Combination Therapy With Intrapleural Doxycycline and Talc in Reduced Doses Is Effective in Producing Pleurodesis in Rabbits*

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Background: **It has been suggested that talc and doxycycline might be acting through different pathways in creating pleurodesis. We hypothesized that combining doxycycline and talc in half the usual doses would be synergistic in inducing pleurodesis.**
Methods: **Thirty-two rabbits were equally allocated into four groups: group 1, half-dose combination (5 mg/kg of doxycycline and 200 mg/kg of talc slurry); group 2, quarter-dose combination (2.5 mg/kg of doxycycline and 100 mg/kg of talc slurry); group 3, half-dose doxycycline (5 mg/kg of doxycycline); and group 4, half-dose talc (100 mg/kg of talc slurry). The pleurodesis scores from historical groups that received a full dose of talc (400 mg/kg) or doxycycline (10 mg/kg) were also compared to those obtained in the current study. Pleural fluid lactate dehydrogenase and protein levels were measured 24 h after the injection. Pleurodesis was graded from 1 (none) to 8 (> 50% symphysis) by two observers blinded to treatment groups. All rabbits underwent an ultrasonic examination on each side of their chest for the evaluation of pleurodesis.**
Results: **The mean pleurodesis score in the half-dose combination group was significantly higher than that in the half-dose talc group, half-dose doxycycline group, and the historical full-dose talc group ($p = 0.009$, $p = 0.01$, and $p < 0.05$, respectively). The quarter-dose combination group also had a significantly higher mean pleurodesis score compared to the half-dose talc group ($p = 0.013$). The difference between the historical full-dose doxycycline and the half-dose combination or quarter-dose combination groups was not significant ($p > 0.05$). A significantly positive correlation existed between the pleurodesis score and the ultrasound scores ($r = 0.876$, $p = 0.000000005$).**
Conclusions: **This study demonstrates that the combination of half doses of talc and doxycycline is more effective than the half dose of either drug alone or the full dose of talc in producing pleurodesis in rabbits. In addition, ultrasound is an accurate imaging modality for the evaluation of pleurodesis, in that the absence of pleural gliding on ultrasound correlates well with the presence of a pleurodesis in rabbits.** ***(CHEST 2005; 128:3735–3742)***

Key words: combination; doxycycline; pleural effusion; talc; ultrasound

Abbreviations: IQR = intraquartile range; LDH = lactate dehydrogenase

Malignancy is the most common etiology for recurrent pleural effusion.[1] It is estimated that annually 200,000 patients in the United States have malignant pleural effusion.[2] The dyspnea caused by malignant pleural effusion lowers the quality of life of the cancer patient with a life expectancy of < 6 months. Although pleurodesis does not improve the patient's survival, it can significantly improve the patient's quality of life by preventing the reaccumulation of malignant effusions.

Many different agents have been used for creating

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This study was supported by the St. Thomas Foundation, Nashville, TN.

Manuscript received April 11, 2005; revision accepted June 15, 2005.

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a pleurodesis. None of the agents are ideal, all with differing degrees of efficacy and adverse effects.[3–6] The ideal agent for chemical pleurodesis should have the following features: low cost, mild or no side effects, worldwide availability, and ease of administration at the bedside. There is a large body of evidence that talc (either as poudrage or slurry) and tetracycline (or its derivatives, especially doxycycline) are two of the most effective sclerosing agents in treatment of malignant pleural effusions.[1–13] Although some studies[1–9] suggested slightly better effectiveness for talc (76 to 94.5%) than doxycycline[10–13] in humans (79 to 88%), the differences were not statistically significant, and the route of administration of the agents was varied in most publications. In a recent, large, randomized controlled study by Dresler at al,[14] the efficacy of talc either in poudrage form (78%) or slurry form (71%) was relatively low. In terms of cost-effectiveness and availability, talc is superior to doxycycline. However, the recent association of talc with serious, and even lethal, respiratory failure has stirred considerable concerns and debate. In the study by Dresler et al,[14] comparing talc administered as an aerosol at thoracoscopy (insufflation) and talc administered as a slurry in 501 patients with documented malignant pleural effusion, a treatment-related mortality was reported in 9 of 242 patients in the talc insufflation group and in 7 of 240 patients in the talc slurry group. However, injection of the tetracycline derivatives is at times extremely painful,[15] and parenteral doxycycline is not available worldwide.

It has been suggested previously that talc and doxycycline might act through different pathways.[16] Also, it has been suggested that serious side effects attributed to talc slurry occur in a dose-dependent manner.[17] Lower doses would be expected to cause less severe side effects but also to be less effective in producing pleurodesis. If this is so, one can speculate that the combination of a lower amount of each agent may generate a synergy and therefore produce a better pleurodesis with lower incidence of side effects. To the best of our knowledge, combining sclerosing agents to provide synergy in the production of pleurodesis has never been studied before. We hypothesized that the combination of half doses of doxycycline and talc slurry would result in a pleurodesis at least as good as each agent by itself.

Materials and Methods

The study protocol was approved by the Vanderbilt University Institutional Animal Care and Use Committee. The methods used were similar to those described in our previous studies.[18–19]

Chest Tube Insertion

New Zealand white rabbits weighing 1.5 to 2 kg were anesthetized with an IM injection of 35 mg/kg of ketamine hydrochloride (Fort Dodge Animal Health Laboratories; Fort Dodge, IA) and 5 mg/kg of xylazine hydrochloride (Fermenta; Kansas City, MO). The chest was shaved, and the skin was sterilized with 10% povidone iodine (Baxter; Deerfield, IL). The rabbit was placed in the left lateral decubitus position, and a skin incision < 2 cm was made midway between the tip of the right scapula and the sternum, approximately 2 cm above the costal margin. A chest tube (silicone tube, 0.062-inch internal diameter and 0.125-inch outer diameter; Braintree Scientific; Braintree, MA) was created with five extra openings near the distal end to enhance drainage. The chest tube was then inserted by blunt dissection into the right pleural cavity and was secured at the muscle layers with purse-string sutures. The proximal end of the chest tube was tunneled underneath the skin and drawn out through the skin posteriorly and superiorly between the two scapulae. A three-way stopcock (Medex; Dublin, OH) was attached to the end of the chest tube via an adapter through which pleural air was evacuated from the pleural space. The three-way stopcock was then removed from the chest tube, and the exterior end of the chest tube was sealed with a one-way valve with a cap (Medex) via the adapter and was sutured to the skin. Any pleural fluid or air that accumulated could be aspirated through the one-way valve. A local anesthetic was applied into the incision area before it was sutured since the rabbits were not administered full general anesthesia. The left pleural cavity was used for control.

Intrapleural Injections

Thirty-two rabbits were allocated into following groups: group 1, half-dose combination ($n = 8$; 5 mg/kg of parenteral doxycycline in 2 mL of saline solution, and 200 mg/kg of talc in 3 mL of saline solution); (2) quarter-dose combination ($n = 8$; 2.5 mg/kg of parenteral doxycycline in 2 mL of saline solution, and 100 mg/kg of talc in 3 mL of saline solution; group 3, half-dose doxycycline ($n = 8$; 5 mg/kg of parenteral doxycycline in 2 mL of saline solution); and (4) half-dose talc ($n = 8$; 100 mg/kg of talc in 3 mL of saline solution). Parenteral doxycycline (Human Label; Burns Veterinary Supply; Norcross, GA) was dissolved in 2 mL of 0.9% sodium chloride (Baxter). Asbestos-free talc powder (Sigma; St. Louis, MO) was gas sterilized using ethylene oxide and was then mixed with the 0.9% sodium chloride solution. In combination groups, each drug was injected separately through the chest tubes, with doxycycline being the first agent followed by talc slurry. The injection of the agents was followed by injection of at least 2 mL of 0.9% sodium chloride to clear the dead space of the chest tube. The total volume that each animal received was completed to 7 mL with the additional 0.9% sodium chloride injection. We also used our historical data for full doses of talc[19] and doxycycline[20] for the statistical comparisons.

Measurements for Pleural Fluid and Follow-up

After the intrapleural injection, the chest tube was aspirated at 24-h intervals for any pleural fluid that had accumulated. The volumes of the aspirated fluids were recorded. The levels of protein and lactate dehydrogenase (LDH) were measured in the fluid collected 24 h after the injection. The protein and LDH levels were determined with an automated analyzer (Johnson & Johnson; Rochester, NY). The lower and upper limits of normal serum LDH are 120 IU/L and 200 IU/L, respectively, by this method. Gentamicin, 2 mg/kg, was administered IM q24h until the removal of the chest tubes. The chest tube was removed under light sedation when the pleural fluid drainage was < 2 mL over the preceding 24 h.