had invaded her home on the previous day (possibility of flea or tick bites?). She was instructed to discontinue the penicillin. A brief trial of diphenhydramine HCl (Benadryl, Parke Davis, Morris Plains, New Jersey) did not improve the symptoms. Later that day she developed chills and joint pains while the itching became even more severe. The itching exacerbated considerably 20 min after injecting one of her doses of Actrapid human insulin. This exacerbation lasted 1–2 h. A. O. was immediately started on oral prednisone, 40 mg/day, in spite of her diabetes. She was instructed to discard the vial of Actrapid she had been using and to use a fresh vial.

The symptoms vanished while she was on a 40 mg of prednisone but her BG, which had been virtually normal around the clock on the new insulin/diet regimen, now became very erratic. Therefore, we began to taper the prednisone on 6/16. On 6/17, she experienced another exacerbation of itching (20 min after injecting Actrapid insulin). Again it lasted 1–2 h. On 6/18, she returned to the office for a routine phlebotomy while on 30 mg/day of prednisone. Her body was now sparsely covered with 1 mm, pink, nearly flat papules. After the venipuncture, a number of scarlet streaks suddenly appeared on her skin. She claimed that these streaks occupied sites that she had previously scratched. A test for dermatographia was, therefore, performed and was strongly positive.

On 6/22, while on 10 mg prednisone/day she complained of new episodes of itching and occasional small hives, all unrelated to the time of insulin injections. Her BGs were now essentially normal. The prednisone was increased to 20 mg/day but a mild itching continued and her BGs again became erratic.

On 6/25, we again began to taper the prednisone but this time instructed the patient to take an oral calcium channel blocker, nifedipine (Procardia, Pfizer Laboratories, New York, New York), 10 mg, at the first sign of symptoms. This was tried at the next attack and successfully terminated all symptoms in less than ½ h. In the ensuing weeks she experienced fine hives or itching or both nearly every day, usually between the hours of 4:30 and 6 p.m. None of the episodes appeared related to insulin injections and all responded to oral nifedipine. In an effort to determine if these events were actually responding to the nifedipine or were terminating spontaneously, the patient was asked to treat subsequent episodes by biting open the nifedipine capsule and holding the liquid nifedipine sublingually for a few minutes. When she did this, the episodes terminated within 10 min. The episodes continued to occur in a progressively milder form until 7/13, about 1 mo after the initial event. Her BGs have been essentially normal throughout each day, except during menses.

Because of this benign outcome, we made no effort to establish a final diagnosis. The symptoms were characteristic of cholinergic urticaria, which is usually treated with antihistamines, specifically cyproheptadine or hydroxyzine. Differential diagnoses include delayed hypersensitivity reactions to insect bites, human insulin, or to penicillin.

Our choice of nifedipine for the treatment of dermatologic eruptions stems in part from its known action as an inhibitor of mast cell degranulation. In this role it prevents the release of histamine, serotonin, SRSA, prostanoids, etc., from mast cells that have migrated into the microvasculature and interstitium of the skin. The advantages of sublingual nifedipine relative to the aforementioned antihistamines reside in its relative freedom from significant adverse side effects and the rapid termination of its activity (about 3 h) after an onset of action within 5–10 min.

It is important to note that this medication should not be used prophylactically for the prevention of urticaria but only to treat an ongoing episode. Chronic usage for the treatment of asthma is known to cause spontaneous "breakthrough" exacerbation of asthmatic symptoms due to the excessive accumulation and resultant release of secretory granules by the mast cell population inhabiting bronchi (personal communication, Arye Rubenstein, M.D.).

To our knowledge, this is the first report of the use of a calcium channel blocking agent for the treatment of urticaria.

RICHARD K. BERNSTEIN, M.D.

**Address reprint requests to Richard K. Bernstein, M.D., 516 West Boston Post Road, Mamaroneck, New York 10543.**

# Rhabdomyolysis Associated with Hyperosmolar Nonketotic Coma

Hyperosmolar nonketotic coma (HNKC) is not rare in the older diabetic population, accounting for 5–15% of all admissions for coma associated with diabetes.[1]

Complications associated with HNKC include severe electrolyte disturbances, phosphate depletion, cerebral edema, arterial thrombosis, myocardial infarction, cardiac dysrhythmia, and azotemia. This study demonstrates another complication of HNKC, rhabdomyolysis, manifested by extreme elevations of creatinine kinase (CK), with levels to 29,000 IU/L.

## Case Report

C. J. is a 55-yr-old black man with a history of NIDDM of 10 yr duration. His diabetes had been well-controlled by diet alone. However, 7 days before admission, the patient noted progressive polyuria and polydipsia. Two days before admission, the onset of lethargy was noted by his family and he was brought to the emergency room. There was no history of trauma, seizures, or drug or alcohol abuse. He had no known cardiovascular, mental, or renal impairment before admission. He denied chest discomfort. He had been on hydrochlorthiazide for several years for treatment of hypertension. His serum potassium levels had always been normal. The dosage had not been changed.

*Physical examination.* On admission to the hospital, he was lethargic but arousable. Blood pressure was 80/40, pulse rate 120, respiratory rate 30, temperature 39°C. Physical exami-

TABLE 1
Laboratory data in a case of rhabdomyolysis associated with HNKC

| Day | Glucose (mg/dl) | CK (IU/L) | K (meq/L) | Phos (mg/dl) | Uric acid (mg/dl) | BUN (mg/dl) | Creat (mg/dl) | pH | $CO_2$ (meq/L) |
|---|---|---|---|---|---|---|---|---|---|
| 1 (a.m.) | 1415 | 6000 | 5.9 | 11.2 | 27 | 85 | 5.8 | 7.33 | 13 |
| 1 (p.m.) | — | 15778 | — | — | — | — | — | — | — |
| 2 | 668 | 29041 | 4.8 | 9.4 | 21 | 67 | 3.7 | 7.45 | 24 |
| 3 | 578 | — | 3.9 | — | — | 50 | — | — | 23 |
| 4 | 482 | 5485 | 4.4 | 4.0 | 10.5 | 45 | 2.0 | — | — |
| 5 | 254 | 1828 | 3.5 | 3.3 | 9.1 | — | 1.4 | — | — |
| 6 | 355 | — | — | — | — | — | — | — | — |
| 7 | 392 | — | 3.6 | — | — | — | — | — | — |
| 8 | 239 | — | — | — | — | — | — | — | — |
| 9 | 194 | 294 | 3.0 | 3.6 | 8.4 | 14 | 1.1 | — | — |
| 10 | 256 | — | — | — | — | — | — | — | — |
| 11 | — | 246 | 3.7 | 3.6 | 7.6 | 12 | 1.0 | — | — |
| 12 | — | — | 3.3 | — | — | 11 | — | — | — |
| 13 | — | 113 | — | — | — | — | — | — | — |

nation was only remarkable for marked dehydration. There was no evidence of infection or trauma. There was no muscle swelling, tenderness, or weakness. He became afebrile 18 h after admission.

*Admission laboratory data* were as follows: blood sugar, 1415 mg/dl; sodium, 140 meq/L; potassium, 5.9 meq/L; chloride, 92 meq/L; $CO_2$ 13 meq/L; blood urea nitrogen, 85 mg/dl; creatinine, 5.8 mg/dl; phosphorus, 11.2 mg/dl; uric acid, 27.0 mg/dl; calcium, 10.2 mg/dl; albumin, 5.4 g/dl; SGOT, 42 U/L; SGPT, 406 U/L; LDH, 485 U/L; hematocrit 52%; WBC 14,900 with 97 segs, 2 bands, 1 lymphocyte; arterial blood gas, pH 7.33. Serum acetone was positive at 1:22, serum creatinine kinase (CK) 6000 IU/L with a negative CK MB isoenzyme. The results of urinalysis were as follows: specific gravity, 1.030; pH 5.0; 1+ protein; 3+ blood; 4+ glucose; 1+ ketones; microscopic: 1–3 RBC/hpf, 10–12 WBC/hpf. The urine orthotolidine test was positive. The test for urine myoglobin was negative. Chest x-ray and EKG were unremarkable.

*Hospital course.* The patient was treated with vigorous rehydration and small doses of intravenous insulin. The blood glucose was slowly lowered to approximately 350 mg/dl within the first 24 h of therapy. A concomitant improvement in the metabolic acidosis was seen with the $CO_2$ content rising to 24 meq/L within the first 5 h of therapy without the administration of sodium bicarbonate. The CK progressively rose from the admission level of 6000 IU/L on admission to a peak level of 29,041 IU/L on the second hospital day. Thereafter, the CK decreased to normal by day 13 of the hospitalization. The CK MB isoenzyme was present only with the peak value of CK. The EKG showed no evidence of infarction. The serum creatinine, blood urea nitrogen, phosphorus, and uric acid all returned rapidly to normal values with rehydration (see Table 1).

All blood and urine cultures were negative. At no time during the hospital course did the patient develop muscle swelling or tenderness. He was discharged on the 13th hospital day on an insulin regimen.

## Discussion

The present case represents an example of HNKC complicated by rhabdomyolysis. Rhabdomyolysis is a clinical and laboratory syndrome resulting from skeletal muscle injury and release of muscle contents into the plasma. In the initial description of the syndrome, crush injuries were the predominant etiology. More recently, it has been appreciated that various nontraumatic etiologies may also give rise to rhabdomyolysis. These include alcohol, drug overdose, and various metabolic disorders including hypokalemia, hyponatremia, hypernatremia, hypophosphatemia, myxedema, and diabetic ketoacidosis.[2] We must now add HNKC to this list. We have been able to find only a single case report in the literature of HNKC complicated by rhabdomyolysis with a moderate CK elevation to 9250 IU/L.[3]

The diagnosis of rhabdomyolysis in our case was made by the marked elevation of CK in the absence of myocardial infarction. Hyperphosphatemia, hyperkalcemia, and elevations of uric acid and albumin were also noted and were due to the marked dehydration. The presence of a positive orthotolidine test in the urine in the absence of hematuria is an important clue to the presence of rhabdomyolysis, and urine myoglobin should be checked. However, the absence of urine myoglobin as in this case should not be taken as evidence against rhabdomyolysis since a positive test for myoglobin is found in only 50% of these patients.[2] While the predominant metabolic derangement was hyperosmolarity in our patient, it must be noted that there was some degree of ketoacidosis. As mentioned earlier, rhabdomyolysis has been associated with diabetic ketoacidosis[4] and this may have played some role in the present patient. Fever, as well, has been associated with rhabdomyolysis,[5] though our patient rapidly defervesed after admission, making this an unlikely cause of

rhabdomyolysis in the present case. Hypokalemia is an additional etiologic possibility, though at no time did the serum potassium significantly fall below normal during the hospitalization, and large replacement doses of potassium were not required. Although there are several possible explanations for rhabdomyolysis in patients with HNKC, the most likely explanation in uncomplicated cases such as this one is the effect of the hyperosmolarity on skeletal muscle.

**Summary**

HNKC is a relatively common condition in older diabetic patients with numerous complications. Rhabdomyolysis is another complication of HNKC and should be suspected in these patients. Elevated CK levels should be recognized as a part of the syndrome.

ERIC SCHLEPPHORST, M.D.
MARVIN E. LEVIN, M.D.

**From the Department of Medicine, The Jewish Hospital of St. Louis, 216 South Kingshighway, St. Louis, Missouri 63110.**

**Address reprint requests to Eric Schlepphorst, M.D., at the above address.**

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# Jaundice and Rash Associated with Chlorpropamide

Sulfonylurea agents may cause a drug hypersensitivity reaction manifested by rash and/or jaundice.[1,2] This case report describes a patient with cholestatic jaundice and rash possibly induced by chlorpropamide.

A 42-yr-old Oriental woman presented to the emergency room with complaints of malaise, rash, fever, and jaundice. The patient had a past diagnosis of diabetes mellitus. Six weeks before admission, the patient was started on 250 mg chlorpropamide daily. Approximately 2 wk before admission, the dose of chlorpropamide was increased to 250 mg twice daily to control her serum glucose. Two days before admission, the patient presented with jaundice to her private physician. Chlorpropamide was discontinued and insulin therapy was initiated.

Previously, the patient, a native of the Philippines, was on 5 mg glibenclamide (Euglocon) twice daily. During the preceding 2 wk, other medications the patient took included *self-prescribed* ampicillin for 2 days to decrease her temperature, followed by 100 mg doxycycline daily for 8 days prescribed by a private physician for a possible urinary tract infection.

The patient had a past infection of ascariasis, which was treated. There was no history of allergies or alcoholism.

Physical examination revealed a thin woman in no acute distress. Her blood pressure was 104/60 mm Hg, pulse 100 beats per minute, and temperature 100°F. There was a diffuse maculopapular rash over her face, arms, neck, back, and thighs. Her skin and sclera were icteric. No spider angiomas, ascites, or hepatosplenomegaly were noted. The remainder of the physical examination was unremarkable.

Initial laboratory evaluation included the following serum levels: glutamicoxaloacetic transaminase, 165 U/L; gamma glutamyl transpeptidase, 625 IU/L; lactic dehydrogenase, 575 U/L; alkaline phosphatase >350 U/L; total bilirubin, 8.6 mg/dl; cholesterol, 347 mg/dl, and glucose, 237 mg/dl. Additional laboratory tests were either within normal limits or negative: hematocrit, white blood cell count with differential, prothrombin time, mono spot, VDRL, rheumatoid factor, antinuclear antibody, antismooth muscle antibody, and stool ova and parasites.

The hepatitis profile was negative for hepatitis A IsM antibody and hepatitis B surface antigen while positive for hepatitis B core antibody and hepatitis B surface antibody. Sonogram of the gallbladder and pancreas was normal without evidence of dilated biliary ducts. Ten days postadmission, after evidence of clinical improvement and progressively decreasing liver function tests, the patient was discharged home on insulin therapy.

Both jaundice and skin rash have been associated with the sulfonylureas, especially chlorpropamide. The incidence of cholestatic jaundice and rash is 0.5% and 1.6%, respectively.[1,2] It is believed that chlorpropamide-induced cholestatic jaundice is a hypersensitivity reaction in that initial cases were associated with a rash and eosinophilia.[3]

Our patient presented with the typical picture of hypersensitivity hepatotoxicity to chlorpropamide. The patient's initial symptoms were malaise, anorexia, fever, and rash. With 5–7 days, the patient had dark urine and jaundice. The onset of jaundice was 6 wk after initiation of chlorpropamide and 2 wk after the dose was increased by 100%. Values for serum liver enzymes and bilirubin were consistent with a picture of cholestatic jaundice.[1–6]

Of interest is that the patient received glibenclamide, a second-generation sulfonylurea, for 3–4 yr. This drug is totally metabolized in the liver to two major metabolites. However, the patient experienced no adverse effects from this sulfonylurea.

The patient had received ampicillin and doxycycline. Am-