

A preliminary study of the effect of guaiphenesin on mucociliary clearance from the human lung

M. L. THOMSON, D. PAVIA, and M. W. McNICOL

TUC Centenary Institute of Occupational Health, London School of Hygiene and Tropical Medicine, Keppel Street (Gower Street), London WC1E 7HT and Central Middlesex Hospital, Park Royal, London NW10 7NT

Thomson, M. L., Pavia, D., and McNicol, M. W. (1973). *Thorax*, 28, 742-747. A preliminary study of the effect of guaiphenesin on mucociliary clearance from the human lung. The effect of guaiphenesin (administered as Robitussin¹) on mucociliary clearance has been assessed in 15 subjects from the rate of removal from the lung of previously inhaled radioactive tracer particles. The guaiphenesin was compared with a positive control preparation consisting of the guaiphenesin vehicle only in two double-blind crossover trials. The first trial examined eight aged 'healthy' volunteer subjects and the second trial examined seven chronic bronchitic patients. Sequential gamma counts were made from the whole lung by scintillation counters for 6 hours after inhalation and the chest was also scanned rectilinearly. In the first 5 hours after inhalation the mean rate of removal of particles and therefore of secretions was faster after guaiphenesin than after the control preparation. This difference was not statistically significant in the healthy volunteers but achieved significance ($P < 0.05$) in the chronic bronchitic patients. Lung scans after inhaling the tracer aerosol indicated that on average the initial penetration of the particles into the lung was similar in the guaiphenesin and control runs. The faster clearance after guaiphenesin was unlikely to be due to bulk movements of mucus caused by coughing since the mean frequency of coughing during the experiment was somewhat less after the drug.

Guaiphenesin is glyceryl guaiacolate ($C_{10}H_{14}O_2$), which is a glyceryl ether of guaiacol. It has been used for many years as an expectorant and it is found in the sputum after oral administration (Chodosh, 1972). It is said to reduce the tenaciousness of the sputum and to diminish the frequency of coughing. The rate of clearance of inhaled radioactive particles from the lungs offers an objective means of assessing the efficiency of this drug in aiding the removal of secretions from the lung. We report below two double-blind crossover trials in 15 subjects using this method to evaluate the expectorant action of this drug.

METHOD

GENERAL The 15 subjects were examined on two occasions by the same standardized technique; eight of these were 'healthy' aged volunteers from old

people's homes (group A) and seven were chronic bronchitics (group B). The full nature of the study had been explained to them before it began. On both occasions the subjects inhaled radioactive particles and their lungs were monitored for gamma radiation for six hours thereafter. One hour prior to both runs the subjects while under observation took either 600 mg of guaiphenesin in the form of Robitussin or a control preparation which consisted of Robitussin without the guaiphenesin; the two preparations were physically indistinguishable and similar in taste. The order in which control and drug were given was randomized (subject to half the subjects taking the drug first) and was not known to subjects or observers until after the results had been analysed.

The technique and radioactive dose have been approved by the Isotope Panel of the United Kingdom Medical Research Council and the ethical subcommittee of the London School of Hygiene and Tropical Medicine and have been passed as safe for similar studies performed on the staff of the United Kingdom Atomic Energy Authority's Research Establishment, Harwell (Booker *et al.*, 1967).

Requests for reprints: Dr. M. L. Thomson, London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London WC1E 7HT

1A. H. Robins Ltd.

TRACER TECHNIQUES The method has been fully

A preliminary study of the effect of guaiphenesin on mucociliary clearance from the human lung 743

described by Thomson and Short (1969). Uniform 5-micron particles of polystyrene were generated by a spinning disc in an airtight tank, from which they were inhaled by the subjects; inhalation was automatically interrupted after a preset volume (here 750 ml). The particles were labelled with technetium-99m (Few, Short, and Thomson, 1970), a gamma-emitter of 6-hour half-life, as tetraphenylarsonium pertechnetate, in which form negligible quantities leached from the particles. The subjects were asked to rinse their mouths and to drink water immediately after the inhalation of the tracer particles in order to remove any particles present in the oropharyngeal region and oesophagus. The rate of clearance from the lungs was subsequently monitored by two opposing scintillation counters (NaI(Tl) crystals); the anterior counter was applied closely to the midpoint of the sternum in the midline and the posterior one to the spine axially opposite. The scintillation detectors were so collimated that their field of view included most of the lungs but virtually excluded the stomach. Counts were taken at frequent intervals over 6 hours and were corrected for radioactive background and decay. A linear change was assumed between successive counts. The subjects were asked to expectorate into a receptacle provided rather than swallow any sputum produced.

Scans of the right lung were made after inhalation using a rectilinear gamma scanner (Dawson *et al.*, 1971). The detector traversed vertical strips at one-inch intervals from the midline of the chest to the periphery. The detector was collimated by a cylindrical lead shield (1 inch diameter) which extended 2 inches

beyond the crystal. The output from the associated ratemeter was recorded on a potentiometric recorder. The count for each traverse was obtained by tracing the graphs on good quality paper and weighing the area under the curves.

During the trial runs the times of all coughs and sputum samples were noted and the type, total weight, and radioactive content of the samples were ascertained.

The ventilatory capacities were measured by Vitalograph (Drew and Hughes, 1969). In group A the forced expiratory volume in 1 second (FEV₁) and the forced vital capacity (FVC) were taken after arrival on the first visit. In group B they were taken after arrival on both visits and 3 hours after administration of drug and control mixtures.

The temperature and humidity of the laboratory air were measured at every trial since they might have affected the consistency of the lung secretions and hence their rate of removal. The mean ambient temperature and relative humidity were almost identical in the control and experimental runs for groups A and B.

RESULTS

SUBJECTS Table I gives the physical characteristics, smoking habits, and ventilatory capacities with their means and standard deviations for groups A and B separately. In group A four subjects had respiratory impairment, according to the regressions assembled in Cotes (1968), although the data of Milne and Williamson (1972) indicate

TABLE I
PHYSICAL CHARACTERISTICS, SMOKING HABITS, AND VENTILATORY CAPACITIES FOR 17 SUBJECTS

Subject and Sex	Age (yr)	Height (m)	Smoking (pack-years) × 10 ³	FEV ₁		FVC		FEV ₁ /FVC		Change in FEV ₁	
				Obs. (litre)	% of Pred.*	Obs. (litre)	% of Pred.*	Obs. (litre)	% of Pred.*	Control	Guaiphenesin
Group A											
1 M	67	1.54	22.2	1.87	78.5	2.78	87.8	67.3	100.7		
2 F	79	1.53	11.0	1.21	89.9	1.73	102.2	69.9	97.6		
3 M	86	1.60	26.3	1.40	80.2	2.01	78.7	69.7	116.2		
4 M	77	1.60	3.5	1.48	74.2	2.14	76.8	69.2	109.5		
5 F	67	1.50	22.2	1.04	62.4	1.46	71.3	71.2	95.2		
6 M	84	1.68	6.0	1.46	69.6	2.27	74.8	64.3	106.1		
7 M	84	1.67	16.9	1.65	79.9	2.25	75.3	73.3	121.3		
8 F	87	1.72	— (NS)	1.06	65.5	1.44	63.7	73.6	105.8		
Mean	78.9	1.63	15.4	1.40	75.0	2.01	78.8	69.8	106.6		
SD	8.1	0.06	8.8	0.29	9.0	0.45	11.6	3.1	9.0		
Group B											
11 M	68	1.59	9.7	0.44	18.0	2.34	75.4	27.5	27.1	-0.11	-0.02
12 M	69	1.60	17.9 (ES)	0.51	21.3	2.09	65.3	24.4	36.9	-0.10	-0.10
13 M	54	1.70	17.5 (ES)	0.50	15.7	2.01	49.6	24.9	34.7	+0.04	-0.02
14 M	65	1.78	58.0	0.79	24.8	2.13	50.4	37.1	54.9	-0.12	-0.09
15 M	64	1.60	9.5	0.59	23.2	2.58	77.9	22.9	29.9	-0.06	-0.18
16 M	59	1.74	93.1	0.53	16.6	1.07	25.8	49.5	70.9	-0.03	-0.04
17 M	67	1.71	0.5 (ES)	0.72	25.2	1.34	36.4	51.8	77.5	-0.19	-0.44
Mean	63.7	1.67	29.5	0.58	20.7	1.94	54.4	34.0	47.4	-0.08	-0.13
SD	2.0	0.03	12.7	0.05	1.5	0.21	7.4	4.6	7.7		

Pack-years = packet of 20 cigarettes or their equivalent × years of smoking; NS = non-smoker; ES = ex-smoker; *Predicted from regressions assembled by Cotes (1968); columns 5-10, ventilatory capacity when first seen; columns 11 and 12, effect on FEV₁ during the trial runs of control (11) and guaiphenesin (12).

SE 0.02 0.06. Mean paired difference 0.05, Student's *t* 1.08, probability *P* not significant.

TABLE II

FREQUENCY OF COUGHS AND SPUTUM SAMPLES AND WEIGHT AND RADIOACTIVITY OF SPUTA DURING THE TRIAL RUNS

Subject	No. of Coughs		No. of Samples		Total Weight(g) of Sputum		Sputum Radioactivity ¹	
	Control	Guaiphenesin	Control	Guaiphenesin	Control	Guaiphenesin	Control	Guaiphenesin
Group A								
1	2	7	0	1	0	2.57	0	9,482
2	10	5	2	0	0.08	0	27,700	0
3	33	8	0	0	0	0	0	0
4	23	23	0	0	0	0	0	0
5	16	22	0	0	0	0	0	0
6	5	4	2	1	12.52	7.35	93,305	78,964
7	6	4	2	1	5.20	3.96	88,405	29,740
8	1	0	0	0	0	0	0	0
Mean	12.0	9.1	0.75	0.38	2.31	1.74	26,176	14,773
SE	4.0	3.0	0.37	0.18	1.59	0.97	14,522	9,879
Mean paired difference	2.9		0.38		0.58		11,403	
Student's <i>t</i>	0.84		1.16		0.76		1.45	
P	NS		NS		NS		NS	
Group B								
11	27	19	0	0	0	0	0	0
12	5	10	4	4	7.42	4.10	299,784	192,837
13	75	13	3	2	6.43	6.40	101,588	113,794
14	57	48	2	3	4.79	6.15	20,294	24,464
15	30	20	0	2	0	0.64	0	15,802
16	18	6	2	2	4.57	4.16	42,393	34,924
17	6	29	2	5	1.67	8.90	53,187	213,085
Mean	31.1	20.7	1.86	2.57	3.55	4.34	73,892	84,987
SE	9.9	5.4	0.55	0.61	1.14	1.20	39,944	33,470
Mean paired difference	10.4		-0.71		-0.78		-11,094	
Student's <i>t</i>	1.07		-1.37		-0.65		-0.38	
P	NS		NS		NS		NS	

¹Observed counts by well counter adjusted for variation about the mean initial lung burden in each group.

lower normal values in the aged. All but one of the eight were smokers. In group B all seven subjects had chronic bronchitis (Medical Research Council, 1965) with greatly impaired ventilatory capacities. Their sputa were graded (Medical Research Council, 1965) as mucoid in five subjects (4 M1, 1 M2) and purulent in the remaining two (P2). All seven were past (3) or present (4) smokers. (The eighth subject in this group had a severe exacerbation between the trial runs and was omitted from the study.)

Table II shows for each subject the number of coughs and sputum samples, total weight of sputum, and its radioactive content expressed as the counts obtained by well-counting adjusted to the mean lung burden in each group. In both groups A and B the mean differences between drug and control runs in all these items were small and not significant.

In group B, the FEV₁ rose on average by 0.093 litre between the first and second runs in six of the seven subjects, irrespective of whether the drug or control run was first. Presumably this is due to a 'learning effect'. In 13 out of 14 control and experimental runs the FEV₁ fell after 3 hours by 0.100 litre on the average ($P < 0.001$). This trend is opposite to that expected as the result of learn-

ing or diurnal rhythm (Walford *et al.*, 1966). The means of the paired differences (-0.08 and -0.13 litres) between runs did not differ significantly.

The answers to questions about change in breathlessness, quantity and type of sputum, and difficulty in expectoration were equivocal.

MUCOCILIARY CLEARANCE Figure 1 shows the mean clearance curves for groups A and B separately for the control and experimental runs. It also shows the paired *t* values and significance of the differences at half-hourly intervals throughout the trials. In both groups clearance was faster after guaiphenesin. In group A, however, although the curves diverged consistently over the first 2.5 hours (where any increase in clearance rate due to the drug would become apparent), the difference between drug and control run was not significant. We are unable to explain the subsequent rise in the lower (guaiphenesin) curve which was due entirely to two subjects (1 and 5).

For group B, after the first hour the difference between the curves was significant at the 5% or higher level. This difference was contributed to by six of the seven subjects; the remaining subject (14) was equivocal.

A preliminary study of the effect of guaiphenesin on mucociliary clearance from the human lung 745

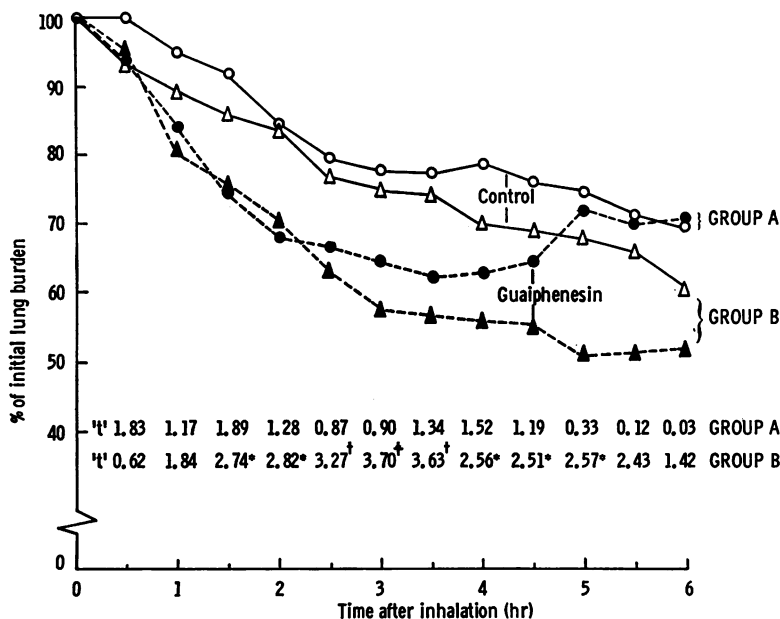


FIG. 1. Mean whole lung clearances of inhaled tracer particles for eight aged 'healthy' volunteers (group A) and seven chronic bronchitics (group B) for control and guaiphenesin trial runs. Also shown are the paired *t* values and significance levels (*, *P* < 0.05; †, *P* < 0.02; ‡, *P* < 0.01) at half-hourly intervals.

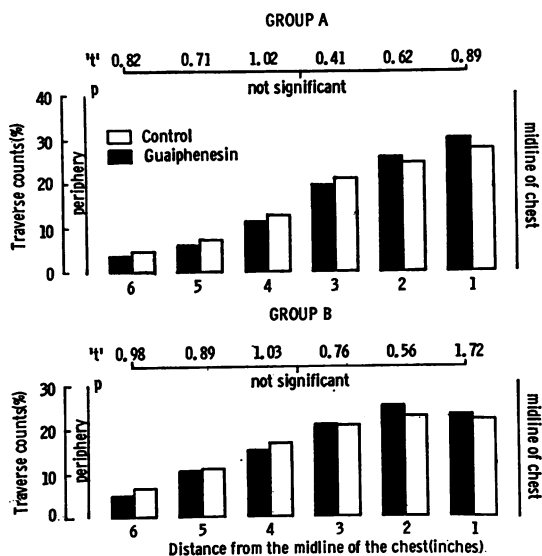


FIG. 2. Lateral distribution of inhaled tracer particles across the right lung for groups A and B. The heights of the columns represent for drug and control runs the means of the individual counts for each traverse of the scan expressed as percentages of the total scan counts. Also shown are the paired *t* values and probabilities for each traverse.

LUNG SCANS Figure 2 summarizes the results of scans of the right lung for groups A and B separately. The counts for the traverses were expressed as percentages of the total count for each individual; the means of these percentages for the two runs in both groups are the heights of the columns in Figure 2. (In one subject in group A the count was too low for accurate scanning.) The left lung scans were slightly affected by radiation from the stomach but in general they followed the same pattern as the right lung. The differences in particle penetration into the lung between the guaiphenesin and control series indicated by the paired *t* values were not significant in either group.

DISCUSSION AND CONCLUSION

Clearance of the inhaled particles from the lung takes place in two stages. In the healthy lung, particles which deposit on the ciliated pathway are removed with a half-life of several hours and this fast or mucociliary clearance phase is usually largely completed in 6 hours or less. Those particles which penetrate beyond the ciliary escalator are removed only very slowly, and for the present

study most of them may be considered to have stayed *in situ* in the lung throughout these trials. Thus, provided there has been equal deposition in control and drug runs beyond the ciliated membrane the activity retained in the lung should be the same in both runs when the mucociliary phase is completed. Therefore, if the curves have diverged over the first part of this phase they must converge in the latter part. Consequently, the first part of the curve is of special interest in comparing rates of clearance (Lourenço, Klimek, and Borowski, 1971; Camner, Philipson, and Arvidsson, 1971), and the divergence of the mean curves over the first 2.5 hours which has been observed here in both groups indicates more rapid clearance after the drug. Also the findings here that the curves in both groups converged towards the same level after 6 hours supports the results of the scans which showed that deposition of the particles beyond the ciliary blanket was similar in drug and control runs. Nevertheless, although particle penetration did not differ significantly between runs it is possible but unlikely that the small difference noted here between the means may have been responsible for the difference in clearance observed.

In chronic bronchitis, an effective coughing mechanism may to some extent take over the function of mucociliary action. Increased expectation does not, however, appear to have played a part here since the frequency of productive coughing and the quantity of radioactive content of the sputa (Table II) were almost the same in both groups. There is no evidence that guaiphenesin increases the frequency of beat of the cilia. On the other hand, comparatively small increases in the width of the sol mucus layer in which the cilia beat could improve the mobility of the mucus without changing sputum viscosity appreciably (Litt, 1970), and this is more likely to be the mechanism responsible for the faster clearance observed here.

In all probability mucus must be present in excess before enhancement of its removal from the lung can be demonstrated. The so-called 'healthy' group A were mainly aged smokers and the majority either produced sputum during the trials or had a history of recurrent productive cough. However, in addition to a greater excess of mucus, the bronchitics had evidence of severe airway obstruction with physical defect in the airways likely to promote greater retention of mucus. It is therefore not surprising that the enhancement of clearance attributable to the drug was greater in the bronchitics than in the 'healthy' group and

that the difference between control and drug series reached significance only in the patients.

In this preliminary study guaiphenesin *per se* was not used because of problems associated with the availability of 600 mg of this low solubility drug in the form of tablets or capsules. The administration of the drug as a single large dose one hour before inhaling the tracer particles has certain advantages in relation to the conduct of the trial. Here it was certain that the full dose had been received by all subjects and they were under observation continuously for 6 hours thereafter so that any early reactions would have been noted. Also the possibility was excluded of random change in the subjects' clinical condition during a more prolonged drug regimen. On the other hand, demonstrable clinical improvement might have occurred after continuous administration of the drug in these fairly severe chronic bronchitics as a result of relief of inflammatory congestion due to the clearance of mucus from blocked airways. This study indicates that the rate of mucociliary clearance has been enhanced by the drug. In order to demonstrate clinical improvement a longer term trial would be required.

We thank the volunteer subjects, and Mrs. S. M. Forsey and Mr. R. Sillett for technical assistance.

REFERENCES

- Booker, D. V., Chamberlain, A. C., Rundo, J., Muir, D. C. F., and Thomson, M. L. (1967). Elimination of 5 micron particles from the human lung. *Nature*, **215**, 30.
- Camner, P., Philipson, K., and Arvidsson, T. (1971). Cigarette smoking in man. Short-term effect on mucociliary transport. *Archives of Environmental Health*, **23**, 421.
- Chodosh, S. (1972). Personal communication.
- Cotes, J. E. (1968). *Lung Function*, 2nd ed. Blackwell Scientific Publications, Oxford.
- Dawson, H., Douglas, R. B., Pavia, D., Reeves, E., Short, M. D., and Thomson, M. L. (1971). An inexpensive automatic two-detector lung scanner. *Physics in Medicine and Biology*, **16**, 691.
- Drew, C. D. M. and Hughes, D. T. D. (1969). Characteristics of the Vitalograph spirometer. *Thorax*, **24**, 703.
- Few, J. D., Short, M. D., and Thomson, M. L. (1970). Preparation of ^{99m}Tc labelled particles for aerosol studies. *Radiochemical and Radioanalytical Letters*, **5**, 275.
- Litt, M. (1970). Mucus rheology. *Archives of Internal Medicine*, **126**, 417.
- Lourenço, R. V., Klimek, M. F., and Borowski, C. J. (1971). Deposition and clearance of 2 micron particles in the tracheobronchial tree of normal subjects—smokers and nonsmokers. *Journal of Clinical Investigation*, **50**, 1411.
- Medical Research Council (1965). Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet*, **1**, 775.

- Milne, J. S. and Williamson, J. (1972). Respiratory function tests in older people. *Clinical Science*, **42**, 371.
- Thomson, M. L. and Short, M. D. (1969). Mucociliary function in health, chronic obstructive airway disease, and asbestosis. *Journal of Applied Physiology*, **26**, 535.
- Walford, J., Lammers, B., Schilling, R. S. F., van den Hoven van Genderen, D., and van der Veen, Y. G. (1966). Diurnal variation in ventilatory capacity. An epidemiological study of cotton and other factory workers employed on shift work. *British Journal of Industrial Medicine*, **23**, 142.