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Review Literature

Glipizide Induced Hepatotoxicity: A Case Report and Review of Literature

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Abstract

Introduction

Sulfonylureas are known to have multiple side effects including weight gain, hypoglycemia and cardiovascular toxicity. Hepatotoxicity has been sparsely described in literature. We present a case of Glipizide induced hepatotoxicity which has not been previously reported in literature.

Case

71 year old female with uncontrolled DM2 presented for evaluation to the endocrine clinic. Type 2 DM was diagnosed during evaluation of polyuria and polydipsia, Hba1c 7.1%. When her Hba1c worsened, Metformin 500 mg BID was initiated. Metformin was maximized to 1000 mg BID as Hba1c increased to 14%. Patient declined insulin. She was started on glipizide 5 mg BID in addition to metformin 1000 mg BID. Four weeks later her routine labs showed elevation of AST to 89 µ/l and ALT to 255 µ/l which were normal previously. Patient was asymptomatic. Labs in four days showed further elevation of AST and ALT to 311 u/l and 446 u/l, respectively. Glipizide was stopped and repeat labs showed improvement in liver enzymes within three days and normalization within a week of stopping the medication. Extensive evaluation including CMV IgM, HBsAg, HBc IgM, EBV DNA, HCV PCR were negative. Gastroenterology suspected glipizide induced liver injury in the setting of significant improvement in liver enzymes after medication cessation. Patient declined a rechallenge.

Discussion

Hepatotoxicity is a rarely reported side effect for sulfonylureas. Previously, liver injury secondary to Glimepiride and Glyburide have been described in case reports. However, this is the first case to our knowledge with glipizide induced hepatotoxicity.

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Introduction

Glipizide is a second generation sulfonylurea which is used in the treatment of type 2 diabetes mellitus. Sulfonylureas to date have been used as first line drugs in the treatment of non-insulin dependent diabetes and are usually well tolerated1. Common side effects include weight gain, hypoglycemia and cardiovascular toxicity [1,2]. Hepatotoxicity is an uncommon side effect from sulfonylureas. It has been sparsely described in literature with Glimepiride, Gliclazide and Gly buride [3-6]. We present a case of Glipizide induced hepatoxicity which has not been previously reported in the literature.

Case Report

A 71 year old female with uncontrolled DM2, HTN, HLD and aplastic anemia presented to her primary care physician with worsening hyperglycemia. Type 2 DM was diagnosed in May 2017 during evaluation of polyuria and polydipsia, Hba1c 7.1%. She was initially managed conservatively with lifestyle modifications. In November 2017, her Hba1c increased to 11%. Metformin 500 mg BID was initiated. Hba1c increased further to 14% in February 2018. Metformin was maximized to 1000 mg BID. She had been on low dose prednisone (1mg) since her bone marrow transplant for aplastic anemia in 2016 which was stopped in February 2018.

In March 2018, she was referred to our clinic due to sudden worsening hyperglycemia with no clear etiology. Her endogenous insulin reserve was tested, fasting C peptide level was 3.5 ng/ml, Glucose 162 and GAD65Ab was negative. Glipizide 5 mg BID was started in addition to metformin 1000 mg BID. Four weeks later her routine labs showed elevation of AST to 89 µ/l and ALT to 255 µ/l which were previously normal. Patient denied any yellowish discoloration of skin, weight changes, appetite changes, fatigue, nausea, vomiting or abdominal pain. No change in the color of stool or urine. She denied using any new medications. Repeat labs within four days showed further elevation of AST and ALT to 311 µ/l and 446 µ/l, respectively. Glipizide was discontinued. Liver enzymes showed improvement in three days and normalized within a week of stopping the medication. Other etiologies of acute hepatitis were tested and were normal - CMV IgM, HBsAg, HBc IgM, EBV DNA, HCV PCR. Patient denied previous history of biliary tract disease, alcohol use, herbal supplements or any other non-prescription medications. No pertinent family history. Physical examination was normal. Patient was diagnosed with acute hepatitis in hepatocellular pattern by Gastroenterology. In the setting of significant improvement in liver enzymes after medication cessation and a negative hepatitis workup, Glipizide induced liver injury was suspected. Patient declined a re-challenge with Glipizide to further confirm its role in acute hepatitis.

Discussion

Drug induced liver injury is the most common cause of acute liver failure [7]. However, hepatotoxicity is a rarely reported side effect for sulfonylureas [8]. This diagnosis requires a high index of suspicion after diligently excluding other causes of abnormal liver enzymes.

Glipizide	Date	AST µ/l	ALT µ/l	AlkPhos µ/l	Total bilirubin mg/dl
	2/12/2018	15	15	73	0.7
Started 3/19/18	4/23/2018	89	255	78	0.5
Stopped 4/20/18	4/27/2018	79	311	446	0.6
	4/30/2018	117	381	89	0.5
	5/04/2018	75	248	92	0.4
	5/11/2018	20	50	70	0.4

Liver enzyme pattern suggesting acute hepatitis. Patient stopped taking Glipizide on 4/29/2018 after which the liver enzymes improved and normalized within two weeks.

Author	Sulfonylurea	Age	Sex	Onset after initiation	Complete resolution of liver enzymes
Chounta A, et al. [3]	Glimeperide (2 mg/day)	65	M	2 weeks	1 month
Van Basten JP, et al. [4]	Glyburide (5 mg BID)	69	F	~ 3 weeks	Fatal outcome
Omar H, et al. [5]	Glimeperide (3 mg daily)	58	M	5 months	2 months
Goodman RC, et al. [6]	Glyburide (10 mg BID)	63	F	4 weeks	1-2 weeks
Goodman RC, et al. [6]	Glyburide (10 mg BID)	61	F	9 weeks	Improving at one week Labs in one year were normal
Chitturi S, et al. [8]	Gliclazide (80 mg BID)	42	F	4 weeks	12-13 weeks
Del-Val A, et al. [9]	Glibenclamide (5 mg TID)	63	M	5 years	Within 6 Months
Wongpaitoon V, et al. [10]	Glibenclamide (10 mg daily)	61	M	5 months	37 days
Saw D, et al. [11]	Glyburide(1.25 mg daily)	46	M	3 years	Alkaline phosphatase remained elevated
Clark BF, et al. [7]	Glibenclamide (20-30mg daily)	67	M	4 weeks	Fatal outcome

Summarizing case reports of sulfonylureas causing hepatotoxicity.

Liver injury secondary to Glimepiride, Glyburide and Gliclazide have been described in case reports [3,4]. We present Glipizide induced hepatotoxicity which has not been previously reported to our knowledge. Roussel Uclaf Causality Assessment Model score was 8 for our patient which represents a probable likelihood of Glipizide causing hepatotoxicity. Most cases with sulfonylurea induced liver toxicity present with reversible liver injury but fatal incidents have also been reported [4,9]. In most of these studies causality was established by excluding other etiologies of liver injury, the pattern of liver enzyme elevation and their normalization after cessation of sulfonylurea use. Pathophysiology behind acute liver injury remains unclear. Hypersensitivity may be a key feature in sulfonylurea induced hepatotoxicity [10].

The onset of hepatotoxicity with Glimepiride varied from a week to five months. Liver enzymes normalized within three days to eight weeks after stopping the medication [3,5]. Liver biopsy report predominantly showed a cholestasis pattern however hepatic necrosis was also noted [3]. With Glyburide and Gliclazide, liver enzyme elevation were commonly seen after two to nine weeks of introduction [6,10]. Rarely, late onset hepatotoxicity has also been described in literature. Adolfo and his team reported a case of a 63 year old male who presented with cholestasis. He had been on Glyburide for three years [11]. Wongpaitoon et al described a case of intrahepatic cholestasis and cutaneous bullae after five months of using Glyburide [12]. In these case reports, liver enzymes normalized between one to two weeks after the medication was discontinued.

Two cases of fatal liver disease have been reported with the use of Glyburide. Clark and associates described a case of severe generalized hypersensitivity reaction with toxic erythema, eosinophilia, visceral arteritis and cholestatic jaundice in a 67 year old male who was taking high dose of Glyburide (30 mg/day) for four weeks [9]. Van Basten and coworkers report a fatal case of a 69 year old woman who developed icterus and pruritus after three weeks of using Glyburide 5 mg BID. Despite discontinuation of Glyburide, patient progressed to liver failure precipitated by bacterial peritonitis and did not survive [4]. In contrast to previous reports, our patient was asymptomatic and was found to have liver enzyme abnormalities consistent with hepatocellular pattern on routine monitoring. In agreement with previous literature, her liver enzymes peaked at four weeks and normalized after a week of discontinuation.

Conclusion

Hepatotoxicity has been described as a rare side effect of sulfonylurea therapy. We present a case of asymptomatic acute liver toxicity from Glipizide which resolved with discontinuation of the medicine. This case emphasizes the importance of monitoring liver function closely once sulfonylureas are initiated. It also highlights the significance of considering sulfonylureas in the differential diagnosis of acute hepatitis.

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