated, followed by a further four days of “known” theophylline at the same dose as that which had previously produced

therapeutic levels, after which tablet B (theophylline or placebo 1, depending on what A had been) was given for four days. This second four-day “known” theophylline period was shorter because the appropriate individual dose to achieve therapeutic levels had been determined in the first seven day period. There was then another tablet-free period of 10–20 days after which tablet C, which was always placebo (placebo 2) was taken for four days. The minimum duration of this second tablet-free period was made twice as long as the first because of our early suspicion that there might be a residual effect of theophylline four days after discontinuation.

There were thus two independent four-day placebo periods, one “double blind” period (placebo 1) and a second “single blind” period (placebo 2) at the end of each study. For the purpose of numbering the days of the experiments the first (5–10 days) and the second (10–20 days) tablet-free periods are standardised to 5 and 10 days respectively for all subjects (fig 1).

Test tablets were stopped after the evening dose in the day preceding, and at least 10 hours before, any $\dot{V}O_2/\dot{V}CO_2$ measurement. The random allocation of theophylline and placebo 1 to tablets A and B was made in the hospital pharmacy and the code was only broken at the end of each study. Both subjects and experimenters were blinded to the nature of all tablets except tablet C which only two experimenters knew to be always placebo. Figure 1 depicts the sequence of tests and interventions.

$\dot{V}O_2$, $\dot{V}CO_2$, and heart rate (obtained from a “Datascop” ECG monitor connected to shoulder and precordial electrodes) were always measured first thing in the morning, between 08.00 and 09.00 hours, 10–12 hours after the last dosing. In addition to the control measurements taken before and on day 0, a further five measurements were taken at the end of each tablet period on days 7, 11, 20, 24, and 38. On days 0, 11, 24, and 38 each set of measurements started by recording baseline $\dot{V}O_2$ and $\dot{V}CO_2$ values and then recording $\dot{V}O_2$ and $\dot{V}CO_2$ at 5, 15, 30, and 60 minutes after the inhalation of 800 μ g salbutamol (eight puffs, through a spacing device). The number and the timing of the post-inhalation data points were chosen based on our previous experience of the minimum points necessary to accurately define an acute response to salbutamol. Venous blood samples for measurement of trough serum theophylline levels were obtained in the morning of day 4 and of days 11, 20, 24, and 38, at the end of each period taking tablets A, B and C. Side effects to both theophylline and salbutamol were noted at the time of indirect calorimetry.

ANALYSIS OF DATA

All subjects acted as their own controls. $\dot{V}O_2$ and $\dot{V}CO_2$ are expressed as mean (SE) values in ml/min/kg and comparisons made using Student’s paired *t* test since previous similar data appeared normally distributed.² Respiratory ex-

Table 1 Mean (SE) resting baseline oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) in ml/kg/min, respiratory exchange ratio (R), and heart rate (HR, beats/min) in 10 subjects taken before the test (control), at the end of 11 days of treatment with theophylline (T), and at the end of two four-day placebo periods (P1 and P2). Paired comparisons between the various groups were made using the Student's paired *t* test.

	$\dot{V}O_2$	$\dot{V}CO_2$	R	HR
Control (C)	3.43 (0.11)	2.69 (0.08)	0.785 (0.007)	60.6 (2.96)
Placebo 1 (P1)	3.52 (0.12)	2.72 (0.11)	0.772 (0.02)	57.1 (2.88)
Placebo 2 (P2)	3.45 (0.11)	2.70 (0.11)	0.783 (0.02)	58.0 (3.08)
Theophylline (T)	3.75 (0.15)	2.85 (0.16)	0.756 (0.02)	61.9 (2.96)
p (T v C)	<0.01	NS	NS	NS
p (T v P1)	<0.05	NS	NS	<0.01
p (C v P1/v P2)	NS	NS	NS	NS

NS = not significant

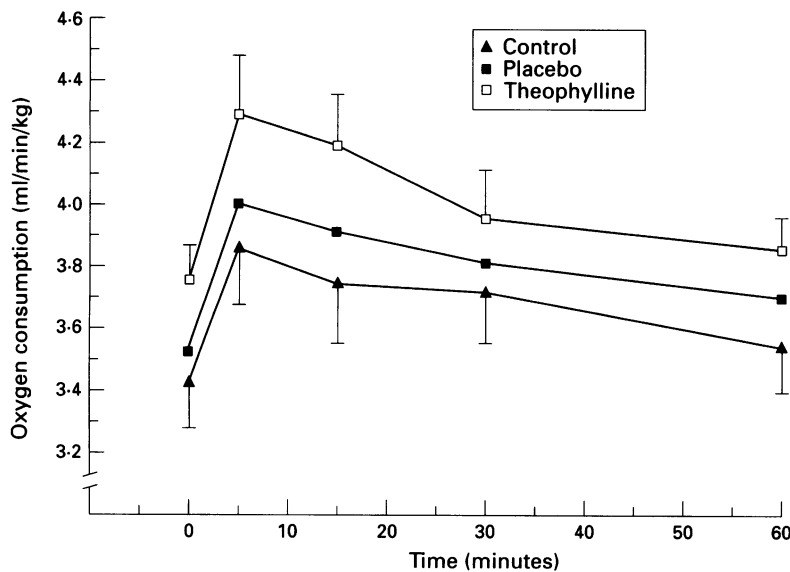


Figure 2 Time course of the changes in mean $\dot{V}O_2$ after the acute inhalation of 800 μ g salbutamol under three test conditions: control (before any tablets were taken), during treatment with placebo tablets, and during theophylline treatment. The order of the treatment with placebo or theophylline tablets was unknown to the subjects. Bars = SE.

change ratio *R* was calculated for all sets of values by dividing $\dot{V}CO_2$ by $\dot{V}O_2$, and the heart rate was measured and averaged over a period of 1–2 minutes during baseline $\dot{V}O_2$ measurements; following inhalation of salbutamol the highest one minute average value of heart rate was recorded.

Paired comparisons of mean $\dot{V}O_2$, $\dot{V}CO_2$, *R*, and heart rate were made between pretest control baseline values and baseline values obtained at the end of each of the three treatment periods (theophylline, placebo 1, and placebo 2). Similar paired comparisons were made between baseline values at the end of placebo 1 and theophylline treatments and between control and placebo 1 and placebo 2 periods.

For the salbutamol tests the preinhalation baseline $\dot{V}O_2$, $\dot{V}CO_2$, *R*, and heart rate values were subtracted from each $\dot{V}O_2$, $\dot{V}CO_2$, *R*, and heart rate value obtained at 5, 15, 30, and 60 minutes after inhalation; curves were thus obtained by drawing straight lines between each time point (as illustrated in fig 2) and the areas under these curves calculated over the 60 minute period. Previous experience showed that the four chosen time points are sufficient to define the response curve to salbutamol.² Paired comparisons were then made between the single "area under the curve" values ob-

tained in control measurements and those obtained at the end of each tablet period and between theophylline and placebo 1 periods.

Results

The range of theophylline dosage required to attain sustained therapeutic levels in all subjects was 400–800 mg/day. At the time of $\dot{V}O_2$ measurements all subjects had serum trough levels within the range 8.4–13.5 mg/l.

BASELINE MEASUREMENTS

There were significant increases in mean resting $\dot{V}O_2$ during theophylline administration, by 6.5% when compared with placebo 1 and by 9% when compared with control. The mean $\dot{V}CO_2$ during theophylline administration was also 5% higher than placebo 1 and 6% higher than control, but these values did not reach significance at the 5% level. Table 1 summarises these results, including values for respiratory exchange ratio (*R*) and heart rate during control, placebo 1, placebo 2, and theophylline periods. Values for placebo 2 were almost identical to the control values and did not significantly differ from placebo 1; thus, there was no difference between a minimum of five and a minimum of 10 days discontinuation of theophylline treatment. During theophylline treatment heart rate was 8.4% higher than during placebo 1 but did not differ significantly from the control value. Respiratory exchange ratio did not differ between any of the test conditions.

Measurements taken at days 7 and 20 (fig 1) at the end of the "known" theophylline administration periods (mean (SE) $\dot{V}O_2$ 3.73 (0.16) ml/kg/min) did not differ in any respect from those obtained during the periods of "unknown" theophylline at days 11 and 24 (mean (SE) $\dot{V}O_2$ 3.75 (0.15) ml/kg/min). Thus, continuing the administration of theophylline for a further four days did not change the baseline $\dot{V}O_2$, $\dot{V}CO_2$, *R*, and heart rate values.

RESPONSES TO SALBUTAMOL

Inhalation of 800 μ g salbutamol transiently increased $\dot{V}O_2$, $\dot{V}CO_2$, and heart rate in all subjects. This was maximal at five minutes and was maintained for up to 60 minutes. Respiratory exchange ratio did not change. Figure 2 illustrates the pattern of this response for $\dot{V}O_2$. The acute response to superimposed salbutamol, integrated over 60 minutes after inhalation, was similar between the theophylline period and the placebo 1 period with regard to $\dot{V}O_2$, $\dot{V}CO_2$, heart rate, and respiratory exchange ratio, despite the higher starting baseline values during theophylline. The effect of salbutamol was simply additive for $\dot{V}O_2$, $\dot{V}CO_2$, and heart rate. The only significant differences found were in the heart rate responses to salbutamol inhalation when comparing theophylline or placebo 1 treatments with the control response. These data are summarised in table 2 which shows values of the areas under the 60 minute curves departing from baseline values, and not absolute values of the respective variables.

Table 2 Mean (SE) values for the differences between baseline measurements of oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and heart rate (HR), and measurements taken over one hour after inhalation of 800 μ g salbutamol at the end of each of three test periods: control (C), placebo (P), and theophylline (T). The baseline values obtained before the inhalations were subtracted from each value obtained at 5, 15, 30, and 60 minutes. These differences from baseline were integrated over the 60 minute period following inhalation and expressed in ml/kg/min for $\dot{V}O_2/\dot{V}CO_2$, and in beats/min for HR. Thus, only the departures from the baseline values are compared between the control, placebo, and theophylline groups.

	$\dot{V}O_2$	$\dot{V}CO_2$	HR
Control	+0.25 (0.08)	+0.09 (0.05)	+ 7.4 (2.4)
Placebo	+0.30 (0.07)	+0.16 (0.05)	+12.3 (2.4)
Theophylline	+0.26 (0.06)	+0.18 (0.08)	+13.9 (3.4)
p (T v C)	NS	NS	<0.01
p (T v P)	NS	NS	NS
p (C v P)	NS	NS	<0.05

NS = not significant

SIDE EFFECTS OF THEOPHYLLINE

Theophylline caused gastrointestinal side effects in most subjects, including mild abdominal discomfort, nausea and diarrhoea, as well as palpitations and insomnia. These effects did not correlate with the serum levels of theophylline and resolved after 2–3 days of theophylline “known” administration in all subjects before starting tablets A or B. Salbutamol produced palpitations and a slight perceived tremor in two of the subjects for the first five minutes following inhalation during the theophylline treatment period only.

Discussion

The increase in $\dot{V}O_2$ associated with theophylline administration in this study may contribute to the previously reported approximately 10% increase noted in patients with chronic airflow limitation.¹

The longest period of continuous theophylline treatment was 11 days (see fig 1) and it was clear that the thermogenic effects of theophylline were present on days 7 and 20 of “known” theophylline and were maintained on days 11 and 24, suggesting that the effect is established by the fourth day without changing up to 11 days of administration. We did not see evidence of accommodation of the response within the period of time tested. Since we did not obtain daily calorimetry measurements during the onset of theophylline treatment we could not define precisely the point at which the effect was established and whether there might be some accommodation within the first four days of treatment. These findings, however, contrast with our previous, similar study on regular salbutamol treatment which showed a clear accommodation of the response to acute inhalation and a lack of a sustained thermogenic effect after 10 days of regular administration.³ Our results do not however rule out a downregulation of the thermogenic effect of theophylline over the first four days of treatment or over a longer period of time (>11 days).

Our present study did not address the question as to whether background theophylline treatment might prevent the downregulation of the thermogenic response to chronic salbutamol administration observed in our earlier study,³ but it was interesting that the acute inhalation of salbutamol, superimposed on the theophylline background, had a merely additive

effect on $\dot{V}O_2$, $\dot{V}CO_2$, and heart rate. A potentiation of the effects of salbutamol by theophylline might be expected in this experiment if theophylline exerted its action by inhibition of intracellular phosphodiesterase activity, thus modulating the β effect of salbutamol in a multiplicative way. There is evidence, however, that plasma therapeutic concentrations of theophylline are not sufficient to produce tissue concentrations of the order required to inhibit phosphodiesterases;⁵ antagonism of adenosine, which mediates at least part of the cardiac effects of theophylline,⁵ is a more likely mechanism for the observed effects in our experiment. Inhibition of extraneuronal inactivation of the catecholamines may also have played a part in the thermogenic effect of theophylline.⁶ In this context it is worth noting that previous authors have reported doubling of the thermogenic effects of ephedrine by methylxanthines⁷ in normal adults and long term maintenance of the thermogenic efficacy of caffeine/ephedrine mixtures.⁸

It is of interest to note that there might have been a placebo effect in the heart rate response to salbutamol because it was significantly potentiated during both test periods (theophylline and placebo 1) compared with the control response. We cannot offer a plausible explanation for this apparent dissociation between thermogenic and cardiac effects of theophylline unless we postulate a much longer effect of theophylline on cardiac tissue compared with other tissues contributing to the increase in $\dot{V}O_2$, for which there is no evidence.

The combined thermogenic effect of the two drugs, when 800 μ g salbutamol is given acutely, is considerable: a 25% increase in $\dot{V}O_2$ and a 27% increase in $\dot{V}CO_2$ above control baseline at 5–15 minutes after inhalation of salbutamol. This increase may be clinically important, especially if larger amounts of salbutamol are given by nebuliser. In this context it should be noted that the recommended maximum dose of nebulised salbutamol in the guidelines for the management of severe acute asthma in adults issued by the British Thoracic Society is 5 mg.

During the initial analysis of our data we suspected that there might be some residual effect of theophylline on $\dot{V}O_2$ four days after stopping treatment, at the end of a placebo period (tablet A or B). An additional test period was therefore added to our protocol after a resting gap of 10–20 days following the A/B test. This additional test provided useful data and we can now rule out an important, residual thermogenic effect of theophylline four days after stopping treatment. The present results also suggest that the thermogenic effects of theophylline are established within four days of starting treatment, but a separate study is needed to elucidate the precise time course of this effect.

The cause of the sustained increased whole body oxygen consumption with theophylline observed in this study is unclear. The associated increase in heart rate may have been either an effect of, or a contributing factor to, this increased metabolic rate. Our subjects were

always studied under resting conditions so it is unlikely that increased physical activity was a factor underlying the increased oxygen consumption during theophylline treatment. In two of our subjects, however, muscle tremor might have contributed to the increase in $\dot{V}O_2$ and $\dot{V}CO_2$ after salbutamol, but we believe that this had a negligible effect on the overall result since it was observed for the first five minutes after inhalation only during the theophylline treatment. The metabolic effects of theophylline were quite clear in our study, despite all our subjects being regular (but moderate) caffeine users. The body mass index of eight of our 10 subjects was within very narrow limits (21.5–26.7) except for two female subjects where the body mass index was 18.2 and 32.2; we have taken the precaution of repeating the comparisons of tables 1 and 2 having removed the values of these two subjects but this did not alter the mean values or change the significance of any of the results.

In premature infants aminophylline has been shown to increase oxygen consumption by about 20% and this was accompanied by increases in minute ventilation and in the central responsiveness to carbon dioxide⁹; although not supported by evidence, the authors attributed this metabolic increase to parallel increases in heart rate and in central nervous system activity. Studies in adult rats have also shown a sustained increase in metabolic rate of approximately 20% with aminophylline, but this was almost certainly due to an increase in physical activity associated with the treatment.¹⁰ In adult humans 100 mg of oral caffeine has been shown to cause an increase in resting metabolic rate¹¹ of about 4% above control. None of the human studies, however, offers evidence as to the cause of the increased meta-

bolism associated with treatment with methylxanthines.

In conclusion, theophylline may significantly contribute to the observed increase in $\dot{V}O_2$ and $\dot{V}CO_2$ in patients with chronic airflow limitation. Acute inhalation of salbutamol on a background of theophylline treatment increases metabolic rate in an additive fashion.

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