Br. J. Dis. Chest (1984) *78*, 358

THE EFFECTS OF THEOPHYLLINE AND SALBUTAMOL ON RIGHT AND LEFT VENTRICULAR FUNCTION IN CHRONIC BRONCHITIS AND EMPHYSEMA

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Summary

We have compared the effects of oral theophylline and salbutamol on right and left ventricular function in twelve patients with chronic bronchitis and emphysema. Right and left ventricular ejection fraction (RVEF and LVEF) were measured using multiple gated radionuclide ventriculography. Theophylline 600 mg and salbutamol 4 mg both produced increases in RVEF and LVEF. There were no significant changes in blood gases after either drug. The clinical significance of the effects of oral bronchodilators on cardiac function in patients with chronic bronchitis and emphysema has yet to be determined.

Introduction

Pulmonary hypertension and right ventricular failure carries a poor prognosis in patients with chronic bronchitis and emphysema (Middleton et al. 1979; Weitzenblum 1981) and there is a need for agents that improve pulmonary haemodynamics and right heart function without adversely affecting arterial oxygen tension. Recently there has been considerable interest in the effect of β_2-agonists on the pulmonary vasculature in patients with chronic bronchitis and emphysema (Macnee et al. 1983; Peacock et al. 1983). Although theophylline compounds are often prescribed for their bronchodilator and other properties, information about their effects on ventricular performance is limited. Using a non-invasive technique we have compared the effects of oral theophylline and salbutamol on right and left ventricular function in chronic bronchitis and emphysema.

Patients and Methods

Twelve patients with chronic bronchitis and emphysema (mean age 62.7, range 44–80 years) gave informed consent to participate in this study. They had no clinical evidence of coronary or valvular heart disease and no patient had systemic hypertension. Five patients had a past history of right ventricular failure but this was not present at the time of the study. Mean FEV_1 was 0.75 litres, SEM 0.09 litres, mean FVC 1.70 litres, SEM 0.15 litre, mean P_{aO_2} 65.5 mmHg, SEM 4.4 mmHg and

mean P_{ACO_2} 43.8 mmHg, SEM 2.2 mmHg. Right and left ventricular ejection fraction (RVEF and LVEF) were measured using multiple gated radionuclide ventriculography. This technique uses an in vivo method of red cell labelling; 0.03 ml/kg Amerscan stannous agent is injected intravenously. After 30 minutes 20 mCi ^{99m}technetium pertechnetate is injected into a peripheral vein. After 5 minutes to allow equilibration in the blood pool the multiple gated study is performed using a Siemens large field gamma camera and Medical Data Systems computer. The patient lies supine with the camera angled 10 degrees caudally and 30 degrees left anterior oblique; in each patient the angle is adjusted to obtain maximum separation of the ventricles. Analysis of two right ventricular regions of interest is performed to calculate RVEF. Fourier phase and amplitude functional images are used to help trace the regions of interest. All studies were analysed by the same observer (J.A.L.). This technique is highly reproducible with minimal intraobserver variation (Winter et al. 1984).

FEV_1 and FVC were measured in duplicate using a portable spirometer (VS 400, Puritan Bennett, Chichester, Sussex) and the better measurement recorded in each case. Oxygen tension (P_{AO_2}), carbon dioxide tension (P_{ACO_2}) and hydrogen ion concentration (pH) were measured from a single radial arterial sample drawn breathing room air (ABL1, Radiometer, Copenhagen).

Patients were taking neither maintenance theophylline derivatives nor oral β_2-sympathomimetic agonists, although the use of salbutamol inhaler was permitted on the day of the study, previous

Table I. The effects of salbutamol 4 mg and theophylline 600 mg on RVEF and LVEF

		0 minute	*60 minutes*	*90 minutes*
Salbutamol 4 mg	RVEF	0.35±0.02	0.41±0.03 ($P<0.001$)	0.37±0.03 ($P<0.05$)
	LVEF	0.56±0.03	0.66±0.03 ($P<0.001$)	0.63±0.03 ($P<0.01$)
Theophylline 600 mg	RVEF	0.33±0.02	0.37±0.03 ($P<0.001$)	0.37±0.02 ($P<0.001$)
	LVEF	0.55±0.03	0.66±0.03 ($P<0.001$)	0.62±0.03 ($P<0.01$)

work having established that this has no effect on RVEF and LVEF in chronic bronchitis and emphysema. No patient was receiving continuous oxygen therapy at the time of the study. Patients were randomized to receive either theophylline choline 600 mg (Choledyl, William R. Warner and company) or salbutamol 4 mg in a double-blind manner on each of two study days. The former preparation was chosen because it is rapidly absorbed, reaching a peak concentration within 1 hour (Jones 1979). Serum theophylline was measured at 60 and 90 minutes by immunoassay (Emit theophylline kit, Pyva, Palo Alto, California) adapted for automated analysis (Centrifichem 400, Baker diagnostics). Spirometry, heart rate and blood pressure were measured prior to and at 60 and 90 minutes after drug ingestion. Arterial blood gases were measured before and 60 minutes after drug ingestion.

Values are stated as means and standard errors of the mean (SEM). Statistical analysis of haemodynamic and pulmonary function variables was performed using Student's *t*-test for paired data.

Results

Table I gives the mean values for RVEF and LVEF prior to and after drug ingestion. Theophylline and salbutamol both produced significant increases in RVEF at 60 and 90 minutes. The increase in RVEF was not related to either the initial ejection fraction or to the serum theophylline levels (Tukey's test for

monotonic association). LVEF increased following both drugs at 60 and 90 minutes.

Changes in Pa_{O_2}, Pa_{CO_2} and heart rate are given in Table II. Although individual responses were variable, with Pa_{CO_2} falling by more than 3 mmHg in seven patients, overall there was no change in Pa_{CO_2}. No changes in mean FEV_1 or FVC were seen during the study. Mean blood pressure did not alter following either drug.

Mean theophylline levels achieved were 10.6, range 6–12 μg/ml at 60 minutes and 10.7, range 8–14 μg/ml at 90 minutes.

Table II. The effects of salbutamol 4 mg and theophylline 600 mg on heart rate and arterial blood gas tensions

		0 minute	*60 minutes*	*90 minutes*
Salbutamol 4 mg	Pa_{O_2} (mmHg)	67.1 SEM 4.6	69.5 SEM 7.4 (NS)	
	Pa_{CO_2} (mmHg)	44.4 SEM 2.5	45.7 SEM 3.6 (NS)	
	HR (min^{-1})	79 SEM 7	93 SEM 7 ($P<0.01$)	72 SEM 5 (NS)
Theophylline 600 mg	Pa_{O_2} (mmHg)	65.5 SEM 5.1	68.6 SEM 6.4 (NS)	
	Pa_{CO_2} (mmHg)	46.0 SEM 4.6	43.0 SEM 3.7 (NS)	
	HR (min^{-1})	84 SEM 5	108 SEM 6 ($P<0.001$)	92 SEM 7 ($P<0.01$)

Discussion

In patients with severe airflow limitation due to chronic bronchitis and emphysema RVEF is reduced at rest (Macnee et al. 1983). We have shown that theophylline, like β_2-sympathomimetic agents, produces a sustained increase in RVEF and LVEF in these patients. In previous studies with simultaneous right and left heart catheterization Parker and colleagues showed a reduction in mean pulmonary artery pressure, right ventricular end-diastolic pressure and pulmonary vascular resistance following theophylline suggesting either a reduction in vascular tone or active dilatation of the pulmonary arterioles (Parker et al. 1967). However, in that study serum levels were not measured and it is likely that the high dose used (1 g intravenously over 30 minutes) produced very high serum levels (Jusko et al. 1977).

This study has demonstrated that theophylline exerts an appreciable effect on the pulmonary vasculature and right ventricle which is apparent even at the lowest therapeutic levels, in keeping with the finding of Ogilvie and co-workers who found that in normal volunteers changes in heart rate and systolic time interval were evident at concentrations above 10 μg/ml (Ogilvie et al. 1977).

Similar improvement in right ventricular performance is seen after salbutamol and this is probably due to a reduction in pulmonary artery pressure and vascular resistance (Timmis et al. 1979).

Like Daly and Howard we found that the effects on arterial blood gas tensions were variable (Daly & Howard 1965). $PaCO_2$ fell by more than 3 mmHg in seven patients but overall this did not reach statistical significance. PaO_2 response was variable with both drugs.

Debate continues about the dominant mechanism by which theophylline exerts its influence on the pulmonary vasculature and right ventricle. Evidence for a direct effect is supported by animal studies that have shown a reduction in pulmonary artery pressure with little change in the cardiac index (Borst et al. 1957; Barer & Gunning 1959). Independent of any effect on the pulmonary vasculature theophylline also has a powerful action on myocardial mechanics. The observation that the response to theophylline is reduced following agents that deplete endogenous catecholamine stores provides evidence that the response to theophylline may be mediated partly by catecholamines (Marcus et al. 1972). Theophylline will inhibit phosphodiesterase and may, like salbutamol, cause an increase in intracellular 3,5-cyclic AMP. Thus salbutamol may, in part, have a shared mechanism of action with theophylline.

We have previously shown that inhaled salbutamol at doses commonly prescribed has no effect on RVEF (Winter et al. 1984). Nevertheless inhaled β_2-agonist therapy is frequently used as the mainstay of treatment in these patients who have severe airflow limitation and pulmonary hypertension. It seems likely that an orally active agent that reduces pulmonary artery pressure would be valuable in this group of patients provided no adverse effect on arterial oxygen saturation were seen. If this were to prove the case then salbutamol with its wider therapeutic index would be preferable to theophylline. As yet there has been no long-term trial of oral β_2-agonists in this group of patients and this is now being undertaken.

References

Barer, G. R. & Gunning, A. J. (1959) Action of a sympathomimetic drug and of theophylline ethylene diamine on the pulmonary circulation. *Circulation Res. 7,* 383.

Borst, H. G., Berglund, E. & McGregor, M. (1957) Effects of pharmacological agents on the pulmonary circulation in the dog: studies of epinepherine, nor-epinepherine, 5-hydroxytryptamine, acetyl choline, histamine and aminophylline. *J. clin. Invest. 38,* 669.

Daly, J. J. & Howard, P. (1965) Effect of intravenous aminophylline on the arterial oxygen in chronic bronchitis. *Thorax 20,* 324.

Jones, R. W. (1979) Comparative pharmacokinetics of two theophylline derivatives in asthmatic patients. *J. Int. Med. Res. 7* (suppl. 1), 16.

Jusko, W. J., Koup, J. R., Vance, J. W., Schentag, J. J. & Kuritzky, P. (1977) Intravenous theophylline therapy: nomogram guidelines. *Ann. intern. Med. 86,* 400.

Macnee, W. J., Wathen, C. G., Hannan, W. J., Flenley, D. C. & Muir, A. L. (1983) Effects of pirbuterol and sodium nitroprusside on pulmonary haemodynamics in hypoxic cor pulmonale. *Br. med. J. 287,* 1169.

Marcus, M. L., Skeleton, C. L., Grauer, L. E. & Epstein, S. E. (1972) Effects of theophylline on myocardial mechanics. *Am. J. Physiol. 222,* 1361.

Middleton, H. C., Peake, M. D. & Howard, P. (1979) Hypoxaemia in chronic bronchitis. *Thorax 34,* 313.

Ogilvie, R. I., Fernandez, P. G. & Winsberg, F. (1977) Cardiovascular response to increasing theophylline concentrations. *Eur. J. clin. Pharmacol. 12,* 409.

Parker, J. O., Ashekian, P. B., Di Giorgi, S. & West , R. O. (1967) Haemodynamic effects of aminophylline in chronic obstructive pulmonary disease. *Circulation 35,* 365.

Peacock, A., Busst, C., Dawkins, K. & Denison, D. M. (1983) Response of the pulmonary circulation to oral pirbuterol in chronic airflow limitation. *Br. med. J. 287,* 1178.

Timmis, A. P., Strak, S. K. & Chamberlin, D. A. (1979) Haemodynamic effects of salbutamol in patients with acute myocardial infarction. *Br. med. J. 2,* 1101.

Weitzenblum, E., Hirth, C., Dulolone, A., Mirhom, R., Rasaholinjanahary, J. & Ehrhart, M. (1981) Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax 36,* 752.

Winter, R. J. D., Langford, J. A. & Rudd, R. M. (1984) Effects of oral and inhaled salbutamol and oral pirbuterol on right and left ventricular function in chronic bronchitis. *Br. med. J. 288,* 824.