Comparisons of Pleurodesis Induced by Talc With or Without Thymol Iodide in Rabbits*

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Study objective: At the present time, talc administered either as a slurry or an aerosol is a popular agent for producing pleurodesis. Some investigators use iodized talc while others use plain talc. The purpose of the present study was to determine if iodized talc slurry produced a better pleurodesis in animals than did plain talc.

Design: New Zealand white male rabbits were randomly assigned to receive talc slurry, 200 mg/kg, with or without the addition of 50 mg iodide intrapleurally. Approximately 10 rabbits in each group were killed 1, 2, 4, 7, 14, and 28 days after the injection. The amount and character of pleural fluid, the degree of pleural adhesions, and the microscopic changes were compared in the two different groups.

Results: The pleural fluid findings, the gross adhesion score for the pleura, and the microscopic changes in the visceral pleura were essentially identical for the rabbits that received iodized talc and those that received plain talc. The injection of both plain talc and iodized talc produced a normoglycemic exudative pleural effusion that had, for the most part, disappeared by the fourth day postinjection. The amount of pleural fluid at 48 h was 3.3±0.6 mL in the plain talc and 2.2±0.5 mL in the iodized talc group. At 28 days, the mean degree of gross pleurodesis in the talc group was 2.6±0.2 compared with 2.3±0.2 in the iodized group, while the mean degree of microscopic fibrosis was 1.4±0.3 in the plain talc group compared with 2.0±0.3 in the iodized talc group.

Conclusion: From this study, we conclude that the addition of 50 mg of iodide does not improve the results with talc slurry pleurodesis in rabbits. (CHEST 1998; 113:795-99)

Key words: pleural effusion; pleurodesis; pneumothorax; talc slurry; thymol iodide

Since Bethune1 introduced insufflation of iodized talc to achieve pleural symphysis in 1935, investigators and clinicians have been using talc for pleurodesis. Since the parenteral form of tetracycline became unavailable in the late 1980s, the use of talc either insufflated or as a slurry has become much more widespread. Usually, talc alone is used for pleurodesis, but at times, iodized talc is used. The clinicians who use iodized talc believe that iodized talc produces a better pleurodesis than plain talc.2,3 However, to our knowledge, there have been only limited studies, in animals or patients, comparing the effectiveness of pleurodesis induced by plain or iodized talc. It has been stated that talc by itself produces an inflammatory reaction.3

Plain talc is a highly effective agent for pleurodesis when administered either via poudrage or slurry in patients with a pleural effusion or a pneumothorax.4 In animal studies, the intrapleural administration of plain talc produced a pleurodesis that was comparable to that produced with tetracycline.5 Furthermore, the intrapleural administration of plain talc slurry in rabbits is not associated with the development of fibrothorax or hemothorax, as is the case with the intrapleural administration of the tetracycline derivatives.5

The purpose of the present study was to determine whether iodized talc resulted in a better pleurodesis than plain talc. We hypothesized that the intrapleural instillation of iodized talc would produce a more severe acute injury than plain talc as manifested by a larger volume of pleural fluid and a higher pleural fluid cellular response. We further
hypothesized that after iodized talc, the pleural effusion would persist longer and that there would be more pleural adhesions.

**Materials and Methods**

The methods we used were similar to those we have described previously. The protocol was approved by the Animal Care Committee of the Veterans Affairs Medical Center Long Beach prior to starting the project. The rabbits were randomized to receive either talc (200 mg/kg) intrapleurally or iodized talc (200 mg/kg talc plus 50 mg thymol iodide) intrapleurally. We selected a dose of 200 mg/kg because we have shown previously that this is the lowest dose of talc slurry that produces a pleurodesis in rabbits. The talc (Sigma Chemical Co; St. Louis) was sterilized at a temperature of 132°C for 2 h. The thymol iodide (Sigma Chemical Co) was stored in the dark below 0°C. Shortly before injection, the talc 200 mg/kg with or without thymol iodide 50 mg was suspended in normal saline solution under sterile conditions. The total volume was 3 mL in 50% of the rabbits and was 6 mL in 50% of the rabbits. The suspension was maintained in the dark until it was injected.

Rabbits were lightly anesthetized with ketamine hydrochloride (Fort Dodge Laboratories, Inc; Fort Dodge, Iowa), 35 mg/kg plus xylazine hydrochloride (Miles Inc, Agriculture Division, Animal Health Products; Shawnee Mission, Kan), 5 mg/kg IM. Under sterile conditions, a 0.5-cm skin incision was made midway between the scapular tip and the sternum. A 16-gauge IV catheter placement unit (Deseret Medical Inc, Becton Dickinson and Company; Sandy, Utah) was then inserted into the pleural space. The plastic catheter plug was removed so that the right lung could collapse, thereby preventing damage to the lung via the catheter's needle. Then the needle was removed and the plastic catheter was left in place. A three-way stopcock was attached to the end of the catheter. Through this stopcock, all air was evacuated from the pleural space. Verification that the tip of the catheter was in the pleural space was obtained by documenting inspiratory pressure drops with a pressure transducer. After the suspension had been shaken vigorously, the talc slurry with or without the iodide was injected through the catheter. The catheter was flushed with 0.3 to 0.5 mL of saline solution. Following the flush, a small amount of fluid was aspirated to verify proper placement of the catheter and the lack of a pneumothorax. After the catheter was removed, the wound site was cleaned with povidone-iodine. The left hemithorax received no injection and served as a control.

After the surgery, the rabbits were closely monitored for clinical evidence of pain (vocalization, tachypnea, and restless- ness). All rabbits received 0.3 mL buprenorphine (Reckitt & Colman Products; Hull, England) immediately after recovery from surgery and every 12 h thereafter when they appeared to have any distress.

To determine the acute and chronic reactions after intrapleural injection of plain talc and iodized talc, rabbits were killed on days 1, 2, 4, 7, 14, and 28. On each of these days, 10 to 12 rabbits that had received plain talc and 10 to 12 rabbits that had received iodized talc were killed. The rabbits were killed by the injection of 40 mg/kg pentobarbital solution (Abbott Laboratories; North Chicago, Ill) into the marginal ear vein. Immediately after the rabbits were killed, attempts were made to aspirate all fluid from both pleural spaces using a posterior transdiaphragmatic approach. The volume of aspirated pleural fluid was recorded and the fluid was saved for analysis.

The thorax was then removed en bloc from the rabbit. Small incisions were made in the diaphragm to allow better access of the fixative (10% formaldehyde solution) to the pleural cavities. The lungs were expanded by injecting 40 to 60 mL formaldehyde solution into a plastic catheter (6 mm diameter) that had been inserted into the esophageal trachea. The trachea was ligated with silk after the injection and then the entire thorax was submerged in 10% formaldehyde solution for at least 48 h.

The levels of glucose and protein were measured as well as the WBC count and differential cell count of the pleural fluid. The glucose level was measured using a glucometer (Accu-Chek II model 792, Boehringer Mannheim Corporation; Indianapolis). The protein level was measured by a refractometer (American Optical; Buffalo, NY). The cell count was performed by a hemocytometer (Haemocytometer; Kodak Ektachem; Rochester, NY). The leukocyte differentials were performed by counting 100 cells on a Wright's stained smear.

The necropsy was performed by two of the investigators (C.X. and R.W.L.) who were blinded as to the treatment and the day of death of the rabbit. Each pleural cavity was carefully exposed by making bilateral incisions through the diaphragms and through all the ribs at approximately the midclavicular line. In this manner, the sternum and the medial portions of the anterior ribs were removed so that the lung and pleural cavities could be evaluated. The presence or absence of hemothorax and the position of the mediastinum in each animal were recorded.

The degree of pleurodesis observed grossly was semiquantitatively graded according to the following scheme as described previously: 0, normal pleural space; 1, no adhesions but pleural space inflamed as evidenced by roughness and fibrin deposition; 2, few scattered adhesions; 3, generalized scattered adhesions; and 4, complete obliteration of the pleural space by adhesions.

Samples of the parietal and visceral pleura were obtained from the anterior lower lobes and placed in neutral buffered 10% formaldehyde solution. These tissue samples for histologic examination were processed routinely and stained with hematoxylineosin. The microscopic slides were evaluated blindly by one of the investigators (N.S.W.) for the presence of inflammation and fibrosis. The degree of inflammation and fibrosis was graded from 0 to 4 for absent, equivocal, mild, moderate, and marked, respectively.

**Statistical Analysis**

All data were expressed as the mean±SE. The results in the two groups were compared using the unpaired t test if the data met criteria for normality and the Mann-Whitney Rank Sum Test for data that failed the test for normality (Sigma Stat; Jandel Scientific; San Raphael, Calif). Differences in the results were considered significant when p<0.05.

**Results**

All rabbits tolerated the procedures and none died prematurely during the study period. At necropsy, all rabbits had talc in the right pleural space and no rabbit had a mediastinal shift. Since there were no significant differences in the fluid characteristics when the total volume was 3 mL or 6 mL, the data for the rabbits that received the two different volumes were combined for data analysis. A mild-to-moderate hemothorax was noted in three (one in plain talc group and another two in the iodized talc group) rabbits. Only one rabbit had fluid on the left side. This rabbit had received iodized talc and was
killed on day 2. This rabbit had 9 mL of pleural fluid on the right and 3 mL of pleural fluid on the left. This was the only rabbit that had >6 mL of pleural fluid on the right side.

The volume of the pleural fluid and the characteristics of the pleural fluid were similar in both groups (Table 1). Pleural fluid was present in the right pleural space in all rabbits in both groups on day 1 and in all but one rabbit on day 2. By day 4, pleural fluid was present in only 3 of 21 rabbits and all three of these rabbits were in the plain talc group. There was no significant difference in the mean amount of pleural fluid in the two groups (Table 1). The mean WBC count and differential cell count did not differ significantly between the two groups (Table 1). There was a significant increase in the leukocyte count between the first and second day postinjection in both groups. Monocytes predominated in both groups at 1 and 2 days postinjection.

The levels of protein and glucose in the pleural fluid are shown in Table 2. The effusions were normoglycemic exudates. There was no significant difference in the pleural fluid protein or glucose levels between the two groups.

The effectiveness of the pleurodesis was nearly identical in the two different groups on all examination days (Fig 1). The pleurodesis was not particularly effective in either group. On day 14, only 3 of 10 rabbits (30%) in the iodized talc group had a good pleurodesis (score of 3 or 4) and only 4 of 12 rabbits (25%) in the control talc group had a good pleurodesis. The numbers were similar on the 28th day on which 3 of 10 rabbits in the iodized talc group had a good pleurodesis while 5 of 10 rabbits (50%) in the control group had a good pleurodesis. The gross adhesion score did tend to increase with time in both groups (Fig 1). In all rabbits with adhesions, the adhesions appeared to be more numerous and thicker in the ventral part of the thorax where the residual talc was found.

When the pleura was examined microscopically, there were no significant differences in the two groups for either the pleural inflammation score (Fig 2) or the pleural fibrosis score (Fig 3) on the injected side. The degree of pleural inflammation tended to decrease slightly with time while the degree of pleural fibrosis tended to increase with time on the injected side. The mean score for pleural inflammation on the contralateral side exceeded 1.0 only on day 2 at which time it was 1.27±0.30 in the plain talc group and 1.30±0.34 in the iodized talc group. The mean score for fibrosis on the contralateral pleura never exceeded 1.0 (data not shown).

### Table 1—The Volume and Cell Counts of Pleural Fluid After Intrapleural Injection of Plain Talc and Iodized Talc

<table>
<thead>
<tr>
<th></th>
<th>Days</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>No. with pleural fluid</td>
<td>10/10</td>
</tr>
<tr>
<td>Plain talc</td>
<td>11/11</td>
</tr>
<tr>
<td>Pleural fluid volume, mL</td>
<td>3.2±1.0</td>
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<tr>
<td>Plain talc</td>
<td>4.0±0.3</td>
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<tr>
<td>Leukocyte, k/L</td>
<td>2.9±0.2</td>
</tr>
<tr>
<td>Plain talc</td>
<td>3.4±1.4</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>41±5</td>
</tr>
<tr>
<td>Plain talc</td>
<td>42±2</td>
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<tr>
<td>Mononuclear cells, %</td>
<td>57±5</td>
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<tr>
<td>Plain talc</td>
<td>57±1</td>
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<tr>
<td>Iodized talc</td>
<td></td>
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</tbody>
</table>

### Table 2—The Chemical Analyses of Pleural Fluid After Intrapleural Injection of Plain Talc and Iodized Talc

<table>
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<th>Days</th>
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<td></td>
<td>1</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
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<tr>
<td>Plain talc</td>
<td>140±10</td>
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<tr>
<td>Iodized talc</td>
<td>146±8</td>
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<tr>
<td>Protein, g/dL</td>
<td></td>
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<tr>
<td>Plain talc</td>
<td>4.3±0.1</td>
</tr>
<tr>
<td>Iodized talc</td>
<td>4.2±0.1</td>
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**Discussion**

The results from the present study demonstrate that in rabbits, the efficacy of pleurodesis with talc slurry is not improved if the talc is iodized.
The use of talc for the creation of a pleurodesis was first reported by Bethune\(^1\) in 1935. He used iodized talc, but gave no reason why iodized rather than noniodized talc was used. Since that time, iodized talc has been used in some studies\(^2,3,7,8\) while noniodized talc has been used in others.\(^4,9-11\) It is unclear why some researchers used iodized talc. It is more difficult to use the iodized talc. Thymol iodide must be maintained in the dark at a low temperature and therefore it is impossible to sterilize with heat. Accordingly, one must worry about its sterility. Although the thymol iodide was not sterilized in this study, we have previously found that cultures of this preparation are sometimes positive.

Despite the widespread utilization of iodized talc for the production of a pleurodesis, there are few studies that compare the capability of noniodized and iodized talc to produce a pleurodesis. Singer et al.\(^12\) studied two rabbits with plain talc and eight rabbits with iodized talc and noted that there was no significant difference in the macroscopic or microscopic findings in the pleural space. These workers also compared the effects of intrapleural thymol iodide alone and talc alone and found that the thymol preparation was less effective.\(^12\) We have also found that the intrapleural injection of 50 mg iodide does not result in a pleurodesis at 28 days (unpublished observations). The results from the present study confirm and extend those reported by Singer and colleagues.\(^12\) The adhesions with plain talc and iodized talc were identical on both gross and microscopic examination. In addition, both preparations produced acute exudative effusions with essentially identical characteristics.

The mechanism by which talc induces a pleurodesis is unknown.\(^6,13\) However, it appears that the initial event after the intrapleural instillation of talc is an injury to the pleura. The intrapleural injection of talc leads to mesothelial denudement and an exudative pleural effusion.\(^13\) The exudative effusion resolves within 4 days, as shown previously\(^13\) and in the present study. After the effusion resolves, the number of adhesions tends to increase with time (Fig 1). The fact that there is no difference between the iodized talc and the noniodized talc groups in the pleural fluid findings (Table 1), the gross adhesion score (Fig 1), and the microscopic scores (Figs 2 and 3) suggests that there is no advantage to using iodized over the noniodized form.

The results of the present study might not be applicable to humans if inappropriate doses of iodide were used or if the results in rabbits cannot be extrapolated to humans. The ratio of iodide to talc in the present study was approximately 1:10. The ratio of iodide to talc in previous studies has varied markedly. It has ranged from a low of <1:100\(^3\) to a high of 3:5,\(^2\) and in some reports the ratio was not provided.\(^5\) Our ratio is within this wide range. However, it is possible that if we had used a ratio of 3:5, the addition of iodide might have improved the results with pleurodesis. However, we believe that this is unlikely since the results using iodized talc or talc alone in humans are very similar for both pneumothoraces and pleural effusions.\(^4\)

In the present study, talc was not particularly effective at producing a pleurodesis. The dose of talc used in the present study (200 mg/kg) is approximately three times that used for treating recurrent pleural effusion or pneumothorax in humans.\(^4\) In humans, the dose most commonly used is 5 g, which
is equivalent to 70 mg/kg in a 70-kg individual. In a previous article, we demonstrated that 400 mg/kg produced a better pleurodesis in rabbits than did 200 mg/kg. A possible explanation for the higher doses required in rabbits is that in the experimental model, no chest tube is inserted, while a chest tube is almost always inserted in humans. It is possible that the approximation of the two pleural surfaces with the chest tube facilitates the creation of the pleurodesis.

In conclusion, the present study demonstrates that in rabbits, the addition of 50 mg iodide to talc (200 mg/kg) does not improve pleurodesis. The results from the present study in conjunction with human studies in the literature show similar results with iodized and noniodized talc. There is no evidence favoring the use of iodized talc to promote pleurodesis in humans.

REFERENCES
3 Jones GR. Treatment of recurrent malignant pleural effusion by iodized talc pleurodesis. Thorax 1969; 24:69-73