Eur Respir J
1988, 1, 161–167

The clinical effect and the effect on the ciliary motility of oral N-acetylcysteine in patients with cystic fibrosis and primary ciliary dyskinesia

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ABSTRACT: The effect of peroral N-acetylcysteine (NAC) in patients with cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) was investigated. 41 CF patients and 13 PCD patients completed the study which was a double-blind, placebo-controlled, cross-over trial. The patients received either NAC or placebo for two periods of three months followed by a three month follow-up period. Active treatment consisted of NAC, either 200 mg × 3 daily (patients weighing < 30 kg) or 400 mg × 2 daily (> 30 kg). The effect was evaluated in terms of a subjective clinical score, weight, sputum bacteriology, blood leucocyte count, sedimentation rate, titres of specific antimicrobial antibodies, lung function parameters and measurement of the ciliary function. No effect was seen in PCD patients, but in CF patients an improved lung functioo was seen in the period when the patients suffer most from lower airway infections.

Eur Respir J. 1988, 1, 161–167.

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Keywords: Cilliary function; cystic fibrosis; double-blind clinical trial; oral N-acetylcysteine; primary ciliary dyskinesia.

Received: January 26, 1987; accepted after revision June 16, 1987.

Inhalation with mucolytics has been used for many years in the treatment of cystic fibrosis (CF) and N-acetylcysteine (NAC) is one of the most extensively used agents [9]. Inhalation therapy is, however, time-consuming and although some older studies claim a beneficial effect [16], this may not be optimal because of faulty deposition in the airways.

Orally administered NAC has, in several studies, shown a positive clinical effect in patients with chronic bronchitis, as judged by changes in sputum consistency, ease of expectoration and decrease in the number of acute exacerbations [1, 3, 5, 6]. Results from investigations performed in CF patients are, however, controversial [4, 10, 15, 20] and we have therefore performed a double-blind, placebo-controlled, cross-over trial of 3+3 months in a larger number of CF patients. We have also included patients with primary ciliary dyskinesia (PCD) since the effect of oral NAC does not seem to have been investigated in these patients.

Since we have recently demonstrated a decrease in ciliary beating frequency (CBF) in human cilia exposed *in vitro* to NAC [19], we included studies on ciliary function *in vitro*.

Patients, materials and methods

Study design

The study was undertaken in the form of a double-blind, placebo-controlled, cross-over trial conducted on an outpatient basis. It consisted of three periods of three months duration. During the first and second period, the patients received either NAC or placebo, followed by a three month follow-up period. In all patients the first period of treatment fell from June to August, and the second from September to November.

During the study the patients followed their normal daily routine of physiotherapy, inhalation of isotonic NaCl with or without salbutamol, supply of pancreatic enzymes and vitamins and administration of antimicrobials when needed. All patients were seen once a month for clinical control including lung function measurements. Blood and nasal scrapings were sampled at the start and at the end of each period.

Patients

Fourty-four CF patients without pseudomonas infection entered the study, and 41 completed (18 females, 23 males, mean age 9.5 yr (2–31)). Patients with a past history of peptic ulcer, liver or kidney disease, or pregnant patients were not included in the study. Two were excluded because of poor co-operation and one because of an allergy to citrus fruits, which was added to both NAC and placebo. The diagnosis of CF was based upon a typical clinical history and several quantitative sweat tests. None of the patients had pulmonary pseudomonas infections and all were in a good clinical condition.

Out of sixteen patients with PCD who entered the study, thirteen completed (7 females, 6 males, mean age 29.7 yr (2–47)). One female could not co-operate, and two suffered bleeding disorders, one while receiving NAC, the other placebo. In both instances, the disorder stopped on discontinuation of the medicine. Six of the

seven females were older than sixteen. PCD was diagnosed on the basis of typical clinical symptoms (recurrent otitis media, recurrent sinusitis, cough and expectoration), combined with repeated *in vitro* studies of ciliary beating frequency and pattern, and at least one study of the ciliary structure.

Throughout the study none of the patients in the two groups experienced major exacerbations and none were hospitalized. Eight CF patients and six PCD patients received some sort of bronchodilator treatment on a regular basis during the whole study.

All patients were seen at nearly the same time of the day each time, which should make the lung function parameters comparable, particularly in patients treated with bronchodilators. At each monthly visit a sample of expectoration was analysed for bacteria. If positive, antibiotics were prescribed routinely for fourteen days according to culture findings.

Treatment

The patients were randomly allocated to receive NAC or placebo in the first period, and the alternative in the second, followed by three months follow-up. Active treatment consisted of NAC, 200 mg × 3 daily (patients weighing < 30 kg), or 400 mg × 2 daily (> 30 kg). Placebo tablets contained bicarbonate only.

Clinical assessments

Once a week the patients completed a chart in which subjective parameters were scored as shown in table I.

Once a month the treatment was evaluated in terms of the subjective score, weight, sputum bacteriology, and pulmonary function parameters (forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow rate (PEFR)), recorded on an electronic spirometer (Spirotron, Dräger).

Every three months a blood test was examined for total white blood cell count (WBC), sedimentation rate (ESR), and titres of specific antibodies to *Staph. aureus*, *H. influenza* and *Pseudomonas aeruginosa*.

Ciliary function

This was studied in twenty CF patients, and in all PCD patients, at the start and at the end of each three month period. Cells from the mucous membrane of the inferior turbinate in the middle part of the nasal cavity were obtained by gentle scraping, using a sharp spoon. The specimen was washed from the spoon into a tube containing Krebs-Ringer medium, into which was added glucose 5 $mmol \cdot l^{-1}$ (KRG). Immediately after, or at least within an hour, the specimen was transferred to a Dvorak-Stotler culture chamber (Nicholson Precision Instrument Inc., Maryland), which was continuously perfused with KRG (12 $ml \cdot l^{-1}$). A glass plate inserted into the chamber reduced the height to about 40 μm, which produced a monolayer arrangement of the cells, without interfering with the free movement of the cilia.

All measurements of ciliary activity were performed at room temperature (22–23°C). Recording of CBF and ciliary beating pattern was done by an anophtral phase contrast microscope (Zetopan, Reichert, Austria), equipped with a microphotometer which transforms the interference of light caused by the ciliary beating to a curve on a mingograph which depicts the frequency as well as the beating pattern (degree of synchrony between individual cilia) [12]. Synchronous ciliary beating results in almost completely uniform oscillations while asynchrony between cilia from the same cell causes an irregular oscillogram [11]. The percentage of cells with motile cilia was calculated, based on the counting of at least 100 ciliated cells. Oscillograms were recorded from twenty cells, selected according to a defined schedule to

Table I. - Symptom score system. The elements of the score and the grading of each parameter.

	0	1	2	3
Cough, frequency of	no cough	once in a while	all day	all 24 h
Mucus, amount of	no mucus	once in a while	all day	all 24 h
Expectoration		easy	difficult	
Expectoration		loose	stuck	
Mucus, mixed with blood		no	yes	
Respiration	normal	wheezing	rattling	difficult
PEP-mask, effect of	better	no improvement	worse	
Physical activity	normal	slightly decreased	very decreased	stopped

PEP: positive expiratory pressure

ensure that the recordings produced a representative expression of the ciliary activity. The asynchrony and beating frequency of each specimen were expressed as mean values of all recordings.

Statistical methods

We used the Wilcoxon test for paired differences and 5% was considered significant.

Results

The results of the subjective clinical scores are given in tables II and III, for CF and PCD patients respectively. There was no difference between NAC and placebo in either patient group.

The patients were selected double-blind and the two groups should therefore be comparable. Nevertheless, when looking at the lung function parameters, there was a difference. FEV_1, FVC and PEFR (as judged by mean observed predicted values during the placebo period) in the group receiving NAC in the autumn were 78%, 81% and 92% respectively of the values for the group receiving NAC during summer time.

Table II. - Number of patients with cystic fibrosis who regard the treatment with NAC either better, equal to or worse than treatment with placebo. (The results are taken from a diary which the patients filled out once a week)

	NAC taken in period 1 (summer) Number of patients			
	n	x<y	x=y	x>y
Frequency of cough	19	10	1	8
Amount of mucus	19	7	3	9
Expectorate				
easy-difficult	12	2	2	8
loose-stuck	12	3	4	5
Mucus mixed with blood	16	0	16	0
Respiration	19	2	13	4
Effect of PEP-mask	19	4	7	8
Physical activity	19	2	14	3

	NAC taken in period 2 (autumn) Number of patients			
	n	x<y	x=y	x>y
Fequency of cough	18	13	2	3
Amount of mucus	18	5	2	11
Expectorate				
easy-difficult	14	7	2	5
loose-stuck	13	7	1	5
Mucus mixed with blood	18	2	15	1
Respiration	18	3	8	7
Effect of PEP-mask	18	9	6	3
Physical activity	19	6	13	0

x: NAC= N-acetylcysteine; y: placebo.

Table III. - Number of patients with primary ciliary dyskinesia who regarded the treatment with NAC either better, equal to or worse than treatment with placebo. (The results are taken from a diary, filled out once a week).

	NAC taken in period 1 (summer) Number of patients			
	n	x<y	x=y	x>y
Frequency of cough	6	2	1	3
Amount of mucus	6	2	1	3
Expectorate				
easy-difficult	6	4	2	0
loose-stuck	6	5	1	0
Mucus mixed with blood	6	0	6	0
Respiration	6	2	2	2
Effect of PEP-mask	7	2	1	4
Physical activity	4	2	1	1

	NAC taken in period 2 (autumn) Number of patients			
	n	x<y	x=y	x>y
Frequency of cough	7	3	1	3
Amount of mucus	7	4	0	3
Expectorate				
easy-difficult	7	5	0	2
loose-stuck	7	6	1	0
Mucus mixed with blood	7	0	7	0
Respiration	7	5	2	0
Effect of PEP-mask	7	4	2	1
Physical activity	4	2	1	1

x: NAC= N-acetylcysteine; y: placebo.

Table IV shows the difference in lung function after three months of treatment with NAC and placebo in the CF patients, when NAC was given in the first period (summer) and placebo in the second (autumn). No difference was found. However, the difference in lung function in CF patients, when placebo was given in the first period (summer) and NAC in the second (autumn) revealed a marked difference in favour of NAC, as shown in table V. This difference reached statistical significance for FEV_1 and FVC but not quite for PEFR. Of the CF patients receiving bronchodilator treatment three (Nos 17, 19, 48) were in one group and two (Nos 36, 42) were in the other. As seen in tables IV and V this treatment did not influence the result. Neither were there any differences between the groups in antibiotic treatment. There was no similar effect of NAC, given in either of the two periods, in the patients with PCD.

None of the other parameters, including blood tests, revealed any differences between NAC and placebo, in either period.

The results of measurements of CBF, ciliary motility pattern, and the number of cells with motile

Table IV. - Difference (Δ) in lung function parameters in % of expected values between treatment with N-acetylcysteine (NAC) and placebo when NAC was given in period 1 (summer) and placebo in period 2 (autumn) to patients with cystic fibrosis.

n	FEV_1 % NAC - placebo	Δ	FVC % NAC - placebo	Δ	PEFR % NAC - placebo	Δ
17	48–60	–12	63–71	–8	85–79	6
19	96–89	7	132–94	38	80–79	1
27	94–99	–5	91–98	–7	74–94	–20
32	74–85	–11	83–90	–7	71–68	3
34	17–16	1	28–22	6	43–52	–9
37	84–86	–2	95–100	–5	77–77	0
38	63–61	2	62–63	–1	81–62	19
44	38–41	–3	41–56	–15	58–69	–11
48	61–61	0	85–74	11	55–57	–2
49	76–83	–7	80–87	–7	65–68	–3
55	88–101	–13	90–100	–10	65–78	–13
mean		–43		–5		–29
		NS		NS		NS

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate. NS: not significant

Table V. - Difference (Δ) in lung function parameters in % of expected values between treatment with N-acetylcysteine (NAC) and placebo when placebo was given in period 1 (summer) and NAC in period 2 (autumn) to patients with cystic fibrosis.

n	FEV_1 % NAC - placebo	Δ	FVC % NAC - placebo	Δ	PEFR % NAC - placebo	Δ
18	73 - 31	42	68 - 38	30	79 - 21	58
20	74 - 39	35	68 - 48	20	80 - 55	25
24	87 - 79	8	86 - 77	9	89 - 67	22
26	51 - 47	4	63 - 46	17	33 - 52	–19
31	106 - 87	19	114 - 101	13	128 - 115	13
33	32 - 40	–8	47 - 47	0	37 - 47	–10
36	77 - 65	12	87 - 71	16	99 - 99	0
41	71 - 70	1	80 - 87	–7	84 - 77	7
42	48 - 58	–10	62 - 74	–12	57 - 68	–11
47	94 - 87	7	112 - 77	35	97 - 100	–3
51	68 - 36	32	72 - 49	23	78 - 45	33
56	38 - 29	9	49 - 41	8	56 - 47	9
mean		151		152		124
		p<0.05		p=0.01		NS

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate. NS: not significant

cilia, are given in tables VI and VII for patients with CF and PCD respectively. No difference between active treatment and placebo was seen in either patient group. Gross changes in motility percentage were seen in individual patients (table VII, patients 8 and 11). These may be due to complicating viral infections [13].

Discussion

NAC cleaves glycoproteins and thereby diminishes the viscosity of mucus [8, 18]. Clinical investigations have indicated that NAC administered orally to patients with chronic bronchitis changes sputum consistency with a resultant ease of expectoration and

Table VI. - Difference (Δ) in ciliary beating frequency (CBF), synchronicity grade of the beating, and motility (cells with motile cilia in % of all ciliated cells seen) between treatment with NAC and placebo for patients with cystic fibrosis.

NAC taken in period 1 (summer)

n	CBF Hz NAC - placebo	Δ	Synchronicity grade[1] NAC - placebo	Δ	Motility %[2] NAC - placebo	Δ
17	3.27 - 8.29	–5.02	0.95 - 0.40	0.55	84 - 90	–6
19	8.29 - 6.58	1.71	0.15 - 0.20	–0.05	93 - 92	1
23	5.56 - 7.35	–1.79	2.00 - 0.70	1.30	100 - 86	14
27	5.50 - 8.00	–2.50	1.00 - 0.70	0.30	79 - 97	–18
32	6.30 - 5.33	0.97	0.40 - 1.07	–0.67	98 - 100	–2
34	8.21 - 7.23	0.98	1.00 - 0.35	0.65	90 - 100	–10
38	6.45 - 8.01	–1.56	0.50 - 0.50	0	100 - 92	8
44	7.45 - 5.78	1.67	0.75 - 0.95	–0.20	80 - 96	–16
48	7.50 - 0.86	6.64	0.25 - 0.25	0	100 - 90	10
52	8.55 - 5.96	2.59	0.35 - 0.35	0	89 - 98	–9
mean		3.69		1.88		–28
		NS		NS		NS

NAC taken in period 2 (autumn)

n	CBF Hz NAC - placebo	Δ	Synchronicity grade[1] NAC - placebo	Δ	Motility %[2] NAC - placebo	Δ
20	6.80 - 7.42	–0.62	0.85 - 0.65	0.20	98 - 87	11
24	9.01 - 8.37	0.64	0.25 - 0.10	0.15	98 - 94	4
26	7.23 - 7.83	–0.60	0.40 - 0.80	–0.40	98 - 88	10
31	7.53 - 6.55	0.98	1.00 - 0.70	0.30	96 - 96	0
33	7.77 - 7.48	0.29	0.20 - 0.35	–0.15	92 - 91	1
41	6.91 - 6.69	0.22	0.40 - 0.50	–0.10	100 - 92	8
42	4.75 - 8.80	–4.05	0.27 - 0.15	0.12	74 - 88	–14
47	5.53 - 6.63	–1.10	0.85 - 0.60	0.25	99 - 98	1
51	3.54 - 7.75	–4.21	1.33 - 0.15	1.18	100 - 100	0
mean		–8.45		1.55		21
		NS		NS		NS

1: Synchronicity grade: Pedersen [12]; 2: Cells with motile cilia in % of all ciliated cells counted; NS: not significant

expectoration of larger volumes [1]. A multicentre, double-blind, parallel study in 744 patients with chronic bronchitis, in which half were given NAC orally, and the other half placebo, revealed that NAC protected against acute exacerbations [6]. This agrees with studies by GRASSI *et al.* [5] and BOMAN *et al.* [3]. The effect on lung function was either very small [6] or absent [3].

In studies in CF patients, GÖTZ *et al.* [4] found a slight but not significant clinical difference between NAC and placebo but no difference in lung function parameters. They followed 21 patients in a double-blind study using NAC, 100 ml × 3 daily or placebo, for periods of fourteen days each. MITCHELL and ELLIOTT [10] gave 200 mg × 3 daily for three months in a placebo-controlled, double-blind, cross-over study to twenty CF patients in good clinical condition. Again neither a clinical difference nor a difference in lung function parameters was found between NAC and placebo. In RATJEN *et al.*'s study [15] NAC (200 mg × 3 daily) was given over a period of three months to CF patients in a mild to moderate clinical state. The study was conducted during the summer months and no clinical differences could be observed between NAC and placebo. STEPHAN *et al.* [20] made a comparison between inhaled NAC (dosage not known) and orally administered NAC (dosage ranged from 50 mg t.i.d. for 2 year old children to 200 mg t.i.d. for adults) in 76 patients. After change-over from inhalation to oral NAC, the

Table VII. - Difference (Δ) in ciliary beating frequency (CBF), synchronicity grade of the beating, and motility (cells with motile cilia in % of all ciliated cells seen) between treatment with NAC and placebo for patients with primary ciliary dyskinesia.

NAC taken in period 1 (summer)

n	CBF Hz NAC - placebo	Δ	Synchronicity grade[1] NAC - placebo	Δ	Motility %[2] NAC - placebo	Δ
2	3.93 - 0	3.93	-	-	0.1 - 0	0.1
3	5.80 - 4.13	1.67	1.60 - 2.35	–0.75	90 - 60	30
5	4.67 - 6.13	–1.46	1.50 - 0.45	1.05	78 - 87	–9
9	0 - 0.69	–0.69	-	-	0 - 0.1	–0.1
11	4.23 - 0.80	3.43	3.05 - 3.30	–0.25	60 - 14	46
14	0 - 1.39	–1.39	-	-	0 - 42	–42
mean		5.49		0.05		25.0
		NS		NS		NS

NAC taken in period 2 (autumn)

n	CBF Hz NAC - placebo	Δ	Synchronicity grade[1] NAC - placebo	Δ	Motility %[2] NAC - placebo	Δ
1	0 - 0.70	–0.70	-	-	0 - 4	–4
7	0.97 - 0.56	0.41	3.60 - 3.95	–0.35	12 - 11	1
8	7.99 - 16.14	–8.15	2.20 - 0.42	1.78	11 - 87	–76
10	4.70 - 2.57	2.13	2.35 - 3.60	–1.25	64 - 53	11
12	1.19 - 1.25	–0.06	3.80 - 3.50	0.30	15 - 3	12
15	0.77 - 0.95	–0.18	4.00 - 4.15	–0.15	2 - 22	–20
16	8.13 - 8.64	–0.51	3.25 - 3.00	0.25	16 - 69	–53
mean		–7.06		0.58		–129
		NS		NS		NS

1: Synchronicity grade: Pedersen [12]; 2: Cells with motile cilia in % of all ciliated cells counted; NS: not significant

pulmonary symptoms were either the same, or improved.

The present double-blind, placebo-controlled, cross-over study was undertaken in a rather large group of CF patients, receiving a moderately high dose of oral NAC for several months. The main finding is that pulmonary function is significantly better during NAC than during placebo treatment, but only when NAC is given in the autumn, not in the summer. None of our patients suffered from chronic *Pseudomonas aeruginosa* infection and were thus generally in a good clinical condition with slight or moderate expectoration. In all age groups, most CF patients experience more lower respiratory tract infections, with more sputum production, during autumn and winter, so if oral NAC had any clinical effect, this might be the time of the year to see it. In the Danish CF centre the patients are seen as outpatients every month and a fourteen day course of antibiotics is given if bacteria are cultured from a sputum sample. There was no difference between the two groups in the amount of positive cultures. The presence or absence of viral infections were not however studied. Even so we find our results correspond well with the study of GRASSI [6], which revealed that during the winter semester, about half as many patients would suffer exacerbations on a regimen of oral NAC as those on placebo. Unfortunately, the responding group in this study had considerably worse FEV_1 and FVC (as judged by mean observed predicted values during the placebo period). This could suggest that the discrepancy might be due to the treatment only being effective in more severe cases.

The studies on ciliary function did not reveal any *in vitro* effect of oral NAC. Recently, we [19] and others [14] have found a decrease in CBF in human nasal epithelial cells exposed to NAC *in vitro*, but the concentrations were effective above 2 $mg \cdot ml^{-1}$ and 10 $mg \cdot ml^{-1}$ respectively, and this is far more than the concentrations found *in vivo* in secretions following oral administration by RODENSTEIN *et al.* [17].

If orally administered NAC exerts any clinical effect by changing the properties of the secretions, it

should pass into the mucus. After an oral intake of 100 mg 35S-acetylcysteine, small amounts of radioactivity were found in the bronchial secretions by RODENSTEIN *et al.* [17]. The concentrations were, however, very small (0.21 $\mu g \cdot ml^{-1}$ protein). This might suggest that NAC exerts its clinical effects through other biological activities. Dampening of inflammation through inhibition of granulocyte-derived toxic oxygen radicals is a possibility [2, 7]. It is interesting that NAC in the present study was found effective only in the autumn, when infections are more common than in the summer.

This study indicates that there may be a positive clinical effect of NAC in CF patients, when given orally in the period of the year when the patients suffer from most infections, or when the patients are more severely ill. The cause of this effect remains unknown, as does the long-term effect of the treatment. There are a number of problems to be solved; precise pharmacokinetic studies on the penetration of orally administered NAC into bronchial secretions are wanted, as are clinical trials in CF patients with higher degrees of pulmonary inflammation. At the same time, there is a need for further *in vitro* and *in vivo* studies on the possible anti-inflammatory effect of NAC in CF patients and other patients with chronic pulmonary disease.

Acknowledgements: The study was supported by ASTRA A/S, Copenhagen.

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RÉSUMÉ: L'effet de la N-acetylcystéine (NAC) administrée oralement a été investigué chez des malades atteints de mucoviscidose (CF) et de dyskinésie ciliaire primaire (PCD). 41 CF et 13 PCD sont arrivés au terme de l'étude contrôlée contre placebo réalisée selon la méthode croisée en double insu. Les malades recevaient soit la NAC soit le placebo pendant deux périodes de trois mois, suivies d'un follow-up de trios mois. Le NAC était donné à la dose quotidienne de 3×200 mg (poids corporel < 30 kg) ou de 2×400 mg (poids > 30 kg). Les effets ont été évalués par un score clinique subjectif, le poids corporel, la bactériologie des crachats, la leucocytose sanguine, la vitesse de sédimentation, les titres d'anticorps antimicrobiens spécifiques, les indices fonctionnels respiratoires et la mesure de la fonction ciliaire. Aucun effet n'a été remarqué en cas de PCD, mais en cas de CF une amélioration fonctionnelle a été constatée pendant la période pendant laquelle les patients souffrent du plus grand nombre d'infections des voies aériennes inférieures.