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Effect of Bronchopulmonary Lavage on Lung Retention and Clearance of Particulate Material in Hamsters

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Hamsters were exposed to an aerosol of fused aluminosilicate particles (FAP) labeled with ^{57}Co. Three groups of animals were given bronchopulmonary lavage, beginning at either 1 week, 1 month, or 6 months after exposure. Each treated group was lavaged eight times over a period of 25 days. Each lavage involved 10 saline washes of the lungs. For each group, about 60–70% of the body content of ^{57}Co at the start of lavage treatment was removed; nearly half of this was recovered in the first two lavages. A positive correlation was demonstrated between the macrophage content and ^{57}Co activity of the washings. The subsequent fractional clearance rate of ^{57}Co from lavaged animals was not significantly different from that in a group of untreated control animals.

Introduction

Bronchopulmonary lavage has been used as a clinical procedure for the treatment of obstructive lung diseases in man for at least 20 years (*1–4*). The technique has been extensively studied in baboons, dogs, and rodents as a possible treatment to reduce lung deposits of insoluble radioactive particles after inhalation (*5–11*). For example, Brightwell and Ellender (*6*) found that repeated lavage of hamsters during the first 4 weeks after inhalation of plutonium dioxide (PuO_2) removed 90% of the initial lung burden. Lavage has been used on one occasion in the United States to remove ^{239}Pu from the lungs of a worker after accidental inhalation (*12*). Two lavages of the right lung and one lavage of the left lung were carried out, and 13% of the estimated total lung burden was removed. Lavage, together with diethylenetriamine pentaacetic acid therapy, removed one-third of the total lung burden.

Measurements on lavage fluid removed from the lungs of rats, hamsters, dogs, and baboons have shown a correlation between the number of macrophages and the amount of activity removed (*6,10,13–15*). Macrophages engulf the inhaled radioactive particles rapidly after their deposition in the lung. In baboons, Nolibé et al. (*10*) showed that 1 day after the inhalation of PuO_2, 96% of particles were taken up by macrophages.

Animal experiments examining the long-term clearance of α-emitting actinides from the lung have shown that high initial lung deposits can result in reduced lung clearance (*16–18*). In addition, the efficiency of lavage in removing such materials from the lung has been shown to decrease with time.

Reduced clearance of particles containing α-emitters, and their reduced availability for removal by lavage, may be due to radiation-induced pathological changes in the lungs (*19,20*). Alternatively, the movement of macrophages within the lung may reduce their availability for normal clearance and for lavage. In this study, hamsters were exposed by inhalation to an aerosol of fused aluminosilicate particles (FAP) labeled with the γ emitter, ^{57}Co. The γ activity was set to give a cumulative radiation dose of less than 0.5 Gy, which would not be expected to cause lung damage or affect macrophage function and pulmonary clearance mechanisms (*18*). The efficiency of lavage treatments starting at different times after inhalation was compared.

Materials and Methods

Animals and Preparation of ^{57}Co-Fused Aluminosilicate Particles

Male DSN hamsters were used (Intersimian Ltd, Milton, Oxon, UK). They were between 80 and 100 g at the time of exposure and were allowed food and water *ad libitum*.

Monodisperse ^{57}Co-labeled FAP were prepared in a single batch using the technique described by Bailey and Strong (*21*). Briefly, a suspension of montmorillonite clay (0.3 mg/mL) was labeled with ^{57}Co (half-life 271 days) by ion exchange; uniform droplets of the suspension were generated with a spinning top (*22*), dried, and fired at 1200°C. The resulting particles were collected on a Millipore filter (0.22 μm). Electron micrographs of the particles were measured to obtain the distribution of geometric mean diameters. A log-normal distribution fitted to the results using a maximium likelihood method (*23*) gave a count

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median diameter of 1.32 μm, with a geometric standard deviation of 1.15. Assuming a specific gravity of 2.26 g/cm^3 (*23*), this would represent an activity median aerodynamic diameter of 1.41 μm.

Exposure of Hamsters to ^{57}Co-Fused Aluminosilicate Particles

The particles were administered to hamsters by nose-only inhalation (*24*). A suspension of the particles in 10 mL ethanol was dispersed using a Retec X70/N compressed air nebulizer (Retec Development Laboratory, Portland, Oregon), operated at 1.41 kg/m^2 (20 psi) giving an output of 6 L/min. The reservoir of the nebulizer was ultrasonically agitated to prevent the settling of particles. The exposure continued for 30 min. Cascade impactor samples (*25*) and filter samples were taken during the exposure to confirm that no change in the size distribution of the particles had taken place during the exposure.

Radiochemical Analysis

Groups of three hamsters were killed at 30 min, 7 days, 30 days, 200 days, and 365 days after exposure. The lungs, thoracic lymph nodes, liver, spleen, kidneys, head, carcass, and pelt were analyzed separately. The samples were dry-ashed at 500°C, dissolved in 4 M HNO_3 to give homogeneous samples of equal volume, and counted using an automatic gamma counter (Intertechnique CG-4000, 78370, Plasir, France). Calibrated standards were also counted (Amersham UK, Bucks) and used to correct for radioactive decay of ^{57}Co.

Whole-Body Counting

Whole-body counting was carried out on four groups of five hamsters at intervals from 7 days after exposure; the initial delay was to allow time for the clearance of particles from the nose and pelt. The 122 keV emissions from the ^{57}Co were measured using a large NaI (Tl) well detector (Quartz et Silice, Paris) coupled to a multichannel analyzer (Canberra Industries Inc., Faringdon, Oxon, UK). Measurements were compared with those from calibrated standards (Amersham UK, Bucks) to correct for radioactive decay and counting efficiency. The standards were placed in the lung position of a hamster phantom to ensure reproducibility of counts. Three of the groups were lavaged and the fourth group acted as a control.

Bronchopulmonary Lavage

The first group was lavaged on days 7, 12, 15, 19, 22, 26, 30, and 34 (1-week group); the second on days 30, 34, 37, 40, 44, 48, 51, and 55 (1-month group), and the third on days 201, 205, 208, 212, 215, 219, 222, and 226 (6-month group).

The technique of bronchopulmonary lavage has been described fully by Brightwell and Ellender (*6*); a brief description is given here. Hamsters were anesthetized using 3% halothane in oxygen. A polythene tube (external diameter 1.3 mm) was passed through the mouth into the trachea, and 2 mL of saline at 37°C was instilled into the lungs. The saline was then removed by suction and drainage. This procedure is referred to as a lung wash. Ten lung washes, each with a fresh aliquot of saline, were performed on each animal during one bronchopulmonary lavage. The animal was then resuscitated using oxygen if necessary, although spontaneous respiration was usually reestablished without aid.

Cell Counts

Cell counts were carried out on the lung washes from the first group of animals (1-week group). For each lung wash, an aliquot of the fluid recovered from the lungs was added to an equal volume of 2% acetic acid containing 50 mg/L of gentian violet. Individual wash volumes were recorded to enable calculation of total macrophage numbers. Gentian violet distinguished macrophages from epithelial cells and leukocytes. Cells were counted in a hemocytometer, and the macrophage content of each lung wash was then determined.

Results

Table 1 shows the distribution of the ^{57}Co in hamsters at intervals from 30 min to 1 year after exposure to ^{57}Co-FAP. The results are expressed as a percentage of total retained activity at each time. The high values obtained for retention of ^{57}Co in the head, pelt, and carcass at 30 min after exposure are attributable to nasal deposition and surface contamination. Retention in the lungs at this time accounted for 32% of total activity. However, from 7 days after exposure, the lungs accounted for 83–98% of total activity, with low levels of activity in other tissues.

The retention of ^{57}Co in control and lavaged hamsters up to 1 year after exposure, as measured by whole-body counting, is shown in Figure 1. The results are expressed as a percentage of the activity measured at 7 days after exposure; the observed

Table 1. Tissue distribution of ^{57}Co in hamsters after inhalation of ^{57}Co-fused aluminosilicate particles.[a]

	% Total retention at days				
Tissue	0	7	30	200	365
Lung	31.5 ± 7.6[b]	83.0 ± 4.0	92.1 ± 1.0	97.18 ± 0.7	90.3 ± 7.3
Trachea	0.86 ± 0.29	1.19 ± 0.34	1.6 ± 0.85	1.24 ± 0.45	5.72 ± 0.52
Thoracic lymph nodes	0.003 ± 0.001	0.03 ± 0.02	0.04 ± 0.03	0.25 ± 0.20	0.48 ± 0.36
Liver	0.52 ± 0.11	0.41 ± 0.09	0.31 ± 0.07	0.09 ± 0.01	0.45 ± 0.36
Kidneys	0.24 ± 0.13	0.28 ± 0.11	0.04 ± 0.005	0.01 ± 0.005	0.001 ± 0.001
Spleen	0.02 ± 0.02	0.07 ± 0.04	0.001 ± 0.002	0.006 ± 0.004	0.001 ± 0.001
Head	2.55 ± 1.20	1.07 ± 0.23	0.63 ± 0.23	0.36 ± 0.06	0.67 ± 0.18
Carcass	13.6 ± 6.0	1.35 ± 0.74	0.46 ± 0.09	0.34 ± 0.19	1.71 ± 1.45
Pelt	50.7 ± 13.0	11.8 ± 4.1	4.85 ± 1.24	0.72 ± 0.17	0.67 ± 0.12

[a]Results are means ± SE; $n = 3$.

[b]The initial lung deposit was 21.6 ± 11.4 kBq.

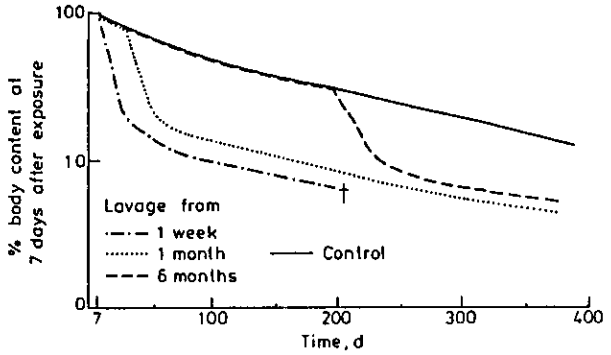

FIGURE 1. The lung retention of ^{57}Co-fused aluminosilicate particles (FAP) in control and lavaged hamsters. Body content is largely due to ^{57}Co-FAP retention in lungs. (†) One animal remaining after this time; results not shown.

clearance can therefore be taken to be largely due to the loss of activity from the lungs. For control animals, the long-term retention from day 7 can be represented by an exponential function with a half-time of 140 days. For lavaged animals, multiple regression analysis of the data for retention after lavage showed that the rates of clearance in each case were not significantly different ($p < 0.05$) from that in controls.

Table 2 compares the effectiveness of lavage started at 1 week, 1 month, and 6 months after exposure. Although proportionately less of the initial activity was removed by lavage at later times, removal as a percentage of the activity retained at the beginning of lavage was similar, at about 60–70%.

Macrophage counts and ^{57}Co measurements were carried out on aliquots of lavage fluid from the 10 individual washes, for each of the 8 lavages of the first group of animals (lavaged at 7 days onward). The total number of macrophages removed was estimated to be about 10^8 for each animal. In each case, about 65% of the macrophages removed by each lavage were contained in washes 2–5. Figure 2 shows the relationship between the macrophage and ^{57}Co content of individual washes, expressed as a percentage of the totals removed for each animal. A high degree of correlation is shown (regression coefficient = 0.98).

Table 2. Effectiveness of bronchopulmonary lavage in removing ^{57}Co-fused aluminosilicate particles from hamster lung.

Time of lavage after inhalation, days	No. of animals	Lavage number	% Removal of: Body content at 7 days[a]	% Removal of: Body content at start of lavage
7[b]	5[c]	1	16.6±3.0[d]	16.6±3.0
	4	2	16.9±2.8	16.9±2.8
	4	3	9.8±1.6	9.8±1.6
	4	4	11.5±1.4	11.5±1.4
	4	5	4.4±0.7	4.4±0.7
	4	6	4.3±1.6	4.3±1.6
	3	7	2.5±0.9	2.5±0.9
	3	8	1.0±0.3	1.0±0.3
	3	Total	67.3±3.7	67.3±3.7
28	5	1	11.4±3.0	15.3±4.1
	5	2	9.0±2.1	12.2±2.9
	5	3	6.5±1.7	8.6±2.2
	4	4	2.8±1.0	3.9±1.5
	4	5	6.3±1.0	8.1±1.1
	4	6	5.2±1.2	6.7±1.4
	4	7	2.6±0.5	3.4±0.6
	4	8	2.5±0.6	3.2±0.7
	4	Total	47.3±5.1	62.5±6.8
180	5	1	7.6±3.4	21.8±6.5
	5	2	5.0±1.3	15.7±1.6
	5	3	1.7±0.7	5.1±1.1
	5	4	1.6±0.4	5.5±0.9
	5	5	2.1±0.9	5.9±1.8
	4	6	2.3±1.0	5.9±1.9
	4	7	1.3±0.3	3.9±0.9
	4	8	1.4±0.7	4.2±2.2
	4	Total	26.1±5.7	69.2±6.3

[a]Body content is largely due to ^{57}Co-fused aluminosilicate particle retention in lungs (see Table 1).
[b]For each group, lavage was carried out eight times over a period of 25 days.
[c]Some animals failed to recover from anesthesia.
[d]Means ± SE.

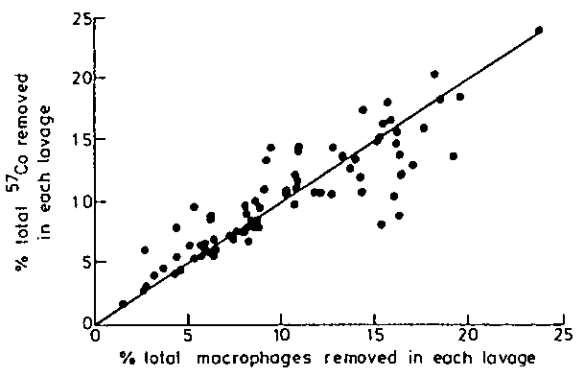

FIGURE 2. The macrophage and ^{57}Co content of lavage fluid.

Discussion

Preparations of ^{57}Co-FAP have been shown to be of low toxicity, and at cumulative doses of < 0.5 Gy caused no observable damage to the lungs of rats over a period of 640 days after inhalation (*18*). Cobalt leached from FAP and translocated to blood has been shown to be rapidly excreted, with only low levels of retention in body tissues (*26,27*). The results obtained in the present study for the distribution of ^{57}Co in hamsters showed that, after the initial clearance of activity from the nose and pelt, the lungs accounted for 83–98% of the total body activity up to 1 year after inhalation. On this basis, whole-body activity was used as a measure of lung retention of ^{57}Co-FAP. As shown previously for rats (*26,27*) and hamsters (*27*), movement of particles to and retention in thoracic lymph nodes was low, accounting for 0.03–0.48% of body activity from 7 days to 1 year after exposure. The low values obtained for retention in other tissues are consistent with reported results for rats (*26,27*) and hamsters (*27*).

Whole-body measurements of the ^{57}Co activity of hamsters from 7 days to 365 days after inhalation of ^{57}Co-FAP indicated that retention in the lungs decreased to about 20% of the initial lung deposit over this period. This appears to be reasonably consistent with the results obtained by Bailey et al. (*26*), which showed retention in hamsters at 300 days after inhalation of FAP to be 12% of the initial lung burden on day 1. Considerable species differences in the lung clearance of FAP have been demonstrated. For example, Snipes et al. (*27*) reported values of retention after 1 year of 48, 3, and 4% in dogs, rats, and mice, respectively.

Bronchopulmonary lavage was carried out on three groups of hamsters, beginning at 1 week, 1 month, and 6 months after ex-

posure. In each case, animals were lavaged 8 times over a period of 25 days, and each lavage involved 10 saline washes of the lungs. For each group, 60–70% of the activity present at the time of the first lavage was removed. This finding contrasts with reports of decreasing efficiency of lavage for the removal of lung deposits of PuO_2. Thus, Nolibé (*28*) showed that for rats with an initial lung deposit of 3.7 kBq of $^{239}PuO_2$, 55% of the lung content could be removed by lavage 4 days after inhalation, decreasing to 45% after 88 days. In animals with an initial lung deposit of about 37 kBq, a similar proportion was removed at 4 days, but only 20% after 35 days. Sanders et al. (*29*) have shown a similar decrease in the efficiency of lavage in rats with initial lung deposits of about 67 kBq of $^{239}PuO_2$. It would appear, therefore, that the reduced availability of $^{239}PuO_2$ for lavage is due to radiation damage and that inert particles remaining in the lungs contained within macrophages do not become less available with time.

Some workers have found evidence that lavage not only mechanically removes inhaled particles from the lung but also leads to mobilization of some of the remaining particles. For example, dogs lavaged after zirconium dioxide (ZrO_2) inhalation (*11*) have shown an enhanced pulmonary clearance of ZrO_2 between successive lavages. This effect was not seen in this experiment; similar rates of clearance were being observed in lavage and control animals.

In conclusion, it appears that bronchopulmonary lavage is capable of removing a similar proportion of alveolar macrophages containing inert particles, independent of the delay after intake. For radiotoxic particles such as PuO_2, however, radiation damage to the lung leads to the accumulation of fibrotic tissue around aggregates of macrophages containing activity. This in turn leads to a reduced avaliability of the macrophages (and particles) for removal and the impairment of mechanical clearance (*30*). Therefore, delay in starting the lavage procedure could make remedial action less effective and lead to greater cumulative absorbed dose to the lung tissue.

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