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Response to Amemiya

We thank Dr. Amemiya (1) for his interest in our study (2). It is worth emphasizing that we studied adult patients with diabetic ketoacidosis and that we do not suggest using our dosage schedule in young children. Dr. Amemiya comments on possible fluid and electrolyte problems with our extended insulin regimen, resulting from a “large amount of infused insulin.” We did not experience any difficulties, although there was a tendency for phosphate concentrations to be lower on the extended insulin regimen. If a variable rate glucose infusion of any concentration is used, overall fluid requirements must be considered independently. As outlined in our study, our approach was to give additional normal saline.

Dr. Amemiya also referred to the late recovery phase (12–36 h). Generally, our extended insulin regimen was not required beyond 12 h (mean 10.8, range 6–19). The constant glucose infusion rate recommended by Amemiya for young adults is similar to that with which we start, because 5 U/h insulin is continued after correction of hyperglycemia. Whatever approach (constant insulin or constant glucose) is used, monitoring of plasma glucose will be required and treatment adjusted accordingly.

M. IVAN WIGGAM, MRCP

MAURICE J. O’KANE, MD

ROY HARPER, MD

A. BREW ATKINSON, MD

DAVID R. HADDEN, MD

ELISABETH R. TRIMBLE, MD

PATRICK M. BELL, MD

From the Sir George E. Clark Metabolic Unit (M.I.W., R.H., A.B.A., D.R.H., P.M.B.) and the Department of Clinical Biochemistry (M.J.O., E.R.T.), Royal Victoria Hospital; and the Department of Clinical Biochem-

istry (E.R.T.), The Queen’s University of Belfast, Belfast, Northern Ireland, U.K.

Address correspondence to Dr. Patrick M. Bell, Sir George E. Clark Metabolic Unit, Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland, U.K.

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Case Report

Pseudohepatotoxicity of metformin

Metformin (dimethylbiguanide) became available in the U.S. for clinical use in 1995, after extensive experience in foreign markets (1). Since its introduction in the late 1950s, metformin has become the second most prescribed oral hypoglycemic agent in Europe. The drug is generally considered to be safe and effective and has been well received in the U.S. (2). The drug’s major side effect is lactic acidosis, and exclusion criteria are weighted toward renal impairment or severe underlying hepatic disease that might predispose the patient to lactic acidosis; the drug is cleared renally (1–3). We wish to report a case of apparent metformin hepatotoxicity that was not confirmed on rechallenge with the drug. We will also briefly review the literature on metformin toxicity and discuss the assessment of an adverse drug reaction.

A 75-year-old white man with a 25-year history of NIDDM was in stable glycemic control on two daily injections of split-and-mixed NPH insulin and regular insulin totaling ~40 U daily. He had no overt diabetic complications and was in general good health, aside from widespread polyostotic Paget’s disease of bone (confirmed by radioisotope bone scans and alkaline phosphatase heat fractionation), hypertension, and hyperlipidemia. He was married, did not smoke, and drank one glass of wine with dinner daily. His medica-

tions included, in addition to insulin, 325 mg/day enteric-coated aspirin, 180 mg/day diltiazem XR, 800 mg ibuprofen thrice daily as needed, and 60 mg/day lovastatin. In an attempt to improve his glycemic control without increasing his insulin dose, he was started on 500 mg metformin twice daily, with a slight reduction in insulin. He tolerated this dose well, and self-monitored glucose tests demonstrated somewhat improved control (predinner glucose values ranged between 4.44 and 6.66 mmol/l (80 and 120 mg/dl) compared with previous values of 5.55–7.77 mmol/l (100–140 mg/dl), as did HbA_{1c} (7.7% at baseline, 7.3% 3 months later). However, 2 months after initiation of metformin, aspartate aminotransferase (AST) increased from a baseline value of 36 (normal = 8–42) to 322 U/l, while alanine aminotransferase (ALT) increased from a baseline of 33 (normal = 0–55) to 413 U/l. Neither total bilirubin nor albumin changed. Alkaline phosphatase, which was consistently elevated in the 470–510 U/l range (normal = 37–107), peaked at 684 U/l after metformin. He felt well, his exam was unremarkable, and he denied travel, unusual foods, drug exposure (including over-the-counter analgesics), and exposure to ill people. Metformin was discontinued. Hepatitis B surface antigen and core antibodies were negative, as were hepatitis C antibodies and hepatitis A IgM antibodies; ultrasound of the abdomen was remarkable only for gallstones. AST and ALT returned to baseline values. Because of the favorable glycemic response to metformin, the patient agreed to rechallenge with 1 month of metformin therapy, at the same dose as before, with repeat liver function testing at the end of the month. On this occasion, there was no elevation of liver enzymes. It was concluded that metformin could not be confirmed as the cause of liver test abnormalities, but the patient preferred to return to his insulin monotherapy.

The primary toxicity of metformin is lactic acidosis, especially in individuals with impaired renal function. Exclusion criteria for the use of this drug take this into account, although individuals with severe underlying liver disease, which might predispose them to lactic acidosis, are also recommended against using metformin (3,4). Hepatic toxicity in response to metformin is exceptionally rare; there is only one previous citation, which is, unfortunately, in Turkish and unavailable to us for review (5). On the other hand,

metformin is absorbed intestinally, passes via the portal circulation into the liver, and exerts some hepatic effect that may underlie its mechanism of action (3,6). The cause for the apparent hepatotoxicity of metformin in this patient, which could not be confirmed on rechallenge, is unclear. A laboratory error is unlikely due to the consistent elevation of alkaline phosphatase and the stability of other chemistry tests. The patient and his wife denied symptoms suggestive of a concurrent subclinical viral illness (the episode took place in winter), binge drinking, or use of other medications. Other potential explanations for the apparent hepatotoxicity include desensitization to metformin so that rechallenge did not provoke the same inflammatory response as the initial challenge or failure of the patient to take the drug on rechallenge out of fear. Both the patient and his wife were emphatic that he had taken the metformin on rechallenge. One explanation for the transient hepatitis, given the ultrasound picture of gallstones, is the passage of a gallstone into the bile ducts. An alternate explanation is a subclinical viral illness. Neither the possibility of an effect of lovastatin or diltiazem nor a possible failure of the patient to take the metformin rechallenge can be excluded, despite our direction and his assurances. While it is disappointing not to be able to confirm the etiology of the apparent metformin-induced hepatotoxicity, it is reassuring that the drug did not appear to be implicated (on the basis of rechallenge). This

observation also confirms the importance of careful ascertainment of adverse drug reactions, including observed rechallenge, to document the role of the putative toxin.

Confirmation of an adverse reaction is difficult and is usually dependent on rechallenge (7-9). In addition, diagnostic criteria and the assiduousness of surveillance differ at the national, institutional, and personal levels. In recognition of this, a European conference on pharmacovigilance recently proposed standard designations of drug-induced liver disorders and criteria for causality assessment (10). Applying these standards here, we can classify this case as demonstrating hepatocellular liver injury with a negative response to readministration of the drug.

ARTHUR L.M. SWISLOCKI, MD, FACP
ROBERT NOTH, MD

From the Medical Service, Department of Veterans Affairs Northern California Health Care System, Martinez; and the Department of Internal Medicine, Division of Endocrinology, University of California, Davis, School of Medicine, Davis, California.

Address correspondence to Arthur Swislocki, MD, FACP, Medical Service (111), VANCHCS, 150 Muir Road, Martinez, CA 94553.

A.L.M.S. has received honoraria for speaking engagements from Bristol-Myers Squibb, Pfizer, and Merck and unrestricted research support from Bristol-Myers Squibb.

Acknowledgments— Supported in part by the Research Service, Department of Veterans Affairs.

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Errata

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The wrong version of this article was printed. Extensive and substantive revisions of this article were requested during the review process. However, the electronic file that was provided with the revised, accepted manuscript corresponded to the original version. The unrevised version was typeset, and proofs were approved by the corresponding author. The version of the article listed above is withdrawn, and the correct version will be printed in an upcoming issue of *Diabetes Care*.

Antonucci T, Whitcomb R, Norris RM, McLain R, Lockwood D: Impaired glucose tolerance is normalized by treatment with the thiazolidinedione troglitazone. *Diabetes Care* 20:188-193, 1997

Rebecca M. Norris, MD, has been added to the list of authors, as shown above. Dr. Norris was employed by the Parke-Davis Research Division of Warner Lambert at the time the research reported in this article was conducted.