OBSERVATIONS

Exenatide-Associated Ischemic Renal Failure

Exenatide is a synthetic peptide that belongs to a new class of antidiabetes agents known as incretin mimetics. Like the endogenous incretin hormone glucagon-like peptide 1 (GLP-1), exenatide effectively lowers blood glucose levels by stimulating insulin release, inhibiting glucagon secretion, and delaying gastric emptying. Nausea and vomiting are the most common adverse reactions, which lead to discontinuation in as many as 14% of patients in one study (1).

We report on four patients (three male and one female; age 52–73 years) with exenatide-associated renal failure who presented with nausea, vomiting, or decreased fluid intake. All patients had type 2 diabetes with or without mild microalbuminuria and hypertension. They were taking stable doses of ACE inhibitors and diuretics. None of the patients were using nonsteroidal anti-inflammatory drugs. No overt hypotension or evidence of acute pancreatitis was observed, and none of the patients required hospitalization during the time of observation. The temporal relationship between exenatide therapy, clinical symptoms, and renal function is summarized in Fig. 1*A–D*. The time between starting exenatide therapy and diagnosis of renal failure varied between 2 and 9 months, and the drug was discontinued within 3 months after the diagnosis except in patient B, whose symptoms improved with dose reduction of exenatide. A renal biopsy showed ischemic glomeruli, with moderate to severe interstitial fibrosis, tubular atrophy, and early diabetic nephropathy. Despite these findings, the patient wished to continue exenatide therapy because of a significant weight loss. In patient D, the dose of sitagliptin was reduced because of the renal impairment; however, subsequently renal function improved toward baseline.

Recovery of renal function was incomplete in three of four patients upon cessation or dose reduction of the medication. Exenatide, by causing nausea, vomiting, or reduced fluid intake, could contribute to extracellular volume contraction. This in turn, when combined with diuretic therapy and the use of ACE inhibitors, leads to an exaggerated decline in glomerular filtration rate (2). In addition, GLP-1 has been shown to induce natriuresis and potentially decrease renal perfusion in healthy subjects and insulin-resistant obese men (3), an effect that may be shared by exenatide. This diuretic effect can be deleterious in the setting of

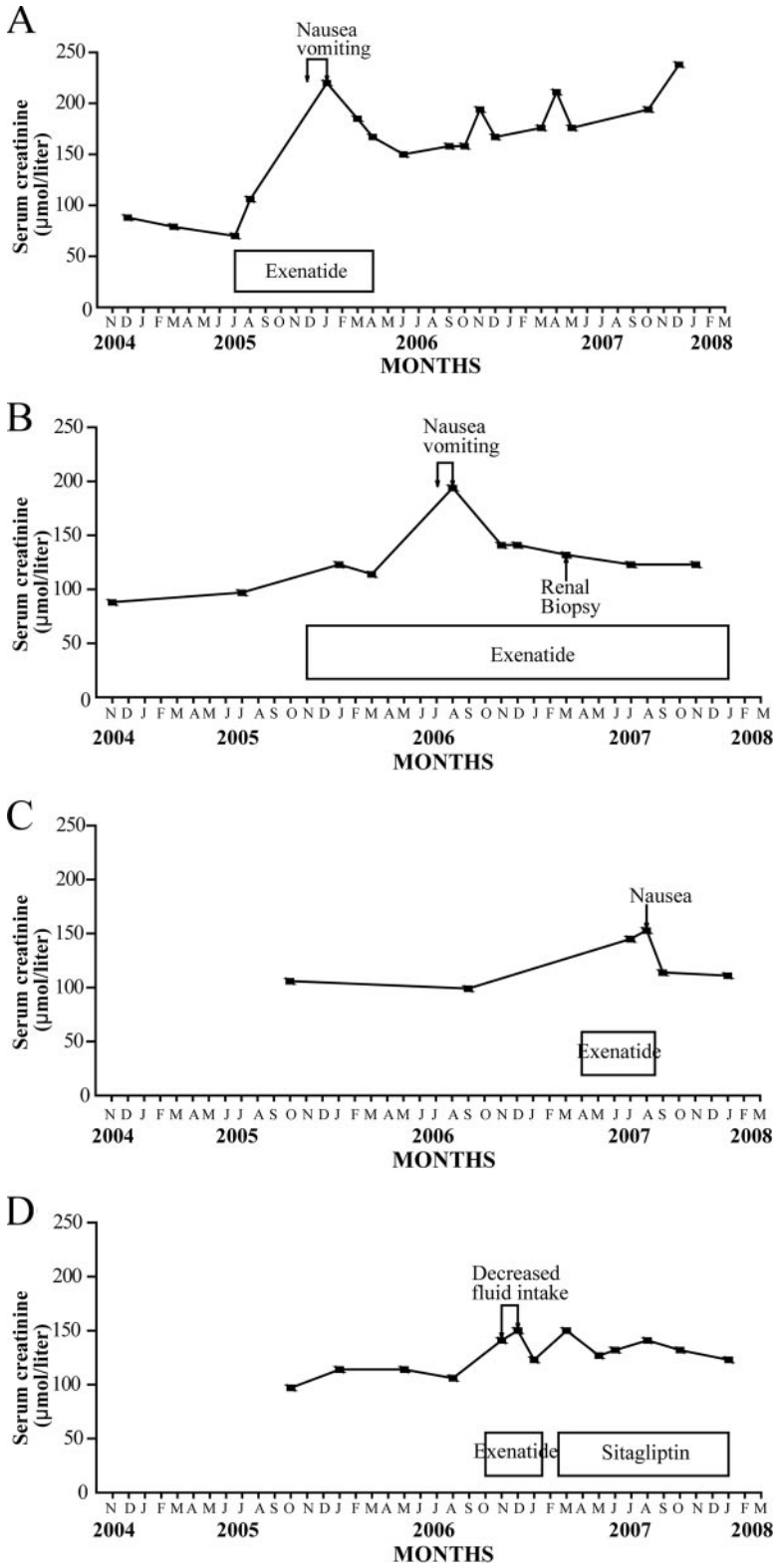

Figure 1—*Changes of serum creatinine in patients A, B, C, and D during treatment with exenatide and sitagliptin.*

volume contraction, and the renal biopsy findings of ischemic glomeruli and extensive tubular-interstitial injury are certainly consistent with this hypothesis. There is no evidence that exenatide is directly nephrotoxic, and we could document normal urinalysis and urine sediments in two patients. Information from the manufacturer indicates rare events of renal failure, which appears reversible with supportive treatment and discontinuation of potentially causative agents, including exenatide (4).

Although exenatide appears relatively safe, published clinical studies included only a limited number of patients for a relatively short time (5). Serious adverse reactions, such as renal failure, may be more apparent when more patients are exposed to the drug. If exenatide therapy is associated with nausea and vomiting, the subsequent hypovolemia may result in ischemic renal failure. Renal function should be monitored regularly in patients receiving exenatide, particularly those who present with nausea, vomiting, or reduced fluid intake.

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