Nephrology Training Program at Stanford University
School of Medicine

The Nephrology Training Program at Stanford University, under the direction of Dr. Bryan Myers, includes 16 full-time faculty members with diverse interests in basic and clinical research. The standard program is 3 yr in duration and comprises 1 yr of training in clinical nephrology and renal transplantation and 2 yr of research. However, for the individual who desires more intensive clinical training, a second clinical year may be arranged. Similarly, for the individual who desires more intensive research experience, additional training is offered. Of the 85 graduates of the training program, approximately one-third currently hold full-time appointments at universities or research institutions.

The first year focuses on clinical nephrology with rotations among the three principal teaching hospitals of Stanford. The Stanford University Hospital consultation service offers a wide variety of nephrologic problems but with emphasis on complex, multifaceted acute renal failure and immunologic renal diseases. The fellow also participates as a member of the kidney/kidney-pancreas transplant team. The other rotations are at the Palo Alto Veterans Administration Medical Center (PAVAMC) and the Santa Clara Valley Medical Center (SCVMC), where the fellow actively participates in the inpatient consultative services and the maintenance dialysis units. The patient population at the PAVAMC consists primarily of middle-aged and elderly men; the patient population at the SCVMC is an extraordinary mixture of patients with common and exotic kidney diseases, which complements the patient population at the other two hospitals to provide a well-rounded clinical experience. Weekly nephrology clinics are held at each of the hospitals. In addition, the fellow is responsible for supervising and teaching Stanford medical residents and medical students. During the research training period, the fellows have a great opportunity to develop skills in research ranging from molecular and cellular biology to the study of important problems in clinical nephrology.

Myoglobinuric Acute Renal Failure in a Cardiac Transplant Patient Taking Lovastatin and Cyclosporine

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ABSTRACT

Acute renal failure can occur in cardiac transplant patients for a variety of reasons. A case of a patient who developed acute renal failure secondarily to drug-induced rhabdomyolysis is reported. The literature regarding acute renal failure and lovastatin and other 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors is reviewed. The potential mechanisms of myoglobinuria and nephrotoxicity and the therapeutic implications are discussed.

Key Words: Rhabdomyolysis, drug induced, organ transplantation, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, cyclosporine

Lovastatin is one of the newer antilipemic drugs that decreases endogenous cholesterol synthesis by inhibiting the rate-limiting step through the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme (1). It effectively lowers cholesterol in patients after cardiac transplantation and may be
of potential benefit in preventing graft atherosclerosis. Its use has been associated with a low incidence of side effects; most important clinically are the skeletal muscle abnormalities that could manifest as asymptomatic creatinine kinase elevation; muscle pain, tenderness and malaise; and rhabdomyolysis (2). Patients at greatest risk of these muscle abnormalities are those who have an underlying illness or those who are concurrently taking medications such as cyclosporine. We present a case of myoglobinuric acute renal failure associated with the concurrent use of cyclosporine and an increased dose of lovastatin.

CASE PRESENTATION

A 57-yr-old man with a history of two heart transplantations was admitted to Stanford University Hospital on March 27, 1992, with acute renal failure. The patient had his first heart transplantation for acute renal failure of variable severity, as depicted in Table 1. Our patient would be the fifth reported case of rhabdomyolysis in cardiac transplant cases. The incidence of lovastatin-induced myopathy is about 30% in patients with concomitant cyclosporin A therapy (8).

CLINICAL AND PATHOLOGIC PRESENTATION

Rhabdomyolysis denotes injury to skeletal muscle cells that liberates their contents into the circulation,
which leads to myoglobinuria. The syndrome could be classified into five categories: (1) exertional rhabdomyolysis occurs when the depletion of muscle energy supplies causes muscle cell dissolution such as vigorous exercise, convulsive seizures, and several hereditary enzymatic disorders that impair energy production, e.g., McArdle's syndrome; (2) hypoxia-induced rhabdomyolysis as in carbon monoxide poisoning and arterial embolism; (3) primary muscle injury secondary to trauma and burns; (4) infectious
diseases affecting muscle, notably gas gangrene and tetanus; and (5) miscellaneous causes, which include numerous drugs and certain toxins including snake venoms (9).

The presenting signs and symptoms of rhabdomyolysis depend on the primary cause but usually manifest with acute muscle pain, cramps, muscular swelling, nausea, vomiting, and dark urine. Muscles may feel "doughy" and characteristically tender on physical examination. Severe myopathy or rhabdomyolysis is characterized by elevated creatine kinase, usually more than 10 times the upper limit of normal (4, 10), and an elevated myoglobin. Acute renal failure occurs in about one-third of cases, frequently associated with hyperkalemia, hyperuricemia, hyperphosphatemia, early hypocalcemia, and late hypercalcemia, which are more pronounced than other types of acute renal failure (11). These abnormalities are due to the efflux of potassium, purines (source of uric acid), and phosphate from damaged muscle cells and the influx of calcium from the extracellular compartment into muscle cells. Hypocalcemia may also be partly due to the associated hyperphosphatemia, which could inhibit vitamin D production (12, 13). During the recovery phase of the syndrome, hypocalcemia manifests as a result of the mobilization of dystrophic calcification from damaged cells and partly as a result of the mobilization of calcium from bone and soft tissues, due to an increased level of parathyroid hormone. The combination of renal hypoperfusion, volume depletion, pigment tubular casts, and renal vasocnstriction leads to acute renal failure (14). The presence of blood on dipstick without significant red blood cells on microscopic urinalysis is an important diagnostic clue and can be confirmed by increased urinary myoglobin. If myoglobin assays are not readily available, the color of the patient’s serum will differentiate if the plasma has hemoglobin or myoglobin. Clear serum denotes that it has normal plasma hemoglobin and there is no hemolysis; hence, myoglobin is causing the reaction in the urine dipstick.

Histology findings on skeletal muscle biopsy include noninflammatory myopathy with vacuolization and focal degeneration of myocytes (15) or edema and necrosis of individual muscle fibers (16). In rat models, light microscopic changes have demonstrated myofiber necrosis with interstitial edema and inflammatory infiltrate in areas of acute injury (17) and mitochondrial damage by electron microscopy (15). Electromyography and nerve conduction velocity studies may be normal despite histologic damage (5).

ETIOLOGY AND PATHOGENESIS

Since its introduction in the United States in September 1987, lovastatin has been reported to cause rhabdomyolysis associated with the concomitant intake of gemfibrozil (18, 19), niacin (2), erythromycin (20), and cyclosporine (2, 5–8). The incidence of rhabdomyolysis with combined lovastatin and cyclosporine appears to be dose-related (3–8, 18). During these episodes, the cyclosporine levels were mostly markedly elevated associated with abnormal liver function tests, which suggest the interplay of cyclosporine and hepatic metabolism with lovastatin intake. Both agents appear to undergo microsomal metabolism by the P450 cytochrome system. Recent studies have suggested possible mechanisms for this interaction.

Smith and coworkers (16) studied four HMG reductase inhibitors (HMGRI), includingLovastatin, given to rats with and without cyclosporine. They observed that high doses of HMGRI have the potential to cause cholestasis as measured by elevated serum conjugated bile acids. The addition of cyclosporine in each group more than doubled the amount of bile acids, suggesting that the interaction between HMGRI and cyclosporine was at least additive. Cyclosporine did not seem to inhibit the metabolism of lovasstatin at the microsomal level. Therefore, the decreased biliary clearance of Lovastatin by cyclosporine increases systemic plasma concentrations of Lovastatin.

Cyclosporine alone has no effect on skeletal muscle histomorphometry (16). In contrast, skeletal muscle from rats treated with high dosages of HMGRI exhibited myofiber injury characterized by necrosis and loss of individual muscle fibers, interstitial edema, inflammatory cell infiltrate, and an increase in the size and number of sarcolemmal nuclei. More severe histologic injury could be seen in animals given a combination of HMGRI and cyclosporine. In fact, comparable muscle injury was noted in rats given high doses of HMGRI and those who were concurrently given lower doses of HMGRI and cyclosporine. This further demonstrated that the interaction was likely at the hepatobiliary level, causing increased levels of lovastatin and Lovastatin enzyme inhibitor (3, 16).

Histochernical evaluation of injured muscle fibers showed that mitochondria-poor, white fibers of rats were most sensitive to HMGRI toxicity, suggesting that myopathy is associated with altered muscle energy metabolism. It was hypothesized that the muscle breakdown was a result of mitochondrial damage due to inadequate synthesis of coenzyme Q (coQ) and heme A, both members of the mitochondrial electron transport system, secondary to toxic levels of lovastatin in blood (15). HMG-CoA reductase converts HMG-CoA to mevalonate, which is also an important precursor of coQ and heme A. Although lovastatin inhibits mevalonate production, a small amount of mevalonate is preferentially diverted to coQ and heme A under ordinary conditions. This preferential diversion of mevalonate may be inadequate with in-
creased levels of lovastatin. When 0.5% mevalonate was coadministered with L647,318, an HMGRI with activity similar to that of lovastatin, skeletal muscle degeneration and the rise in bile acids associated with HMGRI were prevented. Rats supplemented with CoQ both before and during myotoxic dose of HMGRI failed to show protection of CoQ against muscle injury. However, these CoQ may have been metabolized before they reached the target muscle cells. In a preliminary study, isolated neuroblastoma cells exposed to lovastatin had an increased rate of mitochondrial oxygen consumption (16). Whether this mechanism plays a major role in lovastatin-induced rhabdomyolysis remains to be determined.

A significant correlation between renal dysfunction and an increased creatinine kinase level was found in rat models with the coadministration of cyclosporine and lovastatin compared with placebo or either drug alone, further suggesting a greater risk of rhabdomyolysis with combination therapy (17).
The onset of toxicity could not be explained by lovastatin-associated changes in cyclosporine pharmacokinetics. The volume of distribution of cyclosporine in the obese rats was lower than in normolipidemic rats. Cyclosporine in plasma is largely bound to proteins, primarily lipoproteins. A reduction, therefore, of lipoproteins by lovastatin effects the change with increased free serum levels. In our patient, his cholesterol was lowered from 291 to 203 mg/dL with increased lovastatin dose. With a lower lipoprotein level, cyclosporine could have less lipoprotein binding, leading to increased systemic bioavailability and more pronounced drug-associated toxicity, such as cholestasis.

Once rhabdomyolysis ensues, acute renal failure becomes manifest with the presence of myoglobinuria. Volume depletion appears to precipitate rhabdomyolysis-induced renal failure. Myoglobin itself could be toxic to the kidneys (21), especially in aci-
duric conditions when myoglobin dissociates into globin and ferrheme moiety. It was suggested that, aside from causing renovasodistriiction, heme proteins have a direct nephrotoxic effect by promoting hydroxyl radical formation via the Haber Weiss reaction (22), producing proximal tubular cell membrane damage by lipid peroxidation. However, recent evidence failed to show lipid peroxidation in myoglobinuric acute renal failure in rats (23). The exact mechanism by which myoglobinuria effects proximal tubular cell damage remains ill defined. It has been established that, during the initial phase of glycerol-induced myoglobinuric acute renal failure, modest renal ATP depletion occurs and microscopic kidney examination of experimental animals showed findings comparable to experimental ischemic acute renal failure (24). Needless to say, alterations in renal hemodynamics, largely ascribed to intravascular volume depletion, have been a major factor in inducing myoglobinuric acute renal failure.

TREATMENT

The key to the management of lovastatin-induced myoglobinuric acute renal failure is early recognition of the syndrome in the presence of precipitating factors such as volume depletion and concomitant drug intake. Once the diagnosis is confirmed, the offending drugs should be withheld. The timing to restart cyclosporin A to maintain immunosuppression should be based on levels and the course of recovery of renal function.

Volume repletion should be instituted as soon as possible because most of these patients are volume depleted at the time of admission. If iv replacement were inadequate or delayed for more than 6 h, acute renal failure could develop (25). In the earliest stage of oliguria, forced mannitol-alkaline diuresis can be used as prophylaxis for hyperkalemia and renal failure. A regimen of iv fluid consisting of hypotonic sodium chloride and sodium bicarbonate (sodium chloride, 110 mmol/L; bicarbonate, 40 mmol/L) in 5% glucose solution to which 10 g of mannitol per liter is added in 20% solution could be used (14,25). For a young adult weighing about 75 kg, as much as 12 L/day may be required to force a diuresis of 8 L/day or approximately 300 mL/h. Eneas and coworkers advocated that, if patients did not respond to an infusion of 25 g of mannitol and 100 mEq of bicarbonate, no further infusion should be given (21). Mannitol expands intravascular and extracellular fluid volume and decreases blood viscosity, which could improve renal perfusion. It is known to cause renovasodilation and acts as an osmotic diuretic. Bicarbonate, on the other hand, promotes urine alkalization, which appears to be protective because myoglobin is more soluble in alkaline solution. This further prevents tubular obstruction by myoglobin precipitation, which could cause acute renal failure. Maintaining a urinary pH of more than 7.5 completely prevents myoglobin precipitation in human urine, and at a pH of 6.5 to 7.5, only about 4% of myoglobin precipitates (23). In elderly patients, cautious iv fluid administration should be done and loop diuretics such as furosemide are more advisable to induce diuresis.

Despite serum hypocalcemia at the time of admission, calcium infusion is not indicated. Most of the calcium administered is deposited in injured muscle, which could worsen rhabdomyolysis and cause metastatic calcification. Acute dialysis is instituted for anuric acute renal failure, uremia, and hyperkalemia. Dialysis is usually temporary, and patients recover renal function fully.

SUMMARY

There has been increasing awareness of lovastatin-induced rhabdomyolysis with acute renal failure as-

<table>
<thead>
<tr>
<th>Daily Lovastatin Dose (mg)</th>
<th>No. of Patients</th>
<th>% of Patients</th>
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<tbody>
<tr>
<td>10</td>
<td>13</td>
<td>4.7</td>
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<tr>
<td>20</td>
<td>10</td>
<td>3.6</td>
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<tr>
<td>30</td>
<td>1</td>
<td>0.4</td>
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<tr>
<td>40</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>60</td>
<td>1</td>
<td>0.5</td>
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<tr>
<td>Total</td>
<td>30</td>
<td>10.8</td>
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*Only 30 of 277 patients have required lovastatin therapy with only one patient exceeding 40 mg.
TABLE 3. Physicians’ guidelines for transplant patients taking lovastatin and cyclosporin A

| 1. Maintain Lovastatin dose at 20 to 40 mg/day. | 2. Advise patients to report any muscle symptom as soon as possible. |
| 3. Monitor blood levels of creatine kinase (CK), cyclosporine, and liver function tests when either drug is started or increased. | 4. Withdraw or decrease dose of Lovastatin if there is an elevated CK even if the patient is asymptomatic. |
| 5. Avoid combination therapy with other antilipemic drugs such as gemfibrozil, niacin, and clofibrate. | |

associated with cardiac transplant patients taking cyclosporine. The exact mechanism is still unknown, but the incidence appears to be dose related, as shown by the patient presented in this report. Cardiac transplant patients would optimally benefit from the antilipemic effect of Lovastatin at a dose of 20 mg daily to a maximum dose of 40 mg daily (4). Patients should be advised to report any muscle symptom when they are on Lovastatin or any other HMG-CoA reductase inhibitor agents (17). When transplant patients are started on Lovastatin, creatine kinase levels, cyclosporine levels, and liver function tests should be monitored. Lovastatin should be reduced or withdrawn if elevated creatine kinase occurred, even in asymptomatic patients. Combination therapy with other antilipemic drugs such as gemfibrozil, niacin, and clofibrate (26) should be avoided. In our cardiac transplant population, we have tried to maintain a dose of Lovastatin of 40 mg daily or less (Table 2). Physicians should be aware of the potential risks of combined therapy with these drugs in transplant patients.

REFERENCES

