Intrapleural Streptokinase in the Management of Malignant Multiloculated Pleural Effusions*

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Objective: Pleural effusions are a frequent complication of malignancy and cause considerable morbidity from dyspnea. The drainage and control of malignant effusions relieve symptoms and maintain quality of life but these are difficult in patients with multiloculated effusions in whom drainage usually fails. This observational series reports the use of intrapleural streptokinase (IPSK) in the management of malignant multiloculated pleural effusions resistant to standard chest tube drainage.

Methods: Ten consecutive patients with malignant multiloculated pleural effusions, aged 39 to 89 years, were given 250,000-IU doses of IPSK twice daily after failure to drain the effusions with a standard chest tube because of multiloculation and multiseptation, as demonstrated by CT or ultrasound scanning. Outcome was assessed by radiographic improvement and symptom control.

Results: All 10 patients responded to between 500,000 and 1,500,000 IU of streptokinase. There was an increase in pleural fluid drained (mean volume ± SD: pre-IPSK, 843 ± 690 mL; post-IPSK, 2,368 ± 1,051 mL; p < 0.001, paired t test), and radiographic improvement was seen in all 10 patients. All subjects tolerated the instillation of streptokinase well. One subject required opiate analgesia for transient chest pain, and there were no hemorrhagic or allergic complications. One patient died of unrelated septicemia.

Conclusions: This series suggests that IPSK may be useful in the drainage of malignant multiloculated pleural effusions in patients who fail to drain adequately with a standard chest tube. Malignant pleural effusions should not be considered a contraindication to IPSK.

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Key words: intrapleural streptokinase; malignant; pleural effusion

Abbreviation: IPSK = intrapleural streptokinase

Malignant pleural effusion is a frequent complication of malignancy estimated to affect 100,000 patients/yr in the United States and may result in significant morbidity.1 The drainage of malignant effusions promptly relieves dyspnea, maintains quality of life, and can often be achieved by simple thoracocentesis or chest tube drainage. This approach frequently fails in patients with multiloculated effusions, in which fibrinous adhesions impede free fluid drainage, leaving a persistent pleural effusion and dyspnea (Fig 1).1,2 Occasionally, thoracoscopic procedures may be useful in removing fibrin sheets, hence allowing pleurodesis, but this may be unacceptable to some patients.1–3

A prospective, randomized controlled trial shows that intrapleural streptokinase (IPSK) improves pleural drainage in patients with multiloculated pleural fluid collections caused by infection.4–6 In this area, there is published clinical experience to indicate the safety of this approach in several hundred patients.7–17 However, this approach has rarely been reported in the control of malignant effusions, and recent editorial opinion has suggested that IPSK is contraindicated in patients with malignant pleural effusions, despite a lack of evidence in the literature to support this view.18

We therefore report the effects of IPSK in a series of 10 consecutive patients with malignant multiloculated pleural effusions resistant to chest tube drainage alone.

Materials and Methods

During a period of 1 year (September 1996 through August 1997), the records of 10 consecutive patients from one center...
who had malignant multiloculated or multiseptated pleural effusions and had been treated with IPSK were retrospectively reviewed. All patients had cytologically or histologically proven pleural malignancy (Table 1) and were admitted for palliation of their breathlessness.

In all patients, a 12F catheter was inserted under radiologic guidance into the most dependent large fluid locule and was connected to an underwater seal. The catheters were flushed every 6 h with saline and were kept on continuous 20-cm H$_2$O suction until fluid drainage had stopped completely or until the rate of drainage had fallen to $\leq 150$ mL/d. At that time the presence of multiloculation and multiseptation was confirmed by CT or ultrasound scan, and hence patients were considered for IPSK therapy. Streptokinase, 250,000 IU, was dissolved in 30 mL 0.9% saline, and each instillation was retained in the pleural space for 2 h before unclamping the tube. Treatment was continued twice daily either until pleural drainage had ceased or to a maximum of 6 doses. During this period patients were observed for signs of anaphylaxis, chest pain, and bleeding, and patients recorded subjective changes in dyspnea. The volume of fluid drained before the administration of IPSK was recorded and was compared with the volume after IPSK therapy. All patients were considered for tetracycline pleurodesis before removal of the chest tube.

The response to IPSK was assessed radiologically and was judged according to the change in the chest radiographs from presentation (before IPSK administration) to immediately prior to the removal of the chest catheter. The radiographs were scored in consensus by two radiologists (ZT and FG). The change in the size of the pleural opacity was measured as (1) the change in the maximum linear dimension on either the posterioranterior or lateral chest radiograph and (2) the pleural collection size at baseline and post-IPSK administration expressed to the nearest 10% of hemithorax on the chest radiograph, as described previously. $^*$ Bias was avoided through the radiologists being blinded to whether a radiograph was before or after treatment.

**RESULTS**

Table 1 summarizes the clinical characteristics of the 10 patients who received IPSK. The age range was 39 to 89 years, with a mean of 64.7 years. Eight patients had received a previous thoracentesis for the same pleural effusion, and patient 5 had undergone thoracoscopic pleurodesis with talc instillation 2 months previously with subsequent recurrence of multiloculated fluid. The remaining patient had not received any intervention for the effusion before this admission. No patients were receiving systemic therapy that may have influenced the resolution of their effusion. Patient 10 was also receiving hemodialysis for chronic renal failure.

All 10 patients had an increase in the chest tube drainage volume after IPSK administration com-

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**Table 1—Clinical Characteristics**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Cancer Type</th>
<th>Area of Hemithorax Occupied at Presentation, %</th>
<th>Area of Hemithorax Occupied After Treatment, %</th>
<th>Total IPSK Received, IU</th>
<th>Pleurodesis Received Prior to Drain Removal</th>
<th>Survival After Hospital Discharge, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>F</td>
<td>Metastatic malignant fibrosarcoma</td>
<td>40</td>
<td>10</td>
<td>1,500,000</td>
<td>Yes</td>
<td>234</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>F</td>
<td>Adenocarcinoma, breast</td>
<td>50</td>
<td>10</td>
<td>500,000</td>
<td>Yes</td>
<td>53†</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>F</td>
<td>Adenocarcinoma, unknown primary</td>
<td>100</td>
<td>10</td>
<td>1,500,000</td>
<td>No</td>
<td>358</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>M</td>
<td>Mesothelioma</td>
<td>50</td>
<td>10</td>
<td>1,500,000</td>
<td>No</td>
<td>30†</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>Transitional cell carcinoma, bladder</td>
<td>70</td>
<td>10</td>
<td>1,500,000</td>
<td>No</td>
<td>295†</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>M</td>
<td>Mesothelioma</td>
<td>70</td>
<td>10</td>
<td>1,500,000</td>
<td>No</td>
<td>460</td>
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<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>Squamous carcinoma, bronchus</td>
<td>100</td>
<td>10</td>
<td>1,500,000</td>
<td>Yes</td>
<td>Died before discharge</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>M</td>
<td>Adenocarcinoma, bronchus</td>
<td>40</td>
<td>10</td>
<td>1,250,000</td>
<td>Yes</td>
<td>49†</td>
</tr>
<tr>
<td>9</td>
<td>82</td>
<td>F</td>
<td>Adenocarcinoma, breast</td>
<td>40</td>
<td>20</td>
<td>750,000</td>
<td>No</td>
<td>445</td>
</tr>
<tr>
<td>10</td>
<td>89</td>
<td>M</td>
<td>Adenocarcinoma, kidney</td>
<td>40</td>
<td>10</td>
<td>750,000</td>
<td>No</td>
<td>115†</td>
</tr>
</tbody>
</table>

*F = female; M = male.
†Patient dead at time of report.
pared with that before instillation (mean volume ± SD; pre-IPSK, 843 ± 690 mL; post-IPSK, 2,368 ± 1,051 mL; p < 0.001, paired t test). There were no hemorrhagic or allergic complications related to treatment with IPSK. Two of the patients had evidence of trapped lung after the administration of IPSK, but reported improvement in dyspnea. This was only evident on the plain chest radiograph in one patient, but a second patient showed some evidence of trapping on a follow-up CT scan. One patient experienced chest pain after the first dose of IPSK and required IV opiates. It is uncertain whether this was truly related to the IPSK as no pain was experienced during subsequent doses.

All patients reported improvement of their dyspnea after adequate pleural drainage. Radiographic improvement was seen in all patients. There was a reduction in the largest linear dimension in 9 of 10 patients (mean reduction ± SD; 6.75 ± 3.34 cm; p < 0.0001, paired t test). Eight patients had a >75% reduction in the volume of their pleural effusions. After IPSK administration, 9 of 10 patients had only a 10% area of hemithorax occupied by the pleural opacity (Fig 2). All patients reported improvement of their dyspnea.

Four patients received tetracycline pleurodesis before removal of the chest tube. The remaining patients did not receive pleurodesis for a range of reasons, including patient refusal, premature drain removal, patient preference, or poor performance status.

One patient died during admission as a result of staphylococcal sepsis. This was several weeks after drainage of the pleural effusion and chest catheter removal, and death was thought to be secondary to an indwelling IV catheter device. The remaining nine patients were all alive at discharge. Five patients have subsequently died (survival range, 30 to 295 days from discharge), and the remaining four patients are alive 234 to 460 days after discharge. All four patients who received pleurodesis have had no recurrence of effusion to date or had none before death, and of the remaining six patients only one required subsequent thoracentesis for further palliation of dyspnea. There was no difference in survival between patients who received pleurodesis and those who did not (Table 1).

**DISCUSSION**

This study reports the clinical effects of intrapleural fibrinolytics in the drainage of multiloculated malignant pleural effusions in 10 patients. When simple tube drainage had failed to completely drain effusions, the instillation of IPSK into the pleural cavity resulted in effective pleural drainage.

The use of intrapleural fibrinolytics as an adjunct to the drainage of the pleural space has been reported most commonly in pleural infection and in postoperative and traumatic hemothoraces. In these patients, the formation of loculi in the pleural space is caused by an infection-related increase in procoagulant activity and by depressed fibrinolytic activity in the pleural space. This leads to deposition of fibrin sheets, which impair free fluid drainage and which may undergo lysis by a fibrinolytic. In malignant pleural effusion, the primary mechanisms for fluid accumulation are impaired lymphatic drainage, owing to tumor occlusion of stomata on the parietal pleura, and the osmotic effect of proteinaceous malignant fluid. There may also be an inflammatory response between the visceral and parietal surfaces, increasing the procoagulant and
depressing fibrinolytic activity, leading to fibrin strands and therefore to multisepilation and multiloculation (Fig 1).

When pleural fluid becomes loculated in a patient with a malignant pleural effusion, drainage and the subsequent palliation of dyspnea become difficult clinical problems. With the increasing reports on the use of intrapleural fibrinolytics to aid drainage of infected pleural collections, we were interested to see whether IPSK could help with the drainage of malignant multiloculated pleural effusions. Recently, editorial opinion has stated that malignancy is a contraindication to IPSK, although there are no data to support this viewpoint. This concern is presumably because of a theoretical risk of hemorrhage activated by local or systemic fibrinolysis. IPSK has been shown not to activate systemic fibrinolysis in patients with empyema, and it is to be expected that there is less risk of systemic absorption of IPSK from patients with a malignancy, owing to the abnormal pleural surfaces and reduced lymphatic drainage. None of our patients experienced any hemorrhagic complications from therapy, and all subjects tolerated the procedure well. There was only one possible complication in patient 1, who experienced pain after the first streptokinase instillation but was asymptomatic with subsequent doses.

There has only been one other report of a series using intrapleural fibrinolytics, which were used in four patients with multiloculated malignant effusions who were included in a large series of patients with pleural infection. Our report adds to this small series, supporting the safety and efficacy of IPSK in malignant multiloculated effusions.

Care should be taken in the interpretation of increased pleural fluid drainage in patients treated with IPSK and in this series of malignant effusions, as effusions may re-form rapidly and produce substantial volumes of pleural drainage, which differ markedly between subjects. IPSK itself also is known to increase the volumes of fluid generated by the pleural space. The volume of fluid drained is as likely to reflect the rate of production as it is the efficacy of drainage in this clinical setting. Most importantly, in our patients there was improvement in symptoms, and radiographic change confirmed the improved drainage (Fig 2). Two of the patients had evidence of trapped lung after successful pleural fluid drainage. These patients still reported an improvement in dyspnea despite inadequate lung re-expansion.

For a range of reasons, all our patients did not receive sclerosis therapy after the successful drainage of their pleural effusion. Despite this, only one of the six patients not having pleurodesis subsequently required any further thoracentesis. This surprising observation may be because the active fibrinous pleural process responsible for these patients’ multisepilation (Fig 1) leads to pleural symphysis when the visceral and parietal pleural surfaces are brought into apposition. However, until this hypothesis is properly tested, it will remain important for all patients with recurrent pleural effusions secondary to malignancy to be offered sclerosis therapy before removal of the chest tube if there is adequate lung re-expansion.

It is important to recognize the limitations of this series. This is a retrospective review of clinical outcome in a consecutive patient series. These subjects did not, therefore, all follow a consistent therapeutic protocol. This series suggests that IPSK can be a useful adjunct in the management of patients distressed by dyspnea caused by a multiloculated effusion that is resistant to drainage, but the exact estimation of the magnitude of therapeutic benefit in this group will need to be determined from future prospective studies.

In conclusion, we report that the use of IPSK in patients with malignant multiloculated pleural effusions who fail to drain adequately with simple tube drainage can be safe and effective in aiding pleural drainage. After treatment with IPSK all patients reported improvement in dyspnea without significant complications from therapy, and all but one achieved successful long-term pleurodesis. These early data suggest that malignancy and malignant pleural effusions should not be a contraindication to the administration of IPSK to aid drainage of multiloculated fluid.

**References**

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