Sustained release oral aminophylline in patients with airflow obstruction

A P GREENING, E BAILLIE, H R GRIBBIN, AND N B PRIDE

From the Department of Medicine, Hammersmith Hospital, London

ABSTRACT Twenty-four patients with reversible airflow obstruction under suboptimal control on conventional therapy entered a double-blind placebo-controlled trial of additional oral sustained release aminophylline. Assessment was by diary cards, twice daily PEF_R, and weekly FEV₁. Nineteen patients completed the trial satisfactorily. Eleven were improved subjectively by addition of aminophylline. The mean PEF_R for all 19 patients rose from 232 l min⁻¹ SEM ± 5, to 247 l min⁻¹ SEM ± 4 ($p < 0.0001$); nine individuals showed a statistically significant improvement in mean PEF_R and 10 showed an improvement of >200 ml in their FEV₁. Improvement in PEF_R on aminophylline was not at the expense of benefit from inhaled salbutamol. Unwanted effects of nausea, headache, and abdominal discomfort were recorded by 12 of the 24 patients entering the trial. Seventeen of the 19 patients completing the trial had plasma theophylline levels in the accepted therapeutic range of 10–20 mg l⁻¹. The drug doses required to achieve these levels varied from 8.6–30.8 mg kg⁻¹ 24 hr⁻¹ in the patients with no clinical or biochemical evidence of liver disease. Oral aminophylline can improve control of airflow obstruction in patients with moderately severe disease who are already receiving multiple medication, but side-effects often limit its use. The wide dose range required to achieve therapeutic plasma levels indicates that measurements of plasma theophylline are necessary for adequate interpretation of trials of theophylline compounds.

Intravenous theophylline preparations have been used in the management of asthma since 1937. Latterly, the increased availability of plasma theophylline measurements has led to a re-evaluation of intravenous dose schedules.^{1,2} It is generally agreed that peak plasma theophylline levels should be kept below 20 mg l⁻¹ while trough levels should remain above 10 mg l⁻¹. Similar principles apply to oral preparations.^{3,4} The recent development of a sustained release oral aminophylline preparation in a lipid base (Phyllocontin Continus Tablets, Napp Laboratories) has enabled the maintenance of such plasma theophylline levels when the drug is given 12-hourly.⁵ We have examined whether this drug can improve the control of airflow obstruction in patients in whom existing treatment was providing suboptimal control.

Methods

Twenty-four patients, 13 men and 11 women, of mean age 57 years (range 19 to 71 years), with reversible airflow obstruction who attended Hammersmith Hospital regularly were entered into the trial (table 1). Approval of the local ethics committee and informed consent from the patients were obtained. All patients had moderately severe airflow obstruction requiring multiple medication. Twenty were regularly using inhaled steroids and six of these required regular oral steroid therapy in addition. Twenty-three were receiving inhaled, and two oral, β -agonists; one used disodium cromoglycate and one ipratropium bromide. Individual dose requirements of aminophylline were determined during an open phase preceding the trial. Plasma theophylline was measured by high pressure liquid chromatography⁶ at times of peak (four to six hours post dosage) or trough (10 to 12 hours post dosage) plasma levels and were re-

Address for reprint requests: Dr AP Greening, Department of Medicine Hammersmith Hospital, Du Cane Road, London W12 0HS.

Table 1 Age, sex, dose of Phyllocontin, plasma theophylline levels, and side-effects in 24 patients entered into the trial

Trial number	Age (yr)	Sex	Dose (mg/24 hr)	Dose (mg/kg/24 hr)	Plasma theophylline*	Side-effects†
1	61	M	1350	19.2	++	0
2	66	M	2250	30.8	+	0
3	70	F	900	14.4	±	+
4	59	F	900	12.6	++	+++
5	68	F	650	11.8	+	+++
6	26	M	850	11.4	++	+++
7	71	F	900	16.2	+	++
8	19	F	900	18.6	+	0
9	60	M	1100	14.2	++	0
10	55	M	900	12.2	±	0
11‡	63	M	500	7.0	++	+++
12	59	M	900	12.8	++	0
13	68	F	650	12.0	+	++
14	59	M	1350	14.8	+	0
15	68	F	900	20.0	++	+
16	65	F	650	10.8	+	++
17	58	M	800	10.2	±	+++
18	68	F	650	9.7	?§	+++
19	25	F	650	12.6	+	0
20	53	M	1350	19.2	++	0
21	68	M	650	8.6	+	0
22	62	M	1100	12.8	+	0
23	50	M	1350	15.8	++	0
24	41	F	900	13.6	++	++

* ++ = peak level > 15 mg l⁻¹ and/or trough level > 10 mg l⁻¹; + = peak level 10–15 mg l⁻¹ and/or trough level < 10 mg l⁻¹; ± peak level < 10 mg l⁻¹.

† 0 = none; + = present on at least seven of the 28 days but only transient (one to two hours) in nature; ++ = present on most days but of limited duration; +++ = virtually constant.

‡ Patient has alcohol-induced cirrhosis of the liver.

§ Patient discontinued the drug before a plasma theophylline estimation could be made.

|| = unable to complete the trial satisfactorily.

peated if unsatisfactory after a minimum interval of three days. Using these levels the daily doses were adjusted so that, as near as possible, plasma theophylline levels remained in the range 10 to 20 mg l⁻¹ throughout the 12-hour interdosing period.

A double-blind crossover trial design was used with patients receiving four consecutive weeks of active and four consecutive weeks of placebo medication in a randomly allocated order. The tablets were taken 12-hourly. Throughout the period of the trial all patients continued their other medications in unaltered dosage. Eight patients used an inhaled β -agonist regularly four times daily. The others recorded the frequency of their inhaler use. During the trial patients kept a diary of their respiratory symptoms ("better, worse, or no change from usual") and of possible unwanted effects from the medication. They also measured, before any use of β -agonists, their peak expiratory flow rate (PEFR) first thing in the morning and last thing at night and recorded the best value obtained in three attempts. The eight

patients using inhaled β -agonists regularly repeated their PEFR 15 minutes after using the inhaler. Statistical analysis of the PEFR records was by Student's paired *t* test. All patients were seen weekly when their forced expiratory volume in one second (FEV₁) and slow vital capacity (VC) were measured on a dry spirometer. The best value of three estimates was recorded. Weekly blood samples were taken for analysis of plasma theophylline levels. This was performed by one of us (EB) on coded specimens, the trial code to be broken for ethical reasons if any plasma sample had a theophylline level of >25 mg l⁻¹. The results of the plasma theophylline levels were withheld from the clinical assessor until after the end of the trial.

Results

The results from 19 patients were suitable for full analysis. Of the remaining five patients three (5, 17, and 18) withdrew because of side-effects and two were withdrawn because of irregular attendance (24) and irregular compliance with medication (7).

PLASMA THEOPHYLLINE LEVELS

Peak levels were between 15 and 20 mg l⁻¹ in nine patients, between 10 and 15 mg l⁻¹ in eight patients, and below the desired minimum of 10 mg l⁻¹ in two patients (table 1). The daily maintenance dose used to achieve these levels varied between 7.0 and 30.8 mg kg⁻¹, which represented doses from 450 to 2250 mg per 24 hours.

SUBJECTIVE AND OBJECTIVE BENEFITS

Eleven of the 19 patients recorded subjective benefit while on the active drug and none while on the placebo (table 2). The mean PEFR was slightly higher on the active drug (247 l min⁻¹, SEM $\pm$ 4) than on placebo (232 l min⁻¹, SEM $\pm$ 5), ($p < 0.001$) (figure). In nine patients PEFR on the active drug was significantly greater than on placebo, in nine there was no significant difference, and in one there was a small but statistically significant reduction in PEFR while on the active preparation (table 2). The mean weekly FEV₁ during treatment was 201 ml larger than on placebo ($p < 0.001$). Seventeen of the 19 patients showed some improvement in FEV₁, the remaining two showing no change (figure, table 2). All of the eight patients using inhaled β -agonists regularly were responsive to this treatment (mean rise in PEFR during control period of 47 l min⁻¹), but only four (2, 15, 21, and 23) showed a significant improvement in pre-bronchodilator PEFR on aminophylline. These

Figure Comparisons of the mean daily PEFR and mean weekly FEV₁ for 19 patients during periods of treatment with placebo and with sustained release aminophylline tablets. Group means are indicated by the solid circles joined by dashed lines.

Table 2 Patient number, mean weekly FEV₁, and daily PEFR during periods when placebo and active drugs were added to the standard medication in the 19 patients who successfully completed the trial

Patient number	FEV ₁ (l)		FEV ₁ (% best)*		Before bronchodilator			After bronchodilator			Subjective benefit
	Placebo	Active	Placebo	Active	PEFR (l min ⁻¹)†			PEFR (l min ⁻¹)§			
					Placebo	Active	p‡	Placebo	Active	p‡	
1	0.83	0.85	83	85	183 ± 4	218 ± 4	< 0.001				0
2	1.23	1.46	77	91	189 ± 4	230 ± 3	< 0.001	212 ± 3	242 ± 4	< 0.001	+
3	2.16	2.30	90	96	296 ± 6	306 ± 5	0.009				+
4	1.49	1.56	74	78	191 ± 6	193 ± 5	NS	238 ± 4	247 ± 4	0.05	++
6	2.09	2.45	80	94	177 ± 5	170 ± 6	NS				0
8	2.58	2.78	92	99	389 ± 1	390 ± 2	NS				0
9	2.47	3.06	69	85	349 ± 6	395 ± 9	< 0.001				++
10	1.63	1.71	86	90	214 ± 8	215 ± 4	NS	302 ± 4	289 ± 5	0.02	0
11	0.71	0.89	71	89	192 ± 3	193 ± 2	NS	210 ± 3	211 ± 2	NS	+
12	0.95	1.18	68	84	140 ± 6	140 ± 7	0.001				0
13	1.04	1.04	77	77	149 ± 3	142 ± 4	NS				++
14	2.46	2.59	79	83	329 ± 9	340 ± 6	NS				0
15	1.06	1.33	73	92	155 ± 3	189 ± 2	< 0.001	186 ± 3	220 ± 2	< 0.001	++
16	1.16	1.25	68	74	155 ± 6	137 ± 3	0.006	233 ± 5	219 ± 3	0.01	++
19	1.25	1.49	74	88	140 ± 6	140 ± 6	NS				+
20	2.21	2.68	74	89	380 ± 4	400 ± 4	0.005				0
21	1.15	1.43	70	86	167 ± 3	200 ± 5	< 0.001	210 ± 4	244 ± 4	< 0.001	++
22	2.6	2.15	90	90	316 ± 5	324 ± 4	NS				0
23	1.56	1.81	74	86	306 ± 4	350 ± 4	< 0.001	352 ± 3	392 ± 3	< 0.001	++
Mean	1.59	1.79	77	87	232 ± 5	247 ± 4	< 0.001	243 ± 4	258 ± 3	< 0.001	

NS=not significant = $p > 0.05$.

*FEV₁ as a percentage of the best recorded value during the previous three years, including steroid trial periods.

†Mean PEFR (average of morning and evening) ± SEM before use of inhaled β -agonists.

‡p value as determined from paired t test.

§Mean PEFR (average of morning and evening) ± SEM, 15 minutes after use of inhaled β -agonists.

0=no benefit or detriment; +=moderate improvement; ++=marked improvement.

four responders to aminophylline retained their responsiveness to β -agonists (table 2). The other patients, using inhaled β -agonists as required, reduced their daily usage slightly from a mean of 5.4 puffs while on the placebo to 4.2 puffs on the active drug ($p=0.1$).

UNWANTED EFFECTS

Seven of the 19 patients complained of nausea, headache, or upper abdominal discomfort, as did all five of the patients unable to complete the trial satisfactorily. The severity and duration of these symptoms were variable (table 1).

Discussion

We aimed to examine whether sustained release oral aminophylline was a useful addition to the treatment of some of the more poorly-controlled patients attending our asthma clinic. These patients were mainly in late middle age, so our findings do not necessarily reflect the responsiveness of younger patients to aminophylline. The potential for further reversibility of airflow obstruction in our patients was possibly fairly small as the mean weekly FEV₁, while receiving the active preparation, for the whole group reached 87% of the best value recorded during the previous three years, which included periods on high-dose steroid therapy in several patients. This compares with the 77% achieved while on placebo (table 2).

Seven of the 19 patients failed to achieve either a statistically significant increase in daily PEF_R or a mean increase of 200 ml or more in their FEV₁ while receiving the active preparation (table 2). Of these, three (4, 13, and 16) were clearly unresponsive to the drug, since they achieved reasonable plasma levels of theophylline and were submaximally bronchodilated. Of the others, patient 10 was undoubtedly underdosed and patients 14 and 22 also might have benefited from larger doses. In addition patient 22 was already close to maximal bronchodilation. Patient 11 was one of two steroid unresponsive patients in the trial, and the mean increase in his FEV₁ of 180 ml represented a substantial part of his available reversibility.

We have data on the relation between the response to inhaled β -agonists (salbutamol) and to oral aminophylline in eight of the patients (table 2). Four responded to aminophylline and all retained their responsiveness to β -agonists, so that the effects appeared to be additive. We did not attempt to show whether this additional benefit could have been achieved by increasing the dose of salbutamol. The four patients who did not respond to aminophylline nevertheless showed a good response to β -agonists. Our results suggest that a combination of oral aminophylline and salbutamol may be useful, particularly if side-effects from a higher dose of either drug used alone are proving troublesome.

A wide dose range (8.6 to 30.8 mg kg⁻¹ 24 hr⁻¹) was required to achieve similar plasma levels in the 23 patients who had no overt liver disease or cardiac failure (table 1). Variation did not appear to depend on age, which contrasts with data on intravenous aminophylline therapy.⁷ One patient with liver disease required a significantly reduced

dose (7.0 mg kg⁻¹ 24 hr⁻¹), which is in keeping with experience using intravenous aminophylline.⁷ Clearly, as our doses varied from 225 mg up to 1125 mg 12-hourly, the standard recommended dosage of 225 or 450 mg 12-hourly will result in a significant number of patients being underdosed. Measurement of plasma or serum theophylline levels by high pressure liquid chromatography⁶ is quick and accurate but unfortunately not as yet widely available. If such measurements are not available the patient could be started on a low dose, which could be increased progressively to doses greater than 450 mg 12-hourly on occasions. From our experience nausea, headache, or abdominal discomfort are likely to occur before the plasma theophylline level achieves dangerously high levels—that is, 25 mg l⁻¹⁸ above which convulsions and cardiac arrhythmias may occur, but this may not invariably be the case. Only two of our 24 patients would have had subtherapeutic plasma theophylline levels below 10 mg l⁻¹ on dosage regimens of 16 mg kg⁻¹ 24 hr⁻¹ and only three would have potentially been at risk of unacceptably high levels.

We were disappointed with the high incidence of nausea, headache, and abdominal discomfort found in patients receiving the active preparation. Twelve of the original 24 patients complained of such side-effects and in six they were sufficiently severe to exclude maintenance therapy with the drug. The side-effects tended to be most severe four to six hours after taking a dose and thus would coincide with the peak plasma levels.⁵ There was no relationship between the plasma theophylline levels at which side-effects occurred in different patients but in any individual patient the severity of the effects depended on the plasma theophylline concentration.

We conclude that sustained release oral aminophylline can produce modest but useful additional bronchodilatation in some patients whose airflow obstruction is inadequately controlled by other drugs. This may be particularly helpful if it is undesirable to increase the doses of existing medications such as oral steroids. Unfortunately, the high incidence of side-effects and the wide variation in optimum dosage for different patients restrict the drug's usefulness. However, our findings suggest that if asthmatic symptoms are inadequately controlled by inhaled β -agonists then it may be more logical to add oral theophylline compounds rather than further (oral) β -agonist therapy to their treatment. They also underline the need for estimating plasma theophylline levels in clinical trials of theophylline compounds.

We thank Napp Laboratories for provision of the Phyllocontin and placebo tablets and for financial support.

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