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COMPARISON OF ORAL THEOPHYLLINE AND SALBUTAMOL BY INHALATION IN ASTHMATIC PATIENTS

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1 The bronchodilator effects of 375 mg theophylline orally and 200 μg salbutamol by pressurized aerosol were compared in a randomized, cross-over, double-blind trial in fourteen asthmatic patients.

2 The mean peak percentage FEV_1 increase from control was 43.7% at 60 min after salbutamol and 30.3% at 180 min after theophylline.

3 Salbutamol produced significantly greater bronchodilatation than theophylline for the initial 30 min ($P < 0.01$).

4 Theophylline demonstrated a longer duration of action than salbutamol, with a significantly greater FEV_1 response at 360 min ($P < 0.02$).

5 There was no significant difference between the total effect of each drug for the 360 min period, as calculated by the areas under the respective FEV_1 response curves.

Introduction

Oral theophylline derivatives and β_2-adrenoceptor stimulating drugs by inhalation are widely used as bronchodilators in the management of asthma. The purpose of this work was to compare the bronchodilator efficacies of oral theophylline and salbutamol by pressurized aerosol in asthmatic patients.

Methods

Fourteen hospital patients (thirteen males and one female, A.T.), aged from 28-67 years, with chronic, partially reversible airways obstruction due either to asthma or chronic bronchitis with asthma according to the Ciba Guest Symposium Report (1959), were selected for this study. Their age, diagnostic group to which they were assigned, current medical treatment, smoking history and respiratory function before and after bronchodilator (salbutamol (200 μg) by pressurized aerosol) are described in Table 1.

The trial was a randomized, cross-over, double-blind design and was conducted at the same time in the morning on two separate days. Placebo tablets and pressurized aerosols were prepared, identical in appearance and taste to active theophylline tablets (Nuelin, Riker Laboratories Australia Pty Ltd) and salbutamol pressurized aerosols (Ventolin, Allen and Hanburys Ltd) respectively. The treatments for the two trial days were as follows:

1. oral theophylline, 375 mg (three 125 mg tablets), placebo pressurized aerosol (two inhalations).
2. oral placebo (three tablets), salbutamol pressurized aerosol, 200 μg (two 100 μg inhalations).

The doses of salbutamol and theophylline in this study have been recommended for the treatment of acute asthma.

All patients had previously received treatment in hospital for acute exacerbations of airways obstruction, and at the time of the study were in a steady state, established on maintenance treatment prior to their discharge. It was necessary for there to be less than 10% variation between the baseline, control forced expiratory volume in one second (FEV_1) values on the two days of the trial for each patient, and also for each baseline FEV_1 to be between 25 and 70% of predicted normal. All sympathomimetic and xanthine drugs were withdrawn for 12 h prior to each study day, but oral and aerosol corticosteroids and disodium cromoglycate were continued at their maintenance doses.

Ventilatory response was determined by measuring the FEV_1 with a dry spirometer

(Vitalograph). Three resting, baseline FEV_1 readings were taken and the highest value was used as control. After each treatment, three FEV_1 measurements were repeated at 15, 30, 60, 120, 180, 240 and 360 min, the highest value on each occasion used for comparisons. The results were submitted to statistical analysis using the paired Student's *t*-test.

The consent of each patient was obtained after the procedure of the trial had been fully explained.

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 theophylline (mean ± s.e. mean, 1.56 ± 0.17 litres) and salbutamol treatments (mean ± s.e. mean, 1.57 ± 0.17 litres). The mean percentage changes from control values for each drug are graphed in Figure 1. The mean, peak FEV_1 increase was 43.7% at 60 min after salbutamol and 30.3% at 180 min after theophylline. Salbutamol produced significantly greater bronchodilatation than theophylline for the initial 30 min ($P < 0.01$). There was no significant difference between the ventilatory response for each drug from 60 to 240 minutes. However, theophylline appeared to have the longer duration of action, there being a significantly greater FEV_1 response after theophylline at 360 min than after salbutamol ($P < 0.02$). Also, there was a significant decline in FEV_1 from 60 to 360 min only after salbutamol ($P < 0.02$), whereas the action of theophylline plateaued after 60 minutes. As an expression of the total effect of each drug, the areas under the FEV_1 response curves (FEV_1 integrated responses) for each patient were calculated for the 360 min period and are shown in Table 2. There was no significant difference between the mean FEV_1 integrated responses for theophylline and salbutamol. No side-effects were reported by the patients after either treatment.

Table 1 The age, smoking history, diagnostic group assigned according to Ciba Guest Symposium Report (1959), current medical treatment, baseline, forced expiratory volume in one second (FEV_1) as percentage of predicted normal value, and the percentage increase in FEV_1 after inhalation of salbutamol (200 μg) by pressurized aerosol for the fourteen asthmatic patients

Patient	*Age (years)*	*Smoking history*	*Disease*	*Treatment*	*FEV_1 % of predicted normal*	*% FEV_1 response after bronchodilator*
L.R.	60	Previous moderate	Asthma	S, D, B.	31	32
R.D.	57	Previous heavy	Chronic bronchitis with asthma	S, D, B.	51	33
R.R.	45	Previous moderate	Asthma	D, P (10 mg)	45	36
M.B.	51	Nil	Asthma	S	41	43
F.T.	60	Previous moderate	Chronic bronchitis with asthma	S, T, P (10 mg)	48	51
F.A.	56	Previous moderate	Chronic bronchitis with asthma	S, D, P (intermittent)	38	54
D.L.	56	Nil	Asthma	S	45	48
A.T.	60	Nil	Asthma	S, D, T, P (10 mg)	25	133
W.S.	49	Nil	Asthma	S, D, T.	35	31
A.M.	52	Previous light	Asthma	O, D, T, P (20 mg)	25	59
W.W.	50	Previous moderate	Chronic bronchitis with asthma	S, D, T, P, (10 mg)	56	25
C.S.	67	Previous moderate	Asthma	D, T, B.	31	33
A.B.	28	Nil	Asthma	S, D, T P (15 mg)	56	53
D.S.	60	Nil	Asthma	D,T	59	31

Smoking history: light < 10 cigarettes/day, moderate 10 to 20 cigarettes/day, heavy > 20 cigarettes/day
Treatment: S = salbutamol (800 μg/day); B = beclomethasone diproprionate (400 μg/day); D = disodium cromoglycate (80 mg/day); O = orciprenaline aerosol (4000 μg/day); P = prednisone (daily dose); T = theophylline (various preparations and doses)

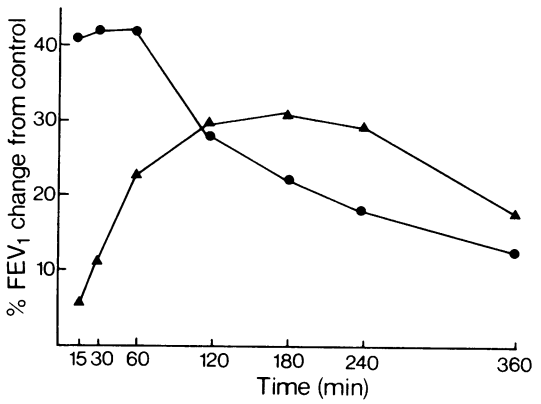

Figure 1 The mean percentage changes in forced expiratory volume in one second (FEV_1) from control values for the fourteen asthmatic patients after 375 mg theophylline (375 mg, ▲) orally and salbutamol (200 μg, ●) by pressurized aerosol.

Discussion

There have been no resported studies evaluating the relative bronchodilator efficacies of oral theophylline derivatives and the more recently available β_2-adrenoceptor stimulating drugs administered by inhalation. Such investigations are required to determine the role of these two classes of drugs and also these two routes of administration in the treatment of asthma.

Table 2 The individual and mean ± s.e. mean forced expiratory volume in one second (FEV_1) integrated responses (the calculated areas under the FEV_1 response curves with respect to time (360 min) for the fourteen asthmatic patients after each treatment, theophylline (375 mg) orally and salbutamol (200 μg) by pressurized aerosol.

Patient	*Salbutamol*	*Theophylline*
L.R.	13.60	96.25
R.D.	229.75	104.45
R.R.	116.85	123.30
M.B.	196.03	202.04
F.T.	62.07	105.66
F.A.	121.35	141.38
D.L.	307.84	264.74
A.T.	284.34	157.29
W.S.	8.94	38.63
A.M.	44.90	192.30
W.W.	144.83	148.11
C.S.	172.14	1.88
A.B.	225.94	153.58
D.S.	88.26	173.14
Mean ± s.e. mean	144.06 ± 25.70	135.91 ± 17.78

The theophylline preparation (Nuelin) used in this study is a microfined tablet which contains only the active bronchodilator with no solubilizing agents or salts. The theophylline tablets have the property of very rapid *in vitro* and *in vivo* dissolution (Graham, Hartnett & Hayter, 1974). These authors observed similar plasma levels in healthy subjects in a cross-over study comparing the rapidly dissolving tablets with an hydro-alcoholic theophylline elixir. Hartnett, Marlin & Graham (1974) showed that a 375 mg dosage of both these theophylline preparations produced equivalent bronchodilatation associated with similar, therapeutic plasma theophylline levels for 4 h, when compared in a placebo-controlled trial in asthmatic patients.

When β_2-adrenoceptor stimulating drugs are administered preferentially to the bronchial tree by inhalation, immediate bronchodilator action occurs, as observed in this study. This rapid onset of bronchodilatation is highly desirable for the effective relief of acute asthmatic symptoms. Unwanted systemic effects, resulting from stimulation of β-adrenoceptors in the heart, peripheral vasculature and skeletal muscle, are minimal, because blood levels of the drugs are very low after pressurized aerosol inhalation (Walker, Evans, Richards & Paterson, 1972). The bronchodilator response after oral theophylline is related to the blood concentration of the drug achieved, and side-effects are negligible within the therapeutic range (Turner-Warwick, 1957; Jackson, McHenry, Moreland, Rayner & Etter, 1964; Jenne, Wyze, Rood & McDonald, 1972). Although the response was slower in onset than after salbutamol, effective bronchodilatation with theophylline was achieved after 1 h and maintained for a further 5 hours. Indeed, the maximal FEV_1 response between 2 and 4 h after theophylline compared more favourably with salbutamol than was expected. If both drugs were administered simultaneously, it is possible that the beneficial, bronchodilator properties of each drug may be additive. Thus, the immediate, peak bronchodilatation resulting from the topical action of inhaled salbutamol might be sustained for a longer period by combination with longer-acting oral theophylline. Whether such a prediction could be realized without producing significant toxicity requires further investigation.

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