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INFLUENCE OF STEROID AEROSOL TREATMENTS ON THE CLEARANCE OF INHALED GOLD PARTICLES.

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ABSTRACT

Female Long Evans rats were used to test the hypothesis that inhaled triamcinolone acetonide accelerates the rate of clearance of particles from the lung. Three groups of animals inhaled a radioactive gold aerosol, which functioned as a tracer of respiratory tract clearance, and then were subjected to various inhalation treatments. The group treated with triamcinolone acetonide aerosol showed a significant acceleration in the rate of early clearance, but the total amount of tracer particles cleared in the first day was not significantly increased. Inhaled triamcinolone acetonide appears to accelerate the translocation of foriegn particles from small airways to larger ones, but stimulation of clearance does not appear to be a large effect.

INTRODUCTION

Aerosolized cortisones are being used increasingly in the medical field for treatment of severe asthmatics. One of the more promising is triamcinolone acetonide (9-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione), a water insoluble synthetic analog of cortisol (1). While reported to be effective, the mode of action for relief of symptoms is uncertain (2). It is possible that a mechanism may be through enhancement of removal of irritants by stimulation of mucociliary clearance. In any case, the possible influence of a medicinal aerosol on respiratory tract clearance should be investigated empirically.

Inhaled foriegn material is removed from the lungs by several pathways, including cough, mucociliary clearance, endocytosis, and dissolution of material (3). The mucociliary transport system works through the action of ciliated epithelial cells of the trachea and bronchi on mucus produced by goblet cells and mucus glands. Clearance of particles deposited in the tracheobronchial region is conveniently described in terms of one or two exponential functions (3,4,5). Particles deposited in the trachea and ciliated bronchi of mammals are removed by ciliary action with half times ranging from minutes to tens of hours (3).

In this experiment, the rate of mucociliary clearance was measured in several groups of rats, including a group which received inhalation treatments of triamcinolone acetonide aerosol. The purpose was to test the hypothesis that the steroid might increase the rate of mucociliary clearance.

MATERIALS AND METHODS

A tracer aerosol of radioactive ^{198}Au microspheres was generated in the center of a 20 liter exposure chamber by means of an exploding wire technique (6). This method of generation produced an aerosol which consisted of small agglomerates of radioactive gold particles, suitable as an indicator of mucociliary clearance.

Female Long Evans (hooded) rats were placed in metal body restrainers and uniformly distributed in three tiers around the exposure chamber, with only their noses protruding into the chamber. A multi-stage cascade impactor (7) was employed to measure the Mass Median Aerodynamic Diameter (MMAD) of the gold tracer while it was being inhaled by the rats. The MMAD was 1.45 micrometers, with a geometric standard deviation of 1.4. The average physical diameter of the individual primary gold particles, as determined by electron microscopy, was 0.03 micrometers, with a standard deviation of 1.2. Analysis of the lung clearance curves indicated that about half of the gold aerosol (by mass) was deposited in the ciliated regions of the lungs, and that the remainder was deposited in the alveolar regions.

The inhaled gold particles established a lung burden of insoluble radioactive particles which was measured at intervals via external radiation detectors. This was accomplished by placing the animals in

plastic restrainers under a 7.62 cm diameter NaI crystal scintillator, which was collimated with lead bricks in such a way that the lung regions of the rats were under the crystal face. The detector assembly was located in a steel vault to decrease background radiation levels. Output of the detector was fed via coaxial cable to a Baird Atomic Spectrometer, Model 530 (Baird Atomic Corporation, Cambridge, Massachusetts). The Gain and window controls were optimized for counting the 0.411 MeV gamma photon emitted by the ^{198}Au.

The animals were divided into three groups. A group of six animals was exposed to the gold aerosol and the activity in their lung regions was counted according to a fixed schedule. This control group provided data which allowed the base line rate of mucociliary clearance from the lung to be determined.

The second group consisted of six animals and functioned as the experimental group. After inhaling the radioactive gold and having their lung regions counted for initial activity, this group received triamcinolone acetonide aerosol treatments for 20 minutes at six hour intervals, for a total of 13 treatments. The triamcinolone was suspended in 0.9% NaCl solution, and was aerosolized by a DeVilbiss Model 900 ultrasonic nebulizer (DeVilbiss Co. Somerset, Pa). The manufacturers specifications for this aerosol generator give a particle diameter range of between 1 and 8 micrometers, with the most common particle being approximately 3 micrometers in diameter. The dose of triamcinolone retained by the rats was calculated to be 28 ± 5 μgm per treatment.

The third group consisted of four animals. These rats received the same gold tracer aerosol as the other two groups, and were given 13 ultrasonic nebulizer treatments of 0.9% NaCl aerosol. This group functioned as a procedural control to evaluate any effects due to ultrasonic NaCl treatments per se, without the triamcinolone preparation present.

The lung regions of each animal were counted immediately after inhalation of the gold to establish the initial activity, and then were counted according to the following schedule:

Every hour for the first 12 hours;
every 2 hours for the next 20 hours;
every 4 hours for the next 16 hours;
every 6 hours for the next 24 hours;
every 24 hours for the last 48 hours.

After every count, background was subtracted and the data were corrected for radioactive decay of the short half life gold aerosol. The results for each group were expressed as percentages of the initial activity in the lungs. Combined data for each group were used to draw clearance curves, which were then fit to the two best exponential components. Slopes and intercepts of these two exponential curves were compared among the three groups. The slopes were assumed to measure clearance rates, while the intercepts were associated with the relative amount of gold that was cleared at each determined rate. The long term slope is generally believed to represent elimination of material initially deposited in the alveolar spaces. The short term mechanism is

assumed to represent mucociliary clearance of particles originally deposited in the tracheobronchial tree (8).

RESULTS

Analysis of the data indicated that each group of animals did indeed eliminate the tracer ^{198}Au microparticles from their lungs by two mechanisms. This is demonstrated by two seperate components of a biphasic curve when the data are plotted on semi-log paper. The long - term clearance observed from 15 hours post exposure to the end of the experiment (118 hours) appears to approximate a straight line for all three groups of animals. By extrapolating these lines back to time t = 0, and subtracting them from the experimental data, the short - term component is obtained. Interest was focused primarily on the short - term (mucociliary) clearance phenomenon.

Clearance rates for each animal are listed by group in table 1, while Figures 1 and 2 graphically demonstrate the particle clearance patterns for all three groups. The short term removal half - time average for the untreated (control) group was 3.1 hours, while the mucociliary clearance rate in the group treated with 0.9% NaCl aerosol was 3.3 hours. These values do not differ statistically, which implies that ultrasonic nebulizer treatments of 0.9% NaCl aerosol had little or no effect on mucociliary clearance of particles in these animals.

The half - time for mucociliary clearance in the experimental group, however, was 2.3 hours, approximately 25% faster than the other two groups. Although this difference between the cortisone and saline or control groups is not large, there was probably ($p < 0.005$) a

Table 1

Mucociliary Clearance Intercepts and Rates

Group	Short Term Intercept	Effective Clearance Half-Time (Hours)
Control Group (Un-treated)	63.0	3.6
	52.1	2.8
	48.3	3.8
	45.8	2.8
	47.6	3.8
	45.6	2.5
Mean Value	50.4	3.2 ± 0.6
Averaged Points Value	47.1	3.1
Procedural Control Group (0.9% NaCl Treatments)	52.5	2.3
	34.5	3.1
	52.7	3.6
	50.1	4.0
Mean Value	47.5	3.3 ± 0.6
Averaged Points Value	60.1	3.3
Experimental Group (Triamcinolone Treatments)	44.5	2.5
	42.4	2.9
	43.4	2.2
	51.8	2.3
	47.3	1.9
	42.3	2.3
Mean Value	45.3	2.4 ± 0.3
Averaged Points Value	65.4	2.3

Clearance Curve Components, Derived From Experimental Data. Averaged Points Values Represent Regression Analysis Curves From Averaged Group Data Points.

transient stimulation of clearance over that of non-treated animals. It also appears that the triamcinolone acetonide treatments may have briefly slowed clearance during the first four hours after deposition of the labeled aerosol, although this interpretation rests on isolated data points and is not statistically supportable.

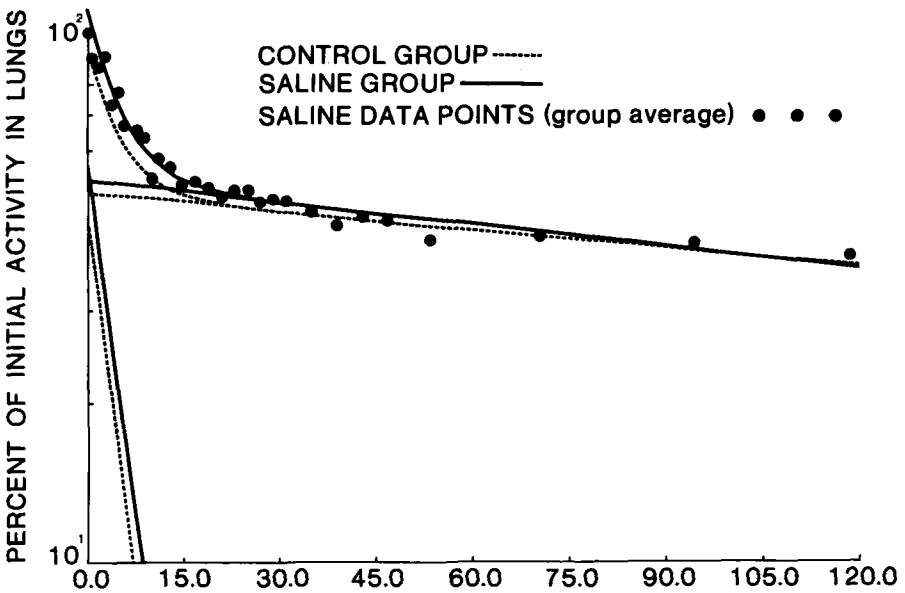

FIGURE 1

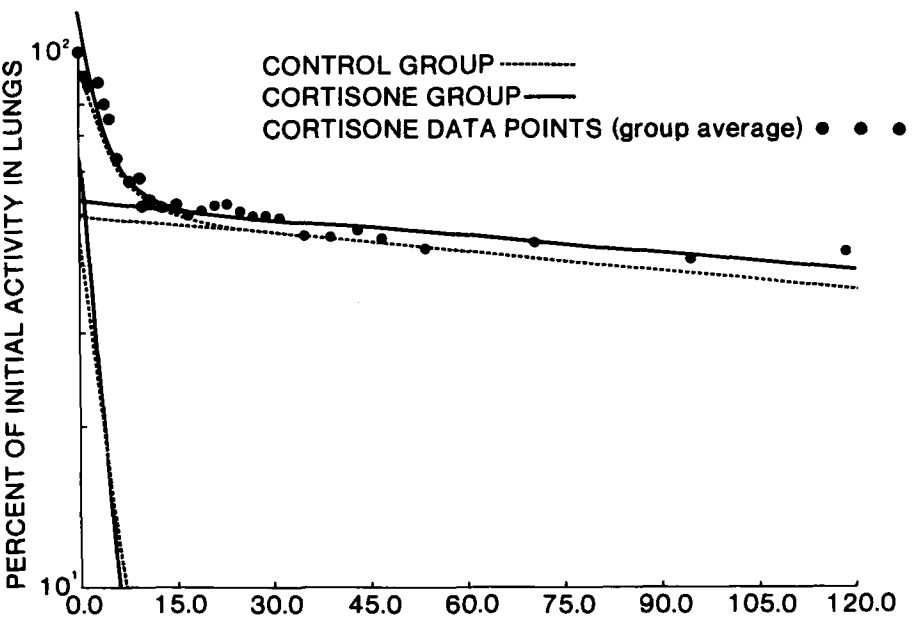

FIGURE 2

The amount of uncleared label remaining at the end of the experiment (118 hours) is slightly higher for the triamcinolone group than for the untreated control group. This difference is not significant at the 95% confidence level.

DISCUSSION

The triamcinolone acetonide (Kenalog - 10, E. R. Squibb and Sons, Inc. Princeton, New Jersey) was suspended in a solution of isotonic NaCl, with 0.9% benzyl alcohol added as a preservative; 0.75% sodium carboxymetholcellulose and 0.04% polysorbate 80 were also present. Small amounts of sodium hydroxide or hydrochloric acid may have been present to adjust the pH of the solution. Though such additives may have had an influence on the treatment response, their action was unlikely to have been significant in view of their small concentrations.

The triamcinolone may have acted as an irritant to the lungs, and any aerosol could have a similiar effect. This possibility would be substantiated if a difference had been appearant in the short term clearance rates between the control and procedural control (0.9% NaCl) groups. There was, however, no statistically significant difference in the short term removal rates in these two groups.

The steroid aerosol itself may have had an effect on the mucous layer in the lung, increasing the efficiency of mucociliary clearance. While this could be the case, previous research on the effect of viscosity of mucus on clearance rates indicates that changes in viscosity tend to slow rather than accelerate particle clearance (9). This appears to occur whether the mucus is thicker or thinner than normal.

The triamcinolone may have had a topical effect on the cilia or ciliated cell membranes. It is conceivable that the efficiency of the ciliary beat could be affected by triamcinolone, although no data other than that already given supports this speculation.

CONCLUSION

In summary, it appears that triamcinolone acetonide aerosol has a transient but observable stimulating effect on clearance of inhaled particles by the mucociliary transport system. Although the statis - tical analysis (t test) of the data indicated a high degree of accep-- tance of the hypothesis that treatment enhanced clearance (99.5%), the effect was not large. That this effect plays a major role in the re - lief of asthmatic symptoms does not seem likely, but the data presented do not preclude the possibility that treatment produces a redistri - bution of mucociliary clearance patterns within the lung.

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REFERENCES

(1) Lertzman, M. M., and Cherniak, R. M: Am Rev Respir Dis, 114, 1145 - 1165, (1976)
(2) Williams, M. H. Jr., Kane, C., and Shim, C. S: Am Rev Respir Dis, 109, 538 - 543, (1974)
(3) Task Group On Lung Dynamics: Health Phys, 12, 173 - 207, (1966)
(4) Adler, K. B., Wooten, O., and Dulfano, M. J: Arch Environ Health, 27, 364 - 369, (1973)
(5) Brain, J. D., and Valburg, P. A: Arch Environ Health, 28, 1 - 11, (1974)
(6) Phalen, R. F: Aerosol Sci, 3, 395 - 406, (1972)
(7) Mercer, T. T., Tillery, M. I., and Newton, G. J: Aerosol Sci, 1 9 - 15, (1970)

(8) Albert, R. E., Lippmann, M., Spiegelman, J., Liuzzi, A., and Nelson, N: Arch Environ Health, 14, 10 - 15, (1967)
(9) Barnet, B., and Miller, C. E: Ann N Y Acad Aci, 130, 891 - 901, (1966)