ASSESSMENT OF COMBINED ORAL THEOPHYLLINE AND INHALED β -ADRENOCEPTOR AGONIST BRONCHODILATOR THERAPY

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- 1 The bronchodilator effects of 500 μ g rimiterol by pressurized aerosol, 375 mg oral theophylline and both drugs in combination were compared in a randomized, placebo-controlled, double-blind trial in eight patients with chronic, partially reversible airways obstruction.
- 2 The four treatments were (i) oral theophylline, placebo aerosol (TP); (ii) oral placebo, rimiterol aerosol (PR); (iii) oral theophylline, rimiterol aerosol (TR) and; (iv) oral placebo, placebo aerosol (PP). The aerosol was administered 2 h after the oral treatment.
- 3 Significant bronchodilatation (% FEV₁ change from control) compared to PP occurred with TP from 60 to 480 min and with TR from 60 to 300 min, whereas with PR only for 45 min ($P < 0.05$).
- 4 The mean, peak % FEV₁ increases from control were 51.8% at 125 min, 31.7% at 125 min, 26.1% at 210 min and 0.9% at 30 min for TR, PR, TP and PP respectively.
- 5 At 125 min (5 min after aerosol inhalation) the mean % FEV₁ change from control with TR (51.8%) was significantly greater than with PR (31.7%), TP (22.2%) ($P < 0.05$) and PP (–2.4%) ($P < 0.01$).
- 6 The mean, peak plasma theophylline levels were 10.19 μ g/ml at 120 min and 9.98 μ g/ml at 180 min with TR and TP respectively. Theophylline half-life ranged between 4.3 and 12.5 h (mean $\pm$ s.e. mean, 8.0 ± 0.8 h).
- 7 Additive bronchodilatation was produced when rimiterol was administered with theophylline at a time when therapeutic plasma theophylline levels were achieved.

Introduction

β -adrenoceptor stimulating drugs by inhalation and oral theophylline derivatives are commonly used either singly or in combination for the maintenance treatment of chronic airways obstruction due to asthma. Cyclic adenosine 3', 5'-monophosphate (Cyclic AMP) appears to regulate bronchodilatation and the immunological mediator release in human lung (Orange, Kaliner, Laraia & Austen, 1971). β -adrenoceptor agonists and theophylline derivatives increase the concentration of cyclic AMP in bronchial smooth muscle and lung, the one by stimulating adenyl cyclase and the other by inhibiting phosphodiesterase. There is some *in vitro* and *in vivo* evidence that these two classes of drugs may act synergistically when administered together (Orange *et al.*, 1971; Duncan, Griffin & Solomon, 1975; Campbell, Middleton, MacKenzie, Shotter, McHardy & Kay, 1976).

This study was performed to compare the bronchodilator effects of a β -adrenoceptor agonist, rimiterol, and an oral theophylline derivative both

singly and in combination in patients with chronic, partially reversible airways obstruction.

Methods

Eight patients with chronic, partially reversible airways obstruction due either to asthma or chronic bronchitis with asthma defined according to the Ciba Guest Symposium Report (1959) were selected for this study. Their sex, age, diagnostic group to which they were assigned, smoking history, current medical treatment and respiratory function before and after bronchodilator (200 μ g salbutamol by pressurized aerosol) are described in Table 1.

The trial was a randomized, balanced, double-blind, Latin square design and was conducted at the same time in the morning on four days separated from each other by at least 72 h. Placebo tablets and pressurized aerosols were prepared identical in appearance to active theophylline tablets (Nuelin, Riker Laboratories

Australia Pty. Ltd) and rimiterol pressurized aerosols (Pulmadil, Riker Laboratories Australia Pty. Ltd) respectively. The treatments for the four trial days were as follows:

1. oral theophylline, placebo aerosol (TP),
2. oral placebo, rimiterol aerosol (PR),
3. oral theophylline, rimiterol aerosol (TR),
4. oral placebo, placebo aerosol (PP).

The dose of oral theophylline was 375 mg (125 mg/tablet) and of rimiterol, 500 µg (250 µg/inhalation by pressurized aerosol). On each day the aerosol was administered two hours after the oral treatment.

All patients were in a steady state of moderate airways obstruction, established on maintenance treatment. It was necessary for there to be less than 15% variation between the baseline, control forced expiratory volume in one second (FEV₁) values on the four trial days for each patient and also for each baseline FEV₁ to be between 25 and 70% of predicted normal. All sympathomimetic drugs were withdrawn for 12 h prior to each study day and theophylline derivatives for 1 week prior to the trial commencement, but oral and aerosol corticosteroids and disodium cromoglycate were continued at their maintenance doses. Three patients were receiving other drugs (F.A.—tolbutamide, digoxin, frusemide, clonidine, imipramine, allopurinol; A.H.—digoxin, frusemide; A.M.—isoniazid, allopurinol). All these drugs were continued at maintenance doses except

frusemide which was withdrawn for 12 h prior to each study day. All patients had normal biochemical renal and hepatic function.

Ventilatory response was determined by measuring the FEV₁ with a dry spirometer (Vitalograph). Three resting, baseline FEV₁ readings were taken and the highest value was used as control. Two FEV₁ measurements were repeated after each oral treatment at 30, 60, 90, 120, 125, 135, 150, 165, 180, 210, 240, 300, 360, 420 and 480 min, the highest value on each occasion used for comparisons. These results were submitted to statistical analysis using the paired Student's *t*-test.

Venous blood samples were collected before and at 60, 90, 120, 150, 180, 240, 300, 360 and 480 min after each oral treatment for plasma theophylline estimations. Theophylline plasma levels were determined by assaying aliquots (4 ml) by the spectrophotometric procedure described by Graham (1974) with the exception that the volume of pH 10.6 buffer used in the final extraction was increased to 6 ml. The absorbance of the final extracts was measured using a Unicam SP 1700 Spectrophotometer incorporating an automatic sampling table and the extracts were scanned over the range of 210–320 nm. The plasma half-life for theophylline was calculated from the terminal phase of the log plasma concentration/time curve. For each patient the equation for the first order disappearance of theophylline from plasma was calculated by the least squares method. The mean equation for all

Table 1 The sex, age, diagnostic group according to the Ciba Guest Symposium Report (1959), smoking history, current medical treatment, baseline forced expiratory volume in one second (FEV₁) as percentage of predicted normal value, and the percentage increase in FEV₁ after inhalation of salbutamol (200 µg) by pressurized aerosol for the eight patients with chronic, partially reversible airways obstruction

Name	Sex	Age (years)	Disease	Smoking history	Treatment	FEV ₁ (% of predicted normal)	% FEV ₁ bronchodilator response
A.B.	M	30	A	Nil	S,D,B,P (4 mg)	49	44
F.A.	M	58	CB-A	Previous moderate	S,T,B,P (8 mg)	55	20
A.H.	M	71	CB-A	Previous moderate	S,T,B	46	33
R.M.	M	63	CB-A	Previous moderate	S,D,B	43	20
R.H.	M	68	CB-A	Previous moderate	S,B	27	88
J.H.	M	58	CB-A	Previous moderate	S,D,B	38	25
A.T.	F	63	A	Nil	S,T,D,B,P (5 mg)	32	84
A.M.	M	54	A	Nil	S,T,B	32	50

Smoking history: moderate 10–20 cigarettes/day.

Disease: A—asthma, CB-A—chronic bronchitis with asthma.

Treatment: S—salbutamol (800 µg/day by pressurized aerosol), T—theophylline (various preparations and doses), B—beclomethasone dipropionate (400 µg/day), D—disodium cromoglycate (80 mg/day), P—prednisone (daily dose).

Figure 1 The mean percentage changes in forced expiratory volume in one second (FEV_1) from control values for the eight patients with chronic, partially reversible airways obstruction after treatments TP $\circ$ (oral theophylline, 375 mg; placebo aerosol) and PP $\blacksquare$ (oral placebo; placebo aerosol). The oral and aerosol treatments were administered at 0 and 2 h respectively.

Figure 2 The mean percentage changes in forced expiratory volume in one second (FEV_1) from control values for the eight patients with chronic, partially reversible airways obstruction after treatments PR $\triangle$ (oral placebo; rimiterol aerosol, 500 μ g) and PP $\blacksquare$ (oral placebo; placebo aerosol). The oral and aerosol treatments were administered at 0 and 2 h respectively.

patients was obtained and the half-life calculated from the equation, half-life ($T_{1/2}$) = $0.693/k$, where k is the rate constant for the disappearance of theophylline from plasma. All patients refrained from caffeine containing drinks for 24 h prior to each study day in order to avoid interference in the theophylline assay.

The written, informed consent of each patient was obtained.

Results

Ventilatory response was expressed as the percentage change in FEV_1 from the control, baseline value. There was no significant difference between the control FEV_1 values before TP (mean $\pm$ s.e. mean, 1.21 ± 0.14 l), PR (mean $\pm$ s.e. mean, 1.19 ± 0.14 l), TR (mean $\pm$ s.e. mean, 1.25 ± 0.14 l) and PP treatments (mean $\pm$ s.e. mean, 1.24 ± 0.15 l). The mean, percentage changes from control, baseline values for each active treatment (TP, PR and TR) and placebo (PP) are graphed in Figures 1, 2 and 3 respectively.

Significant bronchodilatation compared to PP occurred with TP from 60 to 480 min, with PR from 125 to 165 min and with TR from 60 to 300 min ($P < 0.05$). The mean $\pm$ s.e. mean, peak % FEV_1 increases from control were $26.1 \pm 10.4\%$ at 210 min, $31.7 \pm 8.2\%$ at 125 min, $51.8 \pm 13.2\%$ at 125 min and $0.9 \pm 1.5\%$ at 30 min for TP, PR, TR and PP respectively. At 125 min (5 min after aerosol in-

Figure 3 The mean percentage changes in forced expiratory volume in one second (FEV_1) from control values for the eight patients with chronic, partially reversible airways obstruction after treatments TR $\bullet$ (oral theophylline, 375 mg; rimiterol aerosol, 500 μ g) and PP $\blacksquare$ (oral placebo; placebo aerosol). The oral and aerosol treatments were administered at 0 and 2 h respectively.

halation) the mean % FEV₁ change from control with TR (51.8%) was significantly greater than with TP (22.2%), PR (31.7%) ($P<0.05$) and PP (-2.4%) ($P<0.01$). The bronchodilator response after TR was significantly greater than that after PR at all times except 165, 420 and 480 min ($P<0.05$), whereas after TP only at 30, 125, 150 and 180 min ($P<0.05$). TP produced significantly greater bronchodilatation than PR at all times except 30, 125, 150, 165 and 180 min ($P<0.05$) when there was no significant difference. As an expression of the total effect of each treatment, the areas under the FEV₁ response curves (FEV₁ integrated responses) were calculated for the 480 min period. The mean $\pm$ s.e. mean FEV₁ integrated responses were 983 ± 286 , 272 ± 96 , 903 ± 335 and -173 ± 129 for TP, PR, TR and PP respectively, those for TP and TR being significantly greater than for PR ($P<0.02$) and PP ($P<0.01$) but not differing significantly from each other.

The individual and mean $\pm$ s.e. mean plasma theophylline concentrations and plasma half-lives for theophylline for seven patients are shown in Table 2. Data from patient A.M. was discarded because apparent theophylline levels in control, baseline time samples were above 60 $\mu\text{g/ml}$. This patient was also receiving isoniazid and allopurinol, both of which could have interfered in the assay.

There were no side-effects mentioned by any patient throughout the study.

Discussion

Rimiterol, a member of a new series of sympathomimetic amines cyclized about the α -carbon atom, is an effective bronchodilator with a high degree of β_2 -adrenoceptor selectivity similar to salbutamol and a short half-life comparable with isoprenaline (Griffin & Turner, 1971; Phillips, Woolnough, Marinova & Turner, 1972; Svedmyr, Malmberg & Thiringer, 1972; Griffin, Williams & Maughan, 1973; Shenfield & Paterson, 1973; Evans, Shenfield, Thomas, Walker & Paterson, 1974; Bianco, Kam-buroff & Prime, 1975; Marlin & Turner, 1975a, b). The theophylline preparation (Nuelin) used in this trial is a microfinned tablet containing only the active bronchodilator and possessing rapid dissolution properties (Graham, Hartnett & Hayter, 1974). Therapeutic plasma theophylline levels will occur after a single oral dose of 375 mg and peak bronchodilatation will be produced between 2 and 4 h after administration (Hartnett, Marlin & Graham, 1974; Hartnett & Marlin, 1976). For this reason the time of 2 h after theophylline administration was selected to study the combined effect of rimiterol.

There have been no reported studies evaluating the bronchodilator potency of β -adrenoceptor agonists by inhalation and oral theophylline in combination therapy. Such investigations are required to determine the role of these drugs in the maintenance treatment of

Table 2 The individual and mean $\pm$ s.e. mean plasma theophylline concentrations ($\mu\text{g/ml}$) and individual and mean $\pm$ s.e. mean theophylline half-lives for seven patients with chronic, partially reversible airways obstruction during treatments TP (oral theophylline, 375 mg; placebo aerosol) and TR (oral theophylline, 375 mg; rimiterol aerosol, 500 μg)

Patient	Treatment	Plasma theophylline concentration (µg/ml)									Theophylline half-life (h)
		Time (h)									
		1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0	8.0	
A.B.	TP	7.02	7.91	7.85	—	7.44	8.22	7.39	6.81	5.89	8.1
	TR	0.69	5.15	7.18	8.64	8.79	8.64	7.07	6.40	5.89	
F.A.	TP	1.11	1.47	1.84	2.04	2.41	3.96	8.64	8.01	7.29	12.5
	TR	5.21	5.31	5.78	5.72	5.72	7.33	7.18	6.87	6.09	
A.H.	TP	11.34	13.26	12.38	12.12	13.88	11.18	9.46	9.00	7.44	6.5
	TR	12.64	12.64	12.69	12.42	11.75	10.61	8.68	8.38	7.33	
R.M.	TP	9.83	8.64	7.96	7.85	7.59	7.07	6.04	5.26	4.85	6.9
	TR	9.51	8.33	8.16	7.70	7.13	6.81	6.30	4.59	4.48	
R.H.	TP	11.55	10.97	10.45	9.68	10.55	9.36	8.68	7.44	7.44	8.5
	TR	8.90	10.09	10.03	7.75	8.90	8.53	8.01	7.33	5.21	
J.H.	TP	—	7.33	11.18	10.14	9.26	9.10	8.22	7.50	6.40	9.2
	TR	5.21	8.01	9.42	9.42	9.20	9.20	7.81	6.76	6.61	
A.T.	TP	15.85	16.58	15.28	15.08	18.71	12.32	9.68	8.90	6.40	4.3
	TR	—	18.04	18.08	16.84	16.63	14.86	13.56	11.34	9.16	
Mean	TP	9.45	9.47	9.56	9.49	9.98	8.74	8.30	7.56	6.53	8.0
s.e.mean		2.22	2.11	1.71	1.97	2.11	1.13	0.56	0.55	0.40	8.0 (Mean)
Mean	TR	7.03	9.65	10.19	9.78	9.73	9.43	8.37	7.38	6.40	0.8 (s.e.mean)
s.e.mean		1.87	1.84	1.68	1.52	1.46	1.10	0.97	0.84	0.62	0.8

chronic, partially reversible airways obstruction. Hartnett & Marlin (1976) have reported a comparative study between single doses of salbutamol, 200 μ g by pressurised aerosol, and oral theophylline (Nuelin, 375 mg). This work highlighted the immediate, peak bronchodilator effect of a β -adrenoceptor agonist by inhalation compared with the sustained, longer duration response after oral theophylline. Equivalent bronchodilatation was produced by these two drugs between 2 and 4 h after administration.

The present study illustrates the rapid onset and short duration of action of rimiterol, which is related to its metabolism by the enzyme, catechol-o-methyl transferase (Griffin *et al.*, 1973; Evans *et al.*, 1974). Significant bronchodilatation compared with placebo occurred for only 45 min. However, the bronchodilator effect of theophylline plateaued after 2 h and was well sustained during the proceeding 6 h. There was no significant difference between the peak bronchodilator responses of the two drugs. The study failed to demonstrate synergistic activity between the two drugs during combination treatment (TR). Additive bronchodilatation only was produced and there was no evidence that the duration of action of rimiterol was influenced by the prior administration of theophylline. This failure to demonstrate synergism was inherent in the design of the trial because of the change in baseline airways calibre at the time of the aerosol administration in treatments TR and PR. The efficacy of a bronchodilator is known to depend upon the degree of airways obstruction present and also the phase of the disease (Hume & Gandevia, 1957; Hume & Rhys Jones, 1961; Pain & Read, 1962). It is also considered that any bronchodilator drug which sub-maximally increased FEV₁ might non-specifically augment the response to the subsequent administration of a second bronchodilator drug.

The minimal plasma theophylline concentration required to produce peak bronchodilatation lies between 7 and 20 μ g/ml and gastrointestinal toxicity as well as other side-effects will be common above 20 μ g/ml (Turner-Warwick, 1957; Jackson, McHenry,

Moreland, Raymer & Etter, 1964; Jenne, Wyze, Rood & MacDonald, 1972; Mitenko & Ogilvie, 1973; Nicholson & Chick, 1973; Bulow, Larsson & Leideman, 1975). In this study with all seven patients in whom plasma theophylline levels were obtained, therapeutic concentrations were achieved and did not exceed 20 μ g/ml. The mean, peak plasma theophylline levels were 10.19 μ g/ml at 2 h and 9.98 μ g/ml at 3 h with treatments TR and TP respectively, and the mean levels were maintained above 7 μ g/ml between 1 and 6 h after theophylline administration. There was considerable variation in half-lives for theophylline among the seven patients, ranging between 4.3 and 12.5 h (mean $\pm$ s.e. mean, 8.0 ± 0.8 h). Jenne *et al.* (1972) also observed a wide range for theophylline half-life, from 3.0 to 9.5 h, in adult man and postulated that this may be due to variable metabolizing enzyme induction by concurrent or previous drug therapy. Theophylline is partially demethylated and/or oxidized and is largely excreted as a methyl uric acid or methyl xanthine derivative (Ritchie, 1971; Thompson, Nagasawa & Jenne, 1974). Although xanthine oxidase is not involved in theophylline metabolism (Ritchie, 1971), allopurinol, a xanthine oxidase inhibitor, may however interfere with its metabolism. It is noted in this study that patient F.A. receiving allopurinol demonstrated a long theophylline half-life.

In summary, this study demonstrates that additive bronchodilatation was produced by a β -adrenoceptor agonist when administered by pressurized aerosol with oral theophylline at a time when therapeutic plasma theophylline levels were achieved. The clinical efficacy and possible toxicity of combination treatment with inhaled β -adrenoceptor agonists and oral theophylline derivatives in the long-term control of chronic airways obstruction requires further investigation.

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