Creatine Kinase Elevation Associated with 5-Fluorouracil and Levamisole Therapy for Carcinoma of the Colon

A Case Report

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BACKGROUND. There have been no reports of creatine phosphokinase (CK) elevation during levamisole administration. There is only one prior report of CK elevation of noncardiac origin associated with 5-fluorouracil.

METHODS. A 41-year-old man was diagnosed with Stage B2 colon carcinoma and underwent extensive surgical resection. Adjuvant therapy with 5-fluorouracil and levamisole was initiated after surgery. A complete hematologic and chemistry profile was obtained during weekly clinic visits.

RESULTS. The patient's serum CK levels were normal prior to the initiation of chemotherapy but began to rise after 4 weeks of therapy. Isoenzyme analysis revealed that the CK was 100% from skeletal muscle. When the CK level surpassed 1,000 U/L, chemotherapy was discontinued. The CK levels began to decline immediately, falling to normal within 2 months. All attempts to identify a known cause of the enzyme elevation were negative.

CONCLUSIONS. The temporal relationship between chemotherapy administration, enzyme elevation, and the rapid fall in enzyme levels upon discontinuation of treatment argue strongly in favor of chemotherapy as the etiology of CK elevation in this patient. ***Cancer* 1996; 77:1250–3.** © *1996 American Cancer Society.*

KEYWORDS: colon carcinoma, creatine kinase, enzymes, fluorouracil, levamisole.

Colorectal carcinoma is one of the most common malignancies in the United States. It is the third most commonly diagnosed cancer in men (after prostate and lung carcinoma) and women (after breast and lung carcinoma). It is estimated that in 1996, 133,500 people will be diagnosed with colorectal carcinoma and that some 54,900 will die from this disease.[1]

The majority of patients with this disorder will have disease that can be surgically resected. However, many who were thought to have earlier stage disease will be diagnosed with Duke's Stage B2 (T3,T4 N0 M0, penetration through the serosa) or Stage C disease (any T N1–3 M0, regional nodal involvement) at surgery. Although these patients may undergo a complete resection, they are still at significant risk for disease recurrence. These patients have become the center of research on adjuvant therapy. Adjuvant trials have employed radiation, immunotherapy, and chemotherapy.

In 1990, Moertel and colleagues[2] reported the results of a trial of adjuvant levamisole and 5-fluorouracil (5-FU) in over 1,200 patients with Stage B2 or C colon carcinoma. Patients with Stage B2 disease were randomized to observation or levamisole and 5-FU; Stage C patients were randomized to observation, levamisole alone, or levamisole and 5-FU.

After a median follow-up period of 3 years, patients with Stage C disease had a significant reduction in recurrence (41%) with the combination and a 33% reduction in death rate. The results with Stage B2 patients were too preliminary to draw definite conclusions. Similar outcomes were reported in a recent update on 929 patients with Stage III (Duke's C) colon carcinoma who had been followed for 5 years or more (median 6.5 years).[3] Patients receiving fluorouracil and levamisole achieved a 40% reduction in recurrence rate and a 33% reduction in death rate.

In part, as a result of this trial, levamisole was approved in 1990 for use with 5-FU as adjuvant therapy for patients with Stage C colon carcinoma. The most common adverse effects associated with the combination are myelosuppression (leukopenia and thrombocytopenia), nausea and vomiting, diarrhea, and stomatitis.[4] Arthralgias are reported to occur in 4% of patients, and 2% may experience myalgias. There are no indications of creatine kinase (CK) elevations with either levamisole[4] or 5-FU.[5]

CASE REPORT

A 41-year-old white male was diagnosed with cancer of the transverse colon in September, 1994. At surgery, a large mass measuring 10.5 × 13 × 7 cm was found adherent to the abdominal wall, greater curvature of the stomach, and small bowel mesentery. The tumor was poorly differentiated, with penetration through the bowel wall (Dukes Stage B2), with severe acute and chronic inflammation, extensive fibrosis, and abscess formation. A second mass measuring 4 × 3.4 × 0.7 cm was also found in the transverse colon. It was well differentiated, with penetration into the medial muscle but not into the peritoneum (Dukes Stage B1). There was no involvement of local lymph nodes, liver, spleen, pancreas, adrenals, or kidneys, but there was tumor in the peritoneal fat. He underwent a resection of the transverse colon, partial gastric resection, partial omentectomy, and resection of a portion of the right abdominal anterior wall. His carcinoembryonic antigen (CEA) level was 1.5 ng/mL at that time, and his preoperative CK level was within normal limits.

Immediately after surgery, his CK rose to 2,128 U/L, as would be expected after a major surgical procedure. It returned to normal 1 week after surgery. Although his disease was staged as Dukes B2, he was thought to be at high risk for recurrence owing to the poor differentiation, size, and spread of the larger tumor. A decision was made to treat him with adjuvant levamisole and 5-FU for 1 year. His first course of therapy began on October 17, 1994, 4 weeks after surgery. He was begun on 5-FU 450 mg/m^2 i.v. for 5 days and levamisole 50 mg p.o. tid for 3 days. His CK prior to chemotherapy was 47 (normal 0–183 U/L) He received 3 days of levamisole during week 3 and continued to follow the recommended schedule of weekly 5-FU (450 mg/m^2) and levamisole (50 mg tid days 1–3 every other week). His CK levels began to rise in November but remained within normal limits through the first week of December. An excessive elevation of CK was first noted on December 21. CK values remained elevated from that point onward and began a steady rise until March, 1995, when the value exceeded 1,000 U/L for the first time since his surgery (Table 1). Chemotherapy was suspended at this time. One week later, his CK level had fallen by almost two-thirds (from 1,098 to 354 U/L). Other effects associated with the therapy included mild nausea, mild mucositis, and diarrhea after the first cycle, with occasional mucositis or diarrhea thereafter. He also occasionally complained of weakness and fatigue.

TABLE 1
Creatine Kinase Values during Adjuvant 5-FU and Levamisole

Date	5-FU (mg/m^2)	Levamisole (mg/day)	CK (U/L)
10/12	—	—	57
10/17	450[a]	150[b]	47
10/19	—	—	36
10/21	—	—	38
11/2	—	—	51
11/15	450	150	80
11/23	450	—	83
11/29	450	150	113
12/6	450	—	156
12/21	450	150	270
12/27	450	—	243
1/3	450	150	205
1/10	450	—	354
1/24	450	150	346
2/7	450	150	481
2/14	450	—	583
3/2	450	150	289
3/7	—	—	1098
3/15	—	—	354
3/29	—	—	246
5/31	—	—	179

5-FU: 5-fluorouracil; CK: creatine kinase.
[a] Loading dose of 5-FU administered daily for 5 days, maintenance dose administered weekly.
[b] Levamisole administered for 3 days every 2 weeks. CK normal values: 0–183 U/L.

The CK was fractionated and found to be 100% skeletal muscle CK (MM). Tests for antinuclear antibody (ANA) and rheumatoid factor (RF) were negative, and his erythrocyte sedimentation rate was normal. An electromyelogram revealed no abnormalities. He received no i.m. injections and denied any falls, trauma, or vigorous exercise. He was scheduled for a muscle biopsy in early April, 1995, but did not report as scheduled. He was next seen in the Oncology clinic on May 31, 1995, at which time his CK had fallen to 179 U/L.

DISCUSSION

Creatine kinase (formerly called creatine phosphokinase) is an enzyme concentrated in skeletal muscle and the

myocardium, with lesser amounts also found in the brain. Creatine kinase catalyzes the conversion of phosphocreatine to creatine, which results in increased phosphate availability for energy in skeletal and myocardial muscle. CK values become elevated when muscle is damaged by myocardial infarction, alcoholic myopathy, exercise, muscular dystrophy, or delirium tremens or after trauma. CK may also become elevated by pulmonary edema, hypothyroidism, or pulmonary infarction or after acute psychotic reactions.[6]

The characteristics of CK from the brain, myocardium, and skeletal muscle differ, allowing fractionation of serum CK into isoenzymes to tissue of origin. The primary CK released from brain tissue is BB or CK1. Myocardial CK is MB or CK2, and skeletal muscle CK is also known as MM or CK3. Myocardial damage will give rise to both MB (40%) and MM (60%) isoenzymes, whereas the brain releases primarily BB (90%) along with some MM (10%).

Elevation of the MM isoenzyme follows skeletal muscle injury occurring after i.m. injections, surgery, trauma, rhabdomyolysis, and shock. The MM isoenzyme can be elevated after a myocardial infarction along with the MB fraction but only for 4–5 days. Our patient's CK was initially elevated after surgery but fell to normal levels 1 week later. It began to rise again after institution of adjuvant 5-FU and levamisole. He had no history of coronary artery disease and did not suffer from angina. He never complained of chest pain and had no evidence of myocardial infarction. Fractionation of his serum CK revealed 100% MM isoenzyme, indicating skeletal muscle damage. His CK rose steadily over the course of 20 weeks of adjuvant therapy. Upon discontinuation of therapy, the CK levels began to decline very quickly, dropping by almost two-thirds from 1,098 U/L to 354 U/L in 8 days. The temporal relationships between administration of chemotherapy and the steady rise in serum CK values accompanied by a rapid decline upon drug withdrawal strongly implicate the chemotherapy as a cause of the CK elevations.

A review of the literature failed to reveal any reports of CK elevation associated with levamisole administration. The only reference to muscle in the product labeling is an indication of myalgias occurring in 4% of patients during induction therapy with 5-FU and levamisole and in 2% during maintenance therapy with the combination.[4] There are a few reports of CK elevation after 5-FU administration.[7–9] Almost every report involves presumed myocardial damage as the cause of CK elevation. Cardiotoxicity is a well known adverse effect of 5-FU therapy, occurring in 1.6–2.3% of patients.[10] 5-Fluorouracil has been reported to cause chest pain,[8–15] accompanied by diaphoresis and nausea, myocardial infarction,[11,13,15] arrhythmias,[15] cardiac arrest,[9,15] and death.[7,11] The electrocardiogram (ECG) may remain normal or reveal changes consistent with myocardial ischemia. However, enzyme elevation is very uncommon, indicating that myocardial cell destruction does not usually occur. The cardiotoxicity is reversible in most cases, with rapid disappearance of signs and symptoms upon drug withdrawal. Risk factors include radiation therapy and coronary artery disease.

Dent and McColl[7] described chest pain and ECG changes consistent with a myocardial infarction in a 65-year-old man after he received 1 day of a 5-FU infusion (1 gm/day). Enzymes were normal at the time and he continued to receive 5-FU 600 mg accompanied by nausea, vomiting, and anginal pain. During his sixth course he also experienced an increase in serum CK and anginal pain but continued to receive 5-FU until he expired during his sixteenth course of treatment. An autopsy revealed coronary artery disease and evidence of a previous infarction.

Stevenson et al.[8] reported CK and transaminase elevation in a 33-year-old man who received 5-FU, 930 mg i.v. daily for 5 days. He developed chest pain and vomited on day 3, diffuse pleuritic pain on day 4, and chest tightness after the dose on day 5. Later in the day (day 5), he also complained of breathlessness and had ECG abnormalities (ST elevation and T wave inversion) and tachycardia. A chest X-ray revealed pulmonary edema, and he had elevated CK and aspartate transaminase (AST) levels.

There is only one report of CK elevation of noncardiac origin associated with 5-FU administration. A 24-year-old man was treated with topical 5-FU 1.25% solution in propylene glycol twice daily for psoriasis of the fingernails. A biological screening was performed after 110 days of treatment, and a total of 25 ml of solution was administered. Although he denied weakness or myalgia, his CK was elevated to 1,366 U/L (normal 0–270 U/L), with an MB fraction of 34 U/L; his SGOT (AST) was 94 (normal 14–50 U/L), and his LDH was 486 U/L. Therapy was immediately discontinued, and his enzymes fell to within normal limits within 14 days. An ECG performed at the time revealed only bradycardia. Because a literature review failed to reveal rhabdomyolysis secondary to propylene glycol, the authors concluded that the muscle damage was due to the fluorouracil, perhaps with enhanced absorption secondary to the propylene glycol.[14]

Rhabdomyolysis has also been reported with a number of other drugs, including aminocaproic acid, amphetamines, barbiturates, cocaine, colchicine, corticosteroids, opiates, tetracycline, and vincristine.[16] Our patient's only medications at the time that his enzyme levels started increasing were ranitidine 150 mg bid and ferrous sulfate 325 mg tid. Both of these agents were begun 12 days prior to his first dose of chemotherapy but were taken for only 1 month and the prescriptions were never refilled. These

agents would not account for the CK elevation that persisted for over 3 months.

There are no reports of CK elevation after levamisole administration, and levamisole has not been reported to cause muscle damage. The muscle damage caused by 5-FU appears to be seen primarily in the myocardium, skeletal muscle damage being very rare. The mechanism of fluorouracil-induced muscle damage is unknown. Proposed etiologies for the cardiotoxicity include a direct effect on the myocardium, coronary artery vasospasm, or the presence of cardiotoxic impurities in the formulation.[10] Mosseri et al.[17] provided in vitro evidence that 5-fluorouracil can cause ischemia through vasoconstriction secondary to activation of protein kinase-C.

Synergistic cytotoxicity has previously been reported with the combination of 5-FU and levamisole. Moertel et al.[18] evaluated liver function tests among 1,025 patients who were enrolled in their adjuvant trial. Significant elevations of alkaline phosphatase, transaminases, and bilirubin were reported in 149 of 376 patients (39.6%) who received the combination compared with 16.3% who received levamisole alone and 16.1% who received no adjuvant therapy.

CONCLUSIONS

There is a clear association between administration of chemotherapy and CK elevations in our patient. His CK levels began to increase after initiation of chemotherapy and fell dramatically after chemotherapy was discontinued. He had no known risk factors for CK elevation, and it must be assumed that the CK elevations were chemotherapy induced. The most likely cause of the enzyme elevation was 5-FU, although a combined effect of 5-FU and levamisole cannot be ruled out. The mechanism of this effect is unknown at this time. It should be noted that serum CK measurements are not part of the routine chemistry profile for patients who are receiving fluorouracil and levamisole therapy. This may explain why CK elevations have not been reported with this regimen before. Although this patient's CK elevation was asymptomatic and without any significant clinical sequellae, patients receiving chemotherapy with 5-FU and levamisole should be monitored for enzyme elevation.

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