Case Report

An unusual case of glipizide-induced proximal myopathy

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ABSTRACT

This case report outlines a very rare case of glipizide-induced severe proximal myopathy in a 61-year-old diabetic man. After taking 10 mg glipizide for 5 months, diabetes was well controlled but the patient presented with progressive proximal muscle weakness in all the four limbs. Clinical examination and relevant investigations suggested it to be a case of proximal myopathy and might be drug induced. De-challenge was done and was treated resulting in reversal of the diseased state. After 3 more months, controlled re-challenge was done and there was recurrence of proximal muscle weakness. There were no evidences of any other possible metabolic, infective, organic or other pathologic causes giving rise to that condition and Naranjo adverse drug reaction probability scale suggested that it was "probable" that glipizide was responsible for the development of myopathy in this patient.

Key words: Diabetic, glipizide, proximal myopathy, sulfonylurea

INTRODUCTION

Glipizide is a potent hypoglycemic sulfonylurea, widely used in diabetes as monotherapy or in adjunct to other oral hypoglycemic agents. It acts by blocking potassium channels in the beta cells of pancreas and as a result the cell depolarizes leading to opening of voltage-gated calcium channels and insulin release. It also causes the decrease of serum glucagon level and potentiates the action of insulin at the extra pancreatic tissues. The usual recommended dose is 2.5–20 mg/day.[1,2] The most serious adverse effect of this drug is hypoglycemic episodes which can lead to coma. The other reported adverse effects are nausea and vomiting, cholestatic jaundice, agranulocytosis, aplastic and hemolytic anemias, generalized hypersensitivity reactions, neuromuscular and skeletal abnormalities including tremor, myalgia, paresthesia, ocular and dermatological reactions.[3] Rarely, patients treated with these drugs develop an alcohol-induced flush similar to that caused by disulfiram or hyponatremia. It may also increase cardiovascular mortality by a mechanism with expression of the sulfonylurea receptor on vascular smooth muscle cells and cardiac myocytes, where activation of the

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sulfonylurea prevents the beneficial effects of ischemic preconditioning.[1,4] Myalgia and paresthesia are observed in less than 3% of individuals treated with glipizide.[3] We present here an interesting rare case of glipizide-induced proximal myopathy ina 61-year-old diabetic individual.

CASE REPORT

A 61-year-old non-alcoholic, non-smoker and retired man (body weight 68 kg) was diagnosed to be type 2 diabetic for the first time in April 2014 with fasting blood glucose 153 mg/dL, post prandial blood glucose 199 mg/dL and HbA1C 7.2%. He had no other co-morbidities like hypertension, coronary or cerebral arterial diseases, hyperlipidemia, or any other chronic illnesses. Apart from dietary and life style changes, he was prescribed tablet metformin 500 mg once daily by a physician. But, due to severe gastro-intestinal intolerance the drug was discontinued within 1 month and substituted to oral glipizide 5 mg daily. After 2 months of taking this dose of glipizide, his fasting and post-prandial blood glucose levels came down to 145 and 173 mg/dL respectively with 6.7%HbA1C. Then the dose of glipizide was escalated to 10 mg/day and after taking this dose for the next 5 months, the man presented in the block primary health center with symmetrical and progressive weakness of all four limbs, more in the lower ones. The muscle weakness was gradual in onset, mostly in the proximal muscles associated with malaise and fatigue impairing normal daily activities. The bowel and bladder habits and the urine color were normal. On examination, the man had perfect higher mental functions, afebrile with normal vitals and no palpable lymph nodes. Muscle power in both upper limbs (both proximal and distal muscles) was 4/5 and in lower limbs 4/5 in the distal muscles and 3/5 in the proximal ones. There was mild tenderness in the proximal lower limb muscles and the reflexes were normal in both the limbs. No wasting, hypotonia, sensory deficits and skin changes (like patches or papules) were present.

Complete blood count, erythrocyte sedimentation rate, and urinalysis gave a perfectly normal picture. The glycemic status was normal (fasting blood glucose 111 mg/dL and post prandial 132 mg/dL). Serum electrolytes (including calcium and magnesium), liver function, lipid profile and thyroid function came well within normal limits. However, serum creatine kinase (muscle) was 231 U/L (normal: 55–170 U/L), serum creatinine was 1.5 mg/dL (normal: 0.6–1.2 mg/dL), serum urea was 45 mg/dL (normal: 20–40 mg/dL) and serum myoglobin was 179 ng/mL (normal: 0–85 ng/mL). An early stage proximal myopathy was suspected. Electrocardiography and MRI of dorso-lumbar spine was within normal limits. Electromyography and muscle biopsy were however not done as the patient didn't consent.

Autoimmune disease, endocrinopathies, renal insufficiency, alcoholism, periodic paralyses, familial hypokalemic periodic paralysis, muscle dystrophies, metabolic myopathies, infectious-related etiologies were excluded and a diagnosis of chronic fatigue syndrome was made and conservative treatment was started. Diabetes itself was ruled out as a cause of muscle weakness as it was a new onset diabetes without any features of complications, and glycemic status was well maintained with glipizide. The patient didn't improve in 3 weeks and the first suspicion of drug (glipizide)-induced muscle weakness was suspected. Glipizide was withdrawn and substituted with oral vildagliptin 25 mg twice daily and the patient was kept on close regular follow-up. Interestingly, the symptoms of myopathy improved by itself from the end of the first month after stopping glipizide, and almost completely recovered at the end of 3 months, without adding any single other drug for the muscle weakness. Relevant investigations showed fasting glucose 97 mg/dL, post prandial glucose 111 mg/dL, HbA1C 5.9%, normal routine urinalysis results, serum creatine kinase (muscle) 131 U/L, serum creatinine 1.0 mg/dL, serum urea 33 mg/dL and serum myoglobin 53 ng/mL. Under a controlled trial, a low dose (5 mg) glipizide was re-started and again the symptoms of myopathy re-appeared in 3 weeks and glipizide was stopped. Now the patient is perfectly asymptomatic and blood glucose is well controlled with vildagliptin.

DISCUSSION

Drug-induced myopathy may result from several different mechanisms like direct myotoxicity (alcohol, cocaine, glucocorticoids, lipid-lowering drugs, anti-malarials, colchicine, zidovudine), immunologically induced inflammatory myopathy (D-penicillamine) or indirect muscle damage thatcan occur by a variety of mechanisms including drug-induced coma with subsequent ischemic muscle compression, drug-induced hypokalemia (diuretics), drug-induced hyperkinetic states (delirium tremens or seizures secondary to alcohol), dystonic states associated with phenothiazines, hyperthermia related to cocaine use, and the neuroleptic malignant syndrome. In some cases, multiple mechanisms may combine to produce muscle damage. As an example, alcoholic binges may precipitate hypokalemia, hypophosphatemia, coma, or agitation; in addition, direct muscle toxicity may also be present.Intramuscular injections, particularly repeated injections of opiates (e.g., heroin or pentazocine), may cause muscle damage with a fibrotic reaction that can result in muscle contractures. Inadvertent intra-arterial injections may cause ischemic necrosis of muscle tissue.[5] The major symptoms in drug-induced myopathies are proximal muscle weakness, increased muscle enzyme levels, electromyographic changes and histological lesions. Some drug-induced myopathies are also associated with neuropathy.[6]

Among oral hypoglycemic agents, pioglitazone had caused acute rhabdomyolysis in a 52-year-old man.[7] Similar cases were also reported with rosiglitazone and troglitazone.[8,9] Impaired exercise tolerance and skeletal muscle myopathy has been reported in sulfonylurea receptor-2 mutant mice.[10] Till 2012, glipizide caused myopathy in 31 individuals (0.1724%).[11] In March 2015, 0.01% individual on glipizide reported myopathy.[12]

This is a rare case report of glipizide-induced chronic proximal myopathy. Genetic factors involving sulfonylurea receptor might play some role. Patients complaining of muscle weakness after chronic glipizide therapy should be screened for myopathy. Naranjo adverse drug reaction probability scale[13] suggested that it was "probable" that glipizide was responsible for the development of myopathy in this patient.

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Conflicts of interest
There are no conflicts of interest.

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