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Date:	11/13/2002 01:24:26 PM
From:	CN=Saeed Ahmed/OU=AM/O=LLY
Subject:	Re: Clin Diabetes -- McNeely 20 (4) 195.htm

Thanks for forwarding.

To me the clinical pearls at the bottom seem largely consistent with what we have been saying with the possible exception of #1.

Wanted to clarify how strongly we feel that wt gain and hyperglycemia are connected (point 1 in the pearls). Reason I bring that up is that some of the sales forces are using a detail aid that deemphasizes this link (79% of pts who had an episode of hyperglycemia did not experience substantial wt gain in longer term comparative studies; Among those with substantial wt gain, 96% had no glycemic abnormalities at all---benefits/risk detail aid).

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Margaret O Sowell

11/13/2002 12:04 PM

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cc:	Patrizia Cavazzoni/AM/LLY@Lilly
Subject:	Clin Diabetes -- McNeely 20 (4) 195.htm

Tom, Robert, & Saeed -

Below is a case report in the recent issue of Clinical Diabetes.

This is a journal published by the American Diabetes Association directed toward practicing medical clinicians (endocrinologists, internists, and primary care) as opposed to health care providers in the mental health arena. I think there are some valuable discussion points in this letter and that there may be an opportunity to bring additional considerations forward.

Given the US Affiliate's ongoing efforts to work with thought leaders and clinicians in both internal medicine/endocrinology and primary care, I thought it most appropriate that your team decide how best to make use of this opportunity.

Missy

Clinical Diabetes 20:195-196, 2002

Case Study

Case Study: Atypical Antipsychotic Use Associated With Severe Hyperglycemia

Marguerite J. McNeely, MD, MPH

Presentation

A.T. is a 50-year-old woman who developed acute hyperosmolar crisis. She first presented for primary care 5 months before the event. Medical history was notable for longstanding schizo-affective disorder and hyperlipidemia. She denied a history of diabetes. She reported her medication regimen had not changed in more than 1 year; medications included divalproex (Depakote), gabapentin (Neurontin), olanzapine (Zyprexa), and gemfibrozil (Lopid).

A.T.'s weight was 235 lb. A random plasma glucose was 103 mg/dl. Liver function tests, blood urea nitrogen, and creatinine were also normal. One month before the event, hydrochlorothiazide, 25 mg daily, was started for hypertension, and simvastatin (Zocor) was substituted for gemfibrozil to treat hypercholesterolemia.

One month later, A.T. presented to clinic with 1 day of urinary incontinence but no other symptoms of illness and was hospitalized for severe hyperglycemia. Her weight was 219 lb. Urinalysis showed no white blood cells but was strongly positive for glucose and weakly

positive for ketones (trace). Her glucose level was 1,572 mg/dl, and her hemoglobin A_{1c} (A1C) result was >14%. Her serum sodium was 113 mEq/l, potassium was 4.8 mEq/l, and carbon dioxide (bicarbonate) was 36 mEq/l. A.T. was severely volume-depleted as evidenced by postural hypotension, elevated blood urea nitrogen of 47 mg/dl, and elevated creatinine of 2.5 mg/dl. A semiquantitative blood acetone level was positive at a dilution of 1:8 (reference range is negative). A toxicology screen was negative. No evidence of infection, myocardial ischemia, or other acute illness was found. During the hospital stay, A.T. reported earlier treatment with glyburide (DiaBeta, Micronase, and Glynase) and metformin (Glucophage), but stated that those medications had been stopped more than 1 year ago for unknown reasons.

The patient was discharged from the hospital on a regimen of 14 units of NPH insulin with 14 units of regular insulin before breakfast, and 10 units of NPH insulin with 10 units of regular insulin before dinner. Olanzapine and hydrochlorothiazide were stopped, and haloperidol (Haldol) was started.

A few days after hospital discharge, A.T. presented to the clinic. She had skipped lunch, and her glucose was 48 mg/dl. Insulin was stopped.

Three months after stopping all hypoglycemic agents, she weighed 233 lb, her random glucose was 136 mg/dl, and her A1C was 7.5%.

About 4 months after hospital discharge, A.T. weighed 241 lb, and review of her glucose meter memory function showed random glucose levels were all >200 mg/dl. Her A1C was 10.3%. She was started on repaglinide (Prandin), and within a few months, a fixed dose of ultralente insulin was added.

Questions

1. Why did this patient develop severe hyperglycemia?
2. How is diabetes best managed in patients with severe psychiatric disorders?

Commentary

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Hyperosmolar hyperglycemic nonketotic syndrome (HHNS) is defined as glucose >600 mg/dl and serum osmolality >320 mOsm/kg in the absence of significant ketoacidosis.1 Signs and symptoms include acute or subacute changes in mentation, temperature dysregulation (hyperthermia or hypothermia), relative hypotension, and renal insufficiency. The condition typically affects patients with type 2 diabetes who are over age 50. HHNS is often triggered by a physiological stress that causes hyperglycemia and dehydration,

such as infection, myocardial infarction, stroke, or heat stroke. Medications associated with HHNS include glucocorticoids and diuretics. Recently, the newest generation of antipsychotic agents, referred to as "atypical antipsychotics," have been associated with diabetes, severe hyperglycemia, and diabetic ketoacidosis.2

A.T. clearly met the criteria for HHNS, since her calculated serum osmolality was 340 mOsm/kg, using the formula: serum osmolality = 2(Na + K) + (blood urea nitrogen/2.8) + (glucose/18). She did not have obvious acute mental status changes, but subtle deficits may have been masked by her chronic psychosis.

Why she developed HHNS is less clear. It seems unlikely that low-dose hydrochlorothiazide alone triggered such severe hyperglycemia. Olanzapine, an atypical antipsychotic medication, was likely a major factor.

Atypical antipsychotics cause weight gain, and this is thought to be the primary reason that mild to moderate hyperglycemia is often associated with these medications.3 However, severe hyperglycemia that resolves with discontinuation of the medication has also been reported. The mechanism for acute, transient hyperglycemia remains unclear, although one study demonstrated that these medications inhibit glucose transport into cells.4

Atypical antipsychotics offer many benefits over older antipsychotics, and they are now commonly used to treat many psychiatric conditions, including agitation in elderly patients with dementia. Patients who use these medications should be monitored for hyperglycemia. However, as this case demonstrates, severe, acute derangement of glucose control can occur even when a patient has been stable on medication for months to years.5

This case also illustrates the challenges of treating diabetes in patients with severe psychiatric disorders. Members of a multidisciplinary psychiatric team see A.T. several times a week. Nevertheless, she has persistent problems with tangential thoughts, poor judgment, and delusions. Despite inpatient and outpatient diabetes education and frequent reinforcement from her medical providers, she has been unable to apply this knowledge in her daily life. For example, she can test her blood glucose and identify whether the result is low, acceptable, or high. When faced with a low blood glucose, she is able to state that consuming juice and a snack is advisable. However, she may then begin to focus on her desire to lose weight or her frustration with diabetes in general and decide not to follow any advice for treating the hypoglycemia.

Very little is written about managing diabetes in patients with severe psychiatric conditions. Ideally, such patients would live with a responsible person who helps manage their diabetes. For patients without a close friend or relative who is willing to assume this role, alternatives include a paid caretaker or assisted living.

However, poor judgment and lack of insight are inherent features of many psychiatric disorders. Therefore, some psychiatric patients will refuse help with diabetes management. State laws vary with regard to the involuntary confinement and treatment of psychiatric patients who are unable to care for themselves.

Concerns about a patient's capacity for self-care should be discussed with the patient and the patient's psychiatric team. If appropriate, judicial review of the patient's situation should be considered.

Clinical Pearls

Atypical antipsychotics appear to increase the risk of type 2 diabetes by inducing weight gain. Less commonly, they have been associated with severe hyperglycemia that resolves or improves when the medication is stopped.
Managing diabetes in patients with severe psychiatric disorders is especially challenging. Although diabetes education is

important, not all patients will be capable of applying this information appropriately. The diabetes treatment plan should be realistic and account for the patient's situation.

Strategies to minimize the risks of treating diabetes in psychiatric patients include:

Enlisting the help of a caretaker whenever possible.

Treating mild hyperglycemia with medications only in carefully selected patients.

Using oral agents and/or long-acting insulin to control severe chronic hyperglycemia.

Before using metformin, determining whether the patient is likely to stop it if dehydration occurs.

Before using short-acting insulin, determining whether the patient is likely to take it with food.

Prescribing small quantities of insulin using pre-filled syringes or insulin pens when appropriate.

Encouraging patients to wear a medical alert bracelet or necklace that lists diabetes.

In patients for whom tight glucose control is not realistic, other aspects of diabetes care may be especially important, such as treatment of hypertension and hyperlipidemia; regular screening for retinopathy, neuropathy, and nephropathy; and aspirin therapy.

Footnotes

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