Rhinology, 23, 3-10, 1985

Activation of the nasal cilia

Preliminary study in healthy subjects

Juhani Nuutinen, Kuopio, Finland

SUMMARY

The effect of the drug HR-6 containing adenosine triphosphate in three concentrations and of a placebo on nasal mucociliary function was studied in sixteen healthy subjects. Nasal mucociliary function was measured on both sides of the nose with a radioisotopic method before and after the drug administration. The nasal mucociliary transport rate was increased by the active drug, on the average, by 2.0–3.2 mm/min in all three concentrations and by 0.2 mm/min in the placebo group, when one side of the nose was taken into account. When the average of the mucociliary function rate on both sides of the nose was calculated, the active drugs were found to increase the transport rate from 6.0 to 8.9 mm/min. The results of this preliminary study indicate the need for further studies in patients with impaired mucociliary function.

INTRODUCTION

Mucociliary function is the most important defence mechanism of the upper and lower airways against infections and other environmental agents. Primary or secondary disturbance in mucociliary activity is quite clearly a much more common cause of long-term respiratory diseases, nasal infections, sinusitis and otitis media than what has recently been recognized (Nuutinen et al., 1983). In recent years, the so called "immotile cilia syndrome" has been a focus of interest. In this syndrome, inadequate mucociliary function is caused by structural abnormalities in the cilia. The most typical case, observed in ciliary cross sections, is the absence of the dynein arms containing adenosine triphosphatase (Afzelius, 1976; Pedersen and Mygind, 1976).

Ciliary activity has been demonstrated to be caused by sliding of the ciliary microtubules, and its phenomenon is adenosine triphosphate-induced (Summers and Gibbons, 1971). The first studies analyzing ciliary movements were performed on sea urchin sperm flagella, protozoan cilia and mammalian sperm flagella. Dirksen and Zeira (1981) demonstrated that the movement of the cilia in the mammalian trachea and oviduct is caused by the sliding of the ciliary microtubules in a manner similar to that described for invertebrate cilia. They also proved that demembranated cilia are clearly reactivated by adenosine triphosphate (ATP).

Our knowledge about the effect of ATP on the human respiratory mucosa is very scanty. There are only three reports of experiments where the cilia of the human nasal mucosa were activated by ATP or ATPase in vitro (Forrest et al., 1979; Rossman et al., 1980; Lewis et al., 1983).
Robert et al., (1980) found out in eight patients that intranasal ATP solution decreased the ciliostatic effect of the intranasal lidocaine. Their report is the only in vivo experiment stydying the effect of ATP on the nasal mucociliary function. The activation of human respiratory cilia is apparently of great importance in the treatment of respiratory diseases. In the following preliminary study the effect of ATP on the normal nasal mucociliary function is reported.

MATERIAL AND METHODS

Sixteen adult patients (11 females and 5 males), who gave their informed consent, entered the study. The design of the study was accepted by the Ethical Committee of the Kuopio University Central Hospital. The age of the subjects ranged from 22 to 28 years with a mean age of 23.8 years. There were 13 non-smokers, one ex-smoker and two smokers who smoked 10–20 cigarettes per day. None of the subjects had any signs of acute or chronic rhinitis or sinusitis. None of them had had any kind of acute virus infection during the last two weeks. Two of the subjects had had maxillary sinusitis and one had had otitis media over three months ago. None of the subjects had any intranasal or systemic medication.
The nasal mucociliary function was measured with a radioisotopic method described earlier (Kärjä et al., 1982). The tracer used was the 99 Tc labelled human serum albumin. One drop of the tracer (0.01 ml) was placed under visual control on the floor of the nasal meatus, at least 1 cm behind the anterior end of the inferior turbinate. The transport of the tracer substance was monitored by means of a gamma camera from either side of the head at one- to three-minute intervals. The course of the tracer was documented photographically. The result was recorded in millimeters per minute. To eliminate the possible effect of the normal nasal cycle on the mucociliary transport rate, the measurement was performed on both sides of the nose. The drug tested was HR-6, which was the solution containing adenosine triphosphate in three concentrations: 0.1 mg/ml, 1 mg/ml and 10 mg/ml. A solution base not containing the active drug was used as a placebo. The subjects were randomly divided into four groups: active drug 0.1 mg/ml, active drug 1 mg/ml, active drug 10 mg/ml and placebo. After measuring the mucociliary velocity on both sides of the nose, three drops of the tested drug were applied to both sides of the nose and the nose was blowed out. After ten minutes the application of the drug was repeated, and five minutes later the nasal mucociliary function was again measured. The second measurement was performed first on that side of the nose where the mucociliary transport rate was lower. In seven patients the measurement was performed on both sides of the nose also after the drug application.

RESULTS

The measurements of the nasal mucociliary transport velocity were performed on both sides of the nose. The transport velocity of the better side ranged from 4.5 to 15.0 mm/min with a mean of 7.4 mm/min. The mucociliary transport velocity after the application of the tested drug concentrations on the side where the transport was slower, is shown in Table 1. The mucociliary transport was increased by 3.2, 2.0 and 4.3 mm/min in the groups of the active drug 0.1, 1 and 10 mg/ ml, respectively. The mucociliary transport improved only by 0.2 mm/min in the placebo group. In all active groups on the average the improvement of the velocity was 3.1 mm/min and in placebo group 0.2 mm/min (Table 2).

To eliminate the effect of the possibility that the nasal cycle is changed between the two measurements, the mucociliary transport velocity was determined on both sides of the nose in seven subjects also after the drug application. The average of the mucociliary transport rate on both sides of the nose was calculated

Table 1. Nasal mucociliary transport velocity before and after the test drug on the side of the nose with lower initial velocity.

		velocity of transport (mm/min)		
subject no.	test drug	before drug	after drug	change (mm/min)
1.	active 0.1 mg/ml	1.8	6.5	+ 4.7
2.	active 1 mg/ml	7.0	8.8	+ 1.8
3.	active 0.1 mg/ml	3.3	8.2	+ 4.9
4.	placebo	4.0	3.5	− 0.5
5.	placebo	2.7	3.9	+ 1.2
6.	active 0.1 mg/ml	6.0	6.1	+ 0.1
7.	active 1 mg/ml	10.4	10.2	− 0.2
8.	active 10 mg/ml	0	2.0	+ 2.0
9.	active 10 mg/ml	1.2	10.2	+ 9.0
10.	active 10 mg/ml	8.2	14.2	+ 6.0
11.	placebo	1.0	1.0	± 0
12.	active 1 mg/ml	9.5	9.3	− 0.2
13.	active 10 mg/ml	3.7	4.0	+ 0.3
14.	placebo	1.0	1.0	± 0
15.	active 1 mg/ml	0.8	3.6	+ 2.8
16.	active 1 mg/ml	4.8	11.4	+ 6.6

Table 2. The changes in the nasal mucociliary velocity after the drug application.

drug	N	change, average (mm/min)	
active 0.1 mg/ml	3	+ 0.1 - + 4.7	+ 3.2
active 1 mg/ml	5	− 0.2 - + 6.6	+ 2.0
active 10 mg/ml	4	+ 0.3 - + 9.0	+ 4.3
placebo	4	− 0.5 - + 1.2	+ 0.2

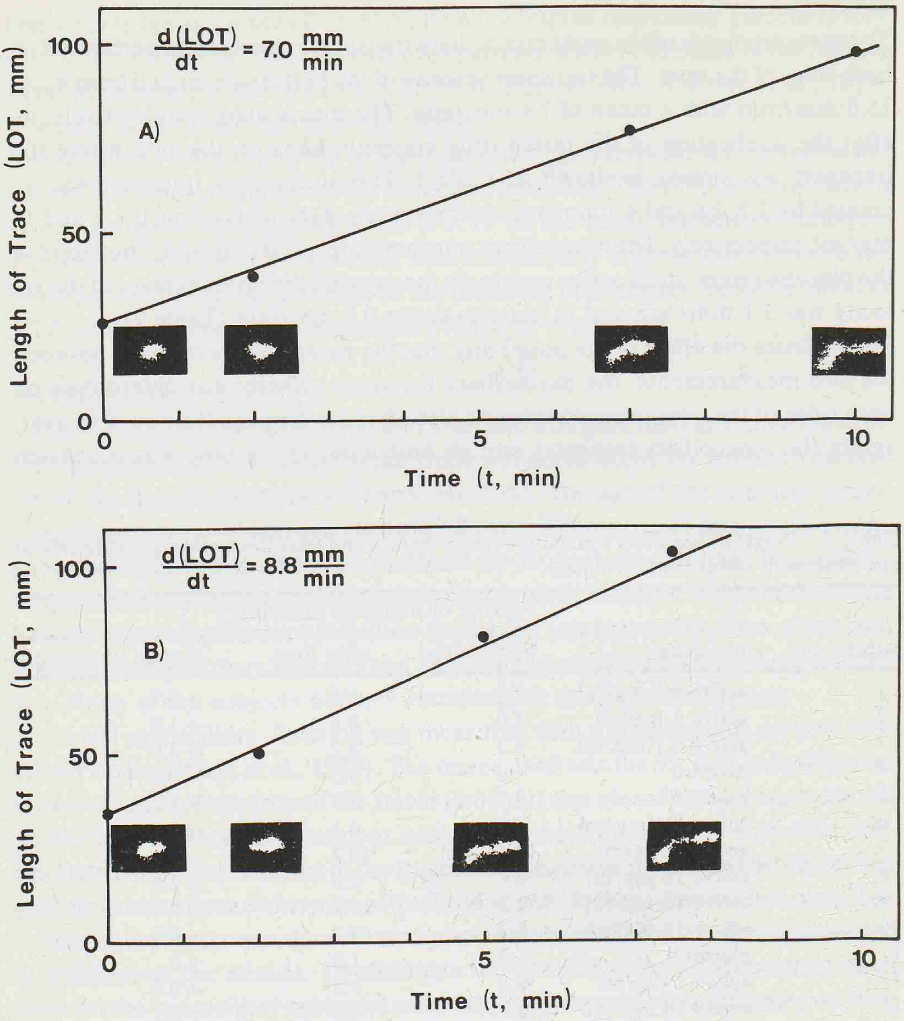

Figure 1. Length of radioactive trace (LOT) in nose and corresponding imaging time (t). Points on line are in correspondence to pictures; magnification coefficient is 6.4. Slightly improved nasal mucociliary function in the subject 2: A) before the drug, B) after the drug.

twice. Table 3 shows that in the active groups, on the average, the transport was improved from 6.0 to 8.9 mm/min. In one patient in the placebo group the transport rate was changed from 3.0 to 2.9 mm/min.

DISCUSSION

The velocity of normal nasal mucociliary function, measured with the radio-

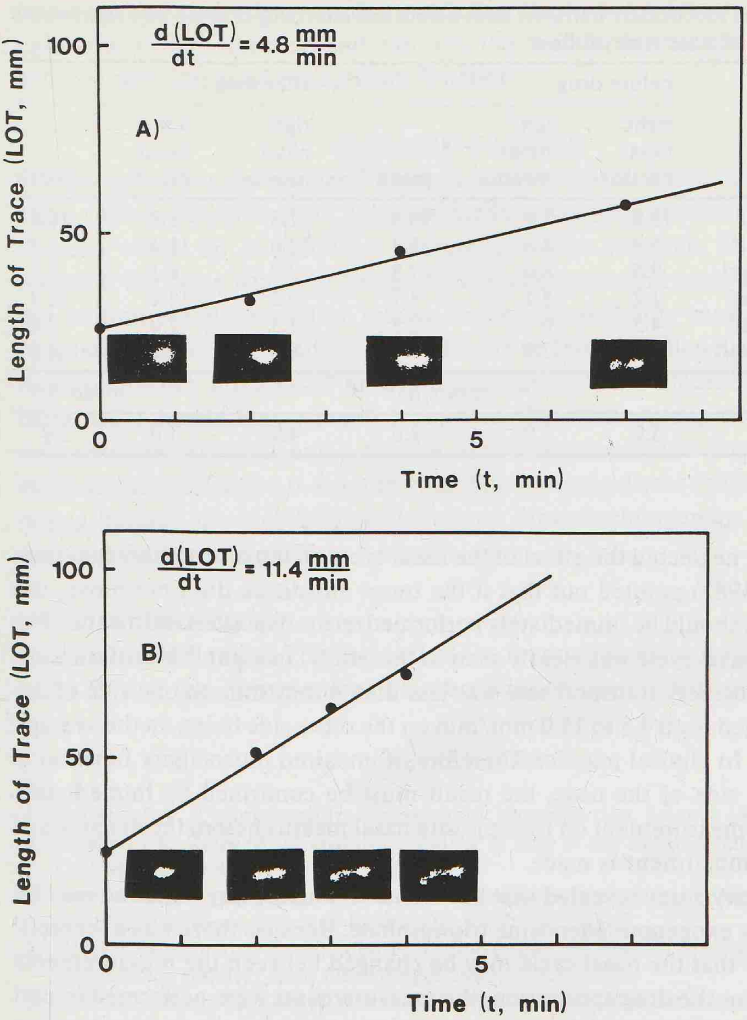

Figure 2. Markedly improved nasal mucociliary function in the case 16: A) before the drug, B) after the drug. Abbreviations, see legend for Figure 1.

isotopic methods, has been reported to be, on the average, from 5 to 7.5 mm/min (Quinlan et al., 1969; Proctor et al., 1973; Kärjä et al., 1982). In several studies it has been observed that the reproducibility of an individual measurement, on different days, is 15% to 25%, but inter-individual variation can clearly be much greater (Puchelle et al., 1979; Yeates, 1975). Also in this study there was a marked inter-individual variation in the mucociliary transport rate. Most of the authors

Table 3. Nasal mucociliary transport rates before and after drug of seven objects in whom the both sides of nose were studied.

	before drug			after drug		
drug	right nasal meatus	left nasal meatus	mean	right nasal meatus	left nasal meatus	mean
active 1 mg/ml	13.8	7.0	10.4	12.8	8.8	10.8
active 1 mg/ml	5.9	4.8	5.4	12.0	11.4	11.7
active 0.1 mg/ml	9.5	6.0	7.8	9.2	6.1	7.7
active 10 mg/ml	1.2	8.1	4.7	10.2	14.2	12.2
active 10 mg/ml	4.5	0	2.3	3.5	2.0	2.8
active 0.1 mg/ml	3.3	7.9	5.6	8.2	8.2	8.2
			mean 6.0			mean 8.9
placebo	5.0	1.0	3.0	4.9	1.0	2.9

have however neglected the effect of the nasal cycle on the mucociliary function. Kärjä et al. (1982) pointed out that if the tracer substance does not move, the measurement should be immediately performed on the opposite nasal meatus. The effect of the nasal cycle was clearly seen in this study. In eight (50%) of the subjects the mucociliary transport rate was less than 4 mm/min on one side of the nose and ranged from 4.5 to 15.0 mm/min on the other side being on the average 7.4 mm/min. In clinical practice, therefore, if impaired mucociliary function is found in one side of the nose, the result must be confirmed by immediately repeating the measurement on the opposite nasal meatus before the diagnosis of mucociliary impairment is made.

This preliminary study revealed that normal nasal mucociliary function may be accelerated by exogenous adenosine triphosphate. Because there was a theoretical possibility that the nasal cycle may be changed between the measurements before and after the drug application, the measurements were performed in part of the patients twice on both sides of the nose. Also in these cases the acceleration of the mucociliary transport by ATP was seen.

The results also show that mucociliary transport is not accelerated by ATP in all cases, especially not in those where the transport rate is faster than on the average. Also Lewis et al. (1983) showed, in vitro, that exogenous ATP or ATPase accelerated the ciliary beat frequency in some of the cilia but not constantly in all cilia. In this study the drugs were applied as nasal drops to the floor of the nasal meatus and so there may be differences in the drug distribution. This may be the explanation for the fact that the differences between the different drug concentrations are not systematic. In clinical practice a metered dosed pump is apparently the best device for the drug application.

However, this preliminary study reveals that the tested ATP solutions improve nasal mucociliary transport and indicates the need for further clinical studies in patients with impaired mucociliary function.

ZUSAMMENFASSUNG

Die Beeinflussung der nasalen Flimmerepithel-Aktivität durch das Arzneimittel HR-6 (Adenocintriphosphat, drei verschiedene Konzentrationen) und durch ein Placebo, wurde an 16 gesunden Versuchspersonen ermittelt. Die mukoziliäre Aktivität der Nase wurde in beiden Nasenhälften vor und nach Verabreichung der Prüfmittel radioisotopisch erfasst. In einer Nasenhälfte wurde die Beförderungsrate des Flimmerepithels durch das aktive Mittel in allen Konzentrationen durchschnittlich um 2,0–3,2 mm/min gesteigert; in der Placebogruppe betrug die entsprechende Steigerung 0,2 mm/min. Die Berechnung der beidseitigen mukoziliären Aktivität ergab für die aktive Substanz eine durchschnittliche Beförderungsrate von 6,0–8,9 mm/min. Die Befunde dieser Präliminaruntersuchung belegen die Notwendigkeit weiterer Untersuchungen an Patienten mit eingeschränkter mukoziliärer Aktivität.

ACKNOWLEDGEMENTS

I wish to thank Remeda Pharmaceutical Co. for providing the drug HR-6 containing ATP and the corresponding placebo solution used in this study.

REFERENCES

1. Afzelius BA. A human syndrome caused by immotile cilia. Science 1976; 193:317–9.
2. Dirksen ER, Zeira M. Microtubule sliding in cilia of the rabbit trachea and oviduct. Cell Motility 1981; 1:247–60.
3. Forrest JB, Rossman CM, Newhouse MT, Ruffin R. Activation of nasal cilia in immotile cilia syndrome. Am Rev Respir Dis 1979; 120:511–5.
4. Kärjä J, Nuutinen J, Karjalainen P. Radioisotopic method for measurement of nasal mucociliary activity. Arch Otolaryngol 1982; 108:99–101.
5. Lewis FH, Beals TF, Carey TE, Baker SR, Matthews KP. Ultrastructural and functional studies of cilia from patients with asthma, aspirin intolerance and nasal polyps. Chest 1983; 83:487–90.
6. Nuutinen J, Kärjä J, Karjalainen P. Measurements of impaired mucociliary activity in children. Eur J Respir Dis 1983; 64 (Suppl 128):454–6.
7. Quinlan MF, Salman SD, Swift DL et al. Measurement of mucociliary function in man. Am Rev Respir Dis 1969; 99:13–23.
8. Pedersen H, Mygind N. Absence of axonemal arms in nasal mucosa cilia in Kartagener's syndrome. Nature 1976; 262:494–5.
9. Proctor DF, Andersen I, Lundqvist G. Clearance of inhaled particles from the human nose. Arch Environ Health 1973; 131:132–9.
10. Puchelle E, Zahm JM, Betrand A. Influence of age on bronchial mucociliary transport. Scand J Respir Dis 1979; 60:307–13.
11. Robert J, Laurens MH, Simeons P et al. Etude du drainage mucociliaire nasal par méthode radioisotopique. Pathol Biol 1980; 28:181–4.

12. Rossman CM, Forrest JB, Ruffin RE, Newhouse MT. Immotile cilia syndrome in persons with and without Kartagener's Syndrome. Am Rev Respir Dis 1980; 121:1011–6.
13. Summers KE, Gibbons IR. Adenosine triphosphate-induced sliding of tubules in trypsin-treated flagella of sea-urchin sperm. Proc Natn Acad Sci 1971; 68:3092–6.
14. Yeates DB, Aspin N, Levison H et al. Mucociliary transport rates in man. J Appl Physiol 1975; 39:487–95.

Juhani Nuutinen, M. D.
University of Kuopio
Department of Otolaryngology
SF-70210 Kuopio
Finland