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New agents for pleurodesis

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Abstract At times when patients have a malignant pleural effusion or a pneumothorax, one wishes to eliminate the pleural space by pleurodesis. This article describes results from attempting pleurodesis with silver nitrate, iodopovidone (betadine), transforming growth factor beta (TGFβ), OK432, and lipoteichoic acid-T. The two most promising agents seem to be silver nitrate and iodopovidone. Both agents induce pleurodesis that is at least comparable with that produced by talc, and neither induced the acute respiratory distress syndrome that sometimes occurs after intrapleural administration of talc.

Keywords Pleural effusion · Malignant pleural effusion · Pleurodesis · Silver nitrate · Iodopovidone (betadine) · Transforming growth factor beta (TGFβ) · OK432 · Lipoteichoic acid-T

Introduction

It is frequently desirable to eradicate the pleural space for patients with malignant pleural effusions, recurrent benign pleural effusions, and pneumothorax. If the pleural space is eradicated, there is no place for liquid or air to accumulate between the lung and the chest wall. Eradication of the pleural space is usually accomplished by injecting an agent into the pleural space that will result in fusion of the visceral and parietal pleura. Fusion of the visceral and parietal pleura is called pleurodesis.

The ideal agent for pleurodesis should be inexpensive, widely available, have no systemic effects, not cause the patient distress, and not require hospitalization. Unfortunately, there is no ideal agent of which I am aware. The agent most commonly used in the English-speaking world is talc [1], but its administration is associated with the development of adult respiratory distress syndrome (ARDS) in a small percentage of patients [2]. The second most commonly used agent is a tetracycline derivative, for example doxycycline or minocycline, but intrapleural injection of these agents sometimes causes intense chest pain [2]. The third most commonly used agent is bleomycin, but it is expensive (~$1000) and it should not be used for pneumothorax because it does not achieve pleurodesis in a normal rabbit [3].

Over the last decade, several new agents have been proposed as good agents for pleurodesis. These include silver nitrate, iodopovidone (betadine), transforming growth factor beta (TGFβ), OK432, and lipoteichoic acid-T. This article summarizes the information available for these agents.

Silver nitrate

Studies on animals have demonstrated that intrapleural silver nitrate is an effective pleurodesing agent. In the past, silver nitrate was used extensively as a pleurodesing agent [4]. However, its use was abandoned because of severe side effects, namely, severe chest pain and the production of pleural effusions. In the past silver nitrate concentrations of 1 to 10 % were used [4]. Vargas and colleagues [4] postulated that silver nitrate could still be an effective pleurodesing agent if lower concentrations were used. They administered, intrapleurally, 2 mL 0.5 % silver nitrate to rabbits and demonstrated that the pleurodesis resulting from this dose of silver nitrate is equivalent to that resulting from 35 mg kg^{-1} tetracycline [4] and better than that resulting from 400 mg kg^{-1} talc [5, 6]. Pleurodesis after intrapleural silver nitrate persists for at least one year [6]. Marchi et al. [7] have shown there is a systemic inflammatory reaction after silver nitrate is given intrapleurally; this is

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manifested by an increase in serum LDH and IL-8 levels and an increase in the VEGF level in serum. This same group demonstrated that if 0.1 % silver nitrate is given three times rather than 0.5 % silver nitrate once, systemic inflammation is markedly reduced, but the extent of pleurodesis is not altered [8]. Tremblay [9] et al. demonstrated that administration of 2 mL 0.05 % silver nitrate daily for 14 days results in adequate pleurodesis. Tremblay et al. [10•] also demonstrated that use of silver nitrate-eluting indwelling catheters in rabbits and lambs over a 14-day period results in pleurodesis.

Silver nitrate was probably the first agent used to produce pleurodesis and is very effective [11]. In the 1980s, silver nitrate was replaced by tetracycline probably because of severe side effects seen after intrapleural injection of high concentrations of this agent. Subsequent studies on rabbits demonstrated that a lower concentration of silver nitrate (0.5 %) was as effective as tetracycline, 35 mg kg^{-1}, in achieving pleurodesis [4]. Moreover, this dose of silver nitrate is superior to 400 mg kg^{-1} talc in producing pleurodesis in rabbits [5].

Two clinical studies have evaluated the efficacy of silver nitrate in inducing pleurodesis in patients with malignant pleural effusions [12, 13••] and one study [14] has evaluated the efficacy of silver nitrate in patients undergoing video-assisted thoracoscopic surgery (VATS) for primary spontaneous pneumothorax. Paschoalini et al. [12] randomized 60 patients with malignant pleural effusion to receive either 5 g talc slurry or 20 mL 0.5 % silver nitrate through a chest tube. For the 47 patients who returned for follow-up, the silver nitrate tended to be more effective than talc [12]. There was no recurrence of the effusion in 96 % of the patients who received silver nitrate and in 84 % of the patients who received talc slurry [12]. In a later study [13••], pleurodesis was performed as an outpatient for 65 patients with malignant pleural effusion; after 30 days recurrence had occurred in 2 of 48 hemithoraces (4 %). Silver nitrate also seems to be effective with pneumothorax. Marcheix et al. [14] subjected 603 patients with primary spontaneous pneumothorax to VATS. At the time of VATS blebs were subjected to endostapling and then the parietal pleural was sprayed with 100 to 150 mL 1 % silver nitrate [14]. Long-term recurrence in this study was only 1.1 % [14]. These studies suggest that silver nitrate should be regarded as a reasonable alternative to other commonly used pleurodesing agents, for example the tetracycline derivatives or talc slurry, for treatment of malignant pleural effusions or pneumothorax.

Iodopovidone (betadine)

Iodopovidone (betadine) is an inexpensive and widely available topical antiseptic. There has been one study on rabbits evaluating the efficacy of iodopovidone [15]. Guo and associates [15] administered 2 mL 2 % or 4 % iodopovidone intrapleurally to rabbits and reported that pleurodesis was equivalent to that produced by 10 mg kg^{-1} doxycycline. If 0.8 mg kg^{-1} triamcinolone was administered weekly intramuscularly to the rabbits that received iodopovidone, the extent of pleurodesis was markedly reduced [15].

It seems that iodopovidone is an effective agent for producing pleurodesis. Olivares-Torres et al. [16] injected 100 mL 2 % iodopovidone into the pleural spaces of 40 patients at the end of a thoracoscopic procedure and to 12 patients via tube thoracostomy. They reported that for 50 of the 52 patients (96 %) there was a complete response with no reaccumulation of the fluid [16]. Three patients developed intense pleuritic pain and systemic hypotension after intrapleural instillation of the iodopovidone, but there were no fatalities [16]. In a second study [17, 18], 37 patients with malignant pleural effusions were given 100 mL 2 % iodopovidone through their chest tube and there was no recurrence of the pleural effusion in 32 (86.5 %) [17, 18]. In a third study [19•], which was a randomized controlled study, 45 patients with metastatic breast carcinoma were randomized to receive 4 g insufflated talc at thoracoscopy or 50 mL 2 % iodopovidone through a chest tube. Post-procedure, 18 % of the patients who received talc and 0 % of the patients who received iodopovidone required analgesics for severe pleuritic chest pain [19•]. Recurrence at mean follow-up of 22.6 months was similar in each group (~10 %) [19•]. Agarwal et al. [20••] recently performed a systematic review and meta-analysis of patients with either malignant pleural effusions or pneumothorax who had received iodopovidone for pleurodesis. They found 13 studies with 499 patients and reported that overall success was 88.7 %. Success was not affected by the method of delivery (thoracoscopy 94.2 %, n=121, tube thoracostomy 89.6 %, n=378) or whether the procedure was performed for malignant pleural effusion (89.2 %, n=361) or pneumothorax (94.9 %, n=138) [20••]. There is one report [21] from Germany of three patients who received 200–500 mL 10 % iodopovidone solution and developed blindness. However, this dose is approximately 25 times larger than the recommended dose. None of the other studies have reported problems with sight. Iodopovidone should also be regarded a reasonable alternative to other commonly used pleurodesing agents, for example tetracycline derivatives or talc slurry.

Transforming growth factor beta (TGF-β)

Without a doubt, cytokines are involved in the production of pleurodesis, but the importance of different cytokines in inducing either fibrosis or repair remains to be determined. It is likely that in the future that pleurodesis will be achieved

by intrapleural injection of cytokines. One cytokine that is an excellent candidate as an effective pleurodesis-inducing agent is transforming growth factor β (TGF-β). TGF-β has several characteristics that would be important for a pleurodesis agent [22]:

1. TGF-β is a potent fibrogenic cytokine that regulates extracellular matrix production. In situations in which there is too much TGF-β, fibrosis results [22]. Transient overexpression of TGF-β in the rat lung leads to marked pleural and interstitial fibrosis [23].
2. Once present, TGF-β can induce its own transcription [24], which suggests that a single injection may be sufficient.
3. Mesothelial cells express and secrete TGF-β; therefore, one intrapleural injection of TGF-β might result in prolonged secretion of TGF-β, which could result in pleurodesis.
4. Incubation of human pleural mesothelial cells with TGF-β results in secretion of increased levels of plasminogen activator inhibitor 1 (PAI-1) [25]. This could facilitate pleurodesis because inhibition of the fibrinolytic system is thought to be necessary for induction of pleurodesis [26].

Our studies on both rabbits [27] and sheep [28, 29] revealed that intrapleural injection of small amounts of TGF-β results in better pleurodesis than does the intrapleural injection of either doxycycline or talc slurry. Pleurodesis occurs faster after TGF-β than after talc [30]. Moreover, the pleural fluid that results from intrapleural injection of TGF-β is characterized by a much lower WBC count and LDH level than the fluid that results from intrapleural injection of doxycycline or talc slurry [27]. The lower pleural fluid WBC count and LDH level suggest there is less inflammation and this might be associated with less chest pain and fever if TGF-β were injected into humans. The pleurodesis after intrapleural TGF-β is not inhibited by corticosteroids [31]. We believe that TGF-β produces a fibrotic reaction in the pleural space without the need for pleural injury. If indeed this is the situation, TGF-β will be an ideal agent for pleurodesis. Clinical trials are necessary to test the effectiveness and safety of TGF-β as an agent for pleurodesis in humans.

OK-432

OK-432 has been used in Asia since 1992 [32]. However, it is included in this article because it is new to the western world. OK-432 is obtained from the SU strain of *Streptococcus pyogenes* and is both immunostimulating and cytotoxic. It has properties similar to *C. parvum* which has been used in the past to induce pleurodesis. In rats, OK-432 (0.3 KE kg^{-1}) is less effective than talc (400 mg kg^{-1}) in inducing pleurodesis at 30 days [33]. In Japan, it is regarded by some as the sclerosing agent of choice [34]. Response as high as 75 % has been achieved. In one study, administration of a combination of OK-432 and 30 mg doxorubicin resulted in complete control of effusion for 80 % of patients [35]. In another study, a combination of OK-432 and cisplatin resulted in complete control of effusion for 180 days in 87 % of 15 patients whereas OK-432 by itself resulted in control in only 47 % of 17 patients [36]. In a recent study [37] of 75 patients with malignant effusions due to breast cancer, overall success was only 70.5 %. These results with OK-432 seem to be inferior to those with silver nitrate or iodopovidone. To my knowledge, OK-432 is available only in Asia.

Lipoteichoic acid-T

Lipoteichoic acid-T (LTA-T) is a cell wall ribitol polymer from Gram-positive organisms which increases inflammation via the Toll-like receptor 2 (TLR2) [38]. There have been no animal studies evaluating this agent. There has been one paper [39] that evaluated the efficacy of this compound in inducing pleurodesis. In this phase one study, 14 patients were given one dose of LTA-T after having an indwelling catheter in place for seven days. Three patients each received 250, 375, 750, and 1500 μg and one patient received 3000 μg [39]. The patient that received 3000 μg developed a systemic inflammatory reaction probably attributable to the trial drug and needed hospitalization [39]. Otherwise there were no other significant adverse effects except for a small but significant increase in peripheral WBC. The rate of pleural fluid production in the seven days after LTA-T was significantly lower than pleural fluid production before LTA-T. Starting seven days after LTA-T administration the pleural catheter was not used unless it was needed. Over the next three weeks only three patients needed to have their pleural fluid drained and after this time 12 of the 13 patients did not require drainage [39]. The results of this study are encouraging and suggest the LTA-T may become an effective adjunct to treatment with indwelling catheters.

Tigocycline

Tigocycline is a new antibiotic structurally related to minocycline with molecular characteristics similar to those of tetracycline [40]. Daddi et al. [40] compared the pleurodesis that resulted from intrapleural injection of 200 mg kg^{-1} talc slurry into normal rabbits with that induced by 0.5 to 50 mg tigocycline. They reported that tigocycline at doses of 25 and 50 mg induced better

pleurodesis than did talc slurry 200 mg kg^{-1}. No human studies of tigocycline-induced pleurodesis have been reported. It is not clear that tigocycline has any advantages over doxycycline or minocycline in inducing pleurodesis.

Conclusion

Silver nitrate, iodopovidone (betadine), transforming growth factor beta (TGFβ), OK432, lipoteichoic acid-T, and tigocycline all seem capable of inducing pleurodesis after intrapleural injection. The two most promising agents seem to be silver nitrate and iodopovidone. Both agents effectively induce pleurodesis in both humans and animals that is comparable with that induced by talc or tetracycline derivatives. Transforming growth factor beta (TGFβ) is the most effective agent in animals but has not been evaluated in humans. OK432 is only available in Asia. Lipoteichoic acid-T has only been evaluated in one study. Tigocycline has not been evaluated in humans.

Conflict of Interest Richard W. Light owns part of the patent on TGF beta for pleurodesis.

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- •• Of major importance

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