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-

picillin-related rash usually appears 4–10 days after therapy and may often resolve even if therapy is continued.[7] Our patient's rash developed 24 h after self-medication with ampicillin. To our knowledge, there are no reports in the literature describing jaundice or a hepatic picture with doxycyline. The tetracycline class may produce clinical manifestations of jaundice within 4–10 days after beginning therapy, but it is usually associated with large intravenous doses, pregnancy, and renal disease.[2]

The patient had a positive serology for hepatitis B core antibody and hepatitis B surface antibody indicating that the patient had hepatitis B in the past but was not manifesting active disease.

We want to alert the practitioner to the possibility of a drug hypersensitivity with hepatotoxicity associated with chlorpropamide. Discontinuance of the drug at the first manifestation of any allergic response such as rash may prevent cholestatic jaundice.

ANNE M. BACIEWICZ, Pharm.D.
RAYMOND DATTILO, M.D.
SANDRA E. WILLIS, Pharm.D.
JANET L. KERSHAW, M.D.

From the Department of Clinical Pharmacy Practice, College of Pharmacy, St. John's University, Jamaica, New York 11439.

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A Generalized Allergic Reaction due to Zinc in Insulin Preparation

Local cutaneous hypersensitivity reactions due to zinc present in commercially available insulin preparations (zinc insulin, zinc sulfate) have been reported.[1] One of our insulin-dependent patients, a man aged 61 yr, with diabetes duration of 21 yr and a history of intermittent treatment with various insulin preparations (NPH, lente, semilente MC, Actrapid, Novo, Copenhagen, Denmark) and/or sulfur drugs, developed an immediate generalized cutaneous allergy (urticaria) when changed from Actrapid MC to Monotard (porcine monocomponent insulin). The same generalized reaction was observed after Monotard HM (human semisynthetic monocomponent insulin).

Skin intradermal tests (Novo kit, Novo, Copenhagen, Denmark) were negative to bovine, porcine, and human insulin, but strongly positive to diluting medium for Monotard and to zinc acetate. Serum insulin-specific IgE were below the detection limit (<0.2 U/ml, Falholt[2]), and insulin IgG were moderately high (4.6 mU/ml, Christiansen[3]). The patient was completely free from allergic manifestations after switching to Actrapid HM (human semisynthetic monocomponent insulin).

This type of systemic allergy due to zinc has not been previously described and could lead to a wrong diagnosis of allergy to Monotard HM. In fact, U-40 preparations like Actrapid (MC or HM), regular insulin, and Velosulin (Nordisk, Denmark) contain the lowest amount of zinc, i.e., only what is present in the dry insulin crystals (5–8 μg Zn^{2+}/ml). Preparations such as Rapitard MC and NPH also contain the lowest amount of zinc (12–18 μg Zn^{2+}/ml). The lente "family" (Monotard MC and HM, Ultralente MC, Ultratard HM, Semilente MC) contains high amounts of zinc (~85 μg Zn^{2+}/ml): half of the zinc is free zinc and the other half is more or less bound to the insulin crystals and/or amorphous insulin. The diluting medium for Actrapid contains no zinc at all, whereas the diluting medium for monotard contains ~50 μg Zn^{2+}/ml.[4]

Specific insulin IgE determination seems to be a discriminating factor in the diagnosis of insulin allergy.

BRUNO BRUNI, M.D.
MARIO CAMPANA, M.D.
SILVIA GAMBA, M.D.
GIORGIO GRASSI, M.D.
ALBERTO BLATTO, B.S.

From the Karen Bruni Diabetes Center, Ospedale Maria Vittoria, Corso Tassoni 44, 10144, Torino, Italy.

Address reprint requests to Bruno Bruni, M.D., at the above address.

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