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BRONCHOSPASM CAUSED
BY ACETYLCYSTEINE IN CHILDREN
WITH BRONCHIAL ASTHMA

By

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N-acetyl-L-cystein (Ac) is a mucolytic preparation which, on comparison with eleven other sputum-liquifying preparations, proved to be the most effective mucolytic agent available for clinical use (15). The mucolytic action of Ac is probably due to the opening of disulfide bonds in the mucus mucoproteins by Ac's sulfydryl group, whereupon the mucus liquifies (5). Inhalation of Ac has been used in mucoviscidosis with good effect and it is one of the important therapeutic agents in this disease (23, 24, 3, 17, 18). In bronchial asthma, increased secretion of mucus forms one of the primary reactions that characterize the disease (1), and the most important cause of obstruction of the respiratory passages in patients who have died in status asthmaticus is plugging of the bronchioles by secretion (27, 11, 8, 28). In prolonged asthmatic states in which secretion accumulates, it is necessary to administer agents that liquify the mucus (27, 4), and since Ac has proved to be such an effective mucolytic agent (10, 14, 15), its use in bronchial asthma would seem to be of value.

Side effects of Ac were among others described by *Webb* (29). In 600 patients (who received several thousand doses of 20 per cent Ac) he found bronchospasm in two, stomatitis in five, nausea and vomiting in six. Five of the patients thought the preparation had a disagreeable odor.

In asthma patients, bronchospasm is the most undesirable side effect. *Webb* (29) studied 13 asthmatics, of whom several had status asthmaticus, and found no increase in bronchospasm following the use of Ac, but on the contrary a decrease in airway obstruction. *Bernstein et al.* (5), on the other hand, found signs of bronchospasm in four of seven asthmatics after inhalation of 20 per cent Ac.

The above partially contradictory reports, only a few limited studies in asthmatics and the lack of studies on a child material motivated this investigation of the possible occurrence of bronchospasm associated with inhalation of Ac in children with bronchial asthma.

METHOD

For measuring changes in the degree of bronchial obstruction, a simple apparatus easy for a child to manipulate was used, namely Wright's peak flow meter (no. 1164, large), (31). The apparatus was calibrated during the course of the study (*Airmed, Harlow*). Measurement of the maximal expiratory flow (peak expiratory flow rate = PEF) has proved to be useful as an indirect measurement of airway obstruction. There are published normal values for children aged 3 to 18 years (21, 7, 22, 12). *Heaf et al.* (12) had no difficulty obtaining satisfactory and reproducible PEF values in children as young as three years of age. However, since the normal variations from person to person are relatively large, the PEF was used in this study only to follow changes in bronchial obstruction in a given individual, and for this purpose the method has been shown to be reliable in both children and adults (9, 13, 30).

MATERIAL

37 children—14 girls and 23 boys—with bronchial asthma (reversible dyspnea, wheezing, a positive skin test and inhalation provocation) aged 5–17 years and with asthma of 1–15

year's duration, inhaled through a Pari-nebulizer (Pari Werk, Starnberg, Germany)—(particle size 0.5 to 5μ) 2 ml of 10 per cent Ac and, 50 minutes later, 2 ml of 20 per cent Ac. After an interval of several hours the patients inhaled 2 ml of Coca's solution (phosphate buffer containing 0.4 per cent phenol), which is customarily used as a control in testing allergens, and 50 minutes later, 2 ml of the diluent used in the Ac solution. Approximately half of the children started nebulization with Coca's solution and after the interval continued with Ac (Table 1). The other children (Table 2) began with Ac and after the interval continued with Coca's solution. For practical reasons only hospitalized patients were used for this study.

TABLE 1.
Children starting nebulization with Coca's solution.

Name	Age years	Asthma years	PEF l/min					
			Morning			Afternoon		
			Before nebuliza- tion	After 2 cc Coca's solution	After 2 cc Diluent	Before nebuliza- tion	After 2 cc 10 % Acetyl- cysteine	After 2 cc 20 % Acetyl- cysteine
Boys								
Å. D.	13	12	180	190	190	220	192	140
Ö. B.	7	3	63	73	52	90	85	63
F. L.	11	10	387	355	350	367	368	360
A. L.	15	1	488	482	527	555	522	550
A. J.	9	7	305	298	307	297	278	287
B. O.	11	10	473	472	443	470	468	468
G. R.	5	3	154	173	163	160	153	140
G. U.	10	7	195	247	228	207	227	228
Girls								
F. A.	8	5	192	192	193	195	195	187
O. L.	10	10	63	85	83	75	113	82
I. A.	7	5	283	282	263	277	263	228
F. M.	9	5	233	227	217	237	85	73
D. C.	13	3	418	415	418	402	395	402
S. B.	17	15	195	223	182	277	233	128

TABLE 2.

Children starting nebulization with 10 per cent Acetylcysteine.

Name	Age years	Asthma years	PEF l/min					
			Morning			Afternoon		
			Before nebuliza- tion	After 2 cc 10 % Acetyl- cysteine	After 2 cc 20 % Acetyl- cysteine	Before nebuliza- tion	After 2 cc Coca's solution	After 2 cc Diluent
Boys								
I. O.	12	6	302	283	277	—	312	327
F. S.	12	9	423	443	433	—	422	427
D. H.	10	5	257	172	168	285	250	287
E. A.	7	5	237	240	220	—	220	197
F. M.	8	7	270	250	258	—	242	167
S. K.	9	1	303	303	305	—	312	302
E. P.	5	5	153	172	162	157	162	157
S. P.	13	10	405	393	417	413	392	393
E. A.	13	9	435	438	445	—	440	440
Å. P.	8	5	308	308	317	307	290	315
L. U.	10	1	314	313	327	—	340	337
J. B.	8	1	247	235	218	217	252	244
H. D.	9	7	278	273	272	270	277	280
V. J.	9	5	274	245	185	257	277	267
N. L.	12	9	218	77	66	243	243	223
Girls								
N. E.	10	6	345	327	318	—	335	313
B. P.	10	9	295	293	282	—	297	295
H. S.	8	3	230	227	232	225	237	230
S. I.	5	4	72	45	40	57	84	77
O. Å.	8	6	160	150	137	167	163	177
J. L.	7	5	122	107	115	113	120	118
G. A.	8	6	293	275	273	283	297	288
K. K.	9	8	158	155	113	155	168	148

In order to avoid the effects of medication with bronchodilators, only patients in a quiescent phase of asthma and not receiving any medication were included. Before the inhalations 7 children (boys D. H., Å. D., Ö. B., girls O. L., S. B., S. I., J. L.) had slight wheezing while 30 were symptomfree.

The day before the test the children were told that they would inhale agents that loosen mucous secretions, but they were not told which agents were to be used. After training with Wright's peak flow meter, the PEF was measured ten times before, and ten times after each inhalation. The averages of the three highest of the ten values before and immediately after the inhalations were calculated and used to express the maximal expiratory flow (PEF)—Table 1 and 2. The PEF was measured immediately after each inhalation, 15 minutes later and after 45 minutes (about 5000 measurements in all). Each time the PEF was measured, the lungs were auscultated and the patient's subjective evaluation of the inhalation solution was noted.

RESULTS

The PEF values are shown in Tables 1 and 2. Some afternoon values „before nebulization“ in Table 2 are missing and these nine children have been omitted when calculating with baseline values for PEF „before the inhalation“. After inhalation of 10 per cent Ac the children had a significant* decrease in PEF ($p < 0.01$) compared with the control values before inhalation. Similarly, there was a significant decrease in the PEF ($p < 0.05$) after inhalation of 10 per cent Ac compared with the values after inhalation of Coca's solution.

After inhalation of 20 per cent Ac there was a significant decrease in the PEF ($p < 0.001$) compared with the control values before inhalation and also a significant decrease in the PEF ($p < 0.01$) compared with the values after inhalation of Coca's solution. Even a comparison of the values obtained after 10 per cent and after 20 per cent Ac, showed a significant decrease ($p < 0.05$) after inhalation of 20 per cent Ac. On the other hand, there was no significant difference between the values obtained after Coca's solution and after

* The statistical treatment (t-test for pairing observations) was performed by fil. kand. Erik Arvidsson, Swedish Medical Research Council's Statistical Service, Umeå University. All tests were performed on the 5 per cent level.

the solvent used in the Ac solution. After the inhalation of Coca's solution there was even an increase in the PEF ($p < 0.05$) compared with the control values before inhalation.

There was no significant difference between the mean values for PEF after Coca's solution, 10 per cent Ac and 20 per cent Ac respectively whether Coca's solution and the solvent used for Ac were inhaled before the two Ac solutions or the Ac solutions were inhaled before Coca's solution and the solvent for Ac. There was no significant difference between the original baseline values for PEF before the inhalation of Coca's solution-diluent on the one hand and 10 per cent–20 per cent Ac on the other. In seven children with wheezing before the inhalations there was no significant change in the PEF after either 10 per cent or 20 per cent Ac, compared with 21 children without wheezing.

27 of the 37 children thought that 10 per cent Ac had an unpleasant odor, and about the same number thought that 20 per cent Ac had an unpleasant odor, whereas 17 and 12 children respectively thought that Coca's solution and the diluent for Ac had unpleasant odors. No stomatitis or nausea was seen.

DISCUSSION

In nebulization the size of the drops is important, since if they are too large they fasten in the pharynx without reaching the lungs, and if too small they are exhaled. The Pari-nebulizer used here produces drops of the size recommended for aerosols (6).

In selecting an investigative technique that would not tire a child, would be easy to learn and as gentle as possible, choice fell on the use of Wright's peak flow meter. *Heaf et al.* (12) described good correlation between the PEF and the one-second FEV in both normal and asthmatic children, whereas *Hoffbrand et al.* (16) found the PEF to be more sensitive to changes in airway resistance than the one-second FEV.

The reliability of the peak flow meter was described by *Fagerberg* (9) and *Herxheimer* (13) and has recently been tested by *Weng et al.* (30), who compared airway resistance in 48 asthmatic children by means of body plethysmograph, spirometer, and Wright's peak flow meter. Although airway conductance (body plethysmograph) was the most sensitive method for measuring changes in airway resistance, they found PEF to be easy to measure, reasonably sensitive, and reliable as an index of airway obstruction. Thus, PEF seemed to be acceptable for our measurements of changes in airway obstruction in a given patient.

Abramowitz et al. (2) investigated whether the PEF values obtained in 50 patients would differ if the following different methods were used: Of 5 successive exhalations the highest value, the average of the last 3 values and the average of the 3 highest values were taken.

Of 10 successive exhalations the highest value, and the average of the 3 highest values were taken.

Of 15 successive exhalations, the highest value, and the average of the last 10 were taken.

They found no significant differences between the results of the different procedures.

In this investigation 10 exhalations were preferred in order to eliminate the possibility that fewer trials would fail to give reliable values for children. I have used average of the 3 highest values when calculating the *maximal* expiratory flow. In my experience, 10 successive exhalations do not cause fatigue, and the maximal values were scattered over the entire range between the first and the tenth trial.

To minimize the source of error that arises on comparison of repeated daily measurements of PEF (and airway resistance) in patients with asthma and which consists of the spontaneous variation in the patient's airway obstruction (26), new baseline values were determined before the inhalations in both the morning and the afternoon.

There was no significant difference between the two baseline values whether the nebulization program began with Ac

or with Coca's solution, and the two baseline values were regarded as equal. The time interval between the two sets of nebulizations should have been sufficient to permit possible bronchospasm to disappear during the interval. This is supported by the fact that there were no significant differences between the average PEF's for the different solutions before and after the interval.

Ac was introduced and is now marketed as a 20 per cent solution. *Hirsch et al.* (14), compared 10 per cent and 20 per cent Ac solutions and found the former to be equally effective as a mucolytic agent. Like *Bernstein et al.* (5), *Hirsch et al.* observed bronchospasm in some of 15 asthmatics after inhalation of 20 per cent Ac. This side effect was reduced if the solution was diluted to 10 per cent (14). However most patients showed no bronchospastic spirometric changes after Ac inhalation. On the other hand *Webb* in 13 asthmatics (29), and *Saarnе*, who tested Ac in 15 asthmatic patients, found no side effects and a favorable response to treatment (25). Neither did *Moser* (20) observe any significant degree of bronchospasm in 50 patients with chronic obstructive pulmonary disease after inhalation of 2 ml 10 per cent Ac. The present results show a statistically significant reduction in PEF (indicative of bronchial obstruction) after both 10 per cent and 20 per cent Ac. The 20 per cent solution produced significantly more bronchial obstruction than did 10 per cent Ac.

The fact that no significant decrease in PEF was obtained after Coca's solution or the solvent for Ac, whereas the PEF was reduced after both 10 per cent and 20 per cent Ac, indicates that the substance causing bronchial obstruction was not in the diluent but was the Ac itself.

How can bronchospasm be counteracted as a possible side effect of Ac therapy when the marked mucolytic effect of Ac is desirable? *Bernstein et al.* (5) found bronchospasm to be slight and transitory and that it could be prevented by adding Isoproterenol to the Ac solution. It might even be possible to add another bronchodilating agent, Orciprenaline (18), but it

is not known whether Ac remains active when mixed with other compounds. This is currently being investigated (14, 19).

CONCLUSION

It has been shown that Ac can produce signs of bronchial obstruction in asthmatic children when used as either a 10 per cent or 20 per cent solution. Since the latter produces signs of a greater degree of bronchial obstruction and the 10 per cent solution has been shown to be equally effective as a mucolytic agent, it is proposed that the 10 per cent solution be used instead of the 20 per cent for inhalation therapy. The possible risk of administering Ac to asthmatic patients should be weighed against its potential benefits.

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