OBSERVATIONS

Exenatide Alters Absorption of Hydrocortisone in a Diabetic Patient With Panhypopituitarism: Iatrogenic Adrenal Insufficiency

Exenatide, which is widely used for patients with type 2 diabetes, inhibits gastric emptying and small intestinal motility (1). We report a diabetic patient with panhypopituitarism who developed general fatigue and appetite loss with hypotension because of absorption delay of hydrocortisone in association with exenatide treatment.

A 50-year-old diabetic woman was admitted to our hospital because of poor glycemic control in December 2011. She had been treated with hydrocortisone and L-thyroxine for hypopituitarism as a result from surgeries and radiotherapy for carniopharyngioma. She was started on treatment with 5 μg exenatide twice a day. Nine days after exenatide treatment, the dose was increased to 10 μg twice a day. Although glycemic control improved rapidly, she complained of general fatigue, appetite loss, and hypotension in the morning, but symptoms improved before noon. We reasoned the symptoms by insufficiency of hydrocortisone replacement but investigated first whether exenatide treatment was the culprit drug. Serum cortisol concentrations were measured before each meal and every 30 min until 4 h. Measurement of serum cortisol concentrations showed maximum concentration (C_{max}) of 21.7 μg/dL and the time of C_{max} (T_{max}) of 90 min after postprandial administration of 10 mg hydrocortisone alone. Administration of hydrocortisone just after exenatide showed a 40% decrease (12.4 μg/dL) in C_{max} and delayed T_{max} (240 min) compared with postprandial administration of hydrocortisone without exenatide.

The hydrocortisone C_{max} and T_{max} values normalized after administration of hydrocortisone before each meal and administration of exenatide at 1.5 h after each meal. Under the last condition, the symptoms of adrenal insufficiency showed complete recovery, together with good glycemic control. We concluded that the delay in the absorption of hydrocortisone by exenatide was the main reason for adrenal insufficiency.

It has already been reported that exenatide delays the absorption of certain drugs. Administration of ethinyl estradiol and levonorgestrel 30 min after exenatide resulted in delays in their T_{max} values by 3 and 3.5 h, respectively, compared with ethinyl estradiol and levonorgestrel alone (2). Similar results were reported with digoxin, warfarin, lovastatin, lisinopril, and acetaminophen (2,3). However, these reports announced no or minor clinical influence on the effects of these drugs due to the lack of changes in steady-state pharmacokinetics or small reductions in area under the curve. Unlike the drugs mentioned above, the half-life of hydrocortisone is shorter, which is 1.7 h (4), and its concentration in blood is more easily affected by absorption delay.

Our report indicates that exenatide may affect the actions of short half-life drugs, including hydrocortisone. The timing of exenatide administration should be considered with care in patients on crucial oral medications.

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References

1. Marathe CS, Rayner CK, Jones KL, Horowitz M. Effects of GLP-1 and incretin-based therapies on gastrointestinal motor function. Exp Diabetes Res 2011;2011:279530
2. Kothare PA, Seger ME, Northrup J, Mace K, Mitchell MI, Linnebjerg H. Effect of exenatide on the pharmacokinetics of a combination oral contraceptive in healthy women: an open-label, randomised, crossover trial. BMC Clin Pharmacol 2012;12:8
3. Blase E, Taylor K, Gao HY, Wintle M, Fineman M. Pharmacokinetics of an oral drug (acetaminophen) administered at various times in relation to subcutaneous injection of exenatide (exendin-4) in healthy subjects. J Clin Pharmacol 2005;45:570–577
4. Derendorf H, Möllmann H, Barth J, Möllmann C, Tunn S, Krieg M. Pharmacokinetics and oral bioavailability of hydrocortisone. J Clin Pharmacol 1991;31:473–476