Br. J. clin, Pharmac. (1981), **11**, 203–208

THEOPHYLLINE-SALBUTAMOL INTERACTION: BRONCHODILATOR RESPONSE TO SALBUTAMOL AT MAXIMALLY EFFECTIVE PLASMA THEOPHYLLINE CONCENTRATIONS

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1 The effect of inhaled salbutamol following a maximally effective dose of theophylline given by intravenous infusion was determined in 12 patients with chronic bronchitis.

2 An initial single intravenous dose study was performed to estimate each patient's theophylline kinetics and to identify those patients who would respond to theophylline.

3 Pulmonary function was assessed at hourly intervals during four to five incremental steady state theophylline infusions over the concentration range 5–25 mg/l.

4 Inhaled salbutamol (400 μg) was administered after the maximum effect from theophylline had been achieved or when theophylline concentrations reached 25 mg/l without maximum effect: pulmonary function was again assessed.

5 Ten patients achieved a further significant improvement in pulmonary function after salbutamol: in five, predicted values for FVC were exceeded.

6 Patients with chronic bronchitis may benefit from the combination of theophylline and salbutamol if steady state theophylline concentrations of 15–20 mg/l are achieved.

Introduction

Theophylline has been in use for 50 years but the ability to control dosage by measuring plasma levels has reawakened interest in the drug. Its possible interaction with β_2-adrenoceptor agonists has not yet been fully explored either at molecular level (Miech & Lohman, 1975; Trembath & Shaw, 1978) or in patients with airways narrowing. Conventional doses have been shown to have some additive effect when combined in asthmatics (Campbell, Middleton, Mackenzie, Shetter, McHardy & Kay, 1976; Wolfe, Tashkin, Calvarese & Simmons, 1978; Marlin, Hartnett & Berend, 1978) but these studies are incomplete since they ignore both individual differences in response and in theophylline clearance. The majority of patients attending our clinic have severe chronic bronchitis, leading to considerable loss of time from work. This prompted us to design a study to determine whether this situation could be improved by adding an effective dose of salbutamol to an individually determined maximally effective dose of theophylline.

Methods

Twelve male patients aged 53 to 72 years with chronic bronchitis (Medical Research Council, 1965) were selected for the study. They had FEV_1 values of approximately 1 l and showed an increase of 20% or more in their untreated FVC after inhalation of 200 μg salbutamol from a metered dose pressurised inhaler. Informed consent and the approval of the hospital's Research and Ethics Committee were obtained. All subjects were out-patients in a clinically stable state: relevant clinical details are presented in Table 1.

The study proceeded in two phases—a 'single dose' study followed by a 'dose-response' study. Subjects attended the Respiratory Laboratory at 11.00 h on both study days so that experimental periods could start at noon. They had been instructed to abstain from tea, coffee, cocoa and theophylline for the previous 48 h and no other bronchodilator was permitted after midnight of the day before the study. Oral or inhaled steroid therapy was, however, uninterrupted.

The subjects sat in an armchair and ECG and pulse

0306–5251/81/020203–06 $01.00

Table 1 Characteristics of the twelve male chronic bronchitic patients studied.

Patient number	*Age (years)*	*Weight (kg)*	*Measured FEV_1 (l)*	*Predicted FEV_1 (l)*
1	68	68	1.1	2.7
2	65	78	0.6	2.8
3	72	69	0.8	2.5
4	68	54	0.9	2.5
5	56	94	1.3	3.4
6	53	55	0.6	3.4
7	62	54	1.1	2.7
8	58	80	0.8	3.8
9	72	72	0.8	3.1
10	71	71	0.9	2.0
11	64	50	0.6	2.4
12	58	95	0.9	3.8

rates were continuously monitored on a Roche Model 123 Memory Oscilloscope. Blood pressures were measured by a Model HEM3 Automatic sphygmomanometer (OMRON, Kyoto) which gave a digital display of systolic and diastolic pressures. Baseline values for response were established by recording one maximal forced expiratory flow-volume (MEFV) curve every minute for 7 min and obtaining a second set of 7 such recordings after 30 min. A Lilly pneumotachograph provided the signal for an electronic spirometer (Mercury Electronics, Glasgow) which gave a digital display of PFR, FEV_1 and FVC and provided an analogue MEFV curve on a DM64 storage oscilloscope (Tectronix, Harpenden) which was photographed with a 'Polaroid' camera. The spirometer was calibrated for flow by means of an air blower and Rotameter and for volume by a 1 l syringe (accuracy 1% at a flow of 200 l/min and a volume of 10 l). To determine the onset of response the upper 95% confidence limit of the 14 baseline forced expirations was calculated.

Single dose study

In the first phase, a single intravenous dose of 500 mg aminophylline (containing 86% anhydrous theophylline) in 20 ml solution was infused over 10 min. Blood samples (5 ml in lithium heparin) were withdrawn from the contralateral arm through an indwelling teflon venous cannula ('Venflon') before the infusion, and at 4, 8, 10, 12, 20, 30, 40 and 50 min and at 1, 2, 4, 6, 8, 10 and 24 h after the end of the infusion. Plasma was separated by centrifugation and stored at −20°C until required for analysis.

Response was assessed by further sets of 7 maximal forced expirations at 1 h and at 2 h after the infusion. Student's *t*-test was applied to these groups of data to detect statistically significant changes in each individual.

Plasma theophylline concentrations were estimated by high pressure liquid chromatography (Gere & Bente, 1977) and post-infusion curves were analysed by nonlinear least squares regression to yield the four parameters A, α, B, and β of the biexponential expression

$$Cp(t) = Ae^{-\alpha t} + Be^{-\beta t}$$

associated with a two compartment pharmacokinetic model (Gibaldi & Perrier, 1975), where Cp(t) is the plasma concentration of theophylline at any time, t; A and B are the extrapolated zero time intercepts on a semilogarithmic plot of concentration vs time and α and β are the rapid and slow disposition rate constants respectively. In two patients, however, the data was insufficient to justify a two compartmental analysis and the post infusion curves were analysed on the basis of the simpler one compartment model. The final estimates of the coefficients of the exponential terms were then used to calculate volumes of distribution (V_d) and clearance (Cl) as presented in Table 2. These values were incorporated into equations proposed by Wagner (1974) which permit the rapid attainment of concentration plateaus by infusing a drug at an initial constant rate, Q_1 for T minutes, and then abruptly lowering the rate to Q_2 which is maintained for as long as steady state is desired. The first two consecutive infusion rates were calculated to achieve an initial plateau concentration of 5 mg/l. The second, slow infusion rate, Q_2, was calculated as follows:

$$Q_2 = \text{theophylline clearance (l/h)} \times 5 \text{ (mg/l)},$$

this infusion to run for 40 min. As the first (loading) infusion, was designed to run for T = 20 min, the ratio of the half-life of the drug ($T_{½}$) to this chosen time T could be calculated and then used to calculate the ratio Q_1/Q_2 from the relationship

$$Q_1/Q_2 = 0.50 + 1.443\ T_{½}/T.$$

Knowing Q_2, Q_1 could be calculated since $Q_1 = (Q_1/Q_2)(Q_2)$. This procedure was accurate if $T_{½}/T \geq 6.93$. If this ratio was < 6.93, Q_1 was calculated by an alternative strategy (Wagner, 1974). These data were then used to establish dose response curves in the 12 subjects.

Dose-response study

Having determined initial Q_1 and Q_2 values, infusion rates for subsequent incremental steps of 5 mg/l, i.e. 10, 15, 20 and 25 mg/l, were calculated on the basis that Q_1 would always remain the same but Q_2 would have to be increased in proportion to the desired plasma concentration, for example for 10 mg/l, the initial Q_2 was doubled, for 15 mg/l, the initial Q_2 was trebled and so on.

These calculations were used to determine the loading doses and infusion rates for each patient in

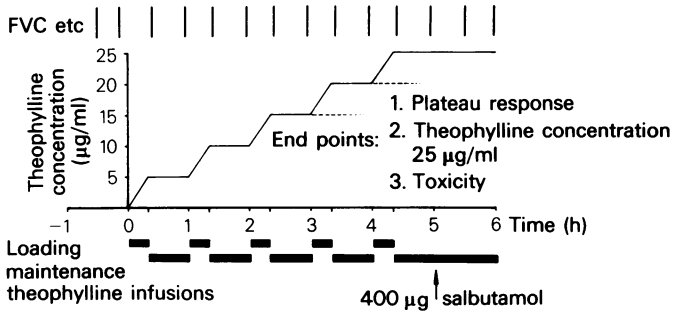

Figure 1 Diagrammatic representation of plan of dose-response study. For details, please refer to text.

the second part of the study which began under identical conditions to the first part. Details of this phase of the study are illustrated in Figure 1. The first loading dose was administered over 20 min and was immediately followed by the constant rate infusion at the calculated rate for 40 min using a Tekmar constant volume infusion pump. Blood samples were taken at baseline, immediately after the loading infusion and 30 min into the steady state infusion. Immediate HPLC analysis provided a useful comparison of actual and predicted theophylline levels which could be used for fine tuning of subsequent infusion rates if this was necessary.

Sets of 7 lung function measurements as described above were obtained at 10 and 37 min after the start of each steady state infusion. This routine (loading dose—steady state infusion—lung function assessment) was arranged so that the loading doses were given at hourly intervals. The dosage increments were continued until the maximum response to theophylline was achieved, as indicated by the failure of an increment to bring about a further significant improvement in the FVC compared with the two sets of data obtained at the previous steady state plasma level. However, two important constraints on this plan were agreed beforehand and strictly observed. No further loading infusion was to be given when measured plasma concentrations indicated that a subsequent loading infusion would increase the plasma theophylline level beyond 25 mg/l and no loading or maintenance infusion was to be given after the appearance of any accepted or possible symptoms or signs of theophylline toxicity.

When a response plateau or the maximal acceptable plasma level was reached, the steady state infusion was continued while the response to 400 μg salbutamol was assessed. Salbutamol was administered by the observer from 100 μg metered dose inhaler and further sets of respiratory data were collected 30 min and 1 h afterwards. At the same times, blood samples were taken to confirm maintenance of plasma theophylline levels.

Results

The pharmacokinetic parameters determined for each subject are listed in Table 2. Table 3 shows the individual loading and maintenance doses calculated to produce the first 5 mg/l step with corresponding predicted and observed plasma levels. The mean difference between the latter was 0.5 ± 1.5 (s.d.) mg/l which is not significantly different from zero (paired *t*-test). Over the entire course of the study, there was a similar good agreement between all predicted and observed levels ($r = 0.8858$, $P < 0.001$). Table 4 shows the plasma levels at which the response reached a plateau, except in patients 8 and 11, in whom no plateau was established below the arbitrary toxic limit. No toxicity was encountered in any subject. Table 5 shows the response to the addition of salbutamol. In each case the FVC values increased and in all but subjects 5 and 11 this increase was significant ($P < 0.05$). Table 6 presents the changes in heart rate and blood pressure throughout the dose response study. After theophylline the heart rate rose by a mean of 9.6 ± 8.8 (s.d.) beats/min ($P < 0.01$) while the systolic pressure fell by 12.3 ± 10.8 (s.d.) mm Hg ($P < 0.01$) and the diastolic pressure fell by 8.6 ± 10.9 (s.d.) mm Hg ($P < 0.01$). Salbutamol subsequently produced no significant change in any of these indices.

Discussion

This study differs from other work in several ways. All the data published so far derives from studies on asthmatics and at best shows that doses of adrenergic agonists and theophylline chosen for approximately equal bronchodilator potency have some additive effect (Wolfe *et al.*, 1978). We chose to study bronchitis because it is a much more common cause of disability and prolonged absence from work than asthma among our patients, even although an irreversible element in the airways narrowing could limit the response available to bronchodilators. In asthmatics

Table 2 Pharmacokinetic parameters derived from single dose studies. V_d refers to the apparent volume of distribution in a two compartment model, except in patients 4 and 9 where the analysis was based on a one compartment model.

Patient number	V_d *(l)*	β *(h^{-1})*	$T_{½}$ *(h)*	*Total body clearance (l/h)*
1	32.2	0.14	4.9	4.5
2	32.7	0.08	8.7	2.6
3	43.8	0.09	7.7	3.9
4	31.6	0.05	13.9	1.6
5	49.1	0.07	9.9	3.4
6	25.0	0.08	8.7	2.0
7	47.1	0.08	8.7	3.8
8	44.2	0.08	8.7	3.5
9	46.0	0.05	13.9	2.3
10	26.0	0.08	8.7	2.1
11	31.3	0.11	6.3	3.4
12	35.4	0.05	13.9	1.8
Mean ± s.d.	37.0 ± 8.5	0.08 ± 0.03	9.5 ± 3.0	2.9 ± 1.0

Table 3 Calculated (20 min) loading infusion and first (40 min) maintenance infusion rates designed to achieve plasma theophylline concentrations of approximately 5 mg/l.

Patient number	*Loading infusion (mg/min)*	*Maintenance infusion (mg/min)*	*Predicted plasma level (mg/l)*	*Measured plasma level (mg/l)*
1	10.3	0.5	5.0	8.2
2	9.1	0.2	5.0	4.4
3	11.1	0.3	4.5	4.5
4	8.0	0.1	5.0	7.9
5	12.0	0.3	6.8	7.4
6	7.0	0.2	5.7	6.2
7	10.1	0.1	5.3	7.4
8	11.2	0.3	6.5	6.0
9	15.0	0.2	5.8	6.5
10	12.6	0.2	5.0	4.4
11	8.0	0.3	6.0	4.8
12	18.0	0.2	5.0	3.9

the response to increasing doses seems limited only by return to the patients' normal values (Wild Bolz, Bachofen & Scherrer, 1978).

In this study we set out to determine each subject's maximum response to theophylline and then added a substantial dose of salbutamol to determine whether a truly additive effect could be obtained. The results show that the maximum response to theophylline was established in 10 patients and that the addition of salbutamol did produce an additive effect. The same result was observed in the other two subjects except that their maximal response to theophylline was determined by the safe plasma level ceiling of 25 mg/l rather than by failure to respond any further. In general, if any limit was imposed by irreversible airways changes it was not attained by theophylline alone and previous laboratory records showed that the response to the theophylline/salbutamol combination was the best result ever obtained in all subjects except one (Table 7). In five, the value was greater than their predicted normal value, and they can therefore be considered to have behaved like asthmatics. We do not know whether the disease process limited the response in the other six.

There was considerable variability in the plasma levels at which maximal responses to theophylline were obtained (Table 4). Two subjects (3 and 10) had already achieved their maximum response at relatively low plasma concentrations (9 mg/l), but in the other ten, the proportion of their eventual response

Table 4 Plasma theophylline levels at which endpoints were observed.

Patient number	*End points*	*Theophylline plasma level (mg/l)*
1	Response plateau	17
2	Response plateau	17
3	Response plateau	9
4	Response plateau	14
5	Response plateau	17
6	Response plateau	20
7	Response plateau	24
9	Response plateau	12
10	Response plateau	9
12	Response plateau	12
8	No plateau by	23
11	approx. 25 mg/l.	23

at the lower end of the therapeutic range (10–20 mg/l) varied from 33 to 93% and in seven, plasma levels of 17 to 23 mg/l were required for maximal effect.

Because the plasma concentrations achieved in this study were carefully controlled, we can conclude that any variability in response was due to differences in the degree of response to theophylline rather than to differences in theophylline clearance. We therefore recommend that, since toxicity should not be a problem, an average steady state plasma level of 15–20 mg/l should normally be aimed at unless it is possible to determine the individual's own dose-concentration-response maximum.

Many previous studies have not included assessment of theophylline plasma levels but the present study clearly demonstrates that individually tailored dosage was only possible through determination of

Table 5 Response to salbutamol after maximal possible theophylline response.

Patient number	*Baseline FVC (l)*	*Final theophylline response (l)*	*Salbutamol response (l)*	*Change in response (l)* [a]
1	3.25	4.50	4.91	0.41
2	0.68	1.33	1.86	0.53
3	1.53	1.60	2.10	0.50
4	1.79	2.69	3.47	0.78
5	2.23	2.49	2.77	0.28 [b]
6	1.65	1.80	2.27	0.47
7	1.66	2.29	3.21	0.92
8	1.13	2.18	2.96	0.80
9	2.07	2.10	2.60	0.50
10	1.40	1.56	2.08	0.52
11	1.55	2.50	2.69	0.19 [b]
12	2.50	2.90	3.62	0.72

(a) Mean (s.d.) of difference between observations = 0.55 (0.21) l ($P < 0.005$).
(b) Not significant.

Table 6 Heart rate and blood pressure changes during the infusion study at baseline, maximum plasma theophylline concentration and following salbutamol.

Patient number	*Heart rate (beats/min)*			*Blood pressure (mm Hg)*		
	Baseline	*Maximum plasma theophylline concentration*	*After salbutamol*	*Baseline*	*Maximum plasma theophylline concentration*	*After salbutamol*
1	100	115	120	143/86	124/85	140/76
2	93	96	96	169/99	150/99	125/89
3	55	65	60	164/85	156/79	152/91
4	96	90	95	164/82	166/78	167/62
5	100	120	110	158/113	145/103	154/99
6	85	100	96	122/83	113/84	123/84
7	75	90	85	157/84	145/73	142/68
8	80	76	76	88/70	96/77	92/78
9	90	96	96	157/82	129/55	153/71
10	80	100	100	129/71	122/61	152/66
11	80	96	96	157/89	128/59	127/76
12	95	100	104	138/93	124/81	119/83

Table 7 Comparison of best previous documented clinical response and that observed during the dose-response study.

Patient number	*Infusion study (theophylline + salbutamol response, FVC (l))*	*Previous best FVC (l)*	*% difference*
1	4.91	2.9	69.3
2	1.86	1.5	24.0
3	2.10	1.6	31.25
4	3.47	2.2	57.7
5	2.77	2.0	38.5
6	2.27	2.2	3.2
7	3.21	2.1	52.8
8	2.96	2.4	23.3
9	2.60	2.3	13.0
10	2.08	2.2	-5.45
11	2.69	2.3	17.0
12	3.62	3.0	20.7
		mean (s.d.)	28.8 (22.3)

theophylline concentrations and relevant pharmacokinetic parameters. Response could then be related to plasma levels, and toxic levels avoided. In the routine clinical situation, however, it would not be practical to apply such an intense effort to every patient. Knowledge of the variability implicit in theophylline clearance and the factors modifying clearance, such as age, smoking, congestive cardiac failure etc—should enable reasonable estimates of dosage to be made, bearing in mind the target concentration of 15–20 mg/l. Dosage adjustment can then be made in the light of clinical response. Patients 8 and 11 in the present study, for example, would require the maximum possible dose whereas patients 3 and 10 would still benefit after a reduction to achieve levels in the 5–10 mg/l range. It is clear that at present, no simple predictive formula can be offered which relates response to plasma level in individual patients.

In conclusion, salbutamol can improve on the maximum bronchodilator theophylline response available in bronchitic patients, and in some, 'total' reversibility of airways obstruction is possible. We have yet to show whether theophylline at maximally effective dosage can add to the maximal effect obtainable from salbutamol. On the present evidence combination therapy is preferable, with the dose of theophylline individually adjusted to provide an average steady state plasma level in the 15–20 mg/l range.

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(*Received May 19, 1980*)