Metformin-Induced Acute Hepatitis

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Abstract

Metformin is considered an initial oral pharmacotherapy of choice for the treatment of hyperglycemia in Type 2 Diabetes Mellitus (T2DM).

Although safe in the vast majority of the population, rare side effects will come to light as the prevalence of type 2 DM continues to rise.

We present a rare case of metformin induced hepatotoxicity. This case report aims to make clinicians aware of this infrequent adverse reaction that can arise with metformin therapy.

Introduction

Metformin is a biguanide that lowers blood glucose levels by inhibiting hepatic gluconeogenesis and increasing insulin sensitivity. It is a first line oral anti-diabetic agent used in the treatment of Type 2 Diabetes Mellitus.

Metformin is generally tolerated well. The most commonly reported adverse reaction to metformin is gastrointestinal distress. However, rare but serious adverse reactions can also occur including hypoglycemia, dehydration, and lactic acidosis [1,2].

Here, we report a case of clinically significant metformin-induced acute hepatitis. To date, only a few cases of this rare adverse reaction have been reported in literature despite the widespread use of metformin for several decades [3-5].

Case Description

A 75-year-old male with a past medical history of T2DM, on metformin therapy, presented with a 1-month history of fatigue, nausea, vomiting, anorexia, and generalized abdominal pain.

He denied the current or recent use of toxins, herbal products, and dietary supplements, preexisting liver disease, and prior abnormal liver labs. He denied the use of new prescription medications but noted a recent increase in his metformin dose from 500mg to 1000mg twice daily a few weeks prior to presentation.

On admission, his vital signs were stable and physical examination revealed trace scleral icterus. Initial laboratory work up was remarkable for a hepatocellular pattern of liver injury (total bilirubin 3.4 mg/dL, aspartate aminotransferase 3,241 units/L, alanine aminotransferase 3,870 units/L, alkaline phosphatase 190 units/L, international normalized ratio 1.3, and serum albumin 2.66g/dL).

Case Description

Work up to evaluate for the various etiologies of acute hepatitis including acute viral hepatitis serologies, metabolic liver diseases, and autoimmune markers were all unremarkable. A complete toxicology screen was also negative.

Abdominal imaging was negative for evidence of cirrhosis, portal hypertension, hepatic steatosis, or congestion. A liver biopsy was not performed due to the patient's preference and the minimal impact it would have in guiding management.

Given the negative work up above, the patient's acute liver injury could not be explained by viral, alcoholic, ischemic, metabolic, and vascular insults. Instead, the pattern of liver injury was highly suspicious of drug-induced hepatitis resulting from an increase in the metformin dose. It was postulated that an increase in the metformin dose resulted in lactic acidosis and subsequently acute hepatitis.

Metformin was withdrawn. Subsequently, the patient's liver enzymes gradually improved as shown below in table 1 and figure 1 and the presenting symptoms resolved. He was then discharged in a stable condition and advised to avoid metformin use in the future.

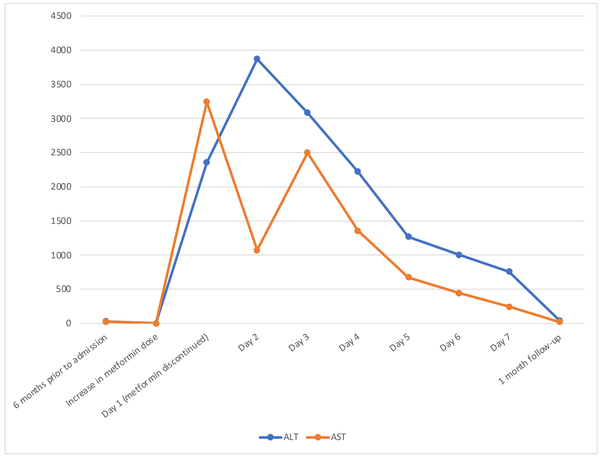
The patient followed up in the Hepatology clinic four weeks after the hospital discharge and was found to be doing well with normalization of the liver enzymes.

Figures

Table 1. Pattern of liver enzyme elevation after an increase in metformin dose 8 weeks prior to hospitalization with gradual return to baseline upon discontinuation of metformin.

	Alkaline Phosphatase (units/L)	Alanine aminotransferase (units/L)	Aspartate aminotransferase (units/L)
6 months prior to admission	126	31	25
Hospital day 1	170	2355	3241
Hospital day 2	187	3870	1070
Hospital day 3	192	3084	2500
Hospital day 4	179	2221	1355
Hospital day 5	167	1270	676
Hospital day 6	165	1006	444
Hospital day 7	168	758	245
1 month follow-up	131	42	20

Chart 1. Dose-dependent metformin induced hepatotoxicity



Discussion

Drug induced liver injury (DILI) is a well-established problem and accounts for nearly 13% of all cases of acute liver failure in the United States [6]. Diagnosing DILI can be especially challenging when hepatotoxicity is caused by a medication that is not considered intrinsically hepatotoxic such as metformin.

When faced with such a conundrum, physicians may find clinical scales useful in the diagnostic process. The Naranjo Adverse Drug Reaction (ADR) Probability Scale was designed to help clinicians determine whether there is a causal relationship between a suspected drug and a clinical event.

Alternatively, clinicians may find it more useful to use the Roussel Uclaf Causality Assessment Method (RUCAM) scale, which was specifically designed to help assess the likelihood of DILI [8].

In our case, the patient had an ADR probability scale score of 7, indicating that the hepatotoxicity was probably due to metformin. To add consistency, the RUCAM scale was applied. Our patient scored 10 points, which correlates with a very high probability of metformin induced hepatoxicity. In light of this, the patient's liver injury was attributed to the recent increase in metformin therapy.

Conclusions

Metformin is the first line therapy in treating T2DM. Although considered safe, metformin may rarely cause severe hepatitis. The exact mechanism of metformin induced hepatic injury is unknown.

In our case, a diabetic patient presented with symptoms of acute hepatitis after an increase in metformin dose, the diagnosis of metformin-induced hepatotoxicity was supported by the causal relationship between an increase in the metformin dose and the onset of liver injury, exclusion of all other causes of liver injury, recovery of liver function on discontinuation of metformin, and clinical scales with an ADR Probability Scale score of 7 and a RUCAM score of 10.

With the rising burden of T2DM worldwide, rare side effects of commonly used anti-diabetic medications will continue to emerge. It is crucial for clinicians to familiarize themselves with these rare but serious adverse reactions.

Through our case report we aim to make clinicians aware of one such dose-dependent reaction, metformin induced severe idiosyncratic acute liver injury.

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