Acute Adrenal Insufficiency in Extreme Hyperglycemia

Lakey W. Tolbert, MD
Birmingham, Alabama

Although the association of diabetes mellitus and adrenal insufficiency has been described, differentiating diabetic ketoacidosis from acute glucocorticoid deficiency with extreme hyperglycemia has not been reported. Because the symptoms of acute adrenal insufficiency and diabetic ketoacidosis may have similar presentations and may be precipitated by the same events, establishing a correct diagnosis can be difficult. A case is reported in which the initial diagnosis of diabetic ketoacidosis was incorrect.

CASE REPORT

A 46-year-old male mechanical engineer presented with a 19-year history of insulin-dependent diabetes mellitus treated with 25 units of NPH insulin and 20 units of insulin in a zinc suspension (Semilente) each morning. Three months before admission, the patient first noted increasing polyuria and polydipsia. Two weeks prior to presentation, the patient developed nausea, vomiting, cramping abdominal pain, and diarrhea.

Physical examination revealed an acutely ill patient. His blood pressure was 78/50 mmHg supine with a postural drop to 60/40 mmHg. He was afebrile but sweating. The pulse rate was 120 beats/min, and respirations were 22/min. The fundi showed no obvious diabetic retinopathy. The thyroid was not enlarged. Examination of the heart and lungs was unremarkable. No abdominal masses or organomegaly was noted. Testicles were bilaterally descended and of normal size. Secondary sexual characteristics were present. Although the patient was torpid, he remained oriented and the neurological examination was otherwise normal. Dry skin and decreased turgor were the only integumentary changes.

The admission blood glucose level was 30.5 mmol/L (550 mg/dL). The initial serum creatinine was 110 μmol/L (1.3 mg/dL), the blood urea nitrogen (BUN) was 21.5 mmol/L (60 mg/dL), and the leukocyte count was elevated to 14.5×10^9/L ($14.5 \times 10^3/\mu L$), with a monocytosis of 0.11. The arterial pH was 7.34 with a partial arterial carbon dioxide pressure of 22 mmHg. The initial electrolytes included a serum sodium value of 121 mmol/L (121 mEq/L) and a potassium level of 7.2 mmol/L (7.2 mEq/L). The urine was positive for ketones, and there was a trace of protein in the urine as well.

The patient was admitted to the intensive care unit with the presumptive diagnosis of diabetic ketoacidosis. He was treated with volume replacement and intravenous infusion of insulin to correct dehydration and hyperglycemia. The blood acetone level was negative. Treatment resulted in the correction of the dehydration and hyperglycemia.

His diarrhea, hypotension, hyponatremia, and hyperkalemia continued. Blood and stool culture findings were negative. Results from examination of stools for blood, ova and parasites, and leukocytes were negative. No drugs were detected by urinalysis. The amylase was 1.98 μkat/L. The cardiac and liver profiles were negative with no creatinine kinase fraction. An elevated BUN of 17.1 mmol/L (48 mg/dL), creatine of 160 μmol/L (1.8 mg/dL), and uric acid of 580 μmol/L (9.8 mg/dL) were also noted. Laboratory findings for thyroxine, triiodothyronine, free thyroxine index, and thyroid-stimulating hormone were normal. The glycosylated hemoglobin was elevated, 9.3 percent. A flat plate of the abdomen, chest film, and computed tomographic (CT) scan of the abdomen were all negative.

A fasting serum cortisol level was markedly reduced to 30 nmol/L (1 μg/dL) (normal, 110 to 520 nmol/L; 4 to 19 μg/dL). After stimulation with 250 μg of cosyntropin intramuscularly, the cortisol failed to stimulate beyond the expected minimum of 190 nmol/L (7 μg/dL) at both 30 and 60 minutes. The cosyntropin stimulation test was repeated with similar results. Thus, a failure of adrenal reserve was demonstrated. The plasma adrenocorticotropic hormone (ACTH) was elevated to 31 pmol/L (140 pg/mL) (normal, 4 to 22 pmol/L; 20 to 100 pg/mL).

Submitted, revised, October 30, 1987.

From Medical Center East, Birmingham, Alabama. Requests for reprints should be addressed to Dr. Lakey Tolbert, P.O. Box 550370, Birmingham, AL 35255.

With a probable diagnosis of primary adrenal insufficiency, the patient was given 50 mg of parenteral hydrocortisone sodium succinate. Rapid improvement in his clinical symptoms and correction of the laboratory findings were noted. Blood glucose values were controlled with twice daily doses of insulin. The patient was discharged on hydrocortisone, 20 mg before breakfast, 2.5 mg before lunch, and 5 mg before supper. Fludrocortisone acetate, 0.05 mg, was provided each morning. In follow-up visits the patient remained free of symptoms. His weight, electrolytes, and urine free cortisol remained within normal limits. The hemoglobin A_{1C} fell to 7.0 percent.

DISCUSSION

Addison's disease is uncommon with an incidence of 39 cases per 1 million population.[1] Adrenal insufficiency and diabetes mellitus are often associated. Ten percent of patients with idiopathic Addison's disease have associated insulin-dependent diabetes mellitus.[2] No such association has been found with non–insulin-dependent diabetes mellitus.

The clinical picture of acute adrenal insufficiency and diabetic ketoacidosis may be similar. The most frequent precipitating event in either disease is infection. Usually, anorexia is followed by nausea, vomiting, and cramping abdominal pain.

Physical signs and laboratory findings are also comparable. In acute adrenal insufficiency, volume depletion of up to 10 percent of the total body fluid occurs with resultant postural hypotension. Hyperkalemia is found in 64 percent of such patients, and hyponatremia is found in 88 percent of patients. Moderate acidosis with plasma bicarbonate levels between 15 and 20 mmol/L (15 to 20 mEq/L) is also common.[3] These physical and laboratory findings are frequently found in patients with diabetic ketoacidoses.

Similar physical and laboratory findings are frequently found in patients with diabetic ketoacidosis. Should the diagnosis of diabetic ketoacidosis be assumed, but not confirmed by serum acetone and other appropriate tests, an error in diagnosis can easily result.

When blood glucose levels are extremely elevated, certain initial findings may suggest underlying adrenal insufficiency. Eosinophilia is commonly associated with low cortisol levels. In chronic Addison's disease, the characteristic hyperpigmentation may be a useful clue. Continued awareness should especially be piqued, however, when symptoms and the above laboratory findings persist despite correction of the hyperglycemia.

Failure to diagnose Addison's disease during extreme hyperglycemia can lead to many complications. The increased insulin sensitivity associated with glucocorticoid deficiency may result in profound hypoglycemia during insulin replacement.[4,5] Further, acute adrenal insufficiency is in itself a life-threatening condition, which requires immediate intervention.

Both diabetic ketoacidosis and acute adrenal insufficiency have similar presentations, and are precipated by similar events. Vigilance should always be maintained when insulin-dependent diabetics present with signs and symptoms suggesting diabetic ketoacidosis.

References

1. Mason SA, Meade TW, Lee JAH, Morris JN: Clinical picture of Addison's disease. Lancet 1968; 2:744–747
2. Irwin WJ, Barnes EW: Adrenocortical insufficiency. Clin Endocrinol Metab 1972; 1:549–594
3. Wilson JD, Foster DW: Textbook of Endocrinology. Philadelphia, WB Saunders, 1985
4. Fain JN: Comparison of glucocorticoid effects on brown and white adipose tissue of the rat. Endocrinology 1965; 76:549–552
5. Frazer RW, Albright F, Smith PH: Carbohydrate metabolism. J Clin Endocrinol 1941; 1:297–306

What starts off as a small lesion on the mouth of an immunocompromised patient can develop into a serious and even life-threatening herpes simplex virus infection.[1] In the compromised host, oral infection may extend opportunistically to involve the esophagus or lungs or may disseminate to the liver, brain, and other organs.[2] Before a limited nonlife-threatening infection reaches this stage, prompt recognition and treatment with ZOVIRAX Ointment 5% can stop viral replication, accelerate healing, and reduce the accompanying pain.[3]

References: 1. Whitley R, Barton N, Collins E, et al: Mucocutaneous herpes simplex virus infections in immunocompromised patients: A model for evaluation of topical antiviral agents. Proceedings of a symposium on acyclovir sponsored by Burroughs Wellcome Co. and the National Institute of Allergy and Infectious Diseases. *Am J Med* 1982;73(1A):236-240. **2.** Nahmias AJ, Roizman B: Infection with herpes-simplex viruses 1 and 2 (third of three parts). *N Engl J Med* 1973;289:781-789. **3.** Whitley RJ, Levin M, Barton N, et al: Infections caused by herpes simplex virus in the immunocompromised host: Natural history and topical acyclovir therapy. *J Infect Dis* 1984;150:323-329.

In most patients, a cold sore is an annoying problem.*

In the immunocompromised, it can become a deadly serious one.

ZOVIRAX®
(acyclovir)
OINTMENT 5%

Stops viral activity and speeds healing.

*Due to herpes simplex virus.

INDICATIONS AND USAGE: Zovirax (Acyclovir) Ointment 5% is indicated in the management of initial herpes genitalis and in limited nonlife-threatening cutaneous Herpes simplex virus infections in immunocompromised patients. In clinical trials of initial herpes genitalis, Zovirax Ointment 5% has shown a decrease in healing time and in some cases a decrease in duration of viral shedding and duration of pain. In studies in immunocompromised patients with mainly herpes labialis, there was a decrease in duration of viral shedding and a slight decrease in duration of pain.

By contrast, in studies of recurrent herpes genitalis and of herpes labialis in nonimmunocompromised patients, there was no evidence of clinical benefit; there was some decrease in duration of viral shedding.

Diagnosis: Whereas cutaneous lesions associated with Herpes simplex infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may assist in the diagnosis.[1] Positive cultures for Herpes simplex virus offer a reliable means for confirmation of the diagnosis. In genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases.

CONTRAINDICATIONS: Zovirax Ointment 5% is contraindicated for patients who develop hypersensitivity or chemical intolerance to the components of the formulation.

WARNINGS: Zovirax Ointment 5% is intended for cutaneous use only and should not be used in the eye.

PRECAUTIONS:

General: The recommended dosage, frequency of applications, and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION). There exist no data which demonstrate that the use of Zovirax Ointment 5% will either prevent transmission of infection to other persons or prevent recurrent infections when applied in the absence of signs and symptoms. Zovirax Ointment 5% should not be used for the prevention of recurrent HSV infections. Although clinically significant viral resistance associated with the use of Zovirax Ointment 5% has not been observed, this possibility exists.

Drug Interactions: Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with Zovirax Ointment 5%.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150 and 450 mg/kg/day given by gavage. These studies showed no statistically significant difference in the incidence of benign and malignant tumors produced in drug-treated as compared to control animals, nor did acyclovir induce the occurrence of tumors earlier in drug-treated animals as compared to controls. In 2 *in vitro* cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive lifetime bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system.

No chromosome damage was observed at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats or Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition, no activity was found in a dominant lethal study in mice. In 9 of 11 microbial and mammalian cell assays, no evidence of mutagenicity was observed. In 2 mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells *in vitro*), positive response for mutagenicity and chromosomal damage occurred, but only at concentrations at least 1000 times the plasma levels achieved in man following topical application.

Acyclovir does not impair fertility or reproduction in mice at oral doses up to 450 mg/kg/day or in rats at subcutaneous doses up to 25 mg/kg/day. In rabbits given a high dose of acyclovir (50 mg/kg/day, s.c.), there was a statistically significant decrease in implantation efficiency.

Pregnancy: *Teratogenic Effects. Pregnancy Category C.* Acyclovir has been known to cause a statistically significant decrease in implantation efficiency in rabbits, when given at subcutaneous doses providing mean plasma levels of drug 2.2 times those expected from use in patients with normal renal function.

Reproduction studies were negative for impairment of fertility or harm to the fetus in mice given oral doses, and in rats given subcutaneous doses providing mean plasma levels of drug 84 times and 4 times (respectively) greater than those expected from use in patients with normal renal function.

Acyclovir was not teratogenic after subcutaneous administration of up to 50 mg/kg/day during the period of organogenesis in rats and rabbits; doses up to 450 mg/kg given daily by gavage to mice were not teratogenic. There are, however, no adequate and well-controlled studies in pregnant women. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zovirax is administered to a nursing woman.

ADVERSE REACTIONS: Because ulcerated genital lesions are characteristically tender and sensitive to any contact or manipulation, patients may experience discomfort upon application of ointment. In the controlled clinical trials, mild pain (including transient burning and stinging) was reported by 103 (28.3%) of 364 patients treated with acyclovir and by 115 (31.1%) of 370 patients treated with placebo; treatment was discontinued in 2 of these patients. Other local reactions among acyclovir-treated patients included pruritus in 15 (4.1%), rash in 1 (0.3%) and vulvitis in 1 (0.3%). Among the placebo-treated patients, pruritus was reported by 17 (4.6%) and rash by 1 (0.3%).

In all studies, there was no significant difference between the drug and placebo group in the rate or type of reported adverse reactions nor were there any differences in abnormal clinical laboratory findings.

DOSAGE AND ADMINISTRATION: Apply sufficient quantity to adequately cover all lesions every 3 hours 6 times per day for 7 days. The dose size per application will vary depending upon the total lesion area but should approximate a one-half inch ribbon of ointment per 4 square inches of surface area. A finger cot or rubber glove should be used when applying Zovirax to prevent autoinoculation of other body sites and transmission of infection to other persons. **Therapy should be initiated as early as possible following onset of signs and symptoms.**

HOW SUPPLIED: Zovirax Ointment 5% is supplied in 15 g tubes (NDC 0081-0993-94). Each gram contains 50 mg acyclovir in a polyethylene glycol base. Store at 15°-25°C (59°-77°F) in a dry place.

REFERENCE: 1. Naib ZM et al. Cancer Res *33*:1452-1463, 1973.
U.S. Patent No. 4199574

Wellcome | **Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

 84-ZOV-8