The Influence of a Secretolytic Drug on Mucociliary Clearance of the Maxillary Sinus

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ABSTRACT

To date, there has not been sufficient experimental evidence to demonstrate the pharmacological effect of secretolytic and mucolytic drugs. Scintigraphic studies to detect the mucociliary clearance in the maxillary sinus before and after application of a secretolytic drug (Gelomyrtol® forte, G.Pohl-Boskamp, Hohenlockstedt, Germanym) were perfomed on four healthy persons and one patient having undergone sinus surgery. The most important parameters was the mucociliary transport velocity of the " region of interest-maxillary sinus " and the increase of radioactivity accumulated in a swab placed in the middle nasal meatus. Measurements were done with a gamma-camera, 99m Technetium-sulphur colloid was used as the radiopharmacon. A dose of 1 Mbq in 0.2 ml NaCl-solution was injected into the maxillary sinus. The results showed a clear increase of mucociliary transport velocity in the maxillary sinus after intake of secretolytics in connection with an increase of radioactivity in the swab. The results can be explained by the secretolytic and secretomotoric effects of the investigated drug. The study reveals that ethereal oils have secretolytic effects and also have a pharmacological effect on the mucociliary apparatus.

KEY WORDS : Mucociliary clearance · Secretolytic drugs · Chronic sinusitis · Pharmacological effect.

INTRODUCTION

Chronic sinusitis is a disease of the mucous membranes within tight and somewhat complicated anatomical structures. The consequence of this inflammation is an imbalance between the production of secretion by the goblet cells and the seromucous glands on the one hand and the clearance of secretion by the ciliated cells. This reduces the mucociliary transport rate.

Therapeutic strategies focus firstly on optimising the anatomical conditions with a view to improving ventilation and drainage of the paranasal sinuses, which is the task of surgical therapy. Concepts for minimal-invasive endoscopic surgery of the paranasal sinuses are now well established and comprehensively documented.[1)2)3)]

Pharmacotherapy, on the other hand, is aimed at softening and liquifying the tenacious or dried secretion. The objective is to reactivate the diturbed mucociliary clearance through the use of drugs which act specifically on the production of secretion, the viscosity of the mucus and ciliary activity. The group of drugs which are effective for this therapeutic indication are collectively known as mucolytics, secretomotoric drugs and secretolytics.[4)]

An assessment of mucolytics and secretolytics as a therapeutic factor in the treatment of chronic sinusitis requires proof of efficacy. Such evidence would provide a tool for measuring the effectiveness of the various substances with a view to formulating an optimal therapeutic strategy.

MATERIALS AND METHODS

Course of study

Four healthy male volunteers and one 58-year-old male patient were examined by nuclear medical techniques. Prior to the investigations the otolaryngological status was established and a nasal endoscopy performed. The subjects showed no signs, either clinical or in their history, of acute, recurrent and chronic sinusitis. The patient had undergone radical maxillary sinus surgery 15 years previously with bilateral endoscopic operation of the ethmoid.

Two sequential scintigraphic function tests were performed, the first before administration of a secretolytic drug (Gelomyrtol forte®, G.Pohl-Boskamp, Hohenlock-stedt, Germany).

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The second sequential scintigraphic function test was performed after four day medication with the secretolytic drug Gelomyrtol forte at a dose rate of one capsule three times daily.

The tests were conducted at the same time each day at room temperature of 23 degree Celsius and 55% humidity.

Participation in the study was entirely voluntary and the subjects had previously been given a full explanation of the radiation exposure during the function study and the possible side-effects of the drug. The radiation exposure per investigation was 0.14 mGy which is less than the 0.17 mGy of a conventional exploration of the paranasal sinuses.

Radioactive tracer

The radioactive tracer used was 99m technetium-labelled sulphur colloid. The examination was performed in the sitting position. After anaesthetising the mucosa of the inferior nasal meatus, the maxillary sinus was punctured through the inferior nasal meatus. 1 Mbq of 99m Tc-labelled sulphur colloid in normal saline was then administered into the maxillary sinus using a Lichtwitz cannula. At the same time a standard swab was inserted into the middle meatus by means of an endoscope.

Gamma camera and evaluation of the readings

The measurement were conducted with an APEX SP 4 gamma camera by ELSCINT (Israel) with a high resolution collimator and a matrix consisting of 64×64 pixels. The distance between camera and patient was 5 cm. The sequential scintigraphic function study in front of the gamma camera was performed with a picture frequency of one frame per minute for a period of 30 minutes in the ventral position.

Regions of interests (ROI) were marked ; 1) above the maxillary sinus floor, 2) the maxillary sinus wall, 3) the ostium.

Computer-aided time activity curves were constructed. The clearance half-lives of the radioactive material were measured via an e-function applied to the descending loop of the time-activity curve. The principal parameter was the half-life of the maxillary sinus floor region. Immediately after the function study in front of the gamma-camera the swab was removed from the middle nasal meatus and the radioactivity measured.

RESULTS

After instillation of the radioactive substance into the maxillary sinus a marked accumulation of 99m Tc-sulphur colloid was observed above the maxillary sinus floor in all tested subjects. In the four healthy volunteers the clearance of the radioactive material proceeded via the secretory routes. In the previously operated patient (state after Caldwell-Luc's operation and ethmoid sinus surgery) no directional clearance of secretion was evident. The secretory route via the lateral wall was seen in 3 subjects, in one case clearance of the radioactive material occurred via the lateral and medial wall, with the two routes joining anterior to the ostium. Therafter drainage proceeded via the lateral nasal wall into the epipharynx and the pharynx.

Compared with the function studies before adminstration of the secretolytic, the second function study, conducted after the secretolytic had caused a bulid-up of radioactivity, revealed marked changes in mucociliary transport velocities, especially in the ROI of the maxillary sinus floor.

In all five cases an accelerated mucociliary clearance was measured in the maxillary sinus during the second sequential scintigraphic function study (after administration of the secretolytic) compared with the preliminary test.

The illustrations (Fig. 1) show nuclear medical findings for mucociliary clearance of the maxillary sinus during the first (without secretolytic) and the second function study (after taking the secretolytic). In each picture the scintigrams of a given time interval are superimposed on each other. The other picutres (Figs. 2 and 3) show the time-activity curves of one volunteer (subject 2).

The radioactivity measurements in the swab from the middle nasal meatus showed markedly higher impulse rates after administrations of secretolytic in all cases, although there were inter-individual differences in the amount of absorbed radioactivity in the swab. For example, the amount of radioactivity found in subject 4 was almost 5 times greater than in subject 2. The percentage increase in the amount of radioactively labelled secretion cleared from the maxillary sinus differed little between individuals. The only exception was subject 3 where the increase in radioactivity was 70% as against 85% in the other subjects (Table 1). The clearance of secretion from the maxillary sinus during the period of investigation was thus considerably higher in all tested subjects after adminstration of the secretolytic.

DISCUSSION

An in vivo pilot study using measurable parameters was carried out to ascertain whether plant-dervied secretolytics such as Gelomyrtol® forte have an influence on the mucociliary apparatus of the paranasal sinuses. Camera sequential scintigraphy using a modified ROI technique is a highly sensitive method for recording changes in mucociliary clearance.[5)6)7)8)]

The principal parameters employed were the mucociliary transport velocity of the maxillary sinus floor as the " region

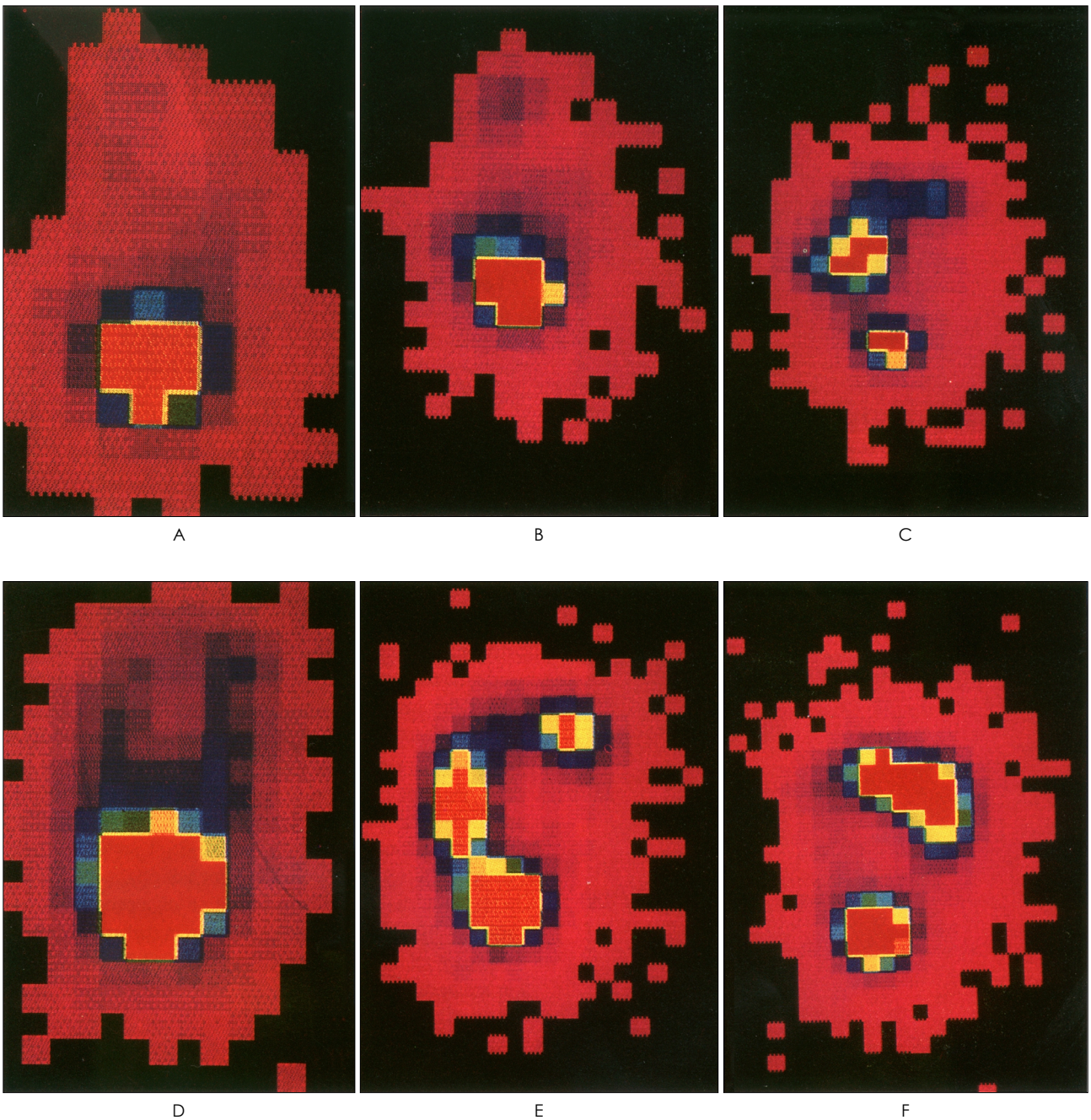

Fig. 1. A) Sequential scintigrams 1 - 2 minute after instillation of 99m Tc-sulphur colloid into the maxillary sinus. Functional study *before* taking Gelomyrtol® forte. Slow clearance of radioactivity from the maxillary sinus floor.
B) Sequential scintigrams 8 - 9 minute after instillation of 99m Tc-sulphur colloid into the maxillary sinus. Functional study *before* taking Gelomyrtol® forte. Clearance of radioactivity via the lateral maxillary sinus wall occurs.
C) Sequential scintigrams 18 - 19 minute after instillation of 99m Tc-sulphur colloid into the maxillary sinus. Functional study *before* taking Gelomyrtol® forte. The radioactive material has reached the maxillary ostium by the lateral secretory route.
D) Sequential scintigrams 1 - 2 minute after instillation of 99m Tc-sulphur colloid into the maxillary sinus. Functional study *after* taking Gelomyrtol® forte. Speedy clearance of radioactivity from the maxillary sinus floor via the secretory routes of the lateral and medial wall.
E) Sequential scintigrams 8 - 9 minute after instillation of 99m Tc-sulphur colloid into the maxillary sinus. Functional study *after* taking Gelomyrtol® forte. Distinctly faster clearance via the lateral wall. In the top right of the picture the radioactivity is already passing the ostium (about 10 min, earlier than in function study 1).
F) Sequential scintigrams 18 - 19 minute after instillation of 99m Tc-sulphur colloid into the maxillary sinus. Functional study *after* taking Gelomyrtol® forte. The radioactivity has passed the maxillary ostium and the infundibulum and is now being transported caudally in the nasopharynx.

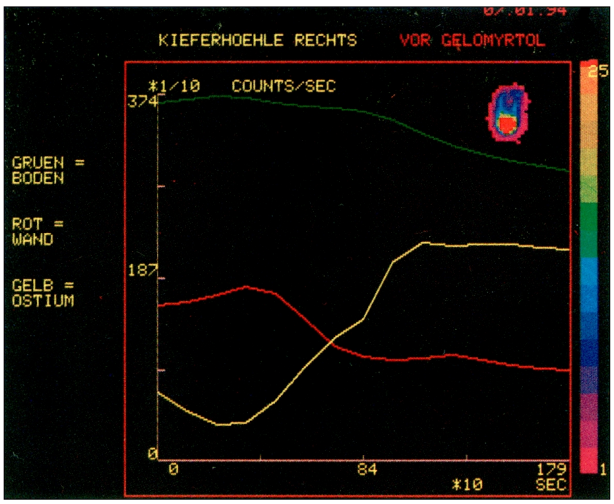

Fig. 2. Time activity curves of subject 2. The function study before administration of the secretolytic drug shows a slow drainage of radioactive material from the maxillary floor (green curve).
Mucociliary transport occurs via the lateral and medial wall (red curve, medial wall) towards the ostium (yellow curve) where a deposit formation occurs (horizontal part of the yellow curve).

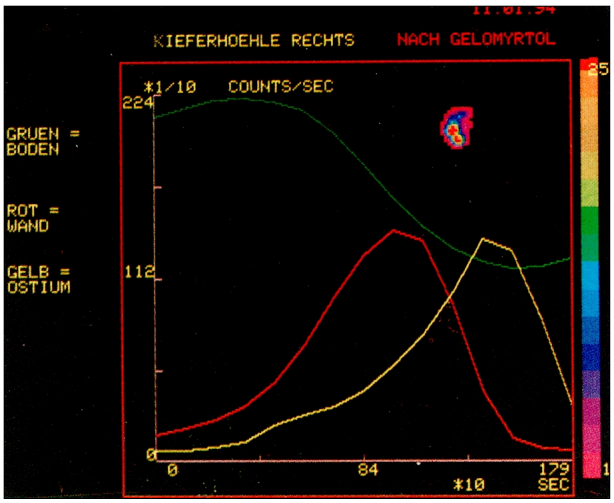

Fig. 3. Time activity curves of subject 2. The function study after administration of the secretolytic shows a markedly accelerated drainage of radioactive material from the maxillary sinus floor (green curve). Speedy clearance occurs via the lateral maxillary sinus wall (red curve). The ostium is reached and passed quickly (yellow curve). No deposit formation.

of interest " and the activity accumulation in a swab placed in the middle nasal meatus. In positioning the swab, care was taken not to obstruct the hiatus semilunaris but to collect the secretion transported from the maxillary sinus via the ethmoidal infundibulum caudally of the hiatus between the lateral surface of the middle concha and the back of the lower concha. Although the subjects were considered to have healthy sinuses, transport times were relatively slow with inter-individual variations in both studies. The crucial result was the comparison between the mucociliary transport velocity before and after administration of the secretoloytic. The radioactivity deposited in the swab must have passed from the maxillary sinus to the middle meatus as a result of active secretory transport, at least in the four healthy subjects.

Table 1. Results of the scintigraphic function studies before and after administration of the secretolytic drug Gelomyrtol forte

a)

	Half-life time of clearance	
	before medication	after medication
Subject 1	47.0	25.2
Subject 2	69.0	12.0
Subject 3	54.8	41.0
Subject 4	103.0	48.9
Subject (5)	37.0	19.2

b)

	Radioactivity in the swab		
	before medication RA_1	after medication RA_2	RA_2 / RA_1
Subject 1	145	1068	86.42
Subject 2	40	256	84.4
Subject 3	102	330	69.1
Subject 4	204	1280	84.07
Subject (5)	310	2140	85.52

RA=radio activity

Table 1 shows a clear acceleration of mucociliary transport in the maxillary transport in the maxillary sinus after ingestion of the secretolytic, accompanied by an increase in radioactivity in the swab. The acceleration cannot be explained by an increased secretion in the goblet cells of the respiratory epithelium alone, but must be due to a secretomotoric effect. The marked difference in activity accumulation in the swab before and after administration of the secretolytic must be due to the fact that more secretion was transported faster from the maxillary sinus to the mucous membrane of the lateral nasal wall via the physiological secretory routes. In the patient with previous radical maxillary sinus surgery the lateral nasal wall on the tested side was virtually non-existent. Thus drainage did not proceed via the usual routes, but there was a marked increase in the amount of secretion.

Critical comment on methodology

One problem with the study is undoubtedly the fact that the influence of a secretolytic on normal mucosa, i.e. non-pathological secretion and non-pathological clearance, is likely to produce a lower measureable yield than in the presence of pathological changes. Nevertheless, we decided to select healthy volunteers for our study because we wanted to keep

the number of variables as low as possible and to concentrate exclusively on the effect of the drug. The results of the study demonstrate that essential oils act as plant-derived secretolytics by exerting a marked influence on the mucociliary apparatus. The difficulty in the pharmacological assessment of mucolytics and secretolytics is due to the lack of a suitable experimental pharmacological model which mimics the human pathological situation. There is also a total absence of standardisation of studies conducted to date in various animal species using a variety of techniques.[9] The method described here for demonstrating mucociliary clearance is reproducible and relatively undemanding in terms of technical resources and time. It would therefore appear to be suitable for use as a standardised procedure for testing the influence of drugs on the mucociliary apparatus in vivo. It also allows the evaluation of physiological mechanisms in pathologically altered paranasal sinuses. This method can enhance the existing knowledge of the various groups of secretolytic, secretomotoric and mucolytic drugs by providing crucial information in efficacy. The choice of a secretolytic from among the essential oils for the present study is based on our own positive clinical experience and several clinical case reports with the test substance.[10)11)12)13)14)] It should be pointed out that the results of the study in healthy volunteers are not necessarily transposable to patients with sinusitis.

Our work is a first step in the pharmacological evaluation of a drug for the mechanism of action under investigation. The efficacy of secretolytics in recurrent and chronic sinusitis will be the subject of further studies.

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