

## ORAL ACETYLCYSTEINE IN BRONCHOPULMONARY DISEASE

Comparative clinical trial with bromhexine.

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### Summary

The efficacy of oral N-Acetylcysteine (NAC) was compared with that of bromhexine in a controlled study carried out on 60 patients with bronchopulmonary disease (31 acute respiratory infections and 29 non-infectious chronic conditions) for 15 days.

Both medications were effective in improving cough, dyspnea, difficulty in raising sputum and sputum thickness.

NAC always showed a better effect than that of bromhexine. This was apparent when NAC was used as coadjuvant therapy to antibacterial treatment in patients with acute forms, and even more markedly in patients with chronic forms.

### INTRODUCTION

Aerosol therapy with N-Acetylcysteine (NAC) is widely used in the mucolytic treatment of thick and viscous bronchopulmonary secretions [1, 2, 3].

This thiol derivative is capable of denaturing mucoprotein and nucleic macromolecules by chemical lysis, acting on both mucous and mucopurulent secretions [2, 4].

The oral use of NAC has only been described recently. RODENSTEIN et al. [5] assessed its absorption in man, demonstrating the high diffusion of this compound in the pulmonary tissue and bronchial secretion. An

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extensive literature reporting its therapeutic efficacy in bronchopulmonary disease is available at present [6, 7, 8, 9, 10].

The aim of our study was to evaluate the activity of orally administered NAC in patients with chronic bronchitis requiring mucolytic treatment only, and in patients with acute respiratory disease requiring mucolytic treatment in addition to antibiotics.

Bromhexine was chosen as the active control, being frequently used in current practice in these indications.

#### MATERIAL AND METHODS

##### *Patients*

The study was carried out on 60 patients (45 males and 15 females) aged 45 to 80 years (average 65.8 yrs), 31 of whom with acute respiratory infections (Group 1) and 29 with simple, non-superinfected chronic forms (Group 2).

##### *Medications*

NAC was administered in the granular form in 200 mg sachets\* at a dose of 3 sachets daily (total 600 mg/die); bromhexine\*\* was given at a dose of 2 x 12 mg tablets 3 times daily (total 24 mg/die).

Both medications were administered for 15 days.

Patient allocation was carried out on a random basis: altogether 17 patients in Group 1 and 14 in Group 2 were treated with NAC, while 14 subjects in Group 1 and 15 in Group 2 received bromhexine.

In addition, all the patients in Group 1 (acute infections) received a standard antibacterial treatment consisting of amoxicillin 2 g daily for 10 days.

##### *Clinical findings*

The following clinical parameters were recorded: cough, dyspnea, difficulty in raising sputum, sputum thickness. Evaluation was carried out at time 0 and after 2, 7 and 15 days of treatment, according to a conventional score from 0 to 3 (0 = normal; 3 = highly pathologic).

Side effects, if any, were also recorded.

\* LYSOMUCIL ®

\*\* BISOLVON ®

*Data analysis*

Results were submitted to statistical analysis by the 4-group covariance analysis (2 clinical conditions and 2 treatments) by means of an IBM computer.

This type of analysis allows the evaluation of the significance level between treatments and between clinical conditions, as well as of the evaluation of the parameters during the 15 days of treatment.

## RESULTS

Figs. 1 and 2 show the time course of the parameters, subdivided into clinical conditions. Values are expressed as percentages of the basal value of each subgroup.

These figures also show probability levels for significance of differences resulting from the statistical analysis of covariance.

A characteristic common to all the parameters is their improvement during the 15 days of observation: in all the groups severity of symptoms shows a high statistical reduction ( $P < 0.001$ ) in patients with acute and chronic disease. However, the entity and rapidity of improvement vary according to the severity of the disease and therapy.

A) *Sputum thickness* (Fig. 1)

For this parameter there are no differences between clinical conditions ( $P > 0.05$ ), while difference between treatments is highly significant ( $P < 0.001$ ).

Sputum thickness was considerably reduced in the first days of treatment and still more in the subsequent days in patients receiving NAC, while the mucolytic effect of bromhexine was slower and on the whole less effective.

B) *Difficulty in raising sputum* (Fig. 1)

Difference between treatments is highly significant ( $P < 0.001$ ); difference between clinical conditions is also significant ( $P < 0.005$ ): expectoration was more difficult in the most severe clinical conditions.

The efficacy of NAC was excellent in both patient groups, while the effect of bromhexine was less evident in subjects with chronic conditions.

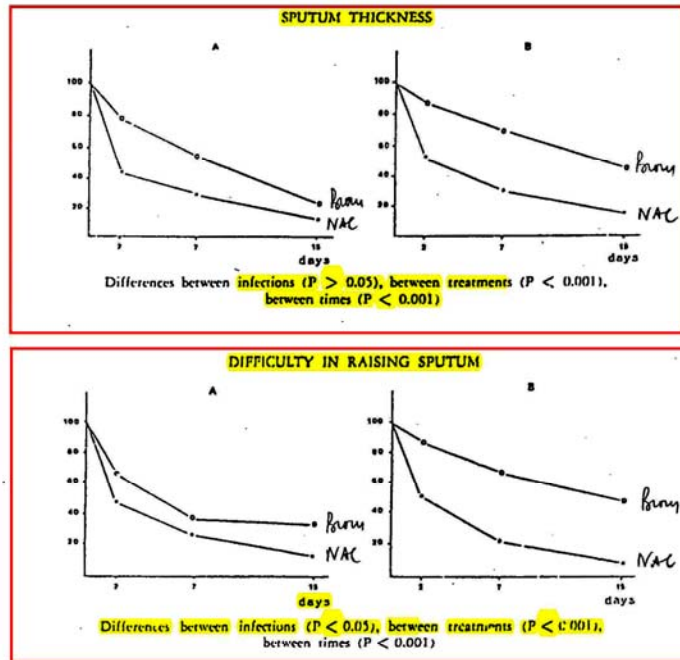


Fig. 1

Clinical evolution of sputum thickness and difficulty in raising sputum in patients with acute respiratory infections (A) and chronic forms (B) orally treated with N-Acetylcysteine (—•—) and bromhexine (---□---).

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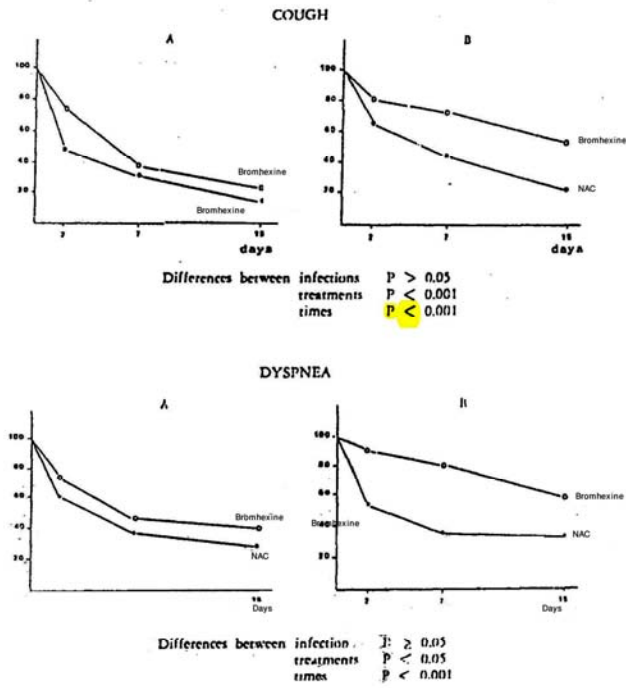


Fig. 2

Clinical evolution of cough and dyspnea in patients with acute respiratory infections (A) and chronic form (B) orally treated with N-Acetylcysteine (●) and bromhexine (○).

C) *Cough* (Fig. 2)

Overall NAC was more effective than bromhexine ( $P < 0.001$ ) on this symptom too, particularly in chronic patients.

D) *Dyspnea* (Fig. 2)

Here significance of difference between treatments ( $P < 0.05$ ) is almost exclusively associated with the different behaviour of the two compounds in chronic patients.

The effect of bromhexine in these patients was scarcely evident, while NAC was equally effective in both patient groups.

E) *Side effects*

No noteworthy adverse effects were observed throughout the duration of treatment (15 days), except nausea in two subjects treated with NAC and in one subject treated with bromhexine.

CONCLUSION

The effect of NAC on each one of the clinical symptoms in the two patient groups under study was considerably more evident than that of bromhexine.

This difference in efficacy is less marked in patients with acute respiratory infections, where the concomitant antibacterial therapy is itself capable of inducing an improvement of the symptomatic clinical picture, as demonstrated by the most rapid positive evolution of the various parameters. The better therapeutic efficacy of NAC is most evident in patients with chronic bronchopulmonary disease. In these subjects the better bronchial drainage resulting from the mucolytic effect of the compound induces a gradual and significant improvement of the whole symptomatology.

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RESUME

L'efficacité de la N-acétylcystéine (NAC) par voie orale fut comparée à celle de la bromhexine au cours d'une étude contrôlée effectuée pendant 15 jours chez 60 patients souffrant d'affections bronchopulmonaires (31 infections respiratoires aiguës et 29 états chroniques non-infectieux).

Les deux médications se sont révélées efficaces et ont amélioré l'évolution de la toux, de la dyspnée, des expectorations ainsi que de la viscosité de ces expectorations.

La NAC procura toujours un effet thérapeutique meilleur que la bromhexine tant comme adjuvant d'un traitement antibactérien chez les patients atteints d'affections aiguës que dans les cas chroniques ou la différence entre les deux médications est la plus importante.

SAMENVATTING

De werkzaamheid van N-acetylcysteïne (NAC) per os werd vergeleken met die van bromhexine tijdens een vijftien dagen lang statistisch gekontro-

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Icde studie bij 60 patiënten met bronchopulmonaire aandoeningen (31 acute ademhalingsinfecties en 29 niet-infectieuze chronische aandoeningen).

Beide medicaties waren werkzaam en verbeterden de evolutie van de hoest, de dyspnoe, de expectoratiefunctie en de viscositeit van het sputum.

NAC gaf op alle punten een beter resultaat dan bromhexine zowel als adjuvans van een antibacteriële behandeling bij patiënten met acute vormen als in chronische gevallen waar het verschil tussen de behandelingen het duidelijkst waren.

#### ZUSAMMENFASSUNG

Die Wirksamkeit von oralem N-Acetylcystein (NAC) wurde mit der des Bromhexin verglichen in einem kontrollierten Versuch, der an 60 Patienten mit broncho-pulmonaren Erkrankungen (31 Akute Atemwegsinfektionen und 29 nicht-infektiöse chronische Fälle) 15 Tage lang durchgeführt wurde.

Beide Medikamente verbesserten Husten, Dyspnoe, Sputum-Ausscheidung und Sputumdichte. Die Wirkung von NAC war jedoch in jedem Fall besser als die des Bromhexin, sei es als Ergänzungstherapie zur antibakteriellen Behandlung von Patienten mit akuten Erkrankungen, oder in chronischen Fällen, wo der Unterschied zwischen den beiden Medikamenten noch deutlicher hervortrat.



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LA ACETILCISTEINA ORAL EN LAS ENFERMEDADES BRONCOPULMONARES

Resumen

En un ensayo clínico controlado efectuado con 60 pacientes que sufrían afecciones broncopulmonares (31 infecciones respiratorias agudas y 29 en condiciones crónicas no infectivas), durante 15 días, se comparó la eficacia de la acetilcisteína oral con la de la bromexina.

Ambos medicamentos se demostraron efectivos en mejorar la tos, disnea, dificultad de expectoración y el espesor del esputo.

La acetilcisteína se mostró siempre más eficaz que la bromexina.

Dicha eficacia fue manifiesta cuando la acetilcisteína fue usada como coadyuvante en el tratamiento antibacteriano en los pacientes con formas agudas y fue más marcada aún en los pacientes con formas crónicas.