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A M E R I C A N C O L L E G E O F
 **C H E S T**
P H Y S I C I A N S

Systemic Distribution of Talc After Intrapleural Administration in Rats*

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Study objectives: Many reports have shown the efficacy of talc to induce an effective pleurodesis. However, there is little information about the side effects related to this sclerosing agent. The objective of this experimental study is to recognize the systemic distribution of talc after its instillation into the pleural space of rats.

Design: Forty animals were assigned to receive talc through a catheter placed in a left minimal thoracotomy. They were randomly divided in two groups: group 1 received 20 mg of talc and group 2 received 10 mg in the same total volume of 1 mL of saline solution. Half of the animals in each group were killed 24 h and the other half 48 h after the procedure. BAL was collected and histologic sections of both lungs, chest wall, liver, kidneys, spleen, heart, and brain were examined. Crystals were tracked using polarized light and we have used a "birefringent particles index of deposition" in an attempt to quantify the amount of talc encountered in different organs.

Results: Talc crystals were found in every organ of all animals studied (100%). There was no statistical difference either on the dose of talc used or in the time of death. The amount of talc was statistically different in the organs, which made us divagate about a route of absorption.

Conclusions: We conclude that there is a progressive deposition of talc particles in the organs examined after its administration into the pleural space of normal rats. This report suggests that there is a rapid absorption of talc through the pleural surface and that the systemic distribution thereafter is not dose related. Further studies are necessary to assess the amount of crystals and the clinical correlation to these findings.

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Key words: malignant pleural effusion; sclerosing agent; talc pleurodesis

Talc was used for the first time by Bethune¹ in 1935 as a pleural sclerosing agent to avoid pulmonary collapse prior to surgery for tuberculosis.

Gaensler² in 1956, as well as Gobbel et al³ in 1963, reported severe complications after intrapleural injection of talc. Despite that, Weissberg⁴ in 1981 said that "The use of talc in pleura is safe and useful. It provides excellent palliation in patients with malignant pleural effusion and cure in the other groups. Excessive concern about complications of using talc is unjustified."

However, recently Lineau et al⁵ in 1993, and Kennedy et al⁶ in 1994, reported pulmonary infiltrate and respiratory distress syndrome in patients undergoing talc pleurodesis.

We have previously reported our experience with 102 patients undergoing talc pleurodesis due to malignant effusion secondary to breast cancer,⁷ recurrent pneumothoraces,⁸ and other benign or undiagnosed pleural effusions.⁹ The overall morbidity in this set of patients was 18.97%.

Presently, many reports have been published comparing talc with other sclerosing agents, and it appears to be the most effective so far available.¹⁰⁻²⁰

Nevertheless, we have been concerned with some cases well documented but not published yet, in which serious complications have been detected following pleurodesis. Furthermore, in these cases, talc was identified outside pleural space such as in BAL, brain, pulmonary artery, and liver. In one case, the embolization to pulmonary artery was the major cause of death at necropsy. Influenced by these experiences, and with the main objective of clarifying the side effects of intrapleural use of talc, an experimental model was designed to verify the distribution of talc after its administration into the pleural space of normal rats.

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MATERIALS AND METHODS

Experimental Design

Forty Wistar rats of similar weight (298 ± 11 g), provided by the Animal Quarters of the Faculty of Medicine—University of São Paulo, were assigned to one of the following groups: in group 1, animals received 20 mg of talc (extrapolated from the usual dose of 5 g in a 70-kg adult man); in group 2, half of this dose was employed, in the same total volume of 1 mL of saline solution. Both groups were divided in two subgroups based on the time of death; in subgroups 1a and 2a, it was performed after 24 h, and in subgroups 1b and 2b, it was performed after 48 h following the intrapleural administration of talc (Table 1), or hydrated magnesium silicate ($\text{Mg}_3\text{Si}_4\text{O}_{10}[\text{OH}]_2$).

The animals were anesthetized in an ether chamber, intubated with a polyethylene tube to provide general anesthesia by inhalation of enflurane (Ethrane) via a nebulizer (Model 1223; Takaoka; Brazil) and a small animal ventilator (Harvard Apparatus; South Natick, MA). Thereafter, a very small left thoracotomy was performed to place a catheter in the fifth intercostal space in order to administer talc as a slurry into the pleural cavity. Drainage of pleural space was accomplished using a polyethylene tube immersed in 0.5 cm H_2O seal. When the animal was wide awake, the tracheal and pleural tubes were removed. The animals were maintained in adequate cages and fed according to the protocol of the animal quarters. After 24 h (groups 1a and 2a) or 48 h (groups 1b and 2b), the animals received intra-abdominal sodium pentobarbital and were killed by exsanguination.

Morphologic Analysis

The obtained lungs, chest wall, liver, kidneys, spleen, heart, and brain were fixed in 10% neutral buffered formalin. After that, they were cut into about 1-cm parasagittal slices and carefully examined for gross abnormalities. Slides 5 μm thick were taken and stained with hematoxylin-eosin. All slides were coded, randomized, and then evaluated by a single observer, who did not have access to the code. In a first approach, we studied all the organs at light microscopy considering the general histoarchitecture and the eventually pathologic process involved. After that, all the specimens were submitted to polarized light with the purpose to look for birefringent particles.

Birefringence Particle Index of Deposition

The analysis was designed to verify the amount of talc crystals deposition along the regions of venous and lymphatic drainage: from thoracotomy site, lungs, heart, and arterial system to possible systemic targets (subpleural connective tissue, axial connective tissue around bronchi and blood vessels and microcirculation). The number of crystal depositions was counted in

five randomly selected bronchovascular bundles and in five fields of $100\times$ along parietal and visceral pleura and microcirculation of heart, spleen, kidneys, and brain. The results of talc crystal were averaged for each case. Figure 1 shows the pattern of talc crystals usually employed for pleurodesis.

Data Analysis

The mean and median scores for talc crystals were compared tabulary for the animals and the different organs by means of a nonparametric test (Kruskal-Wallis). The p values $<\alpha = 0.05$ were considered significant.

RESULTS

All animals did not have any side effects and tolerated both the anesthesia and surgery well. The technique was safe, and no animal suffered any complications from the surgery.

Morphologic Analysis

There were no abnormalities on gross examination of the cut surface of the main organs selected for this study. Microscopically, the most common lesions were observed on chest wall and were represented by an early pneumoconiosis characterized by a stellate interstitial collections of dust-laden macrophages containing pale yellow particles associated with inflammatory infiltrate of lymphocytes with mild fibroblastic proliferation (Fig 2). Polarized light revealed large numbers of irregular, strongly birefringence platy, acicular, and “Maltese Cross” crystals varying in length from 5.7 to 70 μm . In the remaining organs, no pneumoconiosis reactions were observed, although the talc crystals were present mainly inside of the microvessels. Figures 3 and 4, shows the platy birefringent crystalline particulate in the lung tissue and brain.

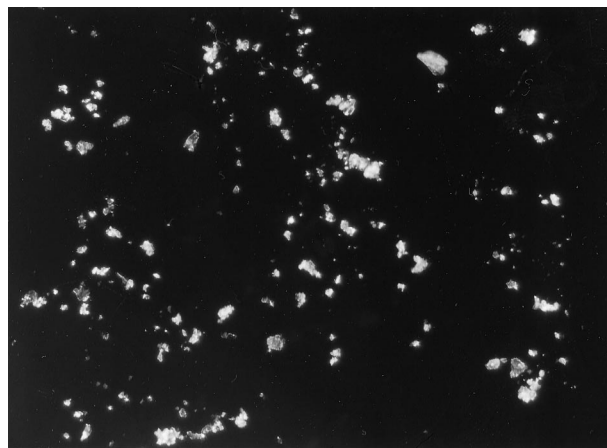


FIGURE 1. The pattern of talc crystals usually employed for pleurodesis (original magnification $\times 100$).

Table 1—Groups of Rats, Compared with Talc Dose and Time of Autopsy

Group	n	Talc Dose, mg	Time of Autopsy, h
1			
a	10	20	24
b	10	20	48
2			
a	9	10	24
b	10	10	48

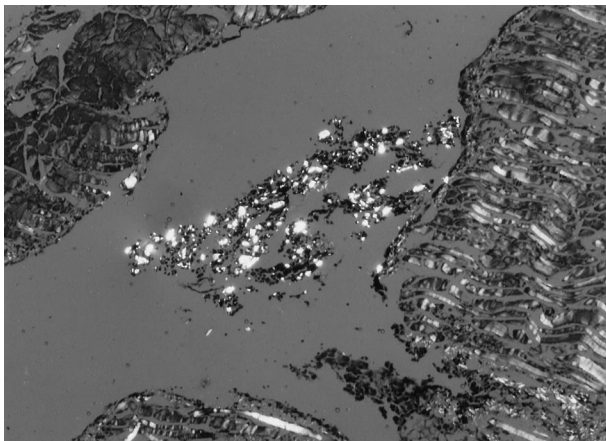


FIGURE 2. Strongly birefringent platy crystalline particulates, talc in chest wall, representing an early pneumoconiosis (original magnification $\times 160$).

Birefringence Particle Index of Deposition

Table 2 shows the mean scores for talc crystals deposition and a comparison for the several organs examined between the two groups (different doses). For chest wall, the mean scores for talc crystals deposition are consistently higher than for other organs.

There is a significant difference in the amount of talc deposition between the two groups for specific organs, like chest wall and lungs, despite the half dose employed in the second group.

Another difference was observed in the density of particles detected among the different organs. Clearly, there is a progressive decrease in the number of particles found in chest wall compared with the kidneys. This observation is a clue for the probable absorption route of the particles.

DISCUSSION

Several reports have been published regarding the potential risk of the indiscriminate use of talc pleu-

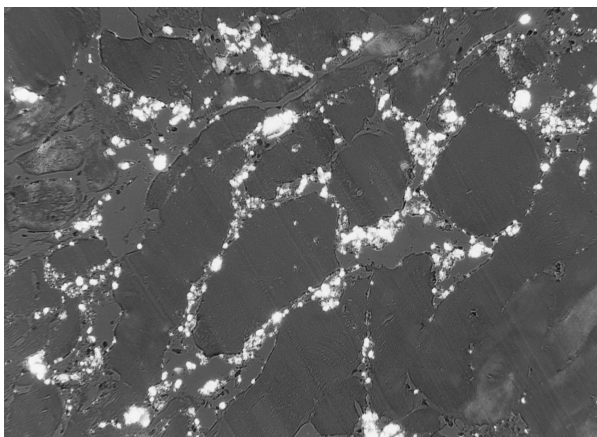


FIGURE 3. Talc crystals in the lung (original magnification $\times 100$).



FIGURE 4. Talc crystals in the brain (original magnification $\times 100$).

rodesis. In 1956, Gaensler,² for the first time (to our knowledge), observed severe effects resulting from pleural poudrage, such as severe pain (worse than the pain observed after thoracotomy) fever, shock, prolonged hospitalization, embolization with hemiplegia, significant changes of the pleura (thickening, granulomas, fibrothorax), and loss of respiratory function. More serious outcome was published by Youmans et al²¹ in 1970, reporting a fatal cardiac arrest of undetermined etiology in a 23-year-old youth immediately after a pleural poudrage.

Weissberg and Zeev,²² in 1993, gathering >10 years of experience with talc, concluded that "purified talc free of asbestos is safe for clinical use. It is the cheapest and most reliable substance in creating pleural adhesions, with effectiveness over 90%. Its use in doses not exceeding 2 g eliminates complications almost completely."

However, some authors such as Schafers and Dresler,¹⁰ in 1995, believe that there are still few reports relating talc itself to the side effects reported in the literature.

Recently, several authors have called attention to

Table 2—Deposition Index of Talc Crystals in Various Organs, and Statistical Comparison Between Groups

Organs	Talc Deposition Index, Mean \pm SD		Comparison Between Groups, p Value
	1	2	
Chest wall	3.58 \pm 0.18	3.90 \pm 0.07	0.0076
Lungs	2.50 \pm 0.24	3.18 \pm 0.13	0.0006
Heart	1.77 \pm 0.10	1.77 \pm 0.13	0.9400
Brain	0.93 \pm 0.26	0.83 \pm 0.13	0.4957
Spleen	0.57 \pm 0.16	0.40 \pm 0.02	0.0591
Kidneys	0.07 \pm 0.01	0.12 \pm 0.02	0.0109
Liver			

ARDS and pulmonary reexpansion edema after talc pleurodesis.⁵⁻⁷ Most of them agree with the fact that even when the indication is well established, the dose to be utilized should be limited to 5 g (in adults), until more data regarding its safety are available.

Our clinical experience has been to use 2 g of insufflated talc through thoracoscopy in 83 patients with benign and 255 patients with malignant diseases of the pleura. Our success rate has been between 88% and 94%. We have observed four patients (1.2%) who developed bilateral pulmonary infiltrates, hypoxemia, hypercapnia, mental confusion, and hypotension within 24 and 48 h after the procedure. All the patients required intubation and mechanical ventilation. Three of the patients died with the diagnosis of ARDS and one recovered after 36 h of mechanical ventilation. All the patients had talc crystals in their BAL performed 10 to 12 h after the thoracoscopy. Necropsy was done on one patient. Talc crystals were found in almost every organ examined.²³

Worried with those facts, we designed this experimental model administrating talc into the pleural space of normal rats, and we could verify that a high incidence of crystals was present in several organs examined. Besides, it was amazing to find talc inside coronary artery, meninges, urinary tract, pulmonary artery, myocardium, and so forth. Secondly, these findings were not dependent on the dose of talc used or on the time of death.

This study suggests that talc is absorbed very rapidly through the pleura, reaching systemic circulation and being deposited on target organs as soon as 24 h after its administration into the pleural cavity. We were not able to demonstrate whether the absorption rate can be influenced by different pleural conditions, since our protocol uses only normal rats. However, these data suggest that morbidity and mortality associated with talc pleurodesis could come from the presence of talc particles.

For this reason, although we can find differences in pleural anatomy, porosity, venous and lymphatic drainage between interspecies, and in permeability of normal vs diseased pleura, until more consistent and definitive data are available, we suggest that talc should be avoided to promote pleurodesis in young patients with benign diseases and even in malignant diseases with a very good prognosis. Maybe we should use another sclerosing agent.

In conclusion, this experimental model with normal rats shows a rapid absorption of talc particles through the pleura. The crystals can be found outside the pleural cavity shortly after the procedure (BAL) and in target organs after 24 h. This is not dose related when an equivalent of 0.036 g/kg is used

(2.5 g for a 70-kg man). We still cannot reach any further conclusion regarding clinical manifestations related to this phenomenon.

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