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# Pharmacokinetics of intrapericardial administration of 5-fluorouracil

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**Abstract** A 30-year-old patient with metastatic breast adenocarcinoma was diagnosed as having a malignant pericardial effusion. *Methods*: The patient was treated with two courses of 200 mg 5-fluorouracil (5-FU) followed by 20 mg cisplatin 5 h later directly infused into the pericardial space through a catheter. The drug levels of the 5-FU were monitored during the second treatment. The half-life of 5-FU in the pericardial space was 168.6 min with a concentration of 0.113 mg/ml still detected at 5 h. The area under the curve (AUC) was estimated to be 4.739 mg h/ml. The plasma concentrations of 5-FU ranged from 0.022 to 0.04 mg/ml throughout the infusion. *Results*: There was no significant change in the patient's blood counts or chemistry profile. She did not experience any side effects during the treatment. A pericardial window was performed 2 days later when balloon pericardiectomy was unsuccessful. The patient eventually succumbed to her disease 4 months later, but without evidence of pericardial effusion. *Conclusions*: We conclude that pericardial infusion of 5-FU allowed a high concentration of 5-FU to be achieved within the pericardial sac with a greatly increased half-life over that of systemic 5-FU treatment (168 min vs 6–20 min), and with little systemic toxicity.

**Key words** 5-Fluorouracil · Pharmacokinetics · Malignant pericardial effusion · Breast cancer

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## Introduction

Pericardial infusions of chemotherapeutic agents have been used infrequently to treat malignant pericardial effusions (for review, see reference 13) from breast [2, 7, 9, 14], cervix [5], and lung [9, 12] cancers. A few cases have been reported and even fewer reports have detailed clinical information or follow-up data, and thus few treatment regimens are available in the literature. There are a few reports of successful pericardial treatment of metastatic breast disease with chemotherapy [2, 7, 14]. Pericardial infusion using cisplatin has also been reported for the treatment of metastases from lung [1, 4, 12] and breast cancer [1, 4]. There is one report of successful 5-fluorouracil (5-FU) treatment in three patients with metastatic cancers of unknown primary [11]. We report here a pharmacokinetic study of intrapericardial administration of 5-FU in a patient with metastatic breast cancer.

## Case history

A 30-year-old Caucasian female was first diagnosed in February 1995 as having adenocarcinoma of the left breast with metastases to the bilateral cervical lymph nodes and the left anterior chest wall. Her disease progressed in spite of chemotherapy with cyclophosphamide, doxorubicin and 5-FU (CAF) as well as paclitaxel and vinorelbine. She was admitted because of increasing bone pain over the thoracic spine and dyspnea. On physical examination, the patient was tachypneic with a respiratory rate of 40/min and sinus tachycardia at 140/min. She had multiple enlarged bilateral cervical and axillary lymph nodes and diffuse skin metastases in the left anterior chest wall. Chest X-radiography showed a bilateral pulmonary infiltrate consistent with lymphangitic metastases, cardiomegaly and new lytic lesions in the thoracic spine. Echocardiography revealed a large pericardial effusion with a collapse of the right atrium

and ventricle during diastole. The patient was deemed too ill to undergo a pericardial window operation. A pericardial catheter was inserted percutaneously to drain the pericardial effusion which was found to contain malignant breast cancer cells. The patient's dyspnea improved following immediate removal of 850 ml of straw-colored pericardial effusion. Over 500 ml of effusion reaccumulated in 24 h, and it was decided to instil chemotherapy into the pericardium to control the pericardial effusion. The patient was also treated with intravenous (i.v.) 130 mg VP-16 and 2000 mg ifosfamide with Mesna daily for 3 days, concurrently with the pericardial infusion.

Because the patient developed fever 2 days later and an attempt at balloon pericardiectomy was unsuccessful, a pericardial window was performed. She also received daily radiation to her spine, vancomycin, tobramycin (for concurrent urinary tract infection with *Klebsiella pneumoniae*) and morphine sulfate. Grade 3 leukopenia occurred in the second week and disappeared in 5 days with the use of granulocyte colony-stimulating factor. Her condition gradually improved, and she was discharged home 3 weeks from the date of admission. She succumbed to her disease 4 months later without clinical evidence of recurrent pericardial effusion. No postmortem examination was done.

## Methods

### Drug administration and sampling

The patient was treated on the first day with 200 mg 5-FU in 100 ml 5% dextrose in water (D5W) into the pericardium. The drug was left in place for 5 h, then all fluid was removed and 100 ml D5W containing 20 mg cisplatin was instilled into the pericardial sac and left overnight. The following day, all fluid present in the pericardium was again removed and the patient received a second infusion of 5-FU 200 mg in 100 ml D5W into the pericardial space over a 10-min time period, which remained in place for 5 h. Pericardial fluid and blood were removed before, and 15, 25, 75, 150, 270 and 330 min after the initiation of the instillation of the 5-FU.

### Specimen preparation

Pericardial fluids were spun at 1500 rpm to remove debris and cellular material and the supernatants were immediately frozen at −20 °C. The blood was collected in heparin-containing tubes and spun at 1500 rpm for 15 min at 4 °C. Plasma was removed and frozen immediately at −20 °C. Prior to high performance liquid chromatography (HPLC) analysis, the samples were thawed and mixed with iced methanol to a final concentration of 60%, left on ice for 15 min, then spun at 2000 rpm for 15 min. The supernatant fluid was transferred to a second tube, then dried in a Speed-Vac (Savant Instruments) for 5 h. The dried samples were stored at −20 °C until used.

### HPLC analysis

The dried samples from the above procedure were reconstituted to 1/10 their original volume in distilled HPLC-grade water. The 5-FU in the extracted samples was measured using HPLC (Varian Instruments, Palo Alto, Calif.). The HPLC was performed using a Waters μBondapak C18 column (4.6 × 250 mm; Millipore; Milford, Mass.) and 5 m*M* $(n\text{-Bu})_4N^+HSO_4^-$ and 5 m*M* potassium phosphate, pH 7, [6] eluting isocratically. The location of the 5-FU peak was confirmed by the use of an authentic 5-FU standard (Sigma; St. Louis, Mo.). The concentrations of the samples were calculated by comparing the peak size with that of a spectrometrically determined concentration of the 5-FU standard. The area under the curve (AUC) was calculated using the trapezoidal rule and the half-life was determined using a linear least squares fit of the measurable data points from the equation for the slope of the line [8].

## Results

### Pericardial and plasma concentrations of 5-FU

The 5-FU instilled into the pericardium at a concentration of 2 mg/ml over a 10-min time period, at its peak 45 min after the initiation of the infusion, was found to be 1.74 mg/ml (13 m*M*; Fig. 1). The actual peak would probably have been higher if measured after a shorter time period. By 5 h the concentration was measurable at 0.113 mg/ml (0.87 m*M*). The AUC was estimated to be 4.739 mg h/ml, and a half-life of 168.6 min was determined. The plasma concentrations were obtained using HPLC (Fig. 1) and remained approximately the same with a range of 0.022 to 0.04 mg/ml (0.16–0.39 m*M*). Extrapolated to zero on the *y*-axis, the concentration line intersected at close to 2 mg/ml (15 m*M*), the starting concentration.

### Patient performance parameters

The patient was monitored carefully in the coronary care unit during pericardial infusion treatment. The morning after the first treatment, the patient reported that she felt

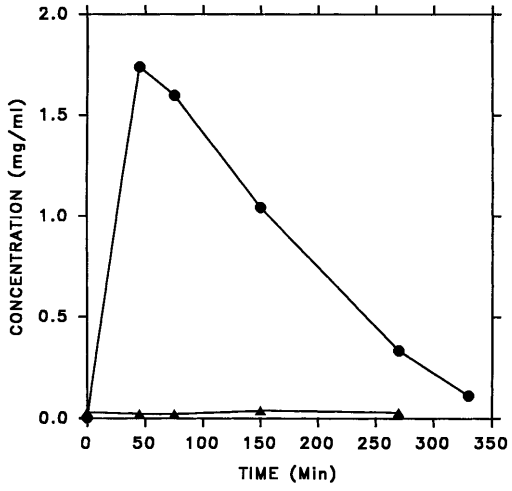


**Fig. 1** Concentration of 5-FU measured in the pericardial sac (●) and in the plasma (▲) over time. 5-FU was instilled into the pericardium immediately following the collection of the time zerosample and remained in the pericardium until all the fluid had been removed at 330 min

better and was breathing more easily. Standard laboratory measurements of electrolytes, liver function, and complete blood counts before and during treatment were unchanged. Throughout the treatments, there were no changes in her vital signs, and the patient reported no chest pain or increase in shortness of breath. There was also no nausea/vomiting, diarrhea or mucositis in the oral cavity. Neutropenia was observed 1 week later and was thought to result from the concurrent i.v. chemotherapy.

## Discussion

There have been sporadic reports of pericardial instillation of drugs for the treatment of various illnesses, including tuberculosis [10] and metastatic effusions (for review, see reference 13). In spite of many of the reports describing successful treatment with good patient tolerance, there are no reports of pericardial and systemic drug levels during treatment, and there are no standardized treatment regimens as the procedure is performed only sporadically. We believe this is the first report of pericardial treatment of metastatic disease during which drug levels in the pericardial fluid and plasma were measured and in which the combination of 5-FU and cisplatin was used.

The patient was severely debilitated, and her disease was rapidly progressing despite previous systemic chemotherapy, including 5-FU. It was determined initially that she was not a good candidate for performing a pericardial window because of poor respiratory risk. We decided to perform pericardial infusion of 5-FU and cisplatin so that a high local concentration of drugs could be achieved at the site of metastasis, with lower systemic toxicity. The patient was also given i.v. chemotherapy in order to control systemic disease.

Despite the patient's debilitated condition, the treatment was well tolerated as reported in nursing notes and by laboratory parameters. The patient succumbed to her systemic disease 4 months later with no evidence of pericardial effusion. According to Smith et al. [9] and Vaitkus et al. [13], if a patient is treated pericardially with no evidence of further effusion, then the patient is considered to have been successfully treated, regardless of the eventual clinical outcome of the underlying disease. Since systemic chemotherapy was given and a pericardial window was also placed later, we cannot attribute the successful local treatment to any one therapy; however, the measurements of 5-FU levels would allow us to administer pericardial chemotherapy better in future patients.

It is apparent that high concentrations of 5-FU (1.7 mg/ml) can be achieved with minimal toxicity by pericardial infusion as compared with systemic treatment. More significantly, the 5-FU half-life of 168.6 min in the pericardial space is much longer than can be achieved when 5-FU is given i.v. (6–20 min) [3]. The higher concentrations and longer half-life should allow a longer duration of 5-FU contact with the cancerous cells with minimal systemic toxicity, since the plasma levels of 5-FU remained low (Fig. 1). This is consistent with the assumption that 5-FU clearance from the pericardial space was limited by the intrinsic inability of the diseased pericardium to clear pericardial fluid. This inability may very among patients with different diseases. Thus our pharmacokinetic results may not be generally applied to other patients. We believe that a higher dose of 5-FU can be administered safely ($>200$ mg) based on our pharmacokinetic study. The optimal dose and schedule of intrapericardial 5-FU remains to be determined, however. This is only one case report and thus extensive conclusions for future treatment are not possible. More cases need to be investigated so that a standard treatment regimen can be formulated.

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