ORIGINAL ARTICLE

Use of Acetyl Cysteine in Respiratory Tract Disease in Children

by

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Abstract

In this study 54 children with respiratory tract disease : bronchopneumonia, bronchial asthma, bronchiolitis and tuberculosis all treated with acetylcysteine and placebo were analysed. In thirty eight patients with bronchopneumonia 20 were treated with acetylcysteine and 16 with placebo; in 9 patients with bronchial asthma 5 were treated with acetylcysteine and 4 with placebo. Of the 5 patients with bronchiolitis, 3 were treated with acetylcysteine and the remainder with placebo. Two children with tuberculosis were given acetylcysteine.

The analysis of patients suffering from bronchopneumonia showed no statistically significant difference between acetylcysteine and placebo. Patients with bronchial asthma also showed no significant difference between both groups. There is a statistically significant difference between the results on the first, third, fifth and seventh day of treatment of the group of patients treated with acetylcysteine.

No attempts were made to analyse bronchiolitis and tuberculosis. No side effects were seen in this study.

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Introduction

Cough is a sign of infection or irritation of the respiratory tract, and is the primitive reflex of defence mechanism especially to clear dirt or sputum from the respiratory tract. (Hofman, 1979; Rodensteine et al., 1978).

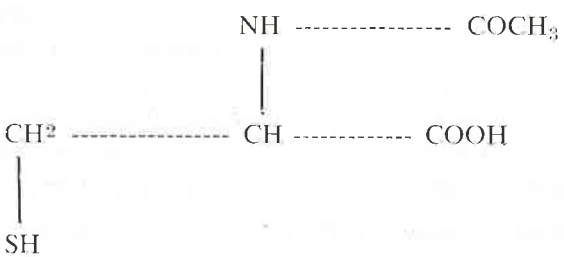
There are many methods to clear the sputum in order to relieve cough and accelerate recovery. One of them is to give mucolytic agents such as acetylcysteine (Armstrong, 1976; Aylward, 1977; Bellomo et al., 1967; Bellomo et al., 1973; Campbell et al., 1975; Hartsell, 1972).

Use of oral acetylcysteine has been reported (Aylward, 1977; Biscatti et al., 1972; Gorringe, 1978; Hartsell, 1972; Nicolic and Korac, 1979). This thiol derivate has the effect on the mucus and mucopurulent secretion (Sheffner, 1964). Rodensteine et al. (1978) showed that there is a high diffusion of this drug into the lung tissues and bronchial secretion (Uro, 1978). N-Acetylcysteine, possessing a free and reactive S-H group, acts principally on the constituent glycoproteins of sputum. Its mucolytic and fluidifying action is consequent on the cleavage of intermolecular disulfide bridges cross-linking the mucoprotein macromolecules.

The objective of the study is to investigate the effect of mucolytic action on children with respiratory tract diseases admitted at the Department of Child Health Dr. Kariadi Hospital Semarang.

Chemical physical properties.

Structural formula of N-Acetylcysteine



Molecular formula : $C_5 H_9 NO_3 S$

N-Acetylcysteine is an acetyl derivative of L-Cysteine, a natural amino acid. It is a white crystalline powder (white), with a sulfur odor and a bitter, acidulous, taste; solubility of N-Acetyl cysteine in water and in solutions, buffered at different pH's is high ($\geq 5\%$) greater than of L-cysteine. At physiological pH values (including the ones) (pH 2-7) N-Acetylcysteine exhibits a good stability to oxydation ($\leq 3\%$ over 24 hours).

Materials and methods

This study was a "double blind" clinical trial done at the Department of Child Health Dr. Kariadi Hospital Semarang since April 1980 until April 1981.

TABLE 1 : *Patients Data*

	N-Acetylcysteine		Placebo		Total	
	Number of patients					
	%		%		%	
Sex : Female	11	18.3	18	30	29	48.3
Male	19	31.6	12	20	31	51.6
Disease :						
Bronchopneumonia	20	33.3	18	30	38	63.3
Bronchiolitis	3	5	2	3.3	5	8.3
Bronchial Asthma	5	8.3	4	10	9	18.3
Pulmonary tuberculosis	2	3.3	—	—	2	3.3
Age (year) :						
> 1 - 5	15	25	13	21.6	28	46.6
< 1	10	16.6	11	18.3	21	35
> 5	5	8.3	6	10	11	18.3

The number of patients was 60, consisting of thirty one boys and 29 girls, their ages varied from 2 months to 13 years; thirty patients was given acetylcysteine (fluimucil) and the remainder placebo.

Of thirty eight children with bronchopneumonia, 18 were treated with placebo and 20 with acetylcysteine. There were 9 children with bronchial asthma : 5 were treated with acetylcysteine and 4 with placebo. Five children suffered from bronchiolitis, 3 were treated with acetylcysteine and 2 with placebo. There were 2 cases of tuberculosis. Six cases were excluded from this trial, 2 died and 4 were discharged without consent before the trial was finished (table 1).

Acetylcysteine was given 3 times 1 sachet of 100 mg fluimucil daily for 5 consecutive days. Patients with acute infection were also given antibiotics (procain penicillin, streptomycin and chloramphenicol) for 10-14 days and patients

with bronchial asthma were given bronchodilator in accordance with the Department's policy.

The clinical parameter for the evaluation of succesful results were : cough, dyspnea, and findings on auscultation and X-ray of the lungs.

The evaluation was done at the first, third, fifth and seventh day of admission, using a scoring system varying from 2 to 8 (2 = severe to 8 = normal).

Examination of SGOT and SGPT were done to determine side effects. Lung function was done only in the patients who were cooperative and bronchoscopy was performed when indicated.

Analysis were done with the "four group covariant" analysis method using Casio FX 102.

Results

TABLE 2 : *Bronchopneumonia.*

Day		Acetylcysteine	Placebo	
I	N	20	18	
	X	11.5	11.44	
	t_0	0.07	0.07	$p > 0.05$
	t_5%	2.042	2.042	
	SD	3.43	2.15	
III	N	20	18	
	X	17.3	17.56	
	t_0	0.29	0.29	$p > 0.05$
	t_5%	2.042	2.042	
	SD	2.36	3.11	
V	N	20	18	
	X	21.3	20.67	
	t_0	2.62	3.29	$p > 0.05$
	t_5%	0.65	0.65	
	SD	2.042	2.042	
VII	N	20	18	
	X	23	22.67	
	t_0	1.89	2.99	$p > 0.05$
	t_5%	0.40	0.40	
	SD	2.042	0.42	

Thirty eight patients with bronchopneumonia, of which 20 were treated with acetylcysteine and 18 with placebo, were analysed. The result showed no statistically significant difference ($p > 0.05$) between both groups.

Statistical analysis revealed no statistically significant difference ($p > 0.05$) at the first, third, fifth and seventh day of treatment between both groups (table 2).

Analysis within the group of bronchopneumonia treated with acetylcysteine though showed a statistically significant difference ($p < 0.05$) at the first, third fifth and seventh day of treatment.

TABLE 3 : *Bronchopneumonia with subacute cor pulmonale*

Day	Bronchopneumonia with subacute cor pulmonale with acetylcysteine	Bronchopneumonia without subacute cor pulmonale with acetylcysteine	
I			
N	4	16	
X	11.5	11.5	
SD	2.52	3.922	$p > 0.05$
t_0	0	0	
t_5%	3.922	3.922	
III			
N	4	16	
X	18.5	17.25	
SD	1.92	2.52	$p > 0.05$
t_0	1.89	1.89	
t_5%	3.922	3.922	
V			
N	4	16	
X	22	20.88	
SD	1.63	3.26	$p > 0.05$
t_0	0.97	0.97	
t_5%	2.101	2.101	
VII			
N	4	16	
X	24	22.75	
SD	0	2.05	$p < 0.05$
t_0	2.45	2.45	
t_5%	2.101	2.101	

Within the group treated with placebo, there was no statistically significant difference ($p > 0.05$). (table 2).

Bronchopneumonia complicating in subacute cor pulmonale treated with acetylcysteine, when compared with bronchopneumonia without complication, showed no difference ($p > 0.05$) at the first, third and fifth day of treatment; while at the seventh day of treatment it showed a statistically significant difference ($p < 0.05$), between both groups (table 3).

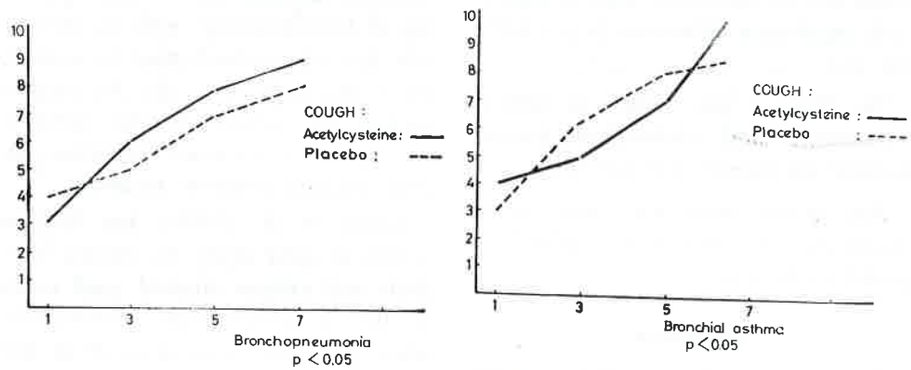
Statistically, patients with bronchial asthma showed no significant difference ($p > 0.05$) at the first, third, fifth and seventh day of treatment - (table 4).

TABLE 4 : *Bronchial asthma*

Day		Acetylcysteine	Placebo	
I	N	5		
	X	12.8	11	
	SD	3.033	2	$p > 0.05$
	t_0	1.06	1.06	
	$t_5\%$	2.365	2.365	
III	N	5		
	X	19.6	20	
	SD	2.607	1	$p > 0.05$
	t_0	0.71	0.71	
	$t_5\%$	2.365	2.365	
V	N	5		
	X		22	
	SD	1.673	2.309	$p > 0.05$
	t_0	0.34	0.34	
	$t_5\%$	2.365	2.365	
VII	N	5		
	X	24	23.5	
	SD	0	1	$p > 0.05$
	t_0	1	1	
	$t_5\%$	2.365	2.365	

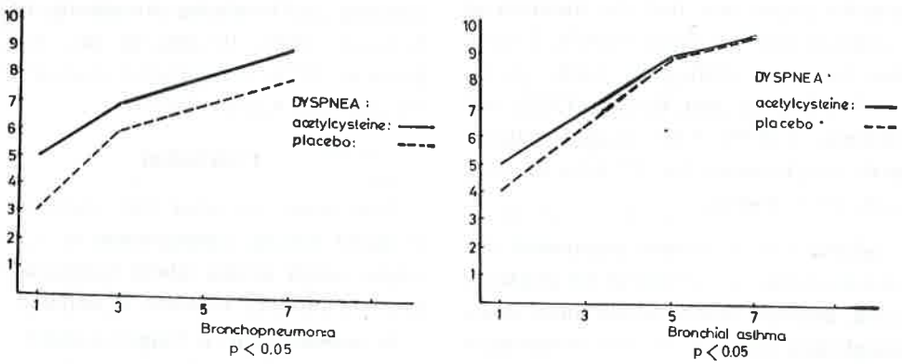
Looking at the symptoms of each patient, it revealed as follows :

Fig. 1 :



Analysis of cough both in bronchopneumonia and bronchial asthma revealed a significant difference ($p < 0.05$) between acetylcysteine and placebo : It showed that the longer acetylcysteine was given the better was the result. (fig. 1)

Fig. 2 :



Dyspnea in bronchopneumonia patients showed rapid changes at the first and third day and especially at the seventh day of treatment, with a statistically significant difference ($p < 0.05$), (fig 2).

No attempt was made to analyse bronchiolitis and tuberculous patients because the number was too small.

Side effects were not observed, as examination for SGOT and SGPT revealed to be normal.

Discussion

Treatment with mucolytic agents within the group of patients with respiratory tract infection (bronchopneumonia) showed satisfactory results as there was an increased effect of treatment when comparing the results at the first, third, fifth and seventh day.

In comparison with placebo this mucolytic effect though revealed no statistically significant difference. One of the possible causes was that the duration of treatment was too short, namely 5 days; this fact was verified by Lemy et al., (1979); Nicolic and Kovac (1979) and Hofman (1979) who treated patients with acetylcysteine for 15 days or over, with good results.

Sheffner et al. (1964) mentioned that acetylcysteine was effective to discharge thick mucous liquid which may cause cough and dyspnea. In our study there was a better result concerning cough and dyspnea within the group treated with acetylcysteine.

In the case of bronchial asthma the result was as could be expected because there were too many factors that might also have influenced the study, e.g. : the use of bronchodilator with its expectorant like effect which must be considered in the evaluation, also the complex etiology of asthma. Another factor is, that asthma is a chronic respiratory disease needing longterm treatment.

Grassi et al. (1976) and Hofman (1979) in their study on chronic bronchitis and asthma attained good results in the treatment with acetylcysteine when given for a duration of at least 15 days.

Several studies showed that there is no significant difference between oral and intramuscular route of acetylcysteine treatment (Bellomo et al., 1973).

In our study no side effects in the treatment with acetylcysteine were observed; examination of SGOT and SGPT showed normal results. Side effects from this drug reported were vomiting and headache (Armstrong, 1976 Aylward, 1977; Biscatti et al., 1972; Hofman, 1979; Lemy Debois et al., 1979; Nikolic and Korac, 1979).

Conclusion

This study revealed that short term (5 days) use of acetylcysteine as a mucolytic agent would relieve symptoms in acute respiratory diseases in children.

It seemed that a longer duration of treatment will give better results especially in chronic cases of respiratory diseases e.g. bronchial asthma.

Acknowledgement

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Assessment Criteria

The following indices were assessed daily from I day before initiation of trial to day 7, 2 days after trial.

All data were recorded on individual clinical data for statistical analysis.

1. Sputum

Quantity :

— abundant, throughout the day 3
— moderate or average, particularly in the morning 2
— sporadic and modest, mainly on waking 1
— absent 0

Type :

— purulent, mainly yellow 3
— mucopurulent, mixed, with yellow and white streaking 2
— mucoid, whitish 1
— absent 0

Viscosity :

— very viscoid and thick, gelatin-like, adhering to the walls of the container 3
— moderately viscid, sirupy, slowly dropping from the walls of the container 2
— fluid, almost watery, albumen-like 1
— absent ("O" in the box corresponding to "quantity") 0

2. Difficulty in raising sputum

— inability to raise sputum, or raised only after considerable and repeated efforts 3
— sputum raised with moderate difficulty, after repeated cough fits ... 2
— sputum raised rather easily or without effort on the first cough fits 1
— absent ("O" in the box corresponding to "quantity") 0

3. Cough :

— repeated fits, almost thoughout the day 3
— repeated fits, but only in the morning or part of day 2
— sporadic fits 1
— absent 0

4. Dyspnea :

— sternal retraction, jugular retraction, pre shock. cyanosis 3
— sternal retraction, intercostal retraction, minimal cyanosis 2
— costal retraction, intercostal retraction, no cyanosis 1
— absent 0

5. Chest semiology :

— Full moist rhales 3
— minimal moist rhales 2
— dry rhales 1
— absent 0

6. Radiological patterns :

— increased bronchovascular marking, diffuse alveolar infiltrate, evidence of parenchymatous diseases 3
— minimal changes of the bronchial-vascular marking evidence of parenchymatous disease 2

— minimal changes of parenchymatous and bronchialvasc. marking 1
— absent 0

7. Side effects :
— strong, interruption of treatment ... 3
— moderate, treatment can be continued, if in case after a short interval 2
— slight 1
— absent 0

REFERENCES

1. ARMSTRONG, M.I. : Double blind crossover trial of bromhexine (bisolvon) in the treatment of chronic bronchitis. Med. Aust. 1 : 612 (1976).
2. AYLWARD, M. : Report on a study on the clinical therapeutic evaluation of N-cysteine (fluimucil) in the treatment of patients with chronic bronchitis : A balanced double blind trial with placebo control. Clinical report (1977).
3. BELLOMO, G.; FRIGERIO, G.; TIRANTELLO, G. : Controlled study of the use of acetylcysteine by intramuscular route in acute respiratory infection in children. Clin. Therap. 43 : 437 (1967).
4. BELLOMO, G.; GIUDICE, S.; GAHCI, C. : Comparative study on efficacy of acetylcysteine administered orally and intramuscular in the pediatric treatment of acute respiratoy infections. Minerva Ped. 25 : 844 (1973).
5. BISCATTI, G.; BRUCELLI, M.; DAMONTE, G.; CAPOZZI, F. : Controlled clinical trial of acetylcysteine administered orally in pediatric respiratory infection. Minerva Ped. 24 : 1075 (1972).
6. CAMPBELL, A.H.; O'CONNEL, J.N.; WILSON, F. : The effect of chest physiotherapy upon FEV in chronic bronchitis. Med. J. Aust. 4 : 117 (1975).
7. GORRINGE, H.R. : Effect of postural drainage, manual percussion and vibration and deep breathing upon MEF in patient with chronic bronchitis. Am. Rev. Resp. Dis. 117 : 202 (1978).
8. GRASSI, C.; MORANDINI, G.C. : A controlled trial of intermittent oral acetylcysteine in the long term treatment of chronic bronchitis. Eur. J. Clin. Pharmacol. 8 : 393 - 396 (1976).
9. HARTSELL, M. : The effects of postural drainage, manual percussion and vibration VS postural drainage, mechanical vibration MEF. Br. Med. J. 2 : 680 (1972).
10. HOFMAN, A. : Acetylcysteine in the treatment of bronchial asthma and disease of upper airways. Intern. Symp. on mucolytic and oral acetylcysteine, Germany, March 5, (1979).
11. LEMY DEBOIS; FRIGERIO, G.; LUALDI, P. : Oral acetylcysteine in bronchopulmonary disease. International Symp. mucolytic and oral acetylcysteine, Germany, March 5, (1979).
12. NIKOLIC, P.; KORAC, D. : The influence of acetylcysteine on respiratory function in children with recurrent bronchitis. Int. Symp. on mucolytic and oral acetylcysteine, Germany, March 5, (1979).
13. RODENSTEINE, D.; De COSTER, A.; GAZZANIGA, A. : Pharmacokinetics of oral acetylcysteine : absorption, binding and metabolism in patient with respiratory disorders. Clin. Pharmacol. 247 (1978).
14. SHEFFNER, A.L.; MEDLER E.M.; YACOBS, L.W.; SARETT, H.P. : The in vitro reduction in viscosity of human tracheo-bronchial secretion by acetylcysteine. Am. Rev. Resp. Dis. 90 : 721 (1964).
15. URO N.J. : A survey of physical methods in the treatment of asthma. Med. J. Aust. 1 : 607 (1978).