EDITORIAL

Pleurodesis: what agent should be used?

Pleurodesis is indicated when one wishes to obliterate the pleural space. The indications for pleurodesis are a symptomatic recurrent pleural effusion or a spontaneous pneumothorax[1]. Over the past 70 years many agents have been injected intrapleurally in an attempt to create a pleurodesis. The agents used have included radioisotopes, quinacrine, antineoplastics (nitrogen mustard, bleomycin, mitoxantrone), tetracycline derivatives (tetracycline, doxycycline, minocycline), talc, erythromycin, sodium hydroxide, silver nitrate, iodopovidone, killed *Corynebacterium parvum* and OK-432 which is an immunostimulant obtained from *Streptococcus pyogenes* [2].

The mechanism for pleurodesis with most of the agents listed above is thought to be the following: an agent is injected into the pleural space which injures the mesothelial cells lining the pleural space[2]. As a result of the injury, pleural inflammation develops usually in association with a pleural effusion. If the injury is sufficiently severe, the resulting inflammation will lead to the formation of collagen and the visceral and parietal pleura will fuse producing a pleurodesis[2].

In the 1960's and 1970's antineoplastic agents were the most popular agents. Nitrogen mustard was most commonly used and was effective in up to 87% of patients[3]. Originally it was thought that the efficacy of the antineoplastic agents was due to their antitumor effects. However, subsequently it was shown that pleurodesis occurred when the tumor was not controlled and the pleurodesis was attributed to the fibrosing effects of the drugs[2]. In recent years, bleomycin has been the antineoplastic agent most commonly used for pleurodesis. This is not due to its greater efficacy, but rather to the fact that the pharmaceutic company who manufactures it completed the necessary paperwork to get it approved by the Federal Drug Administration in the United States. It should be noted that bleomycin does not produce pleurodesis in experimental animals[4]. Mitoxantrone is another antineoplastic agent which has been used as a pleurodesing agent. It is not recommended because doses sufficiently high to induce a pleurodesis in animals produce a cardiomyopathy[5]. Of all the antineoplastics, nitrogen mustard at a dose of 0.8 mg/kg is the most effective in producing a pleurodesis in rabbits[6].

When it was realized that it was the fibrosing effects rather than the antineoplastic effects of the agents that was responsible for producing the pleurodesis, non-specific irritants such as talc, tetracycline, and quinacrine were used for pleurodesis. In the 1980's tetracycline was the most commonly used agent primarily because a study in rabbits demonstrated that it was the most effective agent[7]. However, in the late 1980's the company that produced parenteral tetracycline terminated its production. Subsequently it was shown that doxycycline and minocycline were comparable in efficacy to tetracycline[8,9].

When tetracycline became unavailable, the use of talc as a pleurodesis agent increased rapidly. Indeed, it is the agent most commonly used for pleurodesis at the present time[10]. Talc can be administered either as an aerosol (insufflation) or a suspension (slurry). Talc is the choice of many physicians because it is inexpensive, widely available and is perceived to be the most effective agent[11]. The primary problem with talc is that it has been incriminated in causing the acute respiratory distress syndrome (ARDS) which is fatal in approximately one percent of patients who receive it intrapleurally[12]. The mechanism for the ARDS is not definitely known, but it has been hypothesized that it is due to the systemic absorption of small talc particles[13]. Since the life expectancy of patients with malignancy is very limited, this would not necessarily mean that talc should not be used if it were significantly more effective than the other agents. Although it has been stated in the past that talc was 95% effective and was much more effective than other agents[11], this does not appear to be the case. In one analysis of 433 patients subjected to thoracentesis with talc, tetracycline derivatives or bleomycin, talc was no more effective than the other agents - all agents being approximately 80% effective[14]. In a recent study from Australia, the insufflation of talc at thoracoscopy in 66 malignant pleural effusions resulted in completed control in only 52%[15]. Therefore, other agents should be considered.

There are two other agents that are inexpensive and widely available that may prove to be excellent agents for pleurodesis - silver nitrate and iodopovidone. Vargas and coworkers[16,17] have shown that silver nitrate is at least as good as the tetracycline derivatives or talc in producing pleurodesis in rabbits. Moreover, they have shown that 20 ml of 0.5% silver nitrate produced control of 22 of 23 patients (95%) with malignant effusions [18]. A recent article from Mexico reported that the intrapleural instillation of 20 ml 10% iodopovidone plus 80 ml normal saline resulted in complete control of the effusion

in 50 of 52 patients (96%) (19). In this study the iodopovidone was administered either through a chest tube or at the time of thoracostomy. Three patients did experience intense pleuritic pain and systemic hypotension after the instillation of the sclerosing agent, but they recovered without incident[19]

In view of the above, what agent should be used for pleurodesis in 2003? I prefer not to use talc because of the possibility that its intrapleural instillation can induce ARDS and the fact that it is no more effective than other agents. My agent of choice is doxycycline 500 mg. Acceptable alternatives are silver nitrate and iodopovidone. If I wanted to use an antineoplastic, I would use nitrogen mustard at a dose of 0.8 mg/kg.

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