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Sodium thiophene carboxylate does not facilitate expectoration

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ABSTRACT: A randomised double-blind crossover study compared the clinical effectiveness of a 21-day treatment with 600 mg per day of sodium thiophene carboxylate and placebo in 33 patients with stable chronic bronchial disease. During the seven week trial, subjective symptoms and findings were recorded, pulmonary function tests performed and sputum physical characteristics determined. Side-effects were closely monitored. Both subjective assessment of overall clinical efficacy and statistical analysis of the above mentioned factors failed to show any significant advantage of sodium thiophene carboxylate to placebo. Sodium thiophene carboxylate appears to be an expectorant and mucoregulatory drug, lacking evidence of clinical effectiveness in the treatment of patients with stable chronic bronchitis.
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Drugs which, it is hoped, may change the physiochemical properties of bronchial secretions and facilitate expectoration are used widely despite lack of knowledge about their precise actions and doubts about their clinical usefulness. Moreover, the effects of such drugs are difficult to measure in man [1]. Expectorants, whether secretomotor or secretolytic in action, should be subject to evaluation as stringent as that applied to other classes of drugs.

Sodium thiophene carboxylate (STC) is a mucoregulatory drug, which may correct disturbed intracellular glycoprotein synthesis and normalize the secretory function of the bronchial mucosa [2].

This paper reports a double-blind, placebo-controlled study designed to evaluate the efficacy of STC in patients with stable chronic bronchial diseases with sputum production.

Materials and methods

Design of the study

STC was compared to placebo in a randomized double-blind cross over trial. Prior to the treatment period, a one week wash-out phase with placebo for both groups was maintained, so that the patients had a consistent intake of two capsules daily - either 2×300 mg per day STC or placebo - during the course of the entire seven week trial. In appearance and content STC and placebo capsules were identical except that the latter contained starch in place of the active substance. As shown in figure 1, group 1 received STC from day 8 to day 28, then placebo from day 29 to day 49; group 2 had the reversed order of intake. Examinations were performed on day 0, day 7 and then once a week.

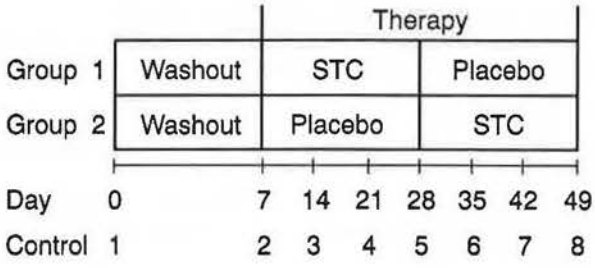

Fig. 1. – Design of study. A randomized double-blind crossover study compared sodium thiophene carboxylate (STC) to placebo in 33 patients with stable chronic bronchial disease during a seven week period. A daily regimen of 2 × 300 mg capsules of either STC or placebo was given during therapy phases in identical capsules. During the washout phase the patients received 2 × 300 mg capsules of placebo. Examinations were performed on day 0 and 7 of the washout phase, at the beginning (day 7–28), two weeks (day 21–42) and after three weeks (day 28–49) of the treatment phases.

Selection of patients

36 outpatients of the Pulmonary Laboratory, Medical Policlinic, University Hospital of Zurich, with stable chronic obstructive pulmonary disease, including chronic bronchitis and both intrinsic and extrinsic forms of chronic bronchial asthma, were initially selected and randomized into two groups [3]. All patients were required to have continuous sputum production during the entire period of the study. Patients

with infectious exacerbations during the study were excluded. Patients maintained their usual medications except secretomotoric and secretolytic drugs which were discontinued two weeks prior to their entry into the study.

Three of the original patients dropped out: one with worsening pulmonary status attributing it to STC, two patients lacking full compliance during the study. Of the remaining 33 patients, averaging 64 yrs of age, 16 (13 men and 3 women) fell into group 1, and 17 (15 men and 2 women) into group 2. In group 1, 14 patients suffered from chronic bronchitis and 2 from chronic bronchial asthma, whereas in group 2, 16 had chronic bronchitis and 1 chronic bronchial asthma. Of all patients, 16 were smokers with an average of 20 cigarettes per day (range 3–100) and a mean value of 33.25 pack yrs (range 3–60). The smoking habits did not change during the study.

Measurements

The following factors were controlled at each examination (day 0, 7, 14, 21, 28).

Symptoms and findings: Cough frequency, cough severity, thickness of sputum, difficulty in raising sputum, wheeze severity, degree of dyspnoea and nature of breath sounds including rales and rhonchi. All symptoms were scored according to the numerical codification of CHODOSH *et al.* [4]. This non-linear graded system, developed to suit each symptom individually, enabled the examiner's assessment of the patient's subjective findings with the following scales: cough frequency: range: 0 (no coughing) – 20 (almost continuous coughing); cough severity: range: 5 (has to concentrate to notice cough) – 19 (cough syncope); difficulty in raising sputum: range: 3 (plugs come up without effort) – 19 (7 or more coughs to raise a plug); dyspnoea: range: 1 (none) – 19 (without effort). The clinican's overall opinion of the efficacy of therapy and possible side-effects were noted.

Pulmonary function tests: FEV_1 (forced expiratory volume in one second), FVC (forced vital capacity), PEFR (peak expiratory flow rate) and $FEF_{25-75\%}$ (expiratory flow at 25–75% of forced vital capacity) were determined.

Sputum analysis: Sputum was collected for 24 hours prior to each visit and was stored in the refrigerator. Sputum volume was computed from the sputum weight using a multiplication factor of 0.9858 [5]. Purulent and mucoid characteristics were estimated in percentage by an experienced laboratory assistant. The ratio of dry weight to wet weight (% solids) of 24 h sputum was determined. During the first 6 h of drying, the sputum was weighed hourly to provide data on the rate of water loss [6].

For the chemical analysis, 5–10 ml of deep frozen 24 h sputum was thawed, ultrasonicated and homogenized, employing a Branson Sonifier for 3.30 s at maximal output (Branson Sonifier Cell Disrupter 1255, Heat Systems Ultrasonics Inc., Plainview, N.Y., U.S.A.), then centrifuged at 1300×g for 10 min. The clear supernatant extracts were used for determination of protein according to the method of FIELDS and CHODOSH [7]. Immunoglobulin A (IgA) and albumin were measured using radial immunodiffusion and monospecific antibodies (Kallestad Laboratories, Austin, TX, USA).

Aliquots of sputum were formalin-fixed, ultrasonicated and homogenized to destroy all fibres without destruction of the cells [5]. Then cell counts (cells×10 ml) were done and cells lost per day calculated.

Fresh untreated 3 h sputum samples, collected by the patients in the morning prior to each visit, were taken for viscosity and elasticity measurements on the low shear Contraves oscillatory rheometer with Couette attachment (Low-shear 30 sinus oscillatory rheometer, Contraves, Zurich, Switzerland [8]). The "apparent" viscosity and elasticity were determined at a shear rate of 2.64 s^{-1} and temperature of 37°C. The results were given in Pa·s and Pa.

The content of acid glycoprotein (AGP) - or mucopolysaccharide (AMPS) - fibres as well as deoxyribonucleic acid (DNA) - fibres of fresh sputum was determined according to the method of BÜRGI [9, 10]. The fibre content was graded semiquantitatively on a scale of 0.1 (rare) to 4.0 (abundant).

Statistical analysis

The mean and standard deviation of the values for each observation time were calculated. Scored data from subjective observations and quantitative data of the above mentioned parameters were analysed first for discrepancy between the groups before treatment using the chi-squared test and the two tailed t-test. Treatment effects in the cross-over trial were assessed using an analysis of variance adapted from HILLS and ARMITAGE [11].

Results

Since neither time nor treatment order affected the response to the currently administered treatment, the results are presented in a simplified manner which allows a direct comparison of the effects of STC and placebo therapy for all patients (tables 1 and 2).

Subjective symptoms (table 1) and data from physical examination (data not shown) remained unchanged during either STC or placebo therapy. The statistical analysis revealed no difference between the two treatment groups. This was also the case for most of the pulmonary function tests (table 1). The only statistically significant difference observed was in the forced expiratory flow at 25 to 75% of vital capacity ($FEF_{25-75\%}$): the value was higher after three weeks of placebo than after three weeks of STC-therapy.

Table 1. – Subjective symptoms and pulmonary function tests in patients with stable chronic bronchial diseases receiving sodium thiophene carboxylate or placebo

	Washout		Sodium Thiophene Carboxylate			Placebo		
Control day	0	7	14	21	28	14	21	28
Number of patients	33	33	31	30	29	31	30	29
Cough frequency (total per day)	20.4±10.2	19.4±10.2	19.2±11.8	19.4±12.6	19.7±13.5	18.7±9.9	18.7±11.1	18.7±11.6
Cough severity (total per day)	23.6±8.8	22.3±9.5	21.4±9.9	20.8±10.3	21.0±9.9	22.4±8.4	21.1±9.0	20.6±8.9
Difficulty in raising sputum (total per day)	22.9±9.8	21.5±9.9	22.3±10.3	19.7±9.5	20.5±9.2	22.8±9.7	22.0±10.9	22.7±10.6
Dyspnoea	8.2±4.8	8.0±4.8	8.0±5.0	7.9±4.6	7.9±4.8	8.2±4.8	8.2±4.9	7.8±4.8
FVC (l)	2.72±0.96	2.68±0.97	2.81±1.04	2.79±1.13	2.68±0.96	2.78±1.04	2.77±1.11	2.72±0.93
FEV_1 (l)	1.52±0.89	1.52±0.86	1.57±0.92	1.57±1.00	1.46±0.87	1.51±0.91	1.59±0.95	1.52±0.88
PEFR ($l \cdot s^{-1}$)	4.48±1.65	4.62±1.54	4.60±2.14	5.11±2.18	4.92±2.13	4.55±1.94	4.96±1.68	4.81±1.91
FEF_{25-75} ($l \cdot s^{-1}$)	0.93±0.97	0.87±1.00	0.92±1.06	0.89±1.09	0.80±0.92*	0.90±0.98	0.91±1.00	0.90±0.95*

$\bar{x}$±SD * Statistically significant difference ($p<0.05$) between sodium thiophene carboxylate and placebo; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; PEFR: peak expiratory flow rate; FEF_{25-75}: forced expiratory flow at 25–75% of vital capacity.

Table 2. – Sputum physiochemical characteristics in patients with stable chronic bronchial diseases receiving sodium thiophene carboxylate or placebo

	Washout		Sodium Thiophene Carboxylate			Placebo		
Control day	0	7	14	21	28	14	21	28
Number of patients	33	33	31	30	29	31	30	29
Volume ($ml \cdot day^{-1}$)	21.4±15.8	19.3±10.9	19.3±10.4	18.9±10.9	19.1±11.4	21.8±16.7	20.2±11.7	19.1±11.8
Purulence (%)	40.2±21.4	34.8±24.2	38.5±25.4	40.6±24.1	36.9±24.3	34.3±21.7	35.4±21.5	42.8±24.1
Sputum cells ($cells \cdot 10^6 ml^{-1}$)	11.1±10.8	13.0±20.1	17.0±22.2	10.4±8.67	10.2±11.3	7.98±5.11*	10.9±10.2	13.4±14.6
Protein ($mg \cdot ml^{-1}$)	8.72±4.49	10.4±5.36	9.97±4.74	9.50±5.48	8.83±3.38	8.05±3.66*	8.77±4.40	9.16±3.31
IgA ($IU \cdot l^{-1}$)	41.4±19.5	44.4±19.0	46.3±20.6	44.7±25.0	51.6±18.0	41.2±20.7	42.5±18.2	51.4±18.6
DNA-fibres **	1.42±1.13	1.44±1.16	1.65±1.17	1.63±1.27	1.25±1.03	1.42±1.24	1.41±1.11	1.36±1.24
AGP-fibres **	1.16±0.95	1.31±1.04	1.35±1.09	1.50±1.15	1.01±0.92	1.14±0.79	1.21±0.89	0.96±0.83
"Apparent" elasticity (Pa)	2.06±3.93	1.98±2.51	1.45±2.25	1.37±1.02	1.82±2.53	1.65±2.27	1.58±2.23	1.80±2.76
"Apparent" viscosity (Pa·s)	8.27±17.23	8.83±12.91	6.07±11.12	5.44±4.95	6.51±9.69	6.61±10.49	6.43±10.07	7.79±13.36

$\bar{x}$±SD * Statistically significant difference ($p<0.05$) between sodium thiophene carboxylate and placebo; ** the fibre content was graded on a scale of 0.1 (rare) to 4.0 (abundant); IgA: Immunoglobulin A; DNA-fibres: deoxyribonucleic acid-fibres; AGP: acid glycoprotein-fibres.

During STC-therapy there was a slight decrease of FVC, FEV_1 and $FEF_{25-75\%}$, whereas PEFR improved. In contrast, FVC, FEV_1 and $FEF_{25-75\%}$ remained unchanged under placebo; PEFR increased slightly.

When comparing the results of the sputum analysis (table 2) at the beginning (day 7) with those at the end (day 28) of each treatment period, the following pattern emerged: sputum volume and dry weight remained practically unchanged. Purulence, cell concentration and protein content decreased slightly during STC therapy whereas the opposite was the case for placebo. "Apparent" viscosity and elasticity as well as sputum IgA increased whereas AGP-fibres decreased during both treatments.

Considering the effects of the two treatments on the various system parameters there were only two statistically significant differences: sputum cell concentration and protein content were higher after one week of STC therapy than after one week of placebo. Otherwise, no statistically significant difference was observed

(24 h sputum volume, purulence, IgA, AGP-fibres, DNA-fibres, dry weight and "apparent" elasticity and viscosity).

Considering the overall clinical response, 9 patients improved and 22 patients remained unchanged after three weeks of STC-therapy. This result is practically the same for placebo: 9 patients improved and 23 remained unchanged. Thus, the clinical efficacy of STC was that of placebo.

Minor side effects (nausea, constipation, meteorism, vertigo, pollakisuria, tiredness, disturbed sleep, sweating, palpitations, pruritus) were observed in 11 patients receiving STC compared to 9 patients on placebo. The symptoms did not necessitate drug withdrawal and disappeared in most cases without specific therapy.

Discussion

Patients' desire for effective expectorant and antitussive medication in diseases linked with excessive quantities of bronchial mucus such as chronic bronchitis or bronchiectasis makes the temptation great to use such drugs despite clinical evidence that they are of little objective effect. Traditional expectorants, with the exception of iodides, have nearly always failed to show an effect when used in controlled trials, though patients sometimes seem to value them [1, 12, 13].

Sodium thiophene carboxylate which contains a cyclised molecule with a sulphur atom in its nucleus is claimed to be a mucoregulatory drug with mucolytic activity. Using a mini-pig model equipped with a tracheal pouch MARRIOTT and MARTIN showed that STC caused a decrease of viscosity and elasticity of mini-pig mucus, which indicates mucolytic activity [14]. At the same time a significant increase in protein concentration of mucus was observed, the fucose content remaining constant. Since the ratio of fucose to protein decreased, the researchers speculated that the secreted glycoprotein was less glycosylated and was released prematurely. The secretion of this immature biopolymer was thought to be the cause of the mucolytic activity. From these data one may conclude that STC is a mucoregulatory drug with mucolytic activity.

Considering the results of clinical studies, BÜRGI observed a decrease of viscosity and AMG-fibres in sputum of thirteen patients with clinically stable chronic bronchitis receiving STC in comparison to eleven patients treated with placebo [15]. In another placebo-controlled study CHEMINAT and AIACHE found just the opposite: viscosity and AMG-fibres content of sputum of chronic bronchitics increased during the treatment with STC, the sputum volume remaining unchanged [2]. Clinically, the patients improved as did their pulmonary function. Based upon the sputum findings which indicated no fluidification of sputum, CHEMINAT and AIACHE considered STC to be a mucoregulatory drug causing reorganisation of the fibrillary structures of mucus.

In contrast to these studies, in the present double-blind crossover trial of STC and placebo, no consistent changes in subjective symptoms, pulmonary function tests or sputum physical characteristics could be detected during the entire length of the treatment periods. In particular, expectoration, *i.e.* the ease of raising sputum, was not improved and cough frequency did not decrease either by STC or placebo. Concerning the typical effects of mucoregulatory drugs on bronchial secretions [16] neither the output of bronchial glycoproteins measured as AGP fibres was increased nor flow properties (viscosity and elasticity) were changed by STC in comparison with placebo. In addition, secretory IgA content remained the same. Occasional statistically significant changes, such as decrease in sputum cell concentration or protein content, elude interpretation because of their inconsistency and lack of correlation to subjective symptoms or other objective measurements.

In view of these negative results the question arises whether our study design, selection of patients and methodology may have been inadequate to demonstrate the presumed pharmacological and therapeutic effects of STC. However, design and methods resembled those of the other two clinical trials, the only difference being the selection of the patients. Whereas our patients had stable bronchial disease during the whole length of the trial - as reflected by the various sputum characteristics - the patients of CHEMINAT and AIACHE had acute exacerbations of their bronchial diseases and were receiving antibiotics [2]. This is a serious disadvantage for the evaluation of the effect of an expectorant - either secretolytic, secretomotor or mucoregulatory drug - since bronchial inflammation profoundly changes chemical composition and flow properties of bronchial secretions [17, 18]. The increase of AGP-fibres and viscosity reported by CHEMINAT and AIACHE may rather be the consequence of decreased bronchial inflammation caused by antibiotics than an effect of STC [2].

From our extensive study we must conclude that no proof exists that STC treatment in the dosage of 600 mg per day has more than a placebo effect. For all the variables measured no consistent statistically significant differences were detectable between STC and placebo given in either sequence. This study documents the clinical inefficacy of STC as mucoregulatory or mucolytic drug in patients with stable chronic bronchial diseases. Whether prolonged treatment with STC will protect patients with chronic bronchial diseases against acute exacerbations - as BOMAN *et al.* have shown for N-acetyl cysteine [19] - remains open, because our trial was not designed to answer this question.

References

1. Richardson PS. – The principles of drug action on cough and on sputum characteristics. *Eur J Respir Dis*, 1980, 61 (Suppl. 110), 67–73.
2. Cheminat JC, Aiache JM. – Etude en double aveugle de l'activité mucorégulatrice du thiophène carboxylate de sodium. *Sem Hôp Paris*, 1981, 57, 307–310.
3. American Thoracic Society. – Chronic bronchitis, asthma and pulmonary emphysema. A statement by the

committee on diagnostic standards for non-tuberculous respiratory diseases. *Am Rev Respir Dis*, 1962, 85, 762–769.
4. Chodosh S, Eichel B, Ellis G, Medici TC, Faling J. – Trimethoprim-sulfamethoxazone compared with ampicillin in acute infectious exacerbations of chronic bronchitis, *J Infect Dis*, 1973, 128 (Suppl.), 710–718.
5. Medici TC, Chodosh S. – Nonmalignant exfoliative sputum cytology. *In:* Sputum, fundamentals and clinical pathology. Dulfano MJ ed. Thomas 1973, Springfield, pp 332–381.
6. Chodosh S. – Objective sputum changes associated with glyceryl guaiacolate in chronic bronchial diseases. *Bull Physiopathol Respir*, 1973, 9, 452–457.
7. Fields JD, Chodosh S. – Quantitation of sputum protein use of the biuret reaction. *Clin Chem*, 1970, 16, 773–775.
8. Davis SS, Dipy JE. – The rheological properties of sputum. *Biorheoloy*, 1969, 6, 11–21.
9. Bürgi H. – Vorkommen und mögliche klinische Bedeutung von Fasersystemen im Bronchialsekret von Asthmatikerm. Mukopolysaccharide. *Schweiz Med Wschr*, 1965, 65, 1677–1679.
10. Bürgi H. – Mucoproteins and sputum viscosity. *Lancet*, 1964, 2, 644.
11. Hills M, Armitage P. – The two-period cross-over clinical trial. *Br J Clin Pharmacol*, 1979, 8, 7–20.
12. Medici TC. – Expektorantien: Sinnvoll oder sinnlos. *Pharmakritik*, 1980, 2, 21–24.
13. Petty TL. – The national mucolytic study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest*, 1990, 97, 75–83
14. Marriott C, Martin GP. – Effect of sodium thiophene carboxylate on the properties of pig tracheal mucus. *Thorax*, 1988, 43, 256 P.
15. Bürgi H. – Etude clinique en double insu d'un agent oral mucolytique sur l'expectoration du bronchiteux chronique. *Méd et Hyg*, 1976, 34, 1430–1431.
16. Puchelle E, Aug F, Polu JM. – Effect of the mucoregulator S-carboxy-methyl-cysteine in patients with chronic bronchitis. *Europ J Pharmacol*, 1978, 14, 177–184.
17. Bürgi H, Wiesmann V, Richterich R, Regli J, Medici TC. – New objective criteria for inflammation in bronchial secretions. *Brit Med J*, 1968; 3, 654–656.
18. Puchelle E, Zahm JM, Polu JM, Sadoul P. – Drug effects on viscoelasticity of mucus. *Eur J Resp Dis*, 1980 (Suppl. 110), 61, 195–203.
19. Boman G, Bäcker U, Larsson S, Melander B, Wåhlander L. – Oral acetyl-cysteine reduces exacerbation rate in chronic bronchitis: report of a trial organized by the Swedish Society for Pulmonary Diseases. *Eur J Respir Dis*, 1983, 64, 405–415.

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RÉSUMÉ: Nous avons comparé, dans une étude randomisée en double aveugle avec permutation croisée, l'efficacité clinique d'un traitement de 21 jours au moyen de caboxylate de thiophène sodique à raison de 600 mg par jour et au moyen de placebo, chez 33 patients atteints de maladie bronchique chronique stable. Pendant la période d'essai qui dura sept semaines, l'on a enregistré les symptômes subjectifs et les constatations objectives, les tests fonctionnels pulmonaires et les caractéristiques physiques de l'expectoration. Les effects collatéraux ont été suivis de près. Tant l'appréciation subjective de l'efficacité clinique globale que l'analyse statistique des facteurs mentionnés ci-dessus, n'ont montré aucun avantage significatif du carboxylate de thiophène sodique sur le placebo. Le carboxylate de thiophène sodique paraît donc un expectorant et un muco-régulateur sans évidence d'efficacité clinique pour le traitement de patients atteints de bronchite chronique stable.
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