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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.

Data were included if the baseline A1C (collected the day of the consult or within 90 days prior) was ≥8.0%, and at least one subsequent A1C, performed after 3 months, was measured. A third A1C was collected in patients who had been seen for ≥6 months at the time of data collection. The mean ± SD A1C was calculated for each of the three time points, and a *t* test was performed to determine statistical significance between levels.

A total of 96 patients met the entry criteria. Of these, 54 (56%) had a third data point. The remainder had not yet been followed long enough at the time of data collection ($n = 32$) or did not adhere to follow up ($n = 9$). The mean A1C at entry was 10.36 ± 1.66%. The mean first and second follow-up A1C levels were 8.06 ± 1.68 and 7.68 ± 1.38%, respectively. Changes from entry to first and second A1C were both statistically significant ($P < 0.001$). Seventy-four percent of patients at first follow-up A1C and 80% at the second demonstrated an A1C decline of ≥1%.

In this brief observation, the majority of patients who were referred for endocrine consultation to evaluate and treat poor diabetes control showed clinically meaningful improvements in A1C. In evaluating quality of care, the DPRP looks at a cross section of randomly chosen patients. In a consultation practice, the diabetes specialist may accumulate many poorly controlled patients. Therefore, the impression is that quality of care is poor. Moreover, provider recognition may be less likely under the current scoring system. Yet, the DCCT demonstrated that reductions in microvascular complications, in particular retinopathy, can be seen with sustained A1C reductions even if the target of <7% is not achieved (5). Change in A1C may be a useful marker for quality of care given by diabetes consultants and can be used as an adjunct to the current DPRP standards, especially if longer-term data are used.

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

Response to Spitz

We thank Dr. Spitz (1) for his letter commenting on the Diabetes Physician Recognition Program (DPRP) criteria regarding HbA_{1c} (A1C) levels. The DPRP criteria were changed in 2000 to coincide with those used in the Health Plan Employer Data and Information Set (HEDIS) program. More recently in 2004, a decision was made to include two measures for A1C, LDL, and blood pressure. In the case of LDL, the change reflected the HEDIS measure, National Cholesterol Education Program guidelines, and the American Diabetes Association recommendation. In the case of A1C and blood pressure, changes were based on current American Diabetes Association recommendations. Using two measures (which some refer to as good and poor control) allows a more comprehensive assessment of how well a group of patients is doing as this approach encourages both attention to persons in relatively poor control as well as allowing ongoing assessment of how the provider is doing in regard to meeting the stated guideline. For example, if only "% of patients with A1C >9%" were used, movement of patients from 9.1 to 8.9% would yield significant improvement, yet most would argue that little had changed. Using measures of "% >9%" and "% <7%", however, would show that little had changed. If patients were moved from an A1C of 9.1 to 6.9%, using only the 9% measure would yield the same results as in the first case, but using both measures the rather significant change would be clearly indicated. Using both measures allows one to see continuing improvement over time as the "% >9%" should continue to decrease and the "% <7%" should continue to increase.

Dr. Spitz suggests that it would be useful (and more fair to those who are referred patients who are not doing well in regard to A1C) to add a measure based on improvement in A1C. The suggestion is well worth considering and has been reviewed in the past by experts in both diabetes as well as measurement. One obvious problem in having a change in A1C measure is that doctors caring for patients who are at goal would appear to not be doing well using this measure, as no improvement would be needed or likely seen. As well, the goal of using measures to document how a population of patients is doing over time would not be part of this metric. Simply awarding points for A1C improvement would create some potential unfairness as well, as it is generally much easier to get a patient doing poorly to reduce his/her A1C 1% (from 10 to 9%, for example) than a patient doing relatively well (to reduce the A1C from 8 to 7%). Secondly, all A1C improvements are not equal in regards to clinical benefit, as an improvement of 1% in A1C offers a different benefit if the change is from 7 to 6% vs. 12 to 11%, for example. Finally there is the problem of setting the time frame for the change and having to review charts for multiple values, not just the most recent.

Dr. Spitz is of course correct that any improvement in A1C is a positive change. The data he cites for his practice are very impressive in regards to the reduction in A1C levels he has achieved. We feel that the current measures, used accurately, fairly capture this aspect of diabetes care, and adding a new measure for A1C change is not likely to add substantial new information to the program. However, we feel it is worthwhile to bring this to the current DPRP advisory committee for discussion at their next meeting.

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