The Use and Efficacy of Mucolytic Agents *

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SUMMARY

A total of 100 patients were tested with different mucolytic agents. In patients with acute obstructive airway disease pancreatic dornase and acetyl-L-cysteine (Airbron) showed excellent mucolytic activity. With Alevaire and Ascoxal we were unable to demonstrate any mucolytic action. Proteolytic enzymes were not tested in view of their uncontrollable action on alveolar epithelium and the recent observation that metaplasia of the bronchial mucosa may be produced by these enzymes.

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NATURE AND COMPOSITION OF BRONCHIAL SECRETION

Normal human bronchial mucus is a semiviscid substance composed almost entirely of mucoprotein and mucopolysaccharide fibres.[1] Its main function appears to be that of trapping and removing foreign particles within the airway, as well as for moistening the bronchial mucosa. It is produced by the bronchial glands in the trachea and bronchi and by goblet cells in the epithelium of these airways.

In acute or chronic bronchitis there is a marked increase in the number and size of mucus glands and in the number of goblet cells. When infection occurs the mucus fibres fragment and are replaced by fibres of deoxyribonucleic acid (DNA).[2,3] DNA is present in purulent sputum because of cellular and tissue breakdown and is not found in the original mucus secretion. The presence of DNA significantly increases the viscosity of sputum and inhibits the lysis of sputum by leukocytic proteases. The purulence of sputum can usually be controlled by suitable antibiotics, but the viscosity and amount of mucoid sputum is not reduced by antibiotics.[4]

Mucus flow and removal of sputum becomes a problem when the rate of mucus production is excessive, when its viscosity interferes with normal ciliary movement, or when infection results in an excessive amount (e.g. in bronchial asthma, postoperatively, etc.). Patients with lung abscesses, bronchiectasis and especially those with cystic fibrosis have this type of involvement.

The purpose of this article is to demonstrate the efficacy of certain well known, widely advertised mucolytic agents. The indications and contra-indications for their use will be discussed.

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METHODS AND MATERIALS

In Vitro Tests

Specimens of purulent and mucoid sputum from patients with chronic chest disease were collected in test tubes. A few drops of the mucolytic agent to be tested were mixed with approximately 2 ml of sputum. The result was read macroscopically after ½ hour as follows: (*i*) sputum completely dissolved 100%; (*ii*) sputum partially dissolved ±50%; and (*iii*) sputum not dissolved 0%.

In Vivo Tests

The expiratory volume was measured with a Wright peak flow meter. A maximum expiratory flow was taken before starting the treatment and 3 readings were taken at ½-, 2- and 4-hour intervals. Finally the total expectoration was measured after 4 hours.

The patients for the study were separated into 2 groups:

The first group of patients (group A) exhibited minor pulmonary diseases which included pneumonitis, acute or chronic bronchitis and bronchopneumonia.

The second group of patients (group B) had a variety of pulmonary diseases which included silicosis, pulmonary emphysema, obstructive airway diseases, as well as bronchial carcinoma and pulmonary tuberculosis. The apparatus we used for the nebulization of the different aerosols by oxygen was a Bird Mark 8 machine. This machine produces a mist with a particle size of 0·5 - 3·0 μ; the inspiratory flow rate, inspiratory pressure, the expiratory flow rate (retarded or accelerated) and the length of the expiratory phase can be controlled independently of each other.

MUCOLYTIC AGENTS USED

Pancreatic Dornase (Deanase*)

Description: Deanase is a deoxyribonuclease extracted from the pancreas.

Action: The highly polymerized nucleic acids or polynucleotides, as they exist in the human sputum, are broken down into smaller components (oligonucleotides) by the action of specific enzymes.[3] Deoxyribonuclease (DNAse) reacts on the bond of deoxyribonucleic acid (DNA), and this reaction is catalysed in the presence of the activator Mg^{++}.[1] This enzymatic reaction causes an irreversible reduction in the viscosity of the sputum.

*Keatings Pharmaceuticals Ltd, Johannesburg.

TABLE I. RESULTS OF ADMINISTRATION OF 50 000 U DEANASE TO 31 PATIENTS

Patient No.	Age	Diagnosis	Maximum expiratory flow: Before	½ hr	2 hrs	4 hrs	Vitro-test %	Total expectoration in 4 hrs (ml)	Additional medication
Group A—Patients with minor pulmonary diseases									
1	24	Pneumonitis	309	316	342	357	100	289	Penbritin
2	27	Pneumonitis	300	308	315	328	100	198	Penbritin
3	34	Pneumonitis	283	291	317	325	100	124	Chloramphenicol
4	45	Pneumonitis	281	289	297	311	100	130	Erythromycin
5	79	Pneumonitis	141	152	163	182	100	156	Chloramphenicol
6	87	Pneumonitis	73	87	108	143	100	416	Chloramphenicol
7	63	Chr. bronchitis	367	382	386	390	100	121	Bactrim
8	57	Chr. bronchitis	348	359	367	371	100	149	Bactrim
9	49	Chr. bronchitis	319	322	329	335	100	108	Bactrim
10	67	Chr. bronchitis	245	249	261	268	100	111	Erythromycin
11	73	Chr. bronchitis	195	208	212	267	100	380	Chloramphenicol
12	57	Bronchial asthma + inf.	209	219	227	230	100	137	Aminophyllin + Bactrim
13	47	Bronchial asthma + inf.	200	211	218	243	100	103	Aminophyllin + Bactrim
14	50	Bronchial asthma + inf.	134	137	158	162	100	167	Aminophyllin
Group B—Patients with a variety of pulmonary diseases									
1	49	Bronchiectasis + inf.*	98	109	111	119	100	348	————
2	57	Bronchiectasis + inf.	101	123	129	145	100	283	————
3	65	Bronchiectasis + inf.	125	131	147	145	100	208	————
4	73	Bronchiectasis + inf.	157	164	169	174	100	178	————
5	61	Silicosis + bronchitis	92	108	110	118	100	248	Bactrim
6	63	Silicosis + bronchitis	167	171	178	181	100	161	Bactrim
7	70	Silicosis + bronchitis	180	192	192	195	100	104	Erythromycin
8	54	Pulm. emphysema + br.	90	93	97	109	100	359	Chloramphenicol
9	72	Pulm. emphysema + br.	131	139	141	143	100	209	Ceporan
10	71	Cor pulmonale + br.	161	170	172	179	100	150	Bactrim
11	80	Cor pulmonale + br.	165	167	170	175	100	100	Chloramphenicol
12	45	Pulm. TB + chr. br.	231	235	238	240	100	191	INH, PAS, streptomycin
13	50	Pulm. TB + chr. br.	308	311	321	320	100	92	INH, PAS, streptomycin
14	55	Pulm. TB + emphysema	56	63	71	75	100	131	INH, PAS, streptomycin Aminophyllin
15	34	Emphysema + chr. bronchial asthma	108	109	121	127	100	172	Aminophyllin
16	45	Lymphangitis carcinoma	78	82	89	92	100	123	Cyclophosphamide
17	65	Interstitial pneumonitis	67	71	76	85	100	131	Chloramphenicol

* Slight haemoptysis.

The effect of DNA upon respiratory secretion is described as follows: It (*i*) increases sputum viscosity; (*ii*) protects protein in nucleoprotein complexes from enzymatic proteolysis; (*iii*) inhibits proteolytic enzymes directly and (*iv*) reduces effectiveness of certain basic antibiotics.[3]

Administration and Dosage: In the following test (Table I) on 31 patients we used 50 000 U of Deanase for each nebulization and pure oxygen was used as the vehicle. Deanase was dissolved in a sterile 2% magnesium sulphate solution.

Comment

After administration of dornase a massive liquefaction of mucus takes place. The cough is greatly increased and becomes very productive. After a single administration of 50 000 U dornase the excretion of mucus up to 600 ml was observed.

Dornase can be mixed with antibiotics, except basic types, and with a bronchodilator in appropriate concentration.[3] The enzyme can be used effectively in either 10% propylene glycol or saline diluent with the addition of Mg^{++}. Propylene glycol is preferred as it provides a soothing effect on the tracheobronchial tree and eases the mobilization of respiratory secretion.

In the abovementioned investigations dornase proved to be an effective mucolytic agent for the mobilization of mucus. In both series the patients were aware of increased air entry after inhalation which corresponded with the obtained MPF readings. In group B the results obtained

TABLE II. RESULTS OF ADMINISTRATION OF 3 ml AIRBRON

Patient No.	Age	Diagnosis	Maximum expiratory flow: Before	½ hr	2 hrs	4 hrs	Vitro-test %	Total expectoration in 4 hrs (ml)	Additional medication
Group A—Patients with minor pulmonary diseases									
1	33	Pneumonitis	357	361	372	385	100	167	Bactrim
2	35	Pneumonitis	292	305	313	338	100	260	Bactrim
3	41	Pneumonitis	290	295	300	331	100	218	Keflin
4	46	Pneumonitis	185	196	232	246	100	279	Keflin
5	74	Pneumonitis	97	114	168	191	100	410	Chloramphenicol
6	81	Pneumonitis	87	92	96	105	100	421	Chloramphenicol
7	64	Chr. bronchitis	234	241	253	263	100	171	Bactrim
8	67	Chr. bronchitis	208	222	235	240	100	197	Erythromycin
9	69	Chr. bronchitis	72	75	82	91	100	82	Bactrim
10	73	Chr. bronchitis	66	69	72	78	100	61	Erythromycin
11	80	Chr. bronchitis	65	69	71	82	100	115	Bactrim
12	62	Inf. bronchial asthma	288	293	298	314	100	306	Bactrim + Aminophyllin
13	65	Inf. bronchial asthma	263	270	284	295	100	255	Keflin + Aminophyllin
14	70	Inf. bronchial asthma	197	196	203	212	100	214	Bactrim + Aminophyllin
15	79	Inf. bronchial asthma	110	115	127	131	100	150	Bactrim + Aminophyllin
Group B—Patients with a variety of pulmonary diseases									
1	36	Pulm. emphysema	110	115	113	123	100	97	———
2	42	Pulm. emphysema	201	225	223	219	100	82	Erythromycin
3	54	Pulm. emphysema	218	223	230	230	100	121	———
4	67	Pulm. emphysema	247	249	253	252	100	105	Bactrim
5	79	Pulm. emphysema	94	98	98	101	100	45	———
6	44	Bronchitis + silicosis	139	140	139	141	100	62	Chloramphenicol
7	49	Bronchitis + silicosis	211	218	239	239	100	211	Chloramphenicol
8	59	Bronchitis + silicosis	101	109	107	108	100	108	Bactrim
9	84	Bronchitis + silicosis	98	98	99	102	100	37	Erythromycin
10	62	Cor Pulmonale	123	127	129	135	100	111	Heparin
11	64	Cor Pulmonale	138	138	145	146	100	78	Heparin + Bactrim
12	45	Pulm. TB + pneumonitis	74	78	87	89	100	123	INH, PAS, streptomycin
13	55	Pulm. TB + bronchitis	178	182	187	193	100	201	INH, PAS, streptomycin
14	66	Pum. TB + lung abcess	62	67	130	149	100	372	INH, PAS, streptomycin
15	45	Scleroderma + chr. bronchitis	95	103	109	111	100	231	Chloramphenicol + peripheral vasodilators
16	69	Silicosis + emphysema + pneumonia	57	60	67	93	100	182	Chloramphenicol + Aminophyllin

were on the average slightly better. Dornase showed no mucolytic activity in normal respiratory secretion.

Side-Effects

The side-effects seen during dornase therapy have been few and minor. In some patients a soreness of the posterior pharynx developed. This can be prevented by having them gargle with water immediately after each treatment to remove the enzyme from the pharyngeal mucosa.

In one of the patients a slight haemoptysis occurred. This may have been related to the advanced bronchiectasis from which the patient suffered.

Airbron†

Description: N-acetyl-L-cysteine 20% in sterile aqueous solution.

Action: The action of Airbron probably depends on the presence of a free sulphydryl group which acts upon the disulfide bonds of mucoprotein and mucopolysaccharide. Deoxyribonucleic acid is also decomposed by L-cysteine.[5]

This action depends on:[6] (*a*) pH (the optimum lies between 7·0 and 9·0), (*b*) the positive pressure breathing (IPPB) and (*c*) the concentration.

The activity of L-cysteine is completely lost by a thousandfold dilution of the commercial 20% material.[3]

†B.D.H. (Pty) Ltd, Johannesburg.

Administration: The apparatus used for the inhalation of L-cysteine should be of glass or plastic as metals and rubber react with the drug. The one we used was the 'Agla' all-glass device (Burroughs Wellcome).

The commercial distributors do not recommend oxygen as a vehicle. It has been reported that high oxygen concentration rapidly inactivates L-cysteine;[7] the commercial preparation contains ethylene diamine tetracetic acid (EDTA) to prevent oxidation and therefore the use of oxygen for nebulization is not contra-indicated.[3]

Dosage: Depending on the tolerance of the patient 3 ml of 10 or 20% Airbron solution up to 4 times a day is recommended. In the following tests (Table II) we used 3 ml of 20% solution of Airbron for each nebulization. Pure oxygen was used as the vehicle.

Comment and Side-Effects

N-acetyl-L-cysteine was effective in both purulent and nonpurulent (mucoid) sputums. In group A, a generalized improvement of the respiratory functions was found. In group B, a reduction in cough and sputum production was noted. The sputum viscosity was considerably reduced and also the colour was clearer.

However, the results that we obtained in group B were not so impressive as they were in the first group. This may be due to the advanced pulmonary pathology of the patients.

Airbron does not have a very pleasant smell and may on occasion cause bronchospasm. The addition of Isuprel or other bronchodilator is recommended. If bronchodilators do not reverse the bronchoconstrictive effects, it may be necessary to discontinue the medication.[6] The irritant effect of L-cysteine in the bronchi is probably due to its hypertonicity and can be prevented by combining the aerosol with a local anaesthetic (lignocaine hydrochloride 4%, amethocaine hydrochloride 2% or cocaine hydrochloride 10%).

It was also reported that L-cysteine inactivates a number of antibiotics (e.g. all the penicillin types).[7]

During this trial 2 patients reacted to Airbron with stomatitis, 3 with nausea and vomiting. Dyspnoea, wheezing, feverfi hoarseness or nasal and eyelid irritation as reported by Robinson *et al.*[14] occurred in my series. Bronchospasm has been reported[8] but did not occur in any of our patients.

Alevaire‡

Description: Alevaire is an alkaline solution containing superinone 0·125%, sodium bicarbonate 2% and glycerine 5%.

Action: It stabilizes aerosol droplets and allows more effective hydration of the respiratory secretion by lowering the surface tension. This action is dependent on the positive pressure breathing (IPPB) and on the effective concentration of aerosol penetrating into the lungs.[6]

Administration: Twenty-four patients with different pulmonary diseases were divided into 2 similar groups. Group A was treated with 5 ml Alevaire using oxygen as the vehicle. Group B was treated with 2% solution of sodium bicarbonate—5 ml solution and oxygen were used.

Comment

Our trial showed that Alevaire is not more effective than the control solution containing bicarbonate. *In vitro* neither purulent nor mucoid sputum was liquefied and none of the patients experienced subjective improvement after Alevaire inhalation.

We are of the opinion that the administration of Alevaire alone has no value which confirms the results of previous studies.[3,6,12]

‡Winthrop, Durban.

TABLE III. RESULTS OF ADMINISTRATION OF 5 ml ALEVAIRE

Patient No.	Age	Diagnosis	Maximum expiratory flow: Before	½ hr	2 hrs	4 hrs	Vitro-test %	Total expectoration in 4 hrs (ml)	Additional medication
1	51	Chr. bronchitis	234	212	208	230	0	12	———
2	62	Chr. bronchitis	317	317	316	318	0	19	———
3	75	Chr. bronchitis	195	195	196	195	0	15	———
4	41	Pneumonitis	340	358	347	352	0	31	Penbritin
5	48	Pneumonitis	351	350	352	350	0	28	Chloramphenicol
6	57	Bronchiectasis	159	156	158	157	0	5	———
7	57	Pulm. TB	259	234	240	251	0	13	INH, PAS, streptomycin
8	67	Sarcoidosis	208	206	207	209	0	17	INH, PAS, streptomycin
9	74	Silicosis	189	191	190	190	0	0	Nethaprin Dospan
10	38	Silicosis	215	218	219	217	0	0	———
11	44	Pulm. emphysema	159	156	157	158	0	9	———
12	71	Ca-bronchus	91	95	94	92	0	2	Cyclophosphamide

TABLE IV. RESULTS OF TREATMENT WITH 5 ml SODIUM BICARBONATE SOLUTION

Patient No.	Age	Diagnosis	Mid-expiratory peak flow: Before	½ hr	2 hrs	4 hrs	Vitro-test %	Total expectoration in 4 hrs (ml)	Additional medication
1	42	Chr. bronchitis	222	225	223	223	0	5	———
2	48	Chr. bronchitis	314	311	312	313	0	7	———
3	57	Chr. bronchitis	323	320	321	321	0	12	———
4	67	Chr. bronchitis	300	300	299	298	0	10	———
5	32	Pneumonitis	248	249	247	248	0	19	Bactrim
6	39	Pneumonitis	375	372	374	376	0	21	Erythromycin
7	47	Pneumonitis	402	404	401	406	0	31	Erythromycin
8	53	Pneumonitis	391	390	391	392	0	23	Chloramphenicol
9	62	Silicosis	223	209	211	219	0	4	Aminophyllin + Bactrim
10	73	Silicosis	189	187	185	188	0	2	Aminophyllin
11	37	Bronchiectasis	321	320	325	322	0	0	Bactrim
12	42	Pulm. TB	241	236	239	240	0	4	INH, PAS, streptomycin

Proteolytic Enzymes

A. **Trypsin preparations** (Tryptar,* Trypure,† Trypsevac‡).

B. **Alpha, delta-chymotrypsin preparations** (Chymar,* Chymovac‡).

These are enzymes which catalyse the cleavage of peptide bonds.[9] *In vitro* the proteolytic enzymes showed an effective mucolytic activity in liquefying purulent and nonpurulent sputum. But the observation of metaplasia in the bronchial mucosa led some to fear that proteolytic enzyme aerosols might be carcinogenic, and their use declined considerably.[9] Recent observations suggest that the use of any proteolytic enzyme aerosols may be dangerous; lung tissue may be digested and the development of emphysema accelerated as a result. Also severe haemoptysis may occur. These agents should only be used with prior evaluation of the antitrypsin status of the patient in view of the high frequency of alpha$_1$-antitrypsin deficiency in patients with chest disease.[9]

Tromasin¶

Tromasin is a purified and standardized extract of proteolytic enzymes from the unripe fruit of the Carica papaya plant. This enzyme is not inhibited by the blood or lung tissues of man and certain animals, and may be dangerous when used as an aerosol.[10] Inhalation of aerosolized papain is an experimental means for producing anatomic emphysema in animals, and it probably owes its success to the lack of innate inhibitors in blood and tissues.

Streptokinase-Streptodornase (Varidase§)

Streptodornase is a deoxyribonuclease-containing enzyme found in certain streptococci. Streptokinase is an activator of plasminogen (profibrinolysin) and is derived from certain haemolytic streptococci.

Streptodornase (dornase) has already been discussed. Streptokinase has not demonstrated any mucolytic activity. However, it acts indirectly upon a substrate of fibrin or fibrinogen by activating a fibrinolytic enzyme in the human serum. The activation of this fibrinolytic system brings a rapid dissolution of blood clots and their fibrinous portions.[11] Theoretically this would mean that: (*i*) streptodornase does influence the sputum viscosity; and (*ii*) streptokinase has an effect on the fibrotic pulmonary tissue.

This fibrinolytic action in the lungs must be controlled. The accumulated tissue fluid must be drained and aspirated, especially in closed spaces; this is because streptokinase may cause a localized leucocytosis and in the presence of infection a lung abscess could result.[11]

In view of the above reasons this preparation may be extremely dangerous if administered as an aerosol.

Ascoxal†

Ascoxal (sodium percarbonate 70 mg, copper sulphate 0·2 mg, ascorbic acid 100 mg) is used as a mucolytic agent and Palmer[12] initially described its excellent mucolytic properties. However, in a subsequent article Palmer[13] reported that this compound failed to demonstrate any mucolytic activity.

In our experiments we used a concentrated Ascoxal solution, prepared from 2 tablets, dissolved in 4 ml water and given by aerosol inhalation.

We were unable to demonstrate any mucolytic action. Ascoxal is no more effective than a control solution containing water only.

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*Armour Pharmaceuticals Ltd, Johannesburg.
†Novo Industries Pharmaceuticals, Johannesburg.
‡Keatings Pharmaceuticals Ltd, Johannesburg.
¶Warner Pharmaceuticals (Pty) Ltd, Johannesburg.
§Lederle (Pty) Ltd, Johannesburg.

†Astra (Remedia).