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# *N*-isobutyrylcysteine, a donor of systemic thiols, does not reduce the exacerbation rate in chronic bronchitis

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N-*isobutyrylcysteine, a donor of systemic thiols, does not reduce the exacerbation rate in chronic bronchitis. A. Ekberg-Jansson, M. Larson, W. MacNee, A. Tunek, L. Wahlgren, E.F.M. Wouters, and S. Larsson for the* N-*isobutyrylcysteine Study Group.* ©*ERS Journals Ltd 1999.*

**ABSTRACT: *N*-isobutyrylcysteine (NIC), a new thiol compound that is not rapidly hydrolysed to give higher levels of free thiols in the body than *N*-acetylcysteine (NAC), was used to test if the effect of NAC on exacerbations in chronic bronchitis was an effect of the unhydrolysed thiol compound.**

**Smokers or exsmokers with chronic bronchitis forced expiratory volume in one second ($FEV_1$) >40% and reversibility ≤10% predicted were treated with oral NIC 300 mg *b.i.d.* or placebo for 24 weeks. Steroids, NAC, antibiotics, and nonsteroid anti-inflammatory drugs use were restricted. Exacerbations were recorded by a respiratory symptom diary card and the time to onset of the first exacerbation after the start of treatment was measured using life-table analysis. Spirometry was performed at each visit.**

**Six hundred and thirty-seven patients were randomized to treatment with NIC (n=316) or placebo (n=321). NIC did not prolong the time to first exacerbation (life-table analysis, p=0.59) and no increase in $FEV_1$ or forced vital capacity was observed. Altered taste perception, taste loss and anosmia occurred more often in the NIC group (p<0.001).**

**In conclusion, *N*-isobutyrylcysteine, a *N*-acetylcysteine-like drug with a greater bioavailability has, contrary to *N*-acetylcysteine, no effect on exacerbations in chronic bronchitis. This suggests that the effect of *N*-acetylcysteine on exacerbations in chronic bronchitis is not due to the relatively low free thiol levels (other than glutathione) produced by *N*-acetylcysteine therapy.**

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*N*-acetylcysteine (NAC) is used to prevent exacerbations in chronic bronchitis [1–5] and to protect against liver toxicity caused by paracetamol overdose [6]. The mechanism of action in preventing paracetamol hepatotoxicity is believed to be the production of glutathione precursors for the liver [7]. Less is known about the mechanisms of the effects observed in the treatment of chronic bronchitis. Thus, it is not known whether NAC itself, or whether any of its metabolites, notably glutathione, is the active molecular species.

The pharmacokinetics of NAC have been investigated. The oral bioavailability in humans is approximately 10% [8, 9]. Following oral intake of NAC in humans, no NAC could be detected in bronchoalveolar lavage fluid [10, 11], suggesting that lung tissue is only minimally exposed to the drug after oral intake.

It was speculated that if a NAC-like compound could be synthesized that possessed greater oral bioavailability than NAC, it might be a better treatment for chronic bronchitis. The mechanism which accounts for the poor bioavailability of NAC is its effective hydrolysis to L-cysteine and acetate during first-pass metabolism [12]. A programme was initiated with the aim of producing a NAC-like compound that did not undergo effective hydrolysis during first-pass metabolism. This resulted in the development of *N*-isobutyrylcysteine (NIC).

NIC is not measurably hydrolysed in any biological system investigated, and its oral bioavailability in humans is up to 80%, depending on food intake *etc.* (G. Almqvist, Astra Draco AB, Lund, Sweden, personal communication). In addition, after oral administration of NIC in humans, it could be detected in bronchoalveolar lavage fluid, albeit at low concentrations (D. Morrison, unpublished data), indicating that lung tissue was actually exposed.

Dose-finding studies in patients with chronic bronchitis (M. Larson, personal communication) indicate that NIC 300 mg *b.i.d.* is the highest tolerable dose. Higher doses give rise to adverse effects at an unacceptable rate, the most serious of which are altered taste perception and reversible taste loss.

The present study evaluates oral NIC as a therapy for chronic bronchitis, particularly during exacerbations. NIC, a thiol that is not rapidly hydrolysed like NAC, has made it possible to test if the effect of NAC on exacerbations is due to an effect of the unhydrolysed thiol compounds.

## Methods

The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki.

### *Study design*

The study was a double-blind, placebo-controlled, parallel-group, multinational multicenter study conducted during the winter season of 1992–93.

After a treatment-free 4 week run-in period, patients were randomized to receive either oral NIC 300 mg *b.i.d.* or placebo for 24 weeks.

The patients attended the clinic for 5 visits: at the start of the run-in period (visit 1), at randomization 4 weeks later (visit 2) and after 2, 4, and 6 months of treatment.

Exacerbations were recorded by a respiratory symptom diary card and by questioning by the doctor at visits 2–5. Lung function was evaluated by spirometry at visits 1–5. Adverse events were noted throughout the whole treatment period. Laboratory tests such as haematology, liver function tests, renal function tests, electrolytes, serum-calcium and erythrocyte sedimentation rate were made at the first, second and at the last visit to the clinic. On the same occasions urinanalysis was performed.

### *Inclusion criteria*

The patients were smokers or exsmokers with chronic bronchitis, defined as recurrent productive cough on most days for at least three months per year for not less than two successive years [13]. In addition, they had to report $\geq 1$ exacerbations during the winter season prior to the study.

Baseline forced expiratory volume in one second ($FEV_1$), at visit 1 was >40% predicted and did not show a reversibility >10% pred after inhalation of 0.5 mg terbutaline sulphate.

All subjects were outpatients.

### *Exclusion criteria*

Patients were recruited while in a clinically stable period with at least 4 weeks since their last exacerbation. Patients who had unstable concurrent nonrespiratory diseases and patients with active pulmonary diseases other than chronic obstructive pulmonary disease were excluded. Patients with almost daily purulent sputum 1 month prior to visit 1 and patients with atopy, lactose intolerance or active peptic ulcer and/or treatment for a peptic ulcer during the prior 2 months, were exluded. Females of fertile age, who were not using contraceptives, were also excluded.

### *Concomitant medication*

There were restrictions on the use of steroids, NAC, antibiotics, and nonsteroid anti-inflammatory drugs during the trial.

Oral steroids initiated >1 month prior to visit 1 in doses of $\leq 5$ mg·day$^{-1}$ prednisolone or equivalent were allowed during the study. Short course treatment with oral steroids in doses >10 mg prednisolone for more than three consecutive days during the run-in period were not allowed.

Inhaled steroids (both oral and nasal) were allowed in doses of $\leq 800$ μg·day$^{-1}$ of budesonide or equivalent. The doses had to remain unchanged during the trial.

NAC treatment in the 4 weeks prior to the start of the study was not allowed.

Daily long-term treatment with antibiotics during the winter season was an exclusion criterion but antibiotics could be given up to two consecutive weeks for reasons other than exacerbations during the treatment period.

If an exacerbation required treatment during the study, the investigator was advised to follow study guidelines defining limitations of the use of antibiotics and steroids. Short course therapy with mucolytics, antibiotics and steroids due to exacerbations were allowed during the study and recorded. Treatment with NAC on two different occasions of only up to seven consecutive days was allowed.

### *Study variables*

The primary objective was to investigate the effect of orally administered NIC, by measuring the time to onset of the first exacerbation after the start of treatment. Secondary objectives were exacerbation rate and the number of exacerbation days.

### *Assessment of exacerbation*

Exacerbations were studied in two ways, by using a questionnaire and by an interview with an investigator at the visits (visits 2–5). A simplified and slightly modified version of the questionnaire published by Boman *et al.* [1] was used. The modification made data processing possible.

Twice weekly the patients recorded their respiratory symptoms, by ticking the appropriate alternative under six different questions (table 1). Increased cough, increased sputum amount, increased problems with expectoration and increased breathlessness, were each scored as 1 point. The development of yellow or green sputum was scored as 2 points.

Table 1. – Diary report and scoring for evaluation of exacerbations

| Questions | Answers | Score |
|---|---|---|
| 1. How much have you been coughing today: | Less than usual | 0 |
| | The same as usual | 0 |
| | More than usual | 1 |
| 2. Today did you have: | No sputum | 0 |
| | Clear sputum | 0 |
| | White sputum | 0 |
| | Yellow or green sputum | 2 |
| | Other colour of sputum | 0 |
| 3. How much sputum have you been coughing up today: | Less than usual | 0 |
| | The same as usual | 0 |
| | More than usual | 1 |
| 4. How difficult did you find it to cough up sputum today: | Did not cough up any sputum | 0 |
| | Less difficult than usual | 0 |
| | The same as usual | 0 |
| | More difficult than usual | 1 |
| 5. How breathless have you been today: | Less than usual | 0 |
| | The same as usual | 0 |
| | More than usual | 1 |
| 6. All things considered, how have your chest symptoms been today: | Better than usual | Global assessment |
| | The same as usual | |
| | Worse than usual | |

The start of an exacerbation was defined as the first given date for a period with a total score of ≥3 for questions 1–5 on two consecutive days and the end as the corresponding date with a score of ≤3 also on two consecutive days. Question 6 was used as a global assessment of the patients' opinion on the condition of their chest symptoms. Since diary recordings were completed twice weekly, each recorded diary period represented 3.5 exacerbation days.

In addition to the questionnaire, the investigator also reported the number of exacerbations and their duration after interviewing the patient at visits 2–5, without using the information in the above mentioned questionnaire. For interview purposes, an exacerbation was defined strictly according to BOMAN *et al.* [1].

### *Lung function*

Spirometry was performed at every visit. A reversibility test was carried out on the initial visit to decide whether the patient should be included or not.

Spirometry was accomplished as the best of three attempts in the sitting position using a spirometer that was calibrated daily. The calculation of predicted FEV1 was based on the reference values defined by the European Respiratory Society [14].

A reversibility test was performed before and 15 min after one inhalation of 0.5 mg terbutaline sulfate from a Bricanyl–Turbuhaler® (Astra Draco AB).

### *Adverse events*

Adverse events, health problems or symptoms not usually associated with chronic bronchitis were recorded at visits 2–5.

### *Statistics*

The statistical evaluation of the diary was carried out by the Dept of Biostatistics and Data Management at Astra Draco AB.

The two treatment groups were compared. The primary variable was analysed by a life-table method. Kaplan-Meier estimates of the "survival curves" and a log rank test were used to test the equality of the two curves. An initial evaluation of efficacy variables was performed in an all-patients-treated analysis.

Statistical significance tests were made for the primary variable only.

## Results

### *Inclusion and exclusion*

Forty-one centers in 10 European countries took part in the study. A total of 638 patients were recruited. One patient never took the study medication which left 637 randomized patients. Three hundred and sixteen were treated with NIC and 321 with placebo.

The characteristics of the patients randomized to NIC and placebo are shown in table 2. There were no significant differences between the groups with regard to current smokers or exsmokers.

Table 2. – Characteristics for subjects recruited

| Characteristics | NIC | Placebo |
|---|---|---|
| Patients n | 316 | 321 |
| Age yrs | 58 (12) | 57 (13) |
| Smokers/exsmokers n/n | 201/115 | 186/135 |
| Tobacco consumption cigarettes·day$^{-1}$ | 18 (10) | 16 (10) |
| Male/female n/n | 192/124 | 199/122 |
| FEV1 % pred | 72.1 (21.7) | 73.2 (22.8) |
| Concomitant medication n | | |
| Inhalation steroids | 91 | 94 |
| Oral steroids | 4 | 4 |

Data are presented as means (SD) or numbers where indicated. NIC: *N*-isobutyrylcysteine.

### *Drop-outs by treatment*

There was a slightly higher frequency of treatment drop-outs, in the NIC group. This was mainly owing to adverse effects and therapeutic failure (table 3). After all drop-outs, 244 and 259 patients remained in the active treatment and placebo groups, respectively.

### *Efficacy*

The life-table analysis was based on the number of patients delivering at least one diary recording, *i.e.* 313 patients treated with NIC and 315 with placebo. Both groups had the same mean number of days of treatment (168 days) and the same compliance with approximately 93% of the issued tablets used.

Figure 1 shows the percentage of patients still free of exacerbation after the start of treatment. The two curves show that NIC did not prolong the time to first exacerbation (p=0.59). At least one exacerbation developed in 174 patients from both groups. The number of exacerbations and exacerbation days, judged from the questionnaire and from the interview, are compared in table 4. There were more exacerbations and exacerbation days recorded in the diary than reported in the interview, but there were no differences between the groups. A detailed analysis of the questionnaire is presented in tables 5 and 6.

There were no differences in short course therapy with steroids, antibiotics and mucolytics between the active and placebo treated group (table 7).

There were no statistically significant changes in the FEV1 or forced vital capacity (FVC) in either group during the study (data not shown).

Table 3. – Randomization and reasons for discontinuation

| | NIC | Placebo | Total |
|---|---|---|---|
| Randomized patients | 316 | 321 | 637 |
| Discontinuations | 72 | 62 | 134 |
| Adverse events | 42 | 25 | 67 |
| Therapeutic failure | 8 | 3 | 11 |
| Other reasons | 22 | 34 | 56 |
| Completed study | 244 | 259 | 503 |

Data presented as numbers of subjects. NIC: *N*-isobutyrylcysteine.

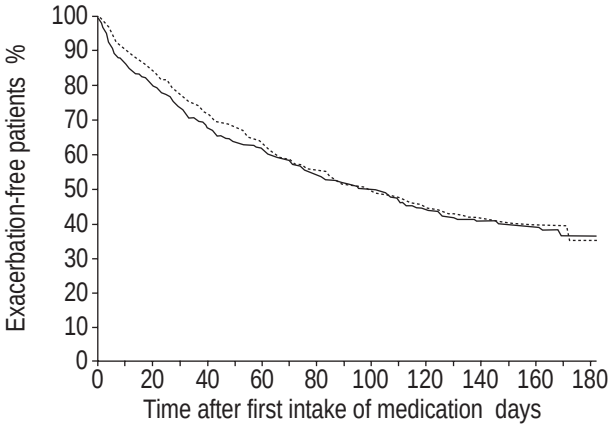


Fig. 1. – Percentage of patients free from exacerbation during the study. ——— : *N*-isobutyrylcysteine; - - - - : placebo.

*Adverse events*

The proportion of patients reporting any adverse event was almost evenly represented in the two groups; 74% and 67% in the NIC and the placebo groups, respectively. Serious adverse events occurred in twice as many cases in the NIC group (n=27) as in the placebo group (n=13) ($p<0.05$). Two thirds of the patients who discontinued the study owing to an adverse event were in the active treatment group. Altered taste perception, taste loss and anosmia occurred more frequently in the NIC group, reported by 23 patients, than in the placebo group, 2 patients ($p<0.001$). These symptoms disappeared when the patients stopped taking the drug. There were more cases of depression reported in the NIC group (8 *versus* 0; $p<0.005$). With respect to laboratory findings there were no differences between the two groups (p=0.8).

## Discussion

This study convincingly shows that the thiol compound *N*-isobutyrylcysteine has no protective effect against exacerbations in patients with chronic bronchitis. No effect was found on the time to the first exacerbation, the number of exacerbations, duration of exacerbations and consumption of antibiotics, steroids or mucolytics. Data for exacerbations were almost identical between placebo and treated patients. Approximately 40% of the patients in both groups did not develop an exacerbation during the study. The large number of patients included makes it highly unlikely that an existing difference could have been overlooked.

The definition of an exacerbation used when analysing the questionnaire did not define mucopurulent sputum as an obligatory criterion. However, mucopurulent sputum was commonly registered where the criteria for an exacerbation was fulfilled (table 5). Furthermore, a good correlation was found between the presence of an exacerbation as defined by the questionnaire and the patient's global assessment of their respiratory problems (table 6). An exacerbation as defined in the analysis of the questionnaire thus reflects increased respiratory problems, commonly, but not always, associated with purulent sputum. Events covered by the questionnaire are probably less specific for bacterial infection of the bronchi than the events picked up by strictly using the definition of BOMAN *et al.* [1]. This might explain why exacerbations were more commonly recorded by questionnaire than by interview with investigators who used the same definition as BOMAN *et al.* [1].

The results of the present study are contrary to those reported for NAC. Several studies on the effect of NAC on exacerbations of chronic obstructive pulmonary disease have been reported [1–5], with variable results. The present study was constructed along the same principles as that of BOMAN *et al.* [1]. Inclusion criteria and the methods of studying exacerbations, using both investigator interview reports and estimations of exacerbations by use of a questionnaire, were also similar. The severity of the patients also appears to have been similar. Mean $FEV_1$ was approximately 80% pred compared to 70% in the present study, with a similar range of the results. Although their

Table 4. – Exacerbations reported in the diary and by the investigator interview

| | NIC (n=313) | Placebo (n=315) |
|---|---|---|
| Diary | | |
| Number of exacerbations | 1.05 (1.30) | 1.02 (1.23) |
| Number of exacerbation days | 15.7 (24.2) | 16.7 (24.9) |
| Investigator | | |
| Number of exacerbations | 0.79 (0.96) | 0.77 (0.99) |
| Number of exacerbation days | 10.1 (15.2) | 10.7 (20.3) |

Data are presented on a per subject basis and expressed as mean (SD). Numbers refer to those subjects with diary data. NIC: *N*-isobutyrylcysteine.

Table 5. – Diary questionnaires: exacerbations and mucopurulent sputum

| Diary points | NIC | Placebo |
|---|---|---|
| 1–2 points | | |
| No mucopurulent sputum | 1827 | 1690 |
| Mucopurulent sputum | 619 | 599 |
| Total | 2446 | 2289 |
| 3–6 points (*i.e.* exacerbation) | | |
| No mucopurulent sputum | 660 | 630 |
| Mucopurulent sputum | 1060 | 952 |
| Total | 1720 | 1582 |

Data are presented as numbers of registrations. NIC: *N*-isobutyrylcysteine.

Table 6. – Diary questionnaires: exacerbations and patient's global evaluation

| Diary points | NIC | Placebo |
|---|---|---|
| 1–2 points | | |
| Better than usual | 30 | 32 |
| The same as usual | 62 | 63 |
| Worse than usual | 8 | 5 |
| 3–6 points (*i.e.* exacerbation) | | |
| Better than usual | 2 | 4 |
| The same as usual | 24 | 31 |
| Worse than usual | 74 | 65 |

Data presented as percentage of subjects in each group. NIC: *N*-isobutyrylcysteine.

Table 7. – Short courses of steroids (Anatomical Therapeutic Chemical Classification System (ATC) code), antibiotics and mucolytics during the study period

| Treatment | NIC | Placebo |
|---|---|---|
| Steroids | 59 | 41 |
| Antiasthmatics, inhalation (R03AB) | 8 | 6 |
| Nasal, inhalation (R01AD) | 1 | 2 |
| Oral (H02AB) | 48 | 30 |
| External (D07AC) | 2 | 3 |
| Mucolytic therapy | 16 | 15 |
| Antibiotic therapy | 170 | 134 |

Data presented as number of courses per treatment period. NIC: *N*-isobutyrylcysteine.

study used a smaller number of patients, it showed a significant effect of NAC. The similarity of their methodology to the present study suggests that there is a difference in the effect of the two thiol compounds on exacerbations of chronic bronchitis. In both studies, patients without airways obstruction or with only mild obstruction were included. Patients with severe airways obstruction are probably less suited for pharmacological studies of drugs with supposed protective effects against exacerbations. In a study on NAC including such patients no significant protective effect was demonstrated [5].

Most investigators are of the opinion that the protective effect against exacerbation of NAC is either due to its antioxidative capacity as a free thiol or due to its antioxidative effect after metabolism to increased glutathione levels. The present study can be thought of as a trial of the free thiol hypothesis in that NIC produces much higher levels of free thiols (other than glutathione) in the human body than NAC. The lack of effect of NIC may therefore indicate that free thiols (other than glutathione) do not protect against exacerbations in chronic bronchitis. In addition, the levels of both NAC and NIC that appear in the airspaces are too low to result in a protective effect (D. Morrison, unpublished data). It is also possible that the effect of NAC on exacerbations has other explanations such as an effect on bacterial colonization of the airways, perhaps mediated by direct effects on bacteria and their ability to adhere to cell membranes [15].

Patients treated with NIC reported altered taste perception, taste loss and anosmia more often than patients given placebo (23 *versus* 2 cases). These adverse effects were the main cause for discontinuation in the treated group and the symptoms disappeared when the patients stopped taking the drug. It was assumed that the influence of NIC on the sense of taste is thiol-dependent. Similar symptoms have previously been reported after treatment with other thiols, *e.g.* captopril and penicillamin [16, 17] but no direct relation of these symptoms to the thiol moiety has yet been reported.

In conclusion, *N*-isobutyrylcysteine, a *N*-acetylcysteine like drug with greater bioavailability producing higher levels of free thiols in the body, has no effect on exacerbations in chronic bronchitis, contrary to *N*-acetylcysteine. This suggests that the effect of *N*-acetylcysteine on exacerbations in chronic bronchitis is not due to the relatively low free thiol levels (other than glutathione) produced by *N*-acetylcysteine therapy.

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