Talc Preparations Used for Pleurodesis Vary Markedly From One Preparation to Another

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Talc Preparations Used for Pleurodesis Vary Markedly From One Preparation to Another*

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Background: **At the present time, talc is the one of the agents most commonly used for the production of a pleurodesis. However, there have been several recent reports of acute pneumonitis developing after the intrapleural administration of talc. The incidence of pneumonitis has varied markedly from center to center.**
Objective: **To compare the physical characteristics of talc used for the production of pleurodesis in various localities.**
Design: **Eight talc preparations (four from the United States, and one each from Brazil, France, Spain, and Taiwan) were analyzed for the distribution of the particle size and the type and amount of impurities.**
Measurements: **The physical characteristics of the talc specimens were determined using radiograph diffraction and scanning electron microscopy.**
Results: **The mean and median particle size varied by more than a factor of three among the eight different talc preparations. In addition, the impurities of the different talc preparations were quite varied.**
Conclusions: **We conclude that there is marked variation in the physical characteristics of the talc preparations used intrapleurally for the production of a pleurodesis. We speculate that different incidences of acute pneumonitis at various centers after intrapleural administration of talc may be due to differences in the physical characteristics of the talc preparations used for pleurodesis.**
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Key words: pleura; pleural effusion; pleurodesis; pneumothorax; talc

At the present time, talc is one of the agents most commonly used for producing a pleurodesis in patients with either a spontaneous pneumothorax or a recurrent pleural effusion. There have been several reports of the ARDS occurring after talc is placed intrapleurally either as a slurry[1–3] or as an insufflated powder.[4,5] Interestingly, most patients who have developed ARDS following talc administration have received talc from the United States. Two large series from Israel[6] and Europe[7] reported no instances of acute respiratory distress.

It has been speculated that the acute lung injury is secondary to the extrapleural dissemination of the talc particles.[8] In the report of Milanez Campos and associates,[4] the talc from Brazil used in the study was found disseminated throughout the body of one patient after insufflation. Kennedy and associates[8] reported that talc (Standard Chemicals; Chicago, IL) was found outside the pleural space in a substantial fraction of rabbits that were administered talc slurry. Werebe and coworkers administered talc slurry (the Brazilian talc used in the present study), 10 or 20 mg, intrapleurally to 40 rats and demonstrated that talc particles were found in both lungs, the chest wall, the liver, the kidney, the spleen, the heart, and the brain of all animals at 24 h and 48 h after injection.[9]

The varying prevalence in different countries of acute respiratory distress following talc intrapleurally suggests that the syndrome might be dependent on the talc preparation. However, there are no pub-

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lished data on the physical and chemical characteristics of the various talc preparations used for pleurodesis. The purpose of the present study was to compare the composition and mean particle size of talc preparations used in various countries to produce pleurodesis. We hypothesized that there would be wide variations in the mean particle size and the impurities in the talc preparations obtained from the various sources.

Materials and Methods

Talc was obtained from four different suppliers in the United States: talc A (Sigma Chemicals; Saint Louis, MO), talc B (Malinckrodt; Chesterfield, MO), talc C (J.T. Baker; Phillipsburg, PA), and talc D (Integra Chemical; Renton, WA); and from one supplier each in Spain (Luzenac talc; Distalc; Barcelona, Spain), France (Luzenac Europe; Toulouse, France), Taiwan (Merck Taiwan LTD; Taipei, Taiwan), and Brazil (Xilolite; Sao Paulo, Brazil). The particle size distribution was determined for each talc preparation using a Laser Mastersizer/E (Malvern Instruments; Malvean, England). Each of these talc preparations has been used clinically for pleurodesis. A sample with a total weight of 150 mg was analyzed by introducing it into a recipient well provided with an agitator and containing distilled water. Optimal dispersion of the talc was obtained by applying ultrasound to the suspension. Variables measured included the particle-size distribution (mean, median, 10th percentile, and 90th percentile) and the specific surface area (meters squared per gram).

The specific surface area is obtained with the following formula:

$$Sw = 6/\rho \times Dm$$

where Sw is the specific surface area, ρ is the density, and Dm is the specific surface area diameter.[11]

The crystalline phases present in the different talc specimens were determined using radiograph diffraction with a Siemens D500 analyzer (Siemens; Karlsruhe, Germany) coupled to a graphite monochromator for Cu K-alpha radiation. For the analysis, talc was placed in a plastic receptacle with a volume of 1.1 mL. Values reported are the intensity of the peak measured in counts per second.

In order to iconographically illustrate the study, some samples were studied by scanning electron microscopy (Phillips 500; Phillips; Eindhoven, Netherlands) fitted to an energy-dispersive radiograph analyzer. These samples were pressed to double-sided carbon adhesive discs affixed to carbon scanning electron microscopy stubs. The energy-dispersive radiograph analyzer permits the identification of the elemental composition of particles detected by scanning electron microscopy.

Statistical Analysis

The talc sizes are presented as the mean diameter, the median diameter, the 10th percentile, and the 90th percentile. The correlation between the mean particle size and specific surface are was analyzed via the Pearson product moment correlation.

Results

There was marked variation in the distribution of the particle sizes from one talc preparation to another (Table 1). The mean particle sized ranged from 10.8 μm for one of the talcs from the United States to > 30 μm for the talcs from France and Taiwan. Similarly, the medium particle size ranged from 7.8 μm for the one talc from the United States to 31.3 μm for the talc from France. Similar wide variations were demonstrated in the 10th and 90th percentiles for the different talcs. The differences in the size of the talc preparations are readily appreciated when the talc particles in Figure 1, *top* (US talc A) are compared with those in Figure 1, *bottom* (French talc).

The specific surface area is the total surface area of all the particles per gram of a material. It is seen that there is a nearly fivefold variation in the specific surface area of the different talcs (Table 2). There was a close inverse relationship between the mean particle size and the specific surface ($r = -0.94$; $p < 0.001$).

There was also a marked variation in the impurities present in the different talc preparations (Table 2). All four of the talcs from the United States were contaminated by quartz (SiO_2) and kaolinite ($2[Al_2Si_2O_5(OH)]_4$), three were contaminated by dolomite ($CaMg[CO_3]_2$), and one was also contaminated by chlorite ($[Mg,Fe,Al]_6[(SiAl)_4O_{10}]\ [OH]_8$). The talc from Spain was the only one that had more than trace contamination by calcite ($Ca\ CO_3$), while only the talc from Brazil was contaminated by forsterite ($MgSiO_4$).

Table 1—*Distributions of Particle Sizes of Various Talc Preparations*

Talc Source	Mean Diameter, μm	Median Diameter, μm	10th Percentile, μm	90th Percentile, μm	Specific Surface Area, m^2/g
US talc A	10.8	7.8	2.4	22.7	0.53
US talc B	19.4	13.2	3.2	46.8	0.30
US talc C	20.1	13.5	3.1	49.5	0.31
Spain	20.1	14.8	3.7	45.7	0.27
US talc D	20.4	13.9	3.1	49.4	0.30
Brazil	25.4	21.5	6.4	50.5	0.16
Taiwan	32.3	28.7	7.2	64.4	0.14
France	33.6	31.3	10.5	60.6	0.13

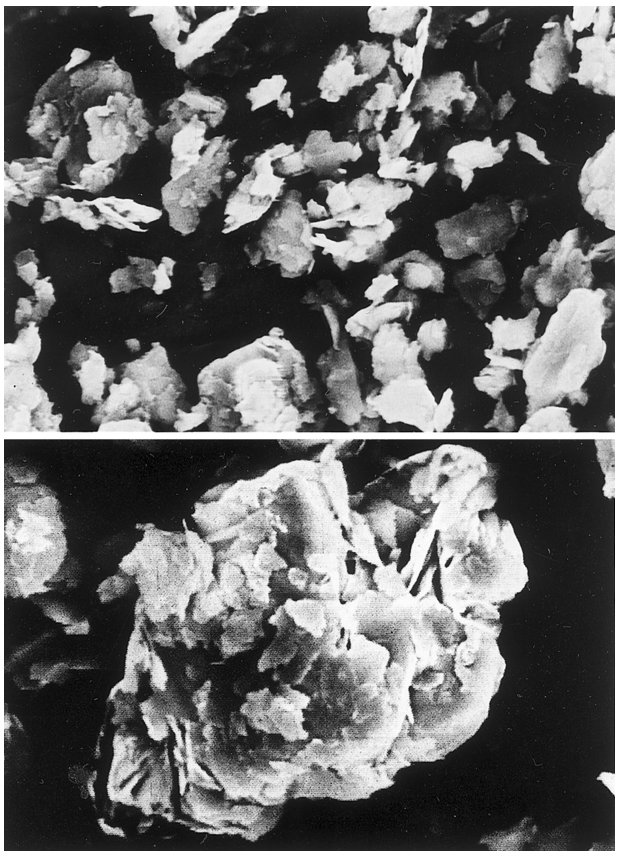

FIGURE 1. *Top*: scanning electron microscopic picture of US talc A (original × 1,500). *Bottom*: scanning electron microscopic picture for French talc (original × 1,500).

DISCUSSION

The present study demonstrates that there is marked variation in the mean particle size from one talc preparation to another. In addition, there are also marked differences in the impurities in the various talc preparations. The differences in the incidences of respiratory distress following the intrapleural administration of talc may be due to differences in the physical characteristics of the preparations.

Talc is a pulverized, natural, sheet-like, hydrated magnesium silicate with the approximate chemical formula of $Mg_3(Si_2O_5)_2(OH)_2$,[12] although calcium, aluminum, and iron are always present in variable amounts. Due to the variety of ways in which the geologic formation of talc is manifest, virtually every talc deposit is unique with regard to both chemistry and morphology. Pure talc is a translucent mineral that appears white when finely ground. The crystal structure of talc is characterized by composite sheet arrangements lying parallel to a common plane. These sheets consist of three sublayers comprising a layer of edge-linked $MgO_4(OH)_2$ octahedra sandwiched between two identical layers of corner-linked SiO_4 tetrahedra. Various talcs have different amounts of elemental substitution within the talc crystal. The most common substitution is a substitution of aluminum for silicon in the tetrahydral positions or aluminum, iron, or manganese for magnesium in the octahedral positions.[12] Nontalc minerals associated with commercial talc vary from deposit to deposit and may include calcite, magnesite, dolomite, chlorite, serpentine, quartz, and others.

After talc has been dug up, it is frequently hand sorted to pick out the whitest pieces. This sorting is called beneficiation. For cosmetic and pharmaceutical purposes, wet beneficiation is frequently done. The talc ore is first crushed and ground to a fineness, which liberates it from other associated nontalc minerals. After washing, the talc is passed through mesh to eliminate the larger-sized talc particles. The size of the final talc preparation depends on the size of the mesh through which it has been passed. The final talc may be 200 mesh, 325 mesh, or 400 mesh. With the 400 mesh, 90 to 95% of the particles are < 37 μm, while with 200 mesh 95 to 99% of the particles are < 74 μm. It appears that all the preparations that we studied were < 400 mesh.

There are serious questions about the safety of talc pleurodesis because it has been associated with some cases of acute lung injury. In the literature, there are published at least 32 cases of acute pneumonitis, 17 of them following talc slurry pleurodesis and the remaining 15 cases after using insufflated talc.[1–5,13–16] In some cases, the patients presented with respiratory failure and required mechanical ventilation. In eight instances, the patients died.[1,4,5,14,16] It seems very probable that these cases of acute lung injury are due to talc since similar cases have not been reported after pleurodesis has been performed with other agents.

The mechanism or mechanisms by which talc produces the acute lung injury is unknown. It has been postulated that the acute lung injury is due to talc itself or its contaminants such as dolomite, quartz, kaolinite, calcite, or chlorite. A reasonable hypothesis is that the acute pneumonitis is related to the systemic absorption of talc with the subsequent elaboration of inflammatory mediators. This hypothesis is supported by the observations, in the case reported by Rinaldo and coworkers,[1] that there were large quantities of talc in the bronchoalveolar fluid of their patient who presented with acute pneumonitis following talc pleurodesis. Talc particles were also found in the BAL in all four patients reported by Milanez Campos et al[4] who had BAL between 10 h and 12 days after the talc insufflation. In addition, one of the patients reported by Milanez Campos et al[4] died, and this patient had talc crystals present in

Table 2—*Contaminants Present in the Different Talc Preparations

Talc Source	Quartz	Calcite	Dolomite	Kaolinite	Chlorite	Forsterite
US talc A	169	0	158	286	194	0
US talc B	T	0	0	65	0	0
US talc C	160	0	121	180	0	0
Spain	160	158	230	0	0	0
US talc D	189	0	156	189	0	0
Brazil	T	T	133	65	360	128
Taiwan	208	0	186	596	241	0
France	0	T	T	349	120	0

*Values are presented as intensity of the peak measured in counts per second; T=trace.

almost every organ at autopsy, including the ipsilateral and contralateral lung, brain, liver, kidney, heart, and skeletal muscle.

Animal studies have demonstrated the extrapleural dissemination of talc administered intrapleurally. In rabbits, talc particles have been detected in 17% of the mediastinal ganglions, 17% of the kidney specimens, and 49% of the spleens.[8] Even though no talc was detected in the lungs of the rabbits in this study, 24 h after pleurodesis, perivascular inflammatory lesions were demonstrated in the lung, which disappeared by 7 days.[8] These authors suggest that the pulmonary lesions are caused by particles of talc that were too small to be detected with the light microscope. When 40 rats were administered talc intrapleurally, talc particles were detected in every organ of each animal killed 24 h and 48 h after talc administration.[9]

If the pneumonitis seen at times after intrapleural talc use is due to the systemic absorption of talc, the results of the present study provide a possible explanation as to why the incidence of talc pneumonitis varies so widely from center to center. If talc with a smaller median particle size is used, there would be many more particles in the pleural space and the particles that are present would be more likely to be absorbed through the lymphatics because they are smaller. In sheep, the diameter of the pleural stomata that are the openings to the lymphatics is approximately 8 to 10 μm in diameter.[17] The diameter of the pleural stomata in humans has been reported to be approximately 6.2 μm in diameter.[18] Therefore, many of the talc particles from the US preparations of talc could easily fit in the stomata. However, animals studies are necessary to document that there is increased systemic distribution when talc with a smaller median particle size is injected intrapleurally.

The present study also provides a possible explanation if the pneumonitis is due to cytokines originating in the pleural space. It has been shown that when mesothelial cells are incubated with talc, cytokines such as interleukin-8 and monocyte chemotactic protein-1 are released.[19] Talc with a higher specific surface area would be likely to create a greater degree of inflammation resulting in the release of more cytokines.

From the present study, we conclude that among the various talc preparations used for pleurodesis, there is marked variation in the mean and median particle size and the types of contaminants. We speculate that differences in the rates of pneumonitis from center to center after intrapleural talc administration may be related to the talc preparation used. However, the differences in these rates could also be due to contaminants such as endotoxin, concomitant procedures such as biopsy, or differences in the size and distribution of the pleurolymphatic communications from patient to patient. It has been suggested[6] that the development of pneumonitis is related to the dose of the talc and that pneumonitis does not occur, if the total dose does not exceed 5 g. This does not appear to be the case, since all four of the cases reported by Milanez Campos and coworkers[4] received only 2 g of talc.

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