

Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis

J.B. Rasmussen, C. Glennow

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ABSTRACT: The clinical effect of N-acetylcysteine (NAC) controlled-release tablets, 300 mg b.i.d., and placebo, in chronic bronchitis was investigated. The study was performed as a double-blind six month comparison between active drug and placebo in two parallel groups, with statistical evaluation after four and six months. The patients were chosen from nine centres. One hundred and sixteen out-patients were included and ninety one of them completed the six month study. The acetylcysteine-treated group had a significantly reduced number of sick-leave days caused by exacerbations of chronic bronchitis after the four winter months December-March compared with the control group (NAC 173, placebo 456). The number of exacerbation days was also very much reduced, however, not significantly (NAC 204, placebo 399). At the end of the six month trial, including also two spring months, the absolute numbers of sick-leave days and exacerbation days were still fewer in the acetylcysteine-treated group, (NAC 260, placebo 739) and (NAC 378, placebo 557) respectively. This study demonstrates a significant reduction in sick-leave days after four months of NAC-treatment. A constant tendency to reduction in the number of exacerbations and exacerbation days was also registered after four and six months. The differences in these parameters were, however, not statistically significant. This was probably due to the small number of patients participating. *Eur Respir J. 1988, 1, 351-355.*

Multicentre trial group. Participating investigators in alphabetical order: J Andersson, Dept of Lung Medicine, University Hospital, Lund. S-G Blanck, Health Care Centre, Höganäs. C Brechter, Dept of Medicine, General Hospital, Trelleborg. K Bülow, Dept of Lung Medicine, General Hospital, Malmö. A Forssell, Dept of Lung Medicine, Orup Hospital, Höör. C Glennow, Dept of Clinical Research, AB Draco, Lund. C Malmberg, Health Care Centre, Skurup. B Månsson, Health Care Centre, Bjärred. J Nyström, Dept of Lung Medicine, Sundsvall Hospital, Sundsvall. JB Rasmussen, Dept of Lung Medicine, General Hospital, Malmö. L Rosenhall, Dept of Lung Medicine, University Hospital, Umeå. C Schrewelius, Dept of Clinical Research, AB Draco, Lund. K Wandt-Strömberg, Dept of Lung Medicine, University Hospital, Lund.

Correspondence: J.B. Rasmussen, Dept. of Lung Medicine, General Hospital, S-214 01 Malmö, Sweden.

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N-acetylcysteine (NAC) has been used as an inhalational drug for more than twenty years [1]. The route of administration has, however, been inconvenient. Inhalation treatment and handling of the equipment are time-consuming. The inhalation solution has an unpleasant smell and taste and may cause local irritation and bronchospasm in some patients.

Oral acetylcysteine given in solution is a safe [2] and well tolerated [3-4] form of administration, which has been found to reduce the viscosity and tenacity of bronchial secretions [5] and to slightly improve lung function [4]. Furthermore, several clinical studies have shown that long-term treatment with oral acetylcysteine reduces the number of exacerbations in patients with chronic bronchitis [4, 6].

The frequency of adverse experiences from the acetylcysteine solution is low. When they occur they are mainly of a mild gastrointestinal nature but can be serious enough for disruption of treatment. The reactions are mainly due to an initial high stomach acetylcysteine concentration or carbon dioxide intolerance. A recently developed controlled-release tablet

containing 300 mg NAC has proved that it can substantially reduce the adverse experiences observed when the fast-dissolving preparations presently on the market are given [7, 8]. The controlled-release tablet produces a more flattened plasma concentration-time curve [9] compared with the solution. This could explain the improved tolerance pattern of the controlled-release tablet.

The aim of this study was to investigate whether or not the efficacy of acetylcysteine solution could be maintained using the controlled-release tablet preparation.

Patients and Methods

Patients

One hundred and sixteen adult out-patients with chronic bronchitis according to the definition and classification of the Medical Research Council [10] were recruited for the investigation. Only smokers or ex-smokers with at least one exacerbation during the previous winter were included. It was, however, not

stated if a patient was a current smoker or not. Treatment with antibiotics for more than two weeks on indications other than exacerbations of chronic bronchitis and pregnancy were considered as exclusion criteria. No concomitant use of mucolytic drugs was allowed during the study. The patients were

Table 1. - Patient data at study entry. No. of patients and mean values are shown

	NAC	Placebo	Total
Number of patients	59	57	116
Sex			
female	28	22	50
male	31	35	66
Age yr	58.8	58.9	58.9
Height cm	167.4	170.0	168.7
Weight kg	67.5	70.3	68.9
PEFR l/min	301	308	305
Duration of disease yr	10.7	13.6	12.1
Diagnosis			
Chr. bronch.	39	37	76
Chr. bronch. + asthma	4	4	8
Chr. bronch + emphysema	12	12	24
Chr. bronch + other disease	3	3	6
Chr. bronch + asthma + emphysema	1	1	2

NAC: N-acetylcysteine

Table 2. - Concomitant COLD therapy

	NAC	Placebo	Total
Patients with no therapy	23	21	44
β-agonist	6	10	16
theophylline	5	3	8
steroid	2	1	3
β-agonist + theophylline	11	10	21
β-agonist + steroid	3	0	3
steroid + theophylline	1	1	2
β-agonist + steroid + theophylline	8	11	19
Total	59	57	116

NAC: N-acetylcysteine

Table 3. - Time and cause of drop-out/withdrawal

Period	Treatment	Number of drop-outs	Adverse experiences	Personal reasons	Exacerbations
0-2 weeks	NAC	6	2	3	1
	placebo	4	2	1	1 ¹
2 weeks - 2 months	NAC	6	5	1	0
	placebo	4	2	1	1 ¹
2 - 4 months	NAC	3	3	0	0
	placebo	2	2	0	0
4 - 6 months	NAC	0	0	0	0
	placebo	1	1 ²	0	0

NAC: N-acetylcysteine. 1) Hospitalization; 2) Is not excluded from statistical evaluation due to late adverse experience

chosen from nine different clinical out-patient centres. Patient data are summarized in table 1.

Most of the patients used concomitant medication for their chronic obstructive lung disease (COLD). Fifty nine patients were treated with β-agonists, 50 with theophyllines and 27 with corticosteroids. These medications were generally used in combination. Forty four patients, however, did not receive any therapy at all for their lung disease. The distribution is given in table 2.

In total, 116 patients, 59 in the acetylcysteine-treated group and 57 in the placebo group, were thus accepted for the statistical evaluation.

Twenty five patients, fifteen in the acetylcysteine-treated group and ten in the placebo group, dropped out during the study. The time and cause of drop-out are given in table 3. Forty four patients in the acetylcysteine group and 47 in the placebo group therefore completed the trial.

Study design

The trial was carried out as a double-blind randomized comparison for six months between active drug and placebo in two parallel groups. The drug was taken twice daily, in the morning and in the evening.

The randomization was made in blocks of four, thereby assuring equal numbers of acetylcysteine and placebo patients at each centre.

Registration of effects

Visits to the clinics were made at the commencement of the trial, after two weeks and after 2, 4 and 6 months. When the patients visited the clinic the physician noted the number of exacerbations, the number of exacerbation days and the type of medication prescribed since the last visit. Exacerbations were defined according to previous trials [6].

Mucopurulent or purulent sputum and new or aggravated cough were regarded as obligatory criteria for a diagnosis of exacerbation. At least one of the following symptoms was also to have been present: general malaise, symptoms of common cold, fever (> 38°C), aggravated breathlessness, increased mucus production, increased sputum thickness, foul-

tasting sputum, increased difficulty in expectoration pneumonia.

If recurrent bouts of exacerbation were separated by at least a two-week interval, they were counted as two different exacerbations. Days on the sick-list, *i.e.* days lost through sickness, were registered and only included illnesses directly related to exacerbations due to chronic bronchitis.

Adverse reactions were registered at home by the patients in diary cards.

Statistical evaluation

A statistical evaluation was performed after four months and after six months of treatment. A two-tailed Wilcoxon-Mann-Whitney test was used. Only p-values equal to or less than 0.05 were considered significant.

Results

The total number of exacerbations, exacerbation days, exacerbations treated with antibiotics and days on the sick-list, as well as mean values after four and six months, are summarized in table 4.

Days on the sick-list

The number of sick-leave days caused by exacerbations due to chronic bronchitis could be studied in 27 (61%) of the patients in the acetylcysteine group and in 28 (59%) in the placebo group as the remainder of patients were not working due to old age (> 65 yrs) or chronic illness.

After four months (December–March) a significant difference in the number of days on the sick-list between the NAC-treated and the placebo group appeared (NAC 173 days, placebo 456 days). The

difference after another two months (April–May) was still very great (NAC 260 days, placebo 739 days), though not statistically significant (table 4).

Exacerbations

Of the 91 patients completing the trial 39 patients, 16 from the acetylcysteine group and 23 from the control group, had at least one exacerbation.

From table 4 it can be seen that the number of exacerbations as well as the number of exacerbation days was lowest in the NAC-treated group. This finding was noted both at the 4-month and 6-month registration. Although the tendency was constant, neither of the differences reached the significance level.

Drop-outs

Characteristics of withdrawn patients appear in table III. Those who completed the study and those who dropped out did not differ significantly in any of the entry parameters. Neither were any differences observed between patients who dropped out during acetylcysteine treatment and placebo treatment.

Adverse experiences

Ten patients in the acetylcysteine treated group and seven patients in the placebo group discontinued therapy because of adverse experiences.

Twenty three patients (39%) in the acetylcysteine group reported a total of 54 adverse symptoms and 21 patients (37%) in the placebo group a total of 66 adverse symptoms. Table 5 summarizes these adverse experiences.

The differences between adverse experiences from placebo and active treatment were not statistically significant.

Table 4. - Total number of exacerbations, exacerbation days, days on the sick-list and antibiotic treatment during four/six months of treatment followed by mean number per patient and in brackets the standard error

		Group of patients completing the trial		
		NAC (44)	Placebo (47)	p-value
no. of exacerbations	4 months	20/0.45 (0.11)	30/0.64 (0.13)	0.35
	6 months	34/0.77 (0.19)	40/0.85 (0.17)	0.45
no. of exacerbation days	4 months	204/4.64 (1.40)	399/8.49 (2.15)	0.18
	6 months	378/8.59 (2.60)	557/11.85 (3.31)	0.14
no. of days on the sick list	4 months	173/6.41 (4.75)	456/16.29 (7.01)	0.049*
	6 months	260/9.63 (7.15)	739/26.39 (10.65)	0.088
no. of exacerbations treated with antibiotics	4 months	13	19	
	6 months	21	26	

NAC: N-acetylcysteine

Table 5. - Adverse experiences

Type of disorder	NAC no. of patients with com- plaints	Placebo no. of patients with com- plaints
Gastrointestinal disorders	10	6
Skin disorders	5	4
CNS disorders	5	8
Others (headache etc.)	24	23
No. of patients with one or more disorders	23	21

NAC: N-acetylcysteine

Discussion

The main finding was a reduction in sick-leave days of about 65% in the N-acetylcysteine group (~6 days/patient) compared with the placebo group (~16 days/patient). In a previous six month trial, also carried out in Sweden [6], a 35% reduction was found. In both trials the differences were statistically significant.

The number of exacerbation days, *i.e.* days when the patient is feeling ill, as well as the number of exacerbations, also appeared to be fewer in the acetylcysteine-treated group than in the placebo group.

The reductions in both days on the sick-list and exacerbation days indicate that infections might be less serious and heal faster with treatment than without.

The tolerance of the drug is very good. About the same number of complaints was found in both the acetylcysteine-treated group and in the placebo group. As expected, the main difference was a somewhat higher frequency of gastrointestinal disturbances in the acetylcysteine treated group (NAC group: ten cases; placebo group: six cases).

N-acetylcysteine controlled-release tablets had a protective effect on acute exacerbations in chronic bronchitis by reducing the severity of the exacerbation. This could be seen by the number of days on the sick-list, which was reduced by 62% when comparing the acetylcysteine and placebo groups, as well as in the number of exacerbation days, which was also reduced. This indicates that the severity of the exacerbations was decreased. The tolerance of the drug was good, with about the same frequency of adverse experiences in both the acetylcysteine and placebo groups.

The patients included in this trial can be categorized as moderately affected by their disease. In some earlier reports patients with severe bronchitis have shown less reversibility in acute mucolytic N-acetylcysteine effects [12]. In a multicentre trial performed by the British Thoracic Society (BTS) this also seems valid for chronic parameters as for example the frequency and severity of acute infections [13]. A difference of about 25% is achieved when the number

of acute exacerbations in the two groups are compared. This difference is smaller than that found in other trials with less severe chronic bronchitis but nevertheless just misses the significance level ($p=0.08$).

The finding of our study agrees with recently published results. In general practice 526 patients with different severity of chronic bronchitis were randomized to either active acetylcysteine or placebo. Significantly fewer patients suffered from 'days when incapacitated' in the acetylcysteine group compared with the placebo patients ($p<0.02$). A tendency towards fewer exacerbations in the acetylcysteine group was also found [14].

In this study we tested a controlled-release tablet preparation of acetylcysteine. On the assumption that the effect of oral treatment depends on local effects in the lung, our results are even more noteworthy, as the bioavailability of acetylcysteine in plasma after the controlled-release preparation is reduced compared to that generated by the solution [9]. This study, however, also demonstrates the effect of controlled-release preparation.

It has not been possible to detect free acetylcysteine in broncho-alveolar lavage fluids or in lung cells in subjects treated with acetylcysteine solution in the same dose as used in this study [11]. This might suggest that effective doses of acetylcysteine do not act by reducing disulphide bridges in mucin.

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RÉSUMÉ: Nous avons investigué l'effet clinique des comprimés de N-acétylcystéine à libération contrôlée à raison de 600 mg par jour, et d'un placebo, chez des sujets atteints de bronchite chronique. L'étude a consisté en une comparaison, en double aveugle, pendant six mois, de la drogue active et du placebo dans deux

groupes parallèles avec évaluation statistique après 4 et 6 mois. Les patients provenaient de neuf centres. L'on a inclus 116 consultants externes dans l'étude, dont 91 ont terminé l'étude de six mois. Dans le groupe traité par l'acétylcystéine, on observe une réduction significative du nombre de jours de maladie dus aux exacerbations de la bronchite chronique après les 4 mois d'hiver (décembre-mars) par comparaison avec le groupe contrôle (NAC 173, placebo 456). Le nombre de jours d'exacerbation, lui aussi, était fortement diminué, quoique de façon non significative (NAC 204, placebo 399). A la fin de l'essai de six mois, quand on inclut également les deux mois de printemps, les nombres absolus d'absence pour maladie et les nombres de journées d'exacerbation restent plus bas dans le groupe traité à l'acétylcystéine que dans le groupe placebo, respectivement (NAC 260, placebo 739) et (NAC 378, placebo 557). Cette étude démontre une réduction significative des journées d'absence pour maladie après 4 mois de traitement à l'acétylcystéine. Une tendance continue dans la réduction du nombre d'exacerbations et de jours d'exacerbation, a été observée également, à la fois après 4 et 6 mois. Les différences entre ces derniers paramètres ne sont toutefois pas statistiquement significatives. Ceci peut être expliqué probablement par le nombre évidemment trop faible de patients ayant participé à l'étude.