COMBINATION OF AMINOPHYLLINE (PHYLLOCONTIN CONTINUS TABLETS) AND SALBUTAMOL IN THE MANAGEMENT OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

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- 1 The effect of a controlled release theophylline derivative (Phyllocontin Continus tablets) and an adrenoceptor agonist (salbutamol) was compared when taken singly and concomitantly in twenty patients with chronic bronchitis and additional reversible airways obstruction using a double-blind crossover technique.
- 2 The pulmonary function data showed a significant improvement in airways obstruction with an associated reduction in hyperinflation on combination therapy, as compared with either drug taken alone.
- 3 No significant improvement in patient symptoms occurred on combination therapy as compared with either drug taken alone.
- 4 A high incidence of side-effects was noted with both Phyllocontin Continus and salbutamol. Combination therapy, however, did not increase the frequency or severity of side-effects seen on either drug alone.
- 5 Although a proportion of patients showed evidence of intercurrent infection during the nine-week trial period, this did not appear to influence the results for the group as a whole.

Introduction

Both β -adrenoceptor agonists and methylxanthines have been shown to cause bronchodilation by increasing levels of cyclic AMP which appears to regulate bronchodilation and immune mediator release in lung (Orange, Kaliner, Laraia & Auster, 1971). Their modes of action are, however, thought to be different, the former stimulating the adenylyl cyclase system and the methylxanthines inhibiting cyclic nucleotide phosphodiesterase. It has been demonstrated *in vivo* in the inotropic response of rabbit atria (Rall & West, 1963) and in human lung (Kaliner, Orange, Koopman Austen & Laraia, 1971), that these two classes of drug act synergistically in raising cyclic AMP concentrations.

Salbutamol is a β_2 -adrenoceptor agonist that is relatively free from cardiac effects (Lands, Luduena & Buzzo, 1967; Cullum, Farmer, Jack & Levy, 1969) and is commonly used both orally and as a pressurized aerosol in the treatment of reversible airways obstruction.

Theophylline rendered soluble as its ethylene diamine complex (aminophylline) has long been used intravenously, orally and rectally in the prevention and relaxation of bronchospasm. Oral aminophylline has required frequent administration to maintain

therapeutic levels on account of the short half life of the drug and has caused distressing irritation of the gastric mucosa in some patients. The recent introduction of a controlled release aminophylline preparation (Phyllocontin Continus Tablets PC) has enabled maintenance of therapeutic theophylline levels on a twice daily dosage and has been reported (Boroda, Miller, Leslie, Nicol & Thomson, 1973) to reduce the incidence of gastric irritation. The aim of the present study was to evaluate the use of a controlled release aminophylline tablet (PC) as a concomitant therapy in patients receiving salbutamol and to determine if the synergism which has been demonstrated in relation to cyclic 3,5-AMP concentrations, is of clinical benefit.

Methods

The forty patients initially selected for the trial fulfilled The Medical Research Council criteria for the diagnosis of chronic bronchitis (chronic or recurrent cough productive of sputum, occurring on most days for at least 3 months of the year and for 3 or more successive years) and showed demonstrable

reversibility of airways obstruction with at least 15% improvement in forced expired volume in 1 s (FEV₁) after a single dose of isoprenaline by aerosol on at least two occasions prior to inclusion in the trial. Those with current pulmonary infection, history of pulmonary tuberculosis, chronic renal failure, cor pulmonale, left ventricular failure, systemic hypertension or ischaemic heart disease, were excluded from consideration. Twenty patients completed the trial, twelve male and eight female, their ages ranging from 31 to 69 years (mean 51 years). All other bronchodilator therapy was discontinued and in one patient on low dose steroid therapy, this was continued unchanged throughout the trial period.

There were three phases of treatment. In Phase I each subject received PC one tablet (225 mg) twice daily for 1 week, then two tablets twice daily for a further 7 days. In Phase II the patients continued with either active PC tablets two twice daily or an identical placebo tablet two twice daily for 3 weeks, with in addition, salbutamol 4 mg three times daily during this period. In Phase III, the PC was changed to placebo or *vice versa* depending on the regime given in Phase II, one tablet twice daily for 1 week followed by two twice daily for a further 3 weeks with in addition, salbutamol 4 mg three times daily during this period. There were four visits in all including the pre-trial interview, which consisted of a clinical assessment and the measurement of pulmonary function tests. Symptoms of cough, sputum production and exertional dyspnoea, were recorded

and graded into one of three categories according to severity. Questions relating to intercurrent chest infection were incorporated in the questionnaire and patients were asked to record any side effects which they experienced. Recordings of pulse and blood pressure were taken at completion of the interview on each occasion. Further assessment of symptoms was obtained from a daily diary kept by the patients in which symptoms of cough, wheeze or chest tightness were graded into one of five categories.

Pulmonary function tests consisted of standard spirometry using a low inertia spirometer and a 'pulmatest' (PK Morgan Limited, London) from which values for vital capacity (VC), FEV₁, functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC) were obtained. Flow volume measurements were completed on each patient with flow rates compared at constant lung volume. Maximum expiratory flow was measured at 60% of total lung capacity. Results were expressed in litres and all volumes were corrected to body temperature and pressure saturated with water vapour. The patients were also asked to record in the daily diary, morning and evening peak flow estimations using a miniwright peak flowmeter (AIRMED, London).

Blood samples were taken at each visit for serological monitoring of antibody titres to common respiratory viruses, including influenza A, B and C, parainfluenza 1, 2 and 3, adenovirus, respiratory syncytial virus, and mycoplasma pneumoniae.

Table 1 Mean values for pulmonary function data ± 2 s.d. from the mean before and during trial period. Volumes expressed in litres (BTPS) and also as a percentage of the mean predicted normal.

Pulmonary function measurements	Pretreatment	Phyllocontin	Salbutamol/ placebo	Salbutamol/ Phyllocontin
Vital capacity				
absolute	3.2 $\pm$ 0.9	3.4 $\pm$ 1.0	3.3 $\pm$ 1.0	3.5 $\pm$ 1.0
% predicted	74.0 $\pm$ 16.8	77.7 $\pm$ 16.9	75.9 $\pm$ 18.7	79.3 $\pm$ 16.9
FEV ₁				
absolute	1.8 $\pm$ 0.9	1.9 $\pm$ 0.9	1.8 $\pm$ 0.9	2.0 $\pm$ 1.0
% predicted	55.3 $\pm$ 21.8	59.6 $\pm$ 25.1	55.9 $\pm$ 22.5	60.8 $\pm$ 23.9
FEV ₁ /FVC ratio	54.8 $\pm$ 14.4	54.1 $\pm$ 15.6	53.9 $\pm$ 15.2	58.3 $\pm$ 16.9
Functional residual capacity (FRC)				
absolute	3.8 $\pm$ 1.2	3.8 $\pm$ 1.0	4.3 $\pm$ 1.1	3.9 $\pm$ 1.1
% predicted	122 $\pm$ 39.0	120 $\pm$ 22.0	136 $\pm$ 33.0	124 $\pm$ 25.0
RV/TLC ratio	46.8 $\pm$ 13.7	42.9 $\pm$ 12.0	47.8 $\pm$ 14.3	45.0 $\pm$ 11.9
Maximum expiratory flow rate (60% TLC)	—	0.8 $\pm$ 1.3	0.6 $\pm$ 0.8	0.7 $\pm$ 0.9
Peak flow	—	3.3 $\pm$ 1.4	3.4 $\pm$ 1.5	3.6 $\pm$ 1.8
Daily peak flow (AIRMED)	—	4.6 $\pm$ 2.6	5.1 $\pm$ 3.7	5.2 $\pm$ 3.7

Analysis of the numerical data was by paired *t*-tests and evaluation of the symptomatic data was by the chi-squared test.

Results

Lung function tests

The results of pulmonary function tests are summarized in Table 1. No significant improvement in airways obstruction occurred, between baseline pre-study lung function data and the periods of the trial in which salbutamol or PL tablets alone were used, apart from an increase in VC of 200 ml ($P < 0.05$) and fall in RV/TLCs of 3.9 ($P < 0.02$) on PC tablets compared with salbutamol alone. However, a significant improvement in airways obstruction occurred with combination therapy as compared with pre-study baseline estimations. FEV₁ increased by 200 ml ($P < 0.05$), mean FEV₁ (expressed as a percentage of predicted normal) by 5% ($P < 0.01$) with an increase in the VC (expressed as a percentage of predicted normal) of 5.3% ($P < 0.01$). The FEV₁/FVC ratio also rose but this change was not statistically significant.

Improvement in airways obstruction was seen on PC therapy alone as compared with salbutamol alone and although marginal, this was present throughout, and reached statistical significance with an increase in FEV₁ (expressed as a percentage of predicted normal) of 3.7 ($P < 0.05$), reduction in FRC of 500 ml ($P < 0.01$) and 15% of mean predicted normal ($P < 0.02$), with a reduction RV/TLC ratio of 4.9% ($P < 0.01$).

Symptoms

Historical data is summarized in Tables 2 and 3. No significant alteration of cough, sputum production, dyspnoea, or severity of chest complaints was seen on analysis of the physician's questionnaire and similarly examination of the patients' diaries showed no significant change in symptoms of cough, wheeze and chest tightness throughout the different phases of treatment.

Respiratory infection

Nine patients reported chest infections of which, one was related to rising titres to Influenza A, one to parainfluenza 3, and 2 to respiratory syncytial virus. Two other individuals had rising viral titres (influenza A, parainfluenza 3) suggestive of infection without clinical symptoms. However, eighteen out of twenty patients had elevated viral titres indicating previous exposure to the respiratory viral pathogens. When the data was re-examined after removing those eleven individuals with documented evidence of intercurrent infection, analysis of FEV₁ expressed as a percentage of mean predicted normal value and FEV₁/FVC ratio of the remaining subjects, showed a similar pattern to those obtained with the group as a whole.

Side effects

The incidence of side effects is shown in Table 4. A significant incidence of side effects was seen with both salbutamol and PC, 24% (7 out of 29) of those receiving salbutamol reported tremor, and 50% (18

Table 2 Physician questionnaire

Assessment	Severity	Pre-treatment	Phyllocontin	Salbutamol/ placebo	Salbutamol/ Phyllocontin	χ^2	P
Chest	Poor	4	4	2	1	3.72	0.5
	Moderate	12	11	11	12		
	Good	4	5	7	7		
Cough	Absent	2	2	3	3	1.45	0.95
	Occasional	12	10	9	11		
	Frequent	6	8	8	6		
Sputum	Less than normal	0	5	5	8	10.48	0.1
	Normal	18	13	12	11		
	More than normal	2	2	3	1		
Exertional dyspnoea	Absent	1	1	2	3	12.18	0.05
	Occasional	7	6	12	13		
	Frequent	12	13	6	4		

out of 36) receiving PC reported side effects, of whom twelve suffered nausea, five heartburn and abdominal discomfort, two headaches and three non-specific symptoms. Overall, however, these side effects were severe enough to warrant withdrawal of the drug in only five patients (13%).

Reasons for withdrawal

Of the twenty patients who failed to complete the trial, five had intercurrent illness, seven complained of side effects of the trial tablets, four were reluctant to continue the required lung function tests, and four defaulted with no reason given.

Discussion

The present study examined the bronchodilator effect of PC tablets, 450 mg twice daily, and salbutamol, 4 mg three times daily, as oral preparations both separately and in combination, using a double-blind crossover technique over a 9-week period. These dosages were chosen since they were the maximum recommended to produce therapeutic benefit without the occurrence of troublesome side effects. The combination of PC tablets with oral salbutamol produced significantly greater bronchodilation and reduction in hyperinflation than either preparation

Table 3 Patient diary data

<i>Assessment</i>	<i>Severity</i>	<i>Phyllocontin</i>	<i>Salbutamol/ placebo</i>	<i>Salbutamol/ Phyllocontin</i>	χ^2	P
Wheeze	None	6	9	10	5.69	NS
	Slight	6	3	2		
	Moderate	7	6	8		
	Severe	1	2	0		
Cough	None	3	5	5	3.50	NS
	Slight	11	9	7		
	Moderate	6	6	7		
	Severe	0	0	1		
Chest tightness	None	9	8	8	3.50	NS
	Slight	5	6	7		
	Moderate	6	5	4		
	Severe	0	1	1		

Table 4 Incidence of side effects attributed to salbutamol and Phyllocontin in the forty patients initially participating in the study.

<i>Drug</i>	<i>Side effect</i>	<i>Incidence %</i>
Salbutamol	Tremor	7 out of 29* 24%
Phyllocontin		18 out of 36† 50%
	Nausea	12
	Heartburn and Abdominal discomfort	5
	Headaches	2
	Non-specific complaints e.g. 'not feeling well'	3

*11 patients discontinued the trial before completing a period on salbutamol therapy.

†4 patients defaulted.

used alone. This observation is similar to that reported by workers using other β -adrenergic receptor agents in combination with methylxanthine derivatives (Smith, Kuo & Steen, 1976; Dyson & Campbell, 1977; Marlin, Hartnett, Berand & Hacket, 1978; Wolfe, Tashkim, Calvanese & Simmons, 1978) and the improvements in pulmonary function which were noted were indicative of an additive rather than a synergistic effect (Marlin *et al.*, 1978). In the present study, the use of PC tablets with oral salbutamol produced no clinical evidence of haemodynamic disturbance, nor any indication of added toxicity so that patients free from side effects with either drug alone may readily tolerate the combined regime and may, thereby, achieve more effective bronchodilation. Despite the clear cut improvement in bronchodilation which was noted when the drugs were used together, no subjective improvement in clinical well-being was recorded by the patients during the course of this study. It has been suggested (Wolfe *et al.*, 1978) that the additive effect noted between these two groups of bronchodilators may permit the use of both drugs in high dosage in subjects where less than adequate bronchodilation was obtained with a high dose of either drug used alone or lower doses may be employed in order to achieve the same degree of bronchodilation but without the risk of side effects which are prevalent at higher doses. It is clear, therefore, that longer term studies would be required to evaluate more completely the extent of the therapeutic advantages when employing combinations of these two classes of oral bronchodilator agents in the management of chronic reversible airways obstruction.

The high incidence of side effects found with Phyllocontin Continus tablets in this study, mainly of nausea, heartburn and abdominal discomfort, was similar to that noted by Greening and his co-workers (Greening, Baillie, Gribbon & Pride, 1979) but in contrast to other reports (Boroda *et al.*, 1973;

Dhatariya, 1975; Maneksha, 1976; Achariya, 1977) in which toxicity was noted to be minimal and gastrointestinal disturbance rare. The explanation for this difference is not clear. A recent review of the factors which affect theophylline clearance (Ogilvie, 1978) implicated increasing age, obesity, smoking and liver dysfunction as important elements which decrease the clearance of this drug and, therefore, which may increase the potential for developing toxicity. In the present study, however, these population characteristics do not appear biased in the direction of reduced theophylline clearance and cannot, therefore, account for the high prevalence of side effects which was observed.

Serological monitoring of antibodies to common respiratory viruses confirmed that a significant number of patients developed respiratory infections during the 9 weeks of the trial period. When the pulmonary function data from those who suffered an infective incident during this time were analysed, they were identical to the data from the group as a whole. So that the overall pattern of pulmonary function throughout the study was not significantly affected by intercurrent infection. It has been suggested, however, that acute viral infective incidents can reduce the clearance of theophylline (Chang, Bell, Lauer & Chai, 1978; Fleetham, Nakatsu & Munt, 1978) so that toxic effects may emerge in these situations. During the course of this work, eleven of the twenty subjects had evidence of recent respiratory infections and eighteen of the total group had elevated viral titres consistent with infection in the recent past. It may be that the relatively high incidence of infection within the series accounted for the increased prevalence of side effects which was noted.

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