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Oral *N*-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction

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ABSTRACT The influence of oral *N*-acetylcysteine on the exacerbation rate in patients with chronic bronchitis and severe airways obstruction has been studied. Two hundred and forty four patients entered the study during October and November 1983 and took placebo sachets for a run in month. One hundred and eighty one who completed this month satisfactorily were randomised to receive either active (acetylcysteine 200 mg three times a day) or matching placebo sachets for five months in a double blind parallel group study. The two groups were well matched. Patients kept detailed daily symptom diaries and were assessed monthly. At the end of the five months' study the outcome in the group taking acetylcysteine appeared a little better, but the differences did not reach conventional levels of statistical significance for the mean (SD) number of exacerbations (2.1 (0.2) for acetylcysteine, 2.6 (0.2) for placebo; $p = 0.08$); total days taking an antibiotic (13.5 (1.7), 18.0 (2.8); $p = 0.17$); total days spent in bed (4.8 (0.8), 5.1 (1.1); $p = 0.9$); number of withdrawals (13 (15%), 20 (21%); $p = 0.4$); incidence of side effects (which were few); drug compliance (which was good); and the patients' assessment of the treatment.

N-Acetylcysteine (NAC: Fabrol, Ciba Geigy) is a mucolytic agent available in sachets for oral use. In multicentre trials from Sweden[1] and Italy[2] acetylcysteine reduced the rate of exacerbations and days lost from work in patients with chronic bronchitis. In both studies the patients had little or no airways obstruction. The present study was conducted to investigate the effect of acetylcysteine in patients with chronic bronchitis complicated by severe airways obstruction.

Methods

Patients were recruited by 31 chest physicians from 26 centres in Britain. Adults of either sex and any age were included if they had a history of chronic bronchitis (defined as the expectoration of sputum on most days during at least three consecutive months in more than two consecutive years), complicated by significant airways obstruction (forced expiratory volume in one second (FEV_1) 50% or less of that predicted for age, height, and sex and FEV_1/vital capacity ratio of less than 70%) and also one or more remembered exacerbations per winter in the three preceding years.

Patients with overt bronchiectasis, insulin dependent diabetes, active peptic ulceration, or possible pregnancy were excluded. Patients were also ineligible if their disease was likely to prevent them from completing the study, if they received continuous prophylactic antibiotics, or if they were already taking a mucolytic and were unwilling to stop. Also excluded were patients who were considered by the clinician to have asthma rather than chronic obstructive bronchitis or who had been shown to have an increase in FEV_1 or peak expiratory flow rate of more than 30% after inhalation of a bronchodilator (tested in all patients).

The study had a double blind, placebo controlled, parallel group design. Patients entered the study during October or November 1983 and took placebo sachets for one month (phase 1). Those completing this phase satisfactorily were randomised in balanced blocks of four to receive active (acetylcysteine 200 mg three times a day) or matching placebo sachets for five months (phase 2). Sucrose in the placebo sachets replaced the acetylcysteine in the active sachets.

Patients kept daily records and scored breathless-

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Table 1 *Details of patients admitted to the acetylcysteine (NAC) study and placebo*

Total number of patients entering phase 1	244	
Withdrawals in phase 1		
Ineligible for study	12	
Side effects while taking placebo	15	
Nausea, vomiting		8*
Non-specific, malaise		5
Unpleasant taste		2*
Diarrhoea		1
Lack of cooperation	6	
Too ill	9	
Death	2	
Total withdrawn in phase 1	44	
	NAC	*Placebo*
Number randomised in phase 2	100	100
Found to be ineligible by trial coordinator	10	4
Lost through administrative error	5	0
Number of evaluable patients	85	96
Treatment not completed (see table 3)	13	20
Treatment completed	72	76

*One patient reported two side effects.

ness, sputum appearance and volume, cough and difficulty in expectoration, days in bed or in hospital, and changes in treatment including antibiotics.

Patients were seen monthly by the clinician and a record was made of the number of exacerbations, number of days taking an antibiotic or staying in bed because of their chest, unwanted side effects, changes in smoking habits, and drug compliance (the remaining sachets were counted). The clinician assessed the number of exacerbations in the preceding month by interviewing the patient and inspecting the diary card. An exacerbation was defined as a new or deteriorating cough with increased sputum purulence lasting for at least 48 hours plus at least one of the following: general malaise, any recorded fever greater than 38°C, increased breathlessness, increased sputum volume or thickness, increased difficulty in expectoration. The FEV_1 and vital capacity (VC) were measured on each visit. At the end of the study the patients made an overall assessment of their condition during the study period, using a five point scale.

STATISTICAL METHODS

In the comparison of the two treatment groups, *t* tests were used to compare mean values when the variable conformed reasonably to a normal distribution (FEV_1, VC) but the non-parametric permutation *t* test[3] was used for other variables (number of exacerbations, days in bed, (or days taking an antibiotic). The data in table 6 were analysed by means of a test for trend in proportions.[4] Two tailed tests of significance were applied throughout.

We present results for those patients satisfying the criteria for entry into the trial who were not withdrawn from the randomised treatment. Separate analyses, however, were also carried out, firstly to include the available data from withdrawn patients, and secondly to include available data from "ineligible" patients. In no instance did these additional analyses produce more than a marginal change in the levels of significance obtained. Similar results were also obtained when analysis was restricted to patients showing good compliance.

Results

Two hundred and forty four patient entered phase 1 of the study. Forty four patients did not proceed to phase 2 for the reasons given in table 1 (although 20 of these were allocated trial numbers in error). Fourteen patients were found to be ineligible by the trial co-ordinator after randomisation. Five patients (from different centres) were randomised but were subsequently untraceable. Thus there were 181 patients successfully randomised, 85 receiving acetylcysteine and 96 placebo. The features of these patients are shown in table 2. The groups formed by randomisation were broadly similar, although there was a tendency for more exacerbations to have occurred in the run in month in those subsequently randomised to receive placebo. The placebo group had a higher proportion of patients who had been admitted to

Table 2 *Comparison of acetylcysteine (NAC) and placebo groups at randomisation*

	NAC (n = 85)	*Placebo (n = 96)*
Sex: No (%) of males	75 (88%)	80 (83%)
Mean (SD) (y)	64.3 (7.3)	62.6 (7.9)
Mean (SD) duration of bronchitis (y)	15.0 (9.7)	17.2 (12.4)
No (%) in smoking category:		
Current smoker	24 (28)	25 (26)
Ex-smoker ≤6 m	3 (4)	8 (8)
Ex-smoker >6 m	58 (68)	61 (64)
Never smoked	0 (0)	2 (2)
Mean (SD) No of exacerbations* in previous winter	3.0 (1.5)	3.3 (1.8)
No (%) of hospital admissions previous year		
0	71 (84)	74 (77)
1	7 (8)	20 (21)
2+	7 (8)	1 (1)
Not recorded	0 (0)	1 (1)
No (%) having following drugs:		
Bronchodilator	78 (92)	89 (93)
Diuretic or digoxin (or both)	23 (27)	28 (29)
Inhaled steroid	19 (22)	27 (28)
Oral steroid	13 (15)	6 (6)
Mean (SD) FEV_1 (l)	0.82 (0.35)	0.89 (0.37)
FEV_1 (% predicted)	29	31
Mean (SD) VC (l)	1.94 (0.67)	1.97 (0.71)
VC (% predicted)	51	53
No (%) having one or more exacerbation in phase 1	25 (29)	40 (42)

*Remembered by patient.

Table 3 *Reasons for withdrawal from phase 2 of acetylcysteine (NAC) trial*

	NAC (n = 85)	Placebo (n = 96)
Lack of co-operation	6	5
Side effects (nausea and vomiting)	1	2
Too ill (chest illness)	2	4
Too ill (other illness)	1	5
Death (chest illness)	1	2
Death (other, not known)	2	0
Not known	0	2
Total number withdrawn	13 (15%)	20 (21%)

Table 4 *Side effects in 181 evaluable patients entering phase 2 of the acetylcysteine (NAC) trial*

	NAC (n = 85) No (%)	Placebo (n = 96) No (%)
Nausea, vomiting	7 (8)	6 (6)
Indigestion, abdominal pain	3 (4)	5 (5)
Change of bowel habit	4 (5)	2 (2)
Weight gain	2 (2)	1 (1)
Unpleasant taste	4 (5)	1 (1)
Total number of patients reporting side effects	16 (19)	15 (16)

hospital in the previous year, whereas the acetylcysteine group contained more patients with two or more hospital admissions. Rather more patients in the acetylcysteine group were taking oral steroids, and fewer used inhaled steroids.

Of the 181 patients, 72 (85%) completed five months' treatment with acetylcysteine and 76 (79%) completed five months of placebo, this difference not being significant. Reasons for withdrawal from the randomised treatment are given in table 3, and showed no significant difference between the treatment groups. Timing of withdrawals was similar in the two groups. Sachet counts showed satisfactory compliance in both groups, 78% of patients taking more than 90% and only 5% taking less than three quarters.

Table 6 *Assessment of changes in condition during the acetylcysteine (NAC) study by the patients themselves (those completing phase 2)*

	NAC (n = 72) No (%)	Placebo (n = 76) No (%)
Much worse than usual	3 (4)	5 (7)
Worse than usual	6 (8)	3 (4)
Same as usual	19 (26)	25 (33)
Better than usual	26 (36)	30 (39)
Much better than usual	16 (22)	12 (16)
No assessment	2 (3)	1 (1)

χ^2 trend = 0.3; p = 0.6.

Side effects were not a major problem in phase 2. Only three patients withdrew for this reason (one with acetylcysteine, two with placebo) table 4 shows that the reported side effects, which were mainly gastrointestinal, were similar in the two treatment groups.

The progress of the 148 patients who completed phase 2 is summarised in table 5. Throughout the study there was little change in FEV_1 or VC from baseline levels. The mean number of days in bed was similar in the two groups, and although the mean number of days of antibiotic treatment was higher in the placebo group this difference is due mainly to three patients in the placebo group who received large amounts of antibiotics. The difference of one half an exacerbation in the number of exacerbations fails to achieve conventional levels of significance (p = 0.08). The approximate 95% confidence limits for the reduction of exacerbations per patient in the acetylcysteine group are −0.05 to +1.20. The placebo group had experienced slightly more exacerbations in phase 1, when both groups were receiving placebo. After stratification of the data according to whether or not there had been an exacerbation in phase 1, the level of significance for

Table 5 *Progress of 148 patients who completed the acetylcysteine (NAC) trial*

		NAC (n = 72)	Placebo (n = 76)	p
Number of exacerbations	0	11	8	
	1	21	20	
	2	16	16	
	3	11	11	
	4	13	21	
Mean (SE) exacerbation rate per patient		2.1 (0.2)	2.6 (0.2)	0.08
Total days in bed	0	34	44	
	1–7	19	18	
	8–14	13	6	
	≥15	6	8	
Mean (SE) No of days in bed		4.8 (0.8)	5.1 (1.1)	0.9
Total No of days taking antibiotics for chest problem	0	20	21	
	1–20	37	32	
	≥21	15	23	
Mean (SE) No of days on an antibiotic		13.5 (1.7)	18.0 (2.8)	0.17
Mean (SE) change in FEV_1 (ml)		−32 (36)	−42 (32)	0.9
Mean (SE) change in VC (ml)		−56 (60)	−82 (45)	0.6

the treatment effect dropped to p = 0.12.

The data were then examined to see whether exacerbation rates in the previous year, the severity of the airways obstruction, or the presence or absence of treated cardiac failure affected the difference in exacerbation rate between the two treatment groups, but no statistically significant interactions were found.

The patients' own assessments of their condition during the study (table 6) show no significant difference between the groups.

Discussion

We were unable to detect a significant benefit for patients with chronic bronchitis and severe airways obstruction who took acetylcysteine regularly for five months during the winter. There was a trend for patients taking the drug to have slightly fewer exacerbations and days taking an antibiotic than those in the placebo group, but neither difference reached conventional levels of significance. The power of our study was such that there was a 90% chance of detecting a mean difference between the groups of one exacerbation over the study period (which we consider a worthwhile and clinically significant difference) as a statistically significant difference at the 5% level. On average the patients who received acetylcysteine had half an exacerbation less during the five month winter period. Confidence limits represent no reduction on the one hand and a reduction of 1.2 exacerbations per winter on the other. The severity of airways obstruction or the presence of treated cardiac failure did not influence the results of analysis. The changes in individual symptoms recorded in the diary cards were not analysed as we were interested in the overall effect on exacerbation rate. Side effects were not a problem with acetylcysteine and this has been the experience in previous studies.

The Swedish study,[1] which was of similar design to ours (except that acetylcysteine was given twice daily), showed 1.2 exacerbations per winter in the acetylcysteine group and 1.7 in the placebo group, which represents a mean reduction of one half an exacerbation—a result very similar to the mean reduction we recorded. The greater number of exacerbations in our patients, however, and the slightly smaller sample size reduced the statistical significance of this difference in our series. The patients in the Swedish study[1] had little or no airways obstruction (the mean FEV_1 was 80% of the predicted value) and most were working, in striking contrast to our patients, who were mostly unable to work owing to illness or age. The lower exacerbation rate in the Swedish study is not surprising.

The Italian study[2] showed a greater difference between the two groups. The mean exacerbation rate for the acetylcysteine group was 0.8 per winter, compared with 2.0 for the placebo group. Patients in the Italian study differed in several ways from ours. Over a third of their patients with chronic bronchitis were non-smokers and 40% were aged 50 years or less. Only 2% of our patients had never smoked. Only a quarter of the patients in the Italian study had "impaired" spirometric values (FEV_1/VC ratio 54%). The definition of an exacerbation is important in comparing studies. Our definition was similar to that used in the Swedish study[1] and was more specific than that used in the Italian study.[2]

Although this study does not show a statistically significant benefit for acetylcysteine, our data in conjunction with those from other studies indicate that regular acetylcysteine treatment may cause a mean reduction of one half an exacerbation per patient per winter. But even if the benefit were at the upper end of the confidence limits obtained from our own study and the Swedish study, the maximum mean reduction of one exacerbation per winter would have to be balanced against the inconvenience, cost, and potential side effects of such regular treatment. Thus long term acetylcysteine seems unlikely to have a routine place in the prevention of exacerbations in patients with chronic bronchitis and severe airways obstruction.

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