Intrapericardial Minocycline Sclerosis for Malignant Pericardial Effusion*

Ilan Lashevsky, MD; Rami Ben Yosef, MD; Diana Rinkевич, MD; Shimon Reisner, MD; and Walter Markiewicz, MD

**Study objective:** To evaluate the effectiveness and safety of minocycline hydrochloride (minocycline) intrapericardially in patients with malignant pericardial effusion.

**Design:** Consecutive patients admitted to the hospital during a 32-month period received intrapericardial minocycline.

**Setting:** A 900-bed university hospital.

**Patients:** Fourteen consecutive patients with malignant pericardial effusion.

**Intervention:** Following percutaneous insertion of a pericardial drain, minocycline was administered at a dosage of 10 mg/kg every 48 h until fluid drainage stopped or until further therapy was deemed necessary.

**Measurements:** Complications associated with therapy, total minocycline requirements, immediate and late failure of therapy, and clinical and echocardiographic follow-up of at least 6 months.

**Results:** Mean amount of minocycline administered was 1.9±1.0 g given in 2.4 divided doses. Total drainage time was 5.4±2.5 days. Recurrence of malignant pericardial effusion was seen in only 1 of 14 patients. Death occurred in 10 patients due to severe metastatic disease in all. Minocycline instillation was associated with severe chest pain in seven patients, and with ECG changes suggesting pericardial or subepicardial injury in two patients.

**Conclusion:** (1) Intrapericardial minocycline instillation is very effective in preventing recurrence of malignant pericardial effusion. (2) Minocycline is irritative to the pericardium and may cause severe chest pain with transient ECG changes, suggesting pericardial or subepicardial injury.

(CHEST 1996; 109:1452-54)

**Key words:** cardiac tamponade; minocycline; pericardial effusion; tetracycline

Cardiac tamponade is an emergency situation that warrants immediate evacuation of the pericardial fluid. The initial therapy consists of evacuation and drainage of the pericardial fluid.1,2 Since the fluid tends to recur, various agents have been instilled into the pericardium to promote adhesion and obliteration of the cavity. The most widely used agent for causing pericardial sclerosis has been tetracycline hydrochloride.2-4 However, tetracycline hydrochloride is no longer manufactured for IV use in many countries, prompting the search for other agents belonging to the tetracycline family. Experimental and clinical data indicate the efficacy of minocycline hydrochloride (minocycline) in causing pleurodesis in malignant pleural effusion.5,6 In a dog model study, intrapericardial instillation of minocycline with drainage caused more cavity obliteration than drainage alone.7 We are not aware of studies evaluating the clinical use of minocycline in patients with pericardial disease. We report our experience with the use of intrapericardial administration of minocycline in consecutive patients with malignant pericardial effusion.

**Materials and Methods**

Between May 1992 and December 1994, all patients with compressive malignant pericardial effusion admitted to Rambam Medical Center were treated with pericardiocentesis and drainage, followed by intrapericardial instillation of minocycline. Pericardiocentesis was performed in the catheterization room under fluoroscopy guidance, using the subxyphoid approach. A 7F or 8F pigtail catheter was introduced into the pericardial sac and most of the fluid was drained. Minocycline was dissolved in sterile water (20 mg/mL) and administered slowly into the pericardial sac at a dose of 10 mg/kg. Drainage was stopped for 24 h to allow prolonged contact between minocycline and the pericardium. After 24 h of closing the drain, the remaining fluid was aspirated and the pericardial fluid was allowed to drain freely for 24 h. This procedure was repeated every 48 h until drainage was less than 50 mL/d. The pigtail catheter was then removed. All patients were followed up clinically and by echocardiography at bimonthly intervals for at least 6 months.

*From the Departments of Cardiology (Drs. Lashevsky, Rinkевич, Reisner, and Markiewicz) and Oncology (Dr. Ben Yosef), Rambam Medical Center, and the Technion-IIT School of Medicine, Haifa, Israel.

Manuscript received September 12, 1995; revision accepted January 17, 1996.

Reprint requests: Dr. Markiewicz, Head, Department of Cardiology, Rambam Medical Center, P.O. Box 9602, Haifa 31086, Israel.
RESULTS

There were 14 patients: 9 women and 5 men. Age range was 32 to 67 years, with mean age of 52±12 years. The primary tumor was located in the lung in five, breast in three, esophagus, stomach, lymphoma, ovary, desmoid tumor of the chest, and mesothelioma of the pericardium, each in one patient. There were 11 patients with and 3 without tamponade. All patients had large pericardial effusion (>500 mL). Mean amount of minocycline administered was 1.9±1.0 g and was given in 2.4 divided doses. The catheter was left in the pericardium for 5.4±2.5 days.

Minocycline instillation was associated with chest pain in seven patients, ECG changes in two patients, vasovagal reaction in one patient, and was followed by transient unexplained fever in one patient. The chest pain was noted during the injection of minocycline itself. The pain was severe enough to require the administration of opiates in all seven patients. In two patients, the pain was associated with diffuse transient ST-T changes on the ECG, suggesting pericardial or subepicardial injury. Mean follow-up was 5.8±5.5 months (11±6.2 months in survivors and 3.6±3.6 months in nonsurvivors). Death occurred in ten patients, and was due to disseminated carcinoma in all. Echocardiographic recurrence of the effusion was noted in 4 of 14 patients (29%): 3 of 4 had stable moderate effusion (calculated amount, 100 to 200 mL) without evidence of hemodynamic impairment; the fourth had primary mesothelioma of the pericardium and had been previously treated by percutaneous intrapericardial drainage with instillation of cyclophosphamide, systemic chemotherapy, and radiotherapy. Tamponade recurred 3 months later. He underwent repeated drainage and intrapericardial instillation of minocycline, but tamponade recurred within 2 months and, therefore, pericardial resection was performed. He was free of subsequent tamponade and death from disseminated carcinoma occurred 7 months later.

DISCUSSION

Pericardial tamponade is a life-threatening emergency requiring immediate diagnosis and relief. Simple pericardiocentesis is associated with a high rate of recurrent tamponade in patients with malignant tamponade, whereas sustained drainage provides better long-term results.1,2,8 Clinical and experimental studies suggest that pericardial drainage associated with intrapericardial instillation of tetracycline might be superior to sustained drainage alone in patients with malignant pericardial effusion.3,4,7 A randomized study is required to test this hypothesis, which was not addressed in our study. Among the many agents used to promote intrapericardial adhesions and, therefore, to reduce further the rate of recurrence, tetracycline has gained widespread acceptance because of its high effectiveness, low cost, and low rate of complications.2,4 However, tetracycline for IV injection is not available in many countries, prompting the search for other effective, nontoxic agents.

Experimental and clinical works indicate that other tetracyclines such as minocycline, oxytetracycline, and doxycycline are effective in producing pleural or pericardial adhesions and promoting cavity obliteration.7,9,10 Light et al6 have compared the effectiveness of tetracycline and minocycline as pleural sclerosing agents in rabbits. The degree of pleurodesis after the injection of 7, 10, 20, or 40 mg/kg of minocycline was comparable to that after the injection of 35 mg/kg of tetracycline, while the dose of 4 mg/kg was less effective. Doses of 20 mg/kg of minocycline were associated with an excess mortality due to the development of hemothorax. Tetracycline derivatives were more effective when the total volume of the solution was 2 mL rather than 1 mL. The mechanisms of action of tetracycline and minocycline in producing early inflammation and subsequent fibrosis of serosa appear similar.5 In a dog model, intrapericardial instillation of minocycline (20 mg/kg) was superior to the effect of drainage alone in causing pericardial adhesions and cavity obliteration.7 No damage to the subepicardium was noted following minocycline administration.7

To our knowledge, the use of intrapericardial minocycline has not been evaluated in the human. The present study indicates that minocycline (10 mg/kg, 20 mg/mL sterile water) is highly effective in preventing the recurrence of malignant pericardial effusion, but it is associated with unpleasant side effects. Pain during injection, ECG changes, and fever are commonly seen following intrapericardial injection of tetracycline.2,4 However, we have been impressed by the severity of pain noted during or immediately after injection of minocycline in seven of our patients. The prominent ECG changes noted in two subjects were not seen in our patients receiving intrapericardial tetracycline hydrochloride in the past.1,2 These side effects might be lessened by adding lidocaine to the solution of minocycline, by pretreating the patients with opiates, or by reducing the dosage or concentration of minocycline. Pharmacy cost of minocycline in Israel compares well with other accepted sclerosing agents: US $39 for one treatment of 700 mg, as compared with US $64 for bleomycin (15 mg) or US $6 for cyclophosphamide (1,000 mg).

The optimal amount of minocycline required to cause cavity obliteration is unknown. Light et al6 suggested 4 mg/kg for use in human pleura. However, higher doses of minocycline tend to cause more intense inflammation of the pleura and presumably more fibrotic response. We chose our dose of 10
mg/kg empirically and based on animal experiments. A lower dosage of minocycline may well have caused less side effects. The optimal concentration and frequency of injection of minocycline have not been determined.

Based on our preliminary experience, we continue to use minocycline, using the same protocol but injecting the drug more slowly (over a 5- to 10-min period) with careful monitoring of the ECG and of the patient response. The injection is stopped immediately if more than mild pain is noted or if ECG changes are seen. We try to ascertain that at least 200 to 300 mL of fluid is still present in the pericardial sac prior to injection and verify that fluid can be aspirated freely from the tip of the pigtail catheter prior to injecting the drug. Too few patients have been so treated to draw conclusions.

Though the prognosis of malignant pericardial effusion is generally poor, many patients may enjoy an appreciable survival with an adequate quality of life following permanent relief of tamponade. Our preliminary experience strongly suggests that intrapericardial minocycline, associated with drainage, may help prevent recurrent tamponade in these patients.

REFERENCES
1 Markiewicz W, Borovik B, Ecker S. Cardiac tamponade in medical patients: treatment and prognosis in the echocardiographic era. Am Heart J 1986; 111:1138-42