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Metformin-Induced Pancreatitis

A possible adverse drug effect during acute renal failure

About 2% of episodes of acute pancreatitis are caused by drugs (1). Phenformin was repeatedly associated with acute pancreatitis (1), but only two case reports highlighted a possible causative role for metformin (2,3). In one case, acute pancreatitis occurred for the coexistence of correct metformin treatment and acute renal failure (2); in the other, metformin overdose was deemed responsible (3).

A 61-year-old woman with diabetes and hypercholesterolemia presented after 5 days of vomiting, followed by oliguria and epigastric pain. At home, the therapy of 3 g/day metformin and 80 mg/day fluvastatin was continued, despite symptoms. Laboratory investigations showed metabolic acidosis with normal lactate, creatinine 13 mg/dl, amylase 270 units/l (normal range 30–110), lipase 1,813 units/l (23–300), and white blood cells 9,000/mm^3 (80% neutrophils). Acute pancreatitis was confirmed by computed tomography. No recognized cause of acute pancreatitis was identified (hypertriglyceridemia, hypercalcemia, alcoholism, gall stones, virus, or trauma). Drugs were suspended, and a treatment of insulin and intravenous fluids normalized amylase, lipase, and blood gases. The patient was discharged with stable creatinine levels of 2.7 mg/dl. She was reexposed to fluvastatin for 1 month, but no symptoms were reported.

Available evidence suggests that acute pancreatitis was caused by metformin accumulation, resulting from a combination of drug overdose and acute renal failure, in turn triggered by vomiting in a patient with concealed renal insufficiency. Because renal failure is a contraindication to metformin, rechallenge was performed only for fluvastatin (1), with negative results. In this case, the association drug/event is considered "probable" (4).

In the presence of appropriate doses and normal renal function, metformin-induced acute pancreatitis was never reported. However, when glomerular filtration rate (GFR) is <60 ml/min, metformin accumulates and adverse effects, mainly lactic acidosis, may occur (5,2). Our and previous observations (2,3) suggest to include acute pancreatitis among the possible metformin-induced adverse events precipitated by renal failure.

A GFR <60 ml/min with normal serum creatinine (concealed renal failure) increases the risk of adverse reactions from hydrosoluble drugs in elderly diabetic patients (6). We reanalyzed the data of hospitalized elderly from the Gruppo Italiano di Farmacovigilanza nell'Anziano study (1993–1998). Of 145 diabetic patients given metformin, 28 subjects had concealed renal failure (mean daily dose 808 ± 303 mg), while the other 28 patients had both reduced GFR and increased creatinine values (mean daily dose 686 ± 470 mg). These patients are at risk of acute renal failure, with critical metformin accumulation and ensuing toxicity, including acute pancreatitis.

Metformin is a precious antidiabetic drug (5). Nonetheless, acute pancreatitis can arise in patients with renal insufficiency. GFR should be carefully monitored in older diabetic patients taking metformin.

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COMMENTS AND RESPONSES

Change in HbA_{1c} as a Measure of Quality of Diabetes Care

The Diabetes Quality Improvement Project established performance indicators that were adopted by The National Committee for Quality Assurance in the Diabetes Physician Recognition Program (DPRP) (1,2). The HbA_{1c} (A1C) factors heavily in the scoring system, accounting for 15 of a possible 80 points. To achieve full credit, <20% of a random sampling of patients may have an A1C >9.0% and at least 40% must be <7.0%. This methodology may bias against diabetes consultants who are referred patients in worse control. Improvements in A1C may more readily reflect quality of care. The American Diabetes Association recommends an A1C of <7.0% (3) and in previous guidelines set ≥8.0% as a level whereupon "additional action is suggested" (4). The Diabetes Control and Complications Trial (DCCT) demonstrated that a decline in the A1C of 1% reduced microvascular complications by 30% or more (5). Therefore, poor control and clinically meaningful improvements may be defined by an A1C of ≥8% and −1%, respectively. The purpose of the present study is to evaluate change in A1C as a marker of quality of care.

Patients from one physician were evaluated, and all were referred from other providers. A1C data were collected prospectively in new patients from 1 January 2003 through 31 December 2004.