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ERDOSTEINE VERSUS N-ACETYLCYSTEINE IN THE TREATMENT OF EXACERBATION OF CHRONIC BRONCHOPNEUMOPATHIES

A double blind clinical trial

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Summary

A double blind controlled clinical trial was carried out to evaluate effectiveness and safety of erdosteine compared with N-acetylcysteine (NAC) in the therapy (combined with antibiotics) of the exacerbation of chronic obstructive bronchopulmonary diseases. The trial involved 50 patients, 31 male and 19 female, aged from 45 to 70 years, divided in two groups and treated for 7-10 days with erdosteine (225 mg thrice a day) or with NAC (200 mg thrice a day). Both drugs induced significant and favourable changes of all efficacy variables: sputum volume, sputum viscosity, sputum appearance, cough severity and frequency signs of catarrh at chest auscultation, difficulty to expectorate, spirometric indices (FVC, FEV1, RAW) and hemogasanalytic indices (pO_2 and pCO_2). The onset of the effect of erdosteine was significantly faster than that of NAC on sputum volume, sputum viscosity and cough frequency. Erdosteine also showed a significantly better tolerance and compliance than NAC.

Key words: erdosteine, N-acetylcysteine, mucus, chronic obstructive bronchopulmonary disease

Riassunto

E' stato attivato uno studio clinico di tipo controllato a cecità doppia, allo scopo di valutare l'efficacia e la sicurezza della erdosteina in confronto all'N-acetilcisteina nella terapia delle broncopneumopatie croniche ostruttive in fase di esacerbazione. L'erdosteina e l'N-acetilcisteina sono state somministrate assieme con antibiotici.

Alla sperimentazione hanno avuto accesso 50 pazienti (31 maschi e 19 femmine) di età compresa fra i 45 ed i 70 anni: essi sono stati distribuiti in due gruppi e trattati per 7-10 giorni con erdosteina (225 mg tre volte al giorno) o con N-acetilcisteina (200 mg tre volte al giorno).

Ambedue i farmaci hanno indotto modificazioni significative e favorevoli di tutte le variabili pertinenti alla efficacia: volume dell'espettorato, aspetto dell'espettorato, severità e frequenza del sintomo tosse, presenza di catarro all'auscultazione, difficoltà ad espettorare, indici spirometrici (FVC, FEV1, RAW) ed emogasanalitici (pO_2, pCO_2).

L'erdosteina, rispetto all'N-acetilcisteina, ha promosso miglioramenti più precoci in termini di significatività relativamente ai seguenti parametri: volume dell'espettorato, viscosità dell'espettorato e frequenza della tosse.

Nei confronti dell'N-acetilcisteina, l'erdosteina ha rivelato una migliore tollerabilità: la terapia con erdosteina ha ottenuto inoltre una migliore adesione da parte dei pazienti.

Parole chiave: erdosteina, N-acetilcisteina, muco, broncopneumopatia cronica ostruttiva.

Introduction

Chronic obstructive bronchopneumopathies (COBP) are commonly encountered in the medical praxis, being favoured by smoking habits and by air pollution. The associated rates of morbidity and mortality are approaching those related to the cardiovascular and rheumatic diseases. Due to mixed manifestations of COBP, their treatment is obviously multifactorial. The concomitant administration of antibiotics and mucolytics is a rational approach during the exacerbation phase. Drugs capable of fluidifying the viscous bronchial secretion facilitate the expectoration of catarrh by cough, thus removing an excellent substratum for bacterial growth. Moreover, it has been shown that the concomitant administration of a mucolytic and an antibiotic increases the bronchial and sputum concentration of the latter (1-4).

The viscosity of bronchopulmonary mucous secretions depends on the concentrations of mucoproteins and, to a lesser extent, of DNA.

The well known mucolytic NAC decreases the viscosity of mucus by means of its free sulfhydryl group, which opens the disulfide bonds of mucoproteins. Clinical studies demonstrated its usefulness in the treatment of lung diseases characterized by abnormal, viscid or thick mucous secretions. The drug is generally well tolerated, however, some patients complain for gastrointestinal side-effects. Compliance is not always very good, since the product has an unpleasant odour and some patients could also taste the smell

during intake, probably due to the free sulfhydryl group (5-8). Recently, a new thiol derivative with two masked SH groups has been synthetized (9): erdosteine, (N-(carboxymethyl thioacetyl) homocysteinethiolactone). This compound could be considered as a prodrug. In fact, the sulfhydryl groups become free and active only after absorption and metabolic transformation (10). This feature may explain the favourable properties of the drug:

- good gastrointestinal tolerance (no interference between blocked thiolic groups and gastric mucus);
- steady effect (the SH groups are protected from oxidation);
- good patient's compliance due to the absence of unpleasant smell and/or taste.

Open and controlled clinical studies have provided evidence of the marked therapeutic activity and good tolerance of erdosteine in the treatment of acute or exacerbated chronic bronchopneumopathies (11-15).

We report here in the results of a double blind trial performed in exacerbated COBP patients treated with erdosteine or NAC. The aim of the trial was to comparatively evaluate efficacy and tolerance.

Materials and Methods

The clinical study involved 50 patients, 31 male and 19 female, aged from 45 to 70 years, suffering from COBP. The patients admission was guided by the following criteria:

- clinical evidence of acute relapse of chronic bronchitis with cough, fever, difficulty in the expectoration for thickness of secretions;
- absence of acute parenchimal or pleuric involvement;
- wash-out period of at least 7 days for previous antibiotics and mucolytics;
- dropping of smoking habits at least three months before;
- no ascertained or presumed pregnancy;
- no history of hypersensitivity to the tested drugs;
- informed consent.

The treatment was performed in double blind conditions for 7-10 days, according to the patient's response. On the basis of a randomization list, patients received erdosteine (*) (ER) or N-acetylcysteine (NAC), in the pharmaceutical form of powder for suspension. The two drugs were supplied in identical sachets containig 225 mg of ER or 200 mg of NAC. The dosage regimen was 1 sachet thrice a day for both drugs. During the trial period all patients received a parenteral antibiotic therapy. No drug able to affect the evaluation of the mucolytic activity of the two compounds under investigation was allowed. The effectiveness of the treatments was assessed as follows. Before starting the trial (basal evaluation), at 2nd, 4th, 6th day of treatment

(*) ERDOSTEINE is the INN of RS[[[(oxo-3-tetrahydrothienyl-3) carbamoil]methyl]thio] 2-acetic acid, compound patented by Refarmed SA - Lugano - CH.

and at the end of observation period (final evaluation) were recorded:

- sputum volume (ml) collected during 3 hours after awakening;
- sputum viscosity (cPs);
- sputum appearance (score from 1=mucoid to 3=purulent);
- severity of cough (score from O=absent to 3=severe);
- frequency of cough (No. of events) recorded during 3 hours after awakening by a tape recorder;
- signs of catarrh at chest auscultation (score from O=absent to 3=severe);
- difficulty to expectorate (score from O=no difficulty to 3=very difficult).

At basal and final evaluation were measured:

- spirometric indices: Forced Vital Capacity (FVC - litres), Forced Expiratory Volume during the first second (FEV1 - litres), Resistance of airway (RAW - cm H_2O/l/s);
- hemogasanalytic indices: partial O_2 pressure (pO_2 - mmHg), Partial CO_2 pressure (pCO_2 - mmHg).

At the end of the treatment a conclusive judgement on mucolytic effect was expressed, according to the following items: positive, doubtful, negative. The safety of the two treatments was observed by performing basal and final hematological and hematochemical analysis (red and white cells count, hemoglobin, BUN, glucose, creatinine, total bilirubin, SGOT, SGPT) and by noting all observed or volunteered side-effects. Drug tolerance and patient's compliance were judged as: good, fair, poor. Statistical evaluation of collected data was performed by means of:

- Analysis of variance for the data concerning sputum viscosity, cough frequency, spirometric, hemogasanalytic and hematochemical parameters;
- Wilcoxon's test (comparisons within group) and Mann-Whitney test (comparisons between groups) for the clinical symptoms;
- Chi square test for analysis of frequency distribution.

Results

Age, sex, diagnosis and duration of treatment are indicated below for each group.

	ER	NAC
No. of patients	**25**	**25**
AGE min.- max.	45 - 68	50 - 70
mean±S.E.	57.4±1.2	58.7±1.2
SEX male	17	14
female	8	11
DIAGNOSIS		
Exacerbation of:		
- COBP	21	19
- Asthmatic COBP	4	6
DURATION OF TREATMENT		
min.-max.	7 - 10	7 - 10
mean±S.E.	8.4±0.2	8.8±0.2

Effectiveness

The mean values ± S.E. of all variables at each measurement time, the mean percent difference versus baseline, the significance level of the differences versus baseline and between groups at each day are shown in tables No. 1 and No. 2.

The administration of both drugs was accompanied by significant and favourable changes of all considered variables. As far as the comparison between groups is concerned, significant differences were observed in the trend of sputum volume, sputum viscosity and cough frequency in favor of ER. The time course of the means of these variables is shown in figure 1. ER is characterized by a faster reduction in sputum viscosity with easier expectoration, as compared with NAC. The other variables presented a similar pattern in both groups.

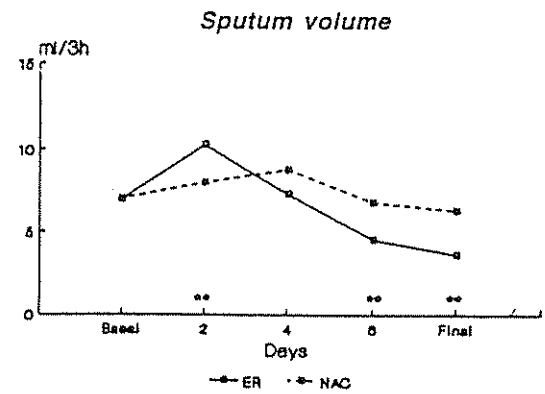
VARIABLES	GROUPS	Mean values ± S.E. at various times				
		Basal	2nd Day	4th Day	6th Day	Final
SPUTUM VOLUME (ml/3h)	ER	6.96±0.43	10.28±0.64 [47.7%] **	7.28±0.68 [4.6%]	4.52±0.29 [-35.1%] **	3.60±0.31 [-48.3%] **
	NAC	7.00±0.54	8.00±0.54 [14.3%]	8.80±0.84 [25.7%]	6.80+0.59 [-2.9%]	6.30±0.55 [-10.0%]
SPUTUM VISCOSITY (cPs)	ER	135.92±2.11	119.92±2.71 [-11.8%] **	104.92±2.40 [-22.8%] **	82.44±2.79 [-39.3%]	75.64±2.73 [-44.4%]
	NAC	138.00±4.86	134.00±4.02 [-2.9%]	117.36±3.24 [-14.9%]	90.36±2.01 [-34.5%]	79.28±2.05 [-42.6%]
SPUTUM APPEARANCE (score)	ER	2.64±0.10	1.96±0.18 [-25.8%]	1.44±0.10 [-45.5%]	1.28±0.09 [-51.5%]	1.12±0.07 [-57.6%]
	NAC	2.56±0.10 [-15.6%]	2.16±0.14 [-37.5%]	1.60±0.10 [-42.2%]	1.48±0.10 [-51.6%]	1.24±0.09
COUGH SEVERITY (score)	ER	2.76±0.09	1.88±0.15 [-31.9%]	1.16±0.11 [-58.0%]	0.84±0.09 [-69.6%]	0.44±0.12 [-84.1%]
	NAC	2.60±0.10	2.08±0.11 [-20.0%]	1.40±0.12 [-46.2%]	0.96±0.09 [-63.1%]	0.56±0.12 [-78.5%]
COUGH FREQUENCY (No./3h)	ER	43.36±2.22	27.28±2.19 [-37.1%] **	15.60±1.30 [-64.0%] **	11.56±1.13 [-73.3%]	7.60±0.75 [-82.5%]
	NAC	44.48±2.31	33.36±1.93 [-25.0%]	22.76±1.25 [-48.8%]	14.52±1.09 [-67.4%]	9.04±0.84 [-79.7%]
CATARRH (score)	ER	2.52±0.10	2.08±0.15 [-17.5%]	1.32±0.10 [-47.6%]	1.04±0.15 [-57.7%]	0.56±0.10 [-77.8%]
	NAC	2.48±0.10	2.00±0.21 [-19.4%]	15.36±0.11 [-45.2%]	1.24±0.12 [-50.0%]	0.76±0.09 [-69.4%]
DIFFICULTY TO EXPECTORATE (score)	ER	2.80±0.08	2.16±0.16 [-22.9%]	1.68±0.16 [-40.0%]	0.96±0.04 [-65.7%]	0.44±0.10 [-84.3%]
	NAC	2.80±0.08	2.40±0.10 [-14.3%]	1.76±0.20 [-37.1%]	1.08±0.13 [-61.4%]	0.60±0.10 [-78.6%]

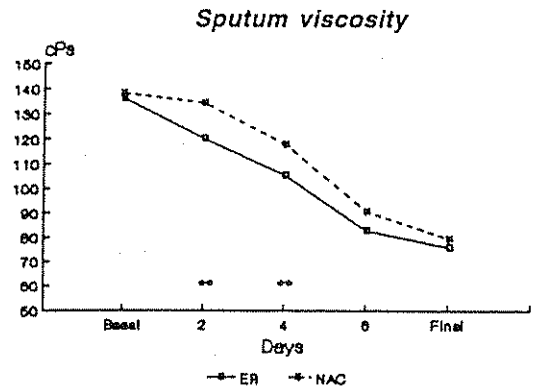
TABLE 1 - Mean values ± standard error at various times before and after erdosteine (ER) and N-acetylcysteine (NAC).
The underlined means are significantly different from their basal (at least at significance level of 5%).
** ($P<0.01$) indicate significant difference between groups at that time.

VARIABLES	GROUPS	Mean values ± S.E. Basal	Final
FVC (litres)	ER (25)	2.94±0.09	3.21±0.07 [9.0 %]
	NAC (25)	2.85±0.12	3.08±0.12 [8.1%]
FEV_1 (litres)	ER (25)	1.55±0.05	1.89±0.08 [22.2%]
	NAC (25)	1.47±0.05	[1.85±0.12] [25.2%]
RAW (cm H_2O/l/s)	ER (25)	7.72±0.17	5.46±0.16 [-29.3%]
	NAC (25)	7.84±0.25	5.73±0.15 [-26.9%]
pO_2 (mmHg)	ER (25)	64.50±0.82	70.60±1.17 [9.5%]
	NAC (25)	63.80±1.18	69.20±1.24 [8.5%]
pCO_2 (mmHg)	ER (25)	41.20±0.55	37.80±0.76 [- 8.3%]
	NAC (25)	42.00±0.92	39.00±0.80 [- 7.1%]

TABLE 2 - Basal and final mean values ± standard error before and after erdosteine (ER) and N-acetylcysteine (NAC).

The underlined means are significantly different from basal (at least at significance level of 5%).
The number of patients is indicated under the group name.





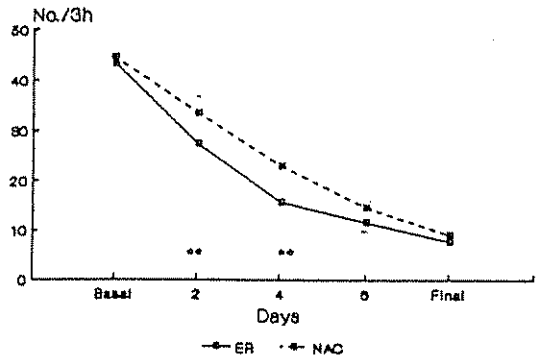


FIGURE 1 - Mean values at various times of Sputum volume, Sputum viscosity and Frequency of cough.
** (P<0.01) between groups at that time.

The conclusive assessment on the mucolytic effect did not point out statistical differences between the two groups, despite a greater percentage of positive judgements in the ER group:

GROUPS	JUDGEMENTS		
	Positive	Doubtful	Negative
ER	21 (84%)	4 (16%)	-
NAC	18 (72%)	6 (24%)	1 (4%)

The statistical comparison of the frequencies of positive and of doubtful+negative judgements did not reveal any difference (Chi square = 0.466; 1 d.f.; N.S.) between groups.

Safety

Mild nausea occurred in 2 (8%) and mild heart-burn in 4 (16%) patients of NAC group. The first two and 5 other patients (28%) of the same group complained of transient unpleasant smell and/or taste when swallowing. In none of the patients did the nature and the severity of the side-effects prevent the prosecution of the treatment. No side-effect was reported by patients of ER group, and, therefore, the tolerance for these patients resulted significantly better than for the others. The compliance of ER was significantly better than that of NAC. No significant changes were observed when comparing the basal and the final values of laboratory tests. The following prospectus summarizes the judgements on the safety and compliance:

GROUPS	SAFETY			CHI SQUARE
	Good	Fair	Poor	(1 d.f.)
ER	25 (100%)	-	-	4 . 735
NAC	19 (76%)	6 (24%)	-	P<0.05
GROUPS	**COMPLIANCE**			**CHI SQUARE**
	Good	**Fair**	**Poor**	**(1 d.f.)**
ER	25 (100%)	-	-	5 . 980
NAC	18 (72%)	7 (28%)	-	P<0.05

Conclusion

The present clinical trial clearly demonstrated the efficacy, safety and compliance of erdosteine in the therapy (combined with antibiotics) of exacerbation of COBP. The drug did very effectively improve sputum viscosity and appearance, which changed from thick and purulent to fluid, more hydrated and easily expectorated. The diminution of irritative stimuli due to viscous secretions probably aided to relieve cough severity and frequency. The favourable action of erdostein on mucus induced relevant advantages in terms of airway patency, as shown by the improvement of spirometric and hemogasanalytic parameters. These results are fully in agreement with those described by other authors and with the pharmacological activity of erdosteine (9-15). The lack of negative effects on laboratory exams, as well as the absence of side-effects, point out the good safety of this compound. The difference between erdosteine and N-acetylcysteine is due to the significantly faster and greater mucolytic activity of erdosteine, and a better compliance of the patient; this one could be explained by the presence of two blocked SH groups in erdosteine molecule.

References

1) BACH P.H., LEARY W.P.P.: *SA. Med. J.* 46, 1512, 1972

2) HADA M.: *Medical treatment* 8, 2079, 1975

3) LAWSON D., SAGGERS B.A.: *Brit Med. J.* 1, 317, 1965.

4) RICEVUTI G. et al.: *Thorax* 43, 585, 1988.

5) WEBB W.R.: *Postgrad. Med.*. 36, 449, 1964.

6) GRASSI C. et al.: *Giorn. It. Mal. Tor.* 13, 2, 1974

7) SHEFFNER A.L., LISH P.M.: *Acetylcysteine and other mucolytic agents.* In: Intern. Encycl. Pharmacol. Ther., H. Salem and D.M. Aviado Eds. Vol. III, New York, Pergamon Press. 1970.

8) *Drug Information For The Health Care Provider.* pp. 17-20-USP DI. 6th - U.S. Pharmacopoeial Convention, Inc. - Rockville, 1986.

9) GOBETTI M., et al.: *Il Farmaco* - Ed. Sc. 41, 69, 1986

10) BERTÈ F.: RV-144: N-(carbossimetil - tio - acetil) - omocisteina tiolattone: rapporto tossico - farmacologico. Farmacologia Medica II dell'Università di Pavia (1984). Data on file - Edmond Pharma - Milano.

11) MORALE M.C., et al.: *Effects of erdosteine on mucus from human lung.* In press. Med. Praxis. 13. (1), 1992

12) SIQUET J.: *Med. Praxis:* 12, 159, 1991
13) TELLINGS J.C.: *Med. Praxis:* 12, 183, 1991
14) HÖTZINGER H.: *Med. Praxis:* 12, 171, 1991
15) FUMAGALLI G. et al.: *It. J. Chest Dis.*, 42, 299, 1988.

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