The Systemic Fibrinolytic Activity of Intrapleural Streptokinase

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Intrapleural fibrinolytics probably improve the drainage of loculated pleural effusions and empyemas. Studies of crude indices of systemic coagulation suggest this effect is accompanied by little systemic fibrinolysis, but few studies have assessed this in detail. This study examines the systemic fibrinolytic activity of two intrapleural streptokinase (IPSK) regimes in detail. Eight patients received a single dose of 250,000 IU IPSK, and a further eight received serial doses of 250,000 IU IPSK every 12 h for 3 d (total dose: 1.5 million IU). Each dose was retained in the pleural cavity for 2 h. Venous blood for prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, and D-dimers due to fibrin degradation were measured before any IPSK. These end points were then remeasured 24 h after IPSK in the single-dose group and after 24, 48, and 72 h in the group receiving serial doses. There were no physiologic or statistical differences in any of the indices after administration of IPSK. IPSK administered up to a dose of 1.5 million IU does not cause significant activation systemic fibrinolysis in humans. Davies CWH, Lok S, Davies RJO. The systemic fibrinolytic activity of intrapleural streptokinase.

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Pleural infection is an important cause of thoracic sepsis for which the traditional therapeutic approaches are catheter or operative drainage combined with systemic antibiotics (1). Several studies suggest that the catheter drainage of an empyema can be improved by the introduction of a fibrinolytic agent into the pleural space (2–15). Two reports suggest intrapleural fibrinolytic agents have little systemic fibrinolytic activity based on studies of simple clotting indices (13, 15), but there is only one study that has quantified this effect in detail. In this report, markers of systemic fibrinolysis were measured in 10 surgical patients given only a single dose of 250,000 IU intra-pleural streptokinase (IPSK) (16). This single dose did not cause detectable systemic fibrinolysis. Despite this encouraging result, there are isolated reports of pleural hemorrhage (13) and a systemic coagulopathy after higher doses of IPSK (17) and cumulative doses of IPSK may cause a bleeding tendency through the progressive depletion of plasma fibrinogen levels (18, 19). The systemic fibrinolytic activity of serial doses of IPSK has not been reported in humans, and without this information the accurate assessment of the safety of IPSK remains uncertain.

This study reports the detailed systemic fibrinolytic effects of both a single dose of 250,000 IU IPSK and serial doses of 250,000 IU given every 12 h for 3 d (cumulative dose of 1.5 million IU).

METHODS

The study was performed in two stages. Eight subjects had detailed measures of the peripheral blood indices of fibrinolytic activity before and after a single dose of 250,000 IU IPSK, and a further eight subjects underwent the same measures before and during cumulative administration of 250,000 IU IPSK every 12 h for 3 d (total dose of 1.5 million IU).

Sequential subjects requiring catheter drainage of a multiloculated complicated parapneumonic pleural effusion or an empyema were studied. Multiloculation was confirmed by computed tomography. Pleural fluid was analyzed for gram stain, culture, pH, lactate dehydrogenase, protein, and glucose. In all subjects, a 14 French catheter (20) was inserted under radiologic guidance and connected to underwater seal. Catheters were flushed every 4 h with saline and kept on -20 cm H_2O suction.

Intra-pleural streptokinase (Streptase; Hoechst, Uxbridge, UK) 250,000 IU was dissolved in 30 ml of 0.9% saline and retained in the pleural space for 2 h after each administration. Eight patients received a single dose of 250,000 IU streptokinase. A further eight received 250,000 IU every 12 h for 3 d (total dose of 1.5 million IU).

Venous blood was collected for prothrombin time (international normalized ration [INR]), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), and D-dimers due to fibrin degradation (DD) at baseline and 24 h after a single dose of 250,000 IU streptokinase and at baseline and within 1 h after administration of the morning dose at 24, 48 and 72 h during the regime of 250,000 IU every 12 h for 3 d. Samples for INR, APTT, and TT were analyzed immediately. Plasma for FIB and DD was stored at -70° C for later analysis. Blood for INR, APTT, TT, and FIB was analyzed by automated technique (Organon Technika, Cambridge, UK). DD were analyzed manually by latex agglutination (Organon Technika).

Changes from baseline of the coagulation indices after the single dose of IPSK were compared by paired *t* testing. Changes in the coagulation indices during the cumulative regimen were compared with analysis of variance for a one-factor experiment corrected with Duncan's multiple range *post hoc* test for multiple comparisons (SAS Software; SAS Institute, Cary, NC).

RESULTS

The clinical characteristics of the 16 subjects are described in Table 1, and the results of the coagulation indices are presented in Tables 2 and 3. There were no changes of either

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TABLE 1

DEMOGRAPHIC, PLEURAL FLUID, AND MICROBIOLOGIC CHARACTERISTICS OF THE STUDIED SUBJECTS

	Single Dose of IPSK (*250,000 IU*)	Cumulative Dose of IPSK (*total dose of 1.5 million IU*)
Subject characteristics		
Sex, male/female	8 (5/3)	8 (6/2)
Median age (range), yr	36 (19–76)	54 (35–89)
Pleural fluid analysis		
pH (median ± 95% range)	7.00 ± 6.79 to 7.14	6.75 ± 6.50 to 7.10
Glucose (median ± 95% range), mmol/L	0.5 ± 0.2 to 1.8	1.0 ± 0.5 to 2.7
Lactate dehydrogenase (median ± 95% range), IU/L	5,215 ± 3,358 to 11,343	3,712 ± 958 to 46,728
Protein (mean ± SD), g/L	46.4 ± 8.0	45.5 ± 7.0
Microbiology		
Streptococcus pneumoniae	2	3
Staphylococcus aureus	1	1
Gram/culture negative	5	4

TABLE 2

EFFECTS OF A SINGLE DOSE OF 250,000 IU IPSK ON SYSTEMIC FIBRINOLYSIS

	Baseline (SD)	Mean (SD) 24 h after IPSK	Mean Difference (SD)	95% CI of the Differences
INR	1.24 (0.11)	1.22 (0.21)	−0.02 (0.25)	−0.239 to 0.19
APTT	1.01 (0.18)	0.99 (0.10)	−0.02 (0.13)	−0.13 to 0.09
TT	1.00 (0.07)	0.88 (0.31)	−0.12 (0.30)	−0.37 to 0.13
FIB, g/L	3.57 (0.77)	3.86 (0.68)	0.31 (0.61)	−0.20 to 0.82
DD, μg/ml	< 0.6 (0.00)	< 0.6 (0.00)	0.00 (0.00)	0.00 to 0.00

Definition of abbreviations: INR = international normalized ratio; APTT = activated partial thromboplastin time; TT = thrombin time; FIB = fibrinogen; DD = D-dimers.

There are no physiologically or statistically significant differences in any of the indices (p = NS, paired *t* test).

physiologic or statistical significance in any index of coagulation at any point after either the single-dose or cumulative higher-dose IPSK regime. No patients in either group reported any symptoms related to IPSK, and there were no complications from its use. In the absence of abnormal indices of clotting on a single-patient basis, systemic bleeding is highly unlikely (18, 19). The statistical power of this small study excludes a 35% difference at 0.05 level (21).

DISCUSSION

This study reports the effects of IPSK on parameters of systemic fibrinolysis in humans. Streptokinase was used in two regimes: 250,000 IU as a single dose and 250,000 IU every 12 h for 3 d to a cumulative dose of 1.5 million IU. The results of this analysis show no physiologically or statistically significant systemic fibrinolysis at either dose.

Intrapleural fibrinolytics may be a useful adjunct in the drainage of the pleural space (2–15). However, prior to this report, there has been limited data on its human safety profile. One previous study has reported its systemic fibrinolytic actions, but this was after only one dose of IPSK when in practice serial-dose regimes are commonly used. The spectrum of doses reported in the literature range from a single dose of 100,000 to 500,000 IU and cumulative instillation doses usually up to 1.5 million IU (1–14). Because streptokinase reduces plasma fibrinogen levels in addition to fibrinolysis, cumulative doses of IPSK might also have depleted plasma fibrinogen levels, causing a bleeding tendency. This report is the first to confirm that these higher doses are still free of measurable systemic fibrinolytic actions in patients with pleural infection. We have not studied patients with a coincident systemic bleeding diathesis who might still be at a greater risk of systemic effects.

The normal systemic coagulation at the higher dose of

TABLE 3

EFFECTS OF A CUMULATIVE DOSE OF 1.5 MILLION IU (250,000 IU EVERY 12 h FOR 3 d) IPSK ON SYSTEMIC FIBRINOLYSIS

	Baseline (SD)	Mean (SD) 24 h after IPSK	Mean (SD) 48 h after IPSK	Mean (SD) 72 h after IPSK
INR	1.31 (0.14)	1.34 (0.16)	1.27 (0.18)	1.29 (0.12)
APTT	1.06 (0.10)	1.08 (0.10)	1.10 (0.12)	1.03 (0.14)
TT	1.02 (0.17)	1.04 (0.23)	1.07 (0.28)	1.06 (0.13)
FIB, g/L	727.0 (276.9)	627.3 (249)	637.5 (232.5)	656.6 (239.1)
DD, μg/ml	< 0.06 (0.00)	< 0.6 (0.00)	< 0.06 (0.00)	< 0.06 (0.00)

Definition of abbreviations: INR = international normalized ratio; APTT = activated partial thromboplastin time; TT = thrombin time; FIB = fibrinogen; DD = D-dimers.

There are no physiologically or statistically significant differences in any of the indices (p = NS, analysis of variance).

IPSK may clarify the one reported case of systemic bleeding after IPSK (16). In this case, a dose of only 500,000 IU total was used, far less than was used in this study, and yet a generalized coagulopathy developed. This patient also had evidence of disseminated intravascular coagulation and the results of our study suggest that this was likely to have been a major contribution to the bleeding in this case.

The plasma half-life of the activator complex after intravenous administration of streptokinase is 23 min with a sustained therapeutic action that leads to vascular reperfusion in myocardial infarction over 20 to 120 min (18, 19), which is the period when coagulation would be expected to be maximally disturbed. Therefore, in our cumulative study, the coagulation indices were measured less than 1 h after administration of the morning dose of IPSK to be sure of identifying the peak fibrinolytic activity.

In conclusion, IPSK administered at doses of 250,000 IU retained in the pleural cavity for up to 2 h to a cumulative dose of 1.5 million IU over 3 d does not cause physiologically significant systemic fibrinolysis and is therefore unlikely to cause systemic bleeding (18, 19). These data suggest it is safe to administer streptokinase locally to patients requiring enhanced drainage of infected pleural effusions, and that large randomized studies to assess definitively the efficacy and safety of this therapeutic approach can proceed.

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