JACC Vol. 4, No. 1
July 1984:183–5

CASE REPORTS

Clinical Failure of Streptokinase Due to an Unsuspected High Titer of Antistreptokinase Antibody

ALLAN S. LEW, MD, FRACP, TOBI NEER, MT, (ASCP), LOIS RODRIGUEZ, RN, BSN, IVOR L. GEFT, MD, FRCP, PREDIMAN K. SHAH, MD, FACC, WILLIAM GANZ, MD, CSc, FACC

Los Angeles, California

Neutralization of streptokinase by an unsuspected high titer of antistreptokinase antibody prevented activation of the fibrinolytic system and induction of a lytic state in a 62 year old man with an acute inferior myocardial infarction. There was no decrease in serum fibrinogen, minimal decrease in serum plasminogen and only a small increase in serum fibrin degradation products after intravenous administration of 1.5 million units of streptokinase. A high titer of antistreptokinase antibody, sufficient to neutralize 1.5 million units of streptokinase, was demonstrated by semiquantitative counterelectrophoresis. There was no clinical evidence of coronary artery reperfusion, and coronary angiography confirmed complete occlusion of the left circumflex artery.

Administration of streptokinase results in thrombolysis and reperfusion of the occluded infarct artery in a high proportion of patients with an evolving myocardial infarction (1–5). Streptokinase is a polypeptide produced by beta-hemolytic streptococcal bacteria that acts as an exogenous indirect activator of the human fibrinolytic system (6). Streptokinase binds to circulating plasminogen, forming a plasminogen-activator complex that generates the proteolytic enzyme plasmin from uncomplexed plasminogen (7). Thrombus-bound plasmin hydrolyzes fibrin resulting in thrombolysis, while circulating plasmin hydrolyzes circulating fibrinogen (8,9).

Antistreptokinase antibodies bind and inactivate streptokinase (10). Although low titers of antistreptokinase antibody are ubiquitous in human subjects due to past streptococcal exposure, several investigators (11,12) have demonstrated that antistreptokinase antibodies are neutralized by less than 250,000 IU of streptokinase in more than 90% of the population. Current dosage regimens allow for neutralization of these antibodies by a portion of the streptokinase administered, while leaving most of the streptokinase free to complex with plasminogen and initiate thrombolysis (12–13). A high titer of antistreptokinase antibody is produced in response to streptokinase administration and acutely after streptococcal infection (6,14). In the presence of a high titer of antibody, the usual dose of streptokinase may be ineffective, fail to activate the fibrinolytic system and, therefore, fail to effect thrombolysis.

We report a case of acute myocardial infarction in which 1.5 million units of streptokinase failed to activate the fibrinolytic system because of an unsuspected high titer of circulating antistreptokinase antibodies.

Case Report

A 62 year old white man was admitted with an acute inferior myocardial infarction after 2 weeks of effort angina. He had a 2 year history of diabetes mellitus of mature onset, had stopped smoking 1 year before this admission and had recently been in good health. There was no history of recent infection and he had not previously received streptokinase.

On the morning of admission, he had experienced a sudden onset of severe retrosternal chest pain, nausea and diaphoresis at home. He was attended by paramedical officers who noted the onset of atrial fibrillation. On arrival in the emergency room, he was pale and diaphoretic with an irregular pulse at a rate of 50 to 70 beats/min and a blood pressure of 100/70 mm Hg. There were no signs of left or right heart failure. The remainder of the examination was noncontributory.

The electrocardiogram demonstrated atrial fibrillation and changes of acute inferoposterior myocardial infarction with 2 mm of ST segment elevation in leads II, III and aVF and 1 to 2 mm ST segment depression in the precordial leads V_1 to V_6.

From the Division of Cardiology, Department of Medicine, Cedars-Sinai Medical Center, University of California, Los Angeles School of Medicine, Los Angeles, California. Manuscript received November 15, 1983; revised manuscript received January 3, 1984, accepted January 6, 1984.

Address for reprints: Allan S. Lew, MD, Department of Cardiology, Room 5314, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, California 90048.

0735-1097/84/$3.00

Laboratory investigation revealed a normal blood urea nitrogen, electrolytes and complete blood count. The white cell count was 11.0 × 10^3 per mm^3 with a normal differential. Plasma glucose was 316 mg/100 ml and the serum creatine kinase level was not elevated at 47 IU/liter with an MB fraction of 1.8 IU/liter. Serum fibrinogen was 260 mg/100 ml and serum plasminogen was 9.6 mg/100 ml (normal value 10 to 20 mg/100 ml).

Informed consent was obtained from the patient to be treated with intravenous streptokinase infusion according to our current research protocol. Hydrocortisone, 100 mg, was administered intravenously, followed by a 15 minute intravenous infusion of 750,000 IU of streptokinase, commencing 2 hours and 15 minutes after the onset of chest pain. Ninety minutes after the streptokinase infusion, there were no clinical signs of coronary artery reperfusion. A second intravenous infusion of 750,000 IU of streptokinase also failed to produce signs of reperfusion. Full anticoagulation was commenced with intravenous heparin.

Serial electrocardiography performed over 24 hours demonstrated evolution of an inferoposterior myocardial infarction with new Q waves and loss of R waves in leads II, III and aVF and a new primary R wave in lead V_1. Serum total creatine kinase and MB fraction peaked at 1,019 and 97 IU/liter, respectively, 22 hours after the onset of chest pain.

Coronary angiography on the fifth hospital day demonstrated complete occlusion of the left circumflex coronary artery and three vessel coronary artery disease. The clinical course was complicated by pericarditis and moderate pulmonary congestion.

Demonstration of antistreptokinse antibodies. Serum fibrinogen was 285 and 280 mg/100 ml at 90 minutes and 4 hours, respectively, after completion of the first and second infusions of streptokinase. Serum plasminogen was 7.8 and 7.2 mg/100 ml at 35 minutes after each of the two infusions, respectively. Fibrin degradation products were slightly elevated at 30 μg/ml, 3 hours after 1.5 million IU of streptokinase (normal value < 10 μg/ml). In this patient, neither serum fibrinongen nor serum plasminogen levels decreased after two intravenous infusions of 750,000 IU of streptokinase. This raised the suspicion that the drug either was ineffective or had been inactivated subsequent to administration. Because streptokinase from the same batch had previously proved effective in nine patients, we concluded that a serum streptokinase inhibitor had inactivated streptokinase before its complexing with plasminogen. The presence of a positive antistreptolysin O screen prompted the search for neutralizing antistreptokinase antibodies.

Antistreptokinase antibodies were demonstrated by counterelectrophoresis, using a modification of the semiquantitative technique described by Spottl and Kaiser (15). Counterelectrophoresis was performed on 1% agarose plates (32 mm × 100 mm × 2 mm) using an electrophoresis chamber and power source. Agarose (Bio-Rad Laboratories, High-M_r) dissolved in Tris, Barbital Sodium Barbital buffer at pH 8.8 was used. Two rows of identical wells, each containing approximately 10 ml, were cut into the agarose plate. The cathodic wells were filled with streptokinase (Hoechst-Roussel) at a concentration of 2,500 IU/ml and the anodic wells were filled with serum to be tested for antistreptokinase antibodies. After a 25 minute run at 25 mA, the plates were incubated at room temperature in a moist chamber for 24 hours. A precipitant line between the rows of wells indicated the presence of streptokinase antibody in the serum.

The specificity of this technique was established by testing for antistreptokinase antibodies in pooled negative serum, pooled negative plasma, pretreatment sera of 12 patients who underwent successful streptokinase thrombolysis and the pretreatment serum of 1 patient in whom streptokinase thrombolysis failed despite activation of the fibrinolytic system. No precipitant line was formed with any of these sera. The sensitivity of the technique was established by demonstration of a precipitant line in all five patients whose serum was also tested 14 days after successful streptokinase therapy, the time when a high titer of antistreptokinase antibody is expected.

Semiquantitative gel counterelectrophoresis confirmed the presence of a high titer of antistreptokinase antibody in both the pre- and posttreatment sera of our patient. A precipitant line was formed up to a dilution of 1 in 4 with pretreatment serum and up to a 1 in 16 dilution with posttreatment serum. Spottl and Kaiser (15) found a good correlation between their semiquantitative and quantitative techniques. According to their report (15), the formation of a precipitant line by counterelectrophoresis correlated with an antistreptokinase antibody titer of greater than 150 IU/ml of serum. On the basis of an estimated blood volume of 5 liters and an hematocrit of 42%, our patient would have been capable of neutralizing more than 1.5 million units of streptokinase.

Discussion

Previous studies of failure of streptokinase thrombolysis. Experimental and clinical studies have confirmed the efficacy of streptokinase as a thrombolytic agent for the treatment of acute myocardial infarction. Athough successful reperfusion has been reported in up to 93% of patients treated with streptokinase, the reasons for failure are usually unclear (16). When streptokinase fails to achieve reperfusion, it is important to determine whether activation of the fibrinolytic system has occurred. Systemic administration of streptokinase results in a marked decrease in serum plasminogen, the generation of circulating plasmin, a decrease in serum fibrinogen and a marked increase in fibrin degradation products. In vitro testing demonstrates increased plasma fibrinolytic activity. These changes are independent of whether or not thrombolysis is successful (17,18).

Failure to achieve thrombolysis and reperfusion after activation of the fibrinolytic system by streptokinase may re-

flect inadequate dosage, low plasminogen concentration in the thrombus, poor thrombus penetration by streptokinase or the presence of an older more organized thrombus in which the fibrin polymer is resistant to hydrolysis. The latter suppositions are supported by the observations that in some patients treated by intracoronary administration of streptokinase, reperfusion was achieved only after mechanical disruption of the thrombus by a guide wire (2,3), and that a delay between the onset of chest pain and the start of streptokinase therapy lowers the success rate for reperfusion (19).

Although circulating antiplasmin factors may inhibit plasmin-mediated fibrinogenolysis, they do not inhibit the formation of the streptokinase-plasminogen activator complex nor the activation of plasminogen by this complex (20). It is unlikely that they inhibit thrombolysis, which is mediated by thrombus-bound and not circulating plasmin. Therefore, in the presence of increased antiplasmin activity, systemic administration of streptokinase results in a decrease in serum plasminogen and the generation of circulating plasmin; fibrinogenolysis is attenuated or inhibited but thrombolysis may still occur.

Present patient. In our patient, streptokinase failed to initiate the fibrinolytic cascade. Neither plasminogen nor fibrinogen was consumed in contrast to the marked decrease in serum plasminogen and fibrinogen levels that accompany the induction of the lytic state by intravenous streptokinase in other patients. In our experience, patients who receive 750,000 IU or more of streptokinase demonstrated a decrease in serum plasminogen to levels less than 1% of control and a decrease in serum fibrinogen to less than 50 mg/100 ml during the 6 hours after the infusion. A small increase in fibrin degradation products, as noted in this case, has been described (21) after acute myocardial infarction, but this increase is much smaller than the marked increase to levels in excess of 500 μg/ml recorded after intravenous streptokinase fibrinogenolysis. Estimation of euglobulin lysis time was not performed in this case, but we believe the failure of streptokinase to produce a lytic state is established.

Our semiquantitative assay for antistreptokinase antibody confirmed that our patient would have been capable of neutralizing in excess of 1.5 million IU of streptokinase. The data suggest that our technique is both sensitive and specific for detecting a moderate to high titer of antistreptokinase antibody and, further, it is unlikely that our technique would identify a low titer because no precipitant line was observed in any of the pretreatment sera, even though in most of these sera, a low titer of antistreptokinase antibody was probably present.

An additional dose of streptokinase may have produced reperfusion in this patient; however, more than 8 hours had elapsed from the onset of chest pain before the mechanism of failure had become apparent, too late to achieve significant myocardial salvage.

Our patient had a positive antistreptolysin O screen without a history of recent infection. Whether this screen can identify the infrequent patient with a high antistreptokinase antibody titer is not known because both the frequency of a positive antistreptolysin O screen and its relation to the antistreptokinase antibody titer in patients undergoing thrombolytic therapy have not been investigated.

References

1. Ganz W, Buchbinder N, Marcus H, et al. Intracoronary thrombolysis in evolving myocardial infarction. Am Heart J 1981;101:4–13.
2. Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris. Circulation 1981;63:307–17.
3. Mathey DG, Kuck KH, Tilsner V, Krebber HJ, Bleifeld W. Nonsurgical coronary artery recanalization in acute transmural myocardial infarction. Circulation 1981;63:489–97.
4. Ganz W, Geft I, Maddahi J, et al. Nonsurgical reperfusion in evolving myocardial infarction. J Am Coll Cardiol 1983;1:1247–53.
5. Anderson JL, Marshall HW, Bray BE, et al. A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. N Engl J Med 1983;308:1312–8.
6. Tillett WS, Edwards LB, Garner RL. Fibrinolytic activity of hemolytic streptococci. The development of resistance to fibrinolysis following acute hemolytic streptococcus infections. J Clin Invest 1934;13:47–78.
7. Brogden RN, Speight TM, Avery GS. Streptokinase: a review of its clinical pharmacology, mechanism of action and therapeutic uses. Drugs 1973;5:357–445.
8. Alkjaersig N, Fletcher AP, Sherry S. The mechanism of clot dissolution by plasmin. J Clin Invest 1959;38:1086–95.
9. Sherry S. Fibrinolysis. Am Rev Med 1968;19:247–68.
10. Fletcher AP, Alkjaersig N, Sherry S. The clearance of heterologous protein from the circulation of normal and immunized man. J Clin Invest 1958;37:1306–15.
11. James DCO. Anti-streptokinase levels in various hospital patient groups. Postgrad Med J 1973;49(suppl):26–9.
12. Hirsh J, O'Sullivan EF, Martin M. Evaluation of a standard dosage schedule with streptokinase. Blood 1970;35:341–9.
13. Verstraete M, Vermylen J, Amery J, Vermylen C. Thrombolytic therapy with streptokinase using a standard dosage scheme. Br Med J 1966;1:454–6.
14. Kostering H, Barth U, Naidu R. Changes of antistreptokinase-titer following long term streptokinase therapy. In: Martin M, Schoop W, Hirsch J, eds. New Concepts in Streptokinase Dosimetry. Bern, Stuttgart, Vienna: Hans Huber Publishers, 1978:110–5.
15. Spottl F, Kaiser R. Rapid detection and quantitation of precipitating streptokinase-antibodies. Thromb Diathes Haemorrh 1974;32:608–15.
16. Dhall DP, Dawson AA, Mavor GE. Problems of resistant thrombolysis and early recurrent thrombosis in streptokinase therapy. Surg Gynecol Obstet 1978;146:15–20.
17. Fletcher AP, Alkjaersig N, Sherry S. The maintenance of a sustained thrombolytic state in man. I. Induction and effects. J Clin Invest 1959;38:1096–110.
18. Fletcher AP, Alkjaersig N, Sherry S. Pathogenesis of the coagulation defect developing during pathological plasma proteolytic ("fibrinolytic") states. I. The significance of fibrinogen proteolysis and circulating fibrinogen breakdown products. J Clin Invest 1962;41:896–916.
19. Schröder R, Biamino G, Leitner ERV, et al. Intravenous short-term infusion of streptokinase in acute myocardial infarction. Circulation 1983;67:536–48.
20. Spottl F, Holzknecht F. The influence of inhibitors of plasmin and plasminogen activation on the streptokinase-induced fibrinolytic state. Thromb Diathes Haemorrh 1970;24:101–12.
21. Okuno T, Nelson C. Value of determination of serum fibrin-fibrinogen degradation products in acute myocardial infarction. Am J Clin Pathol 1974;61:155–9.