

Deterioration of Glycemic Control Induced by Pentoxifylline and Cilostazol in a Diabetic Patient with Peripheral Vascular Disease

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ABSTRACT

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A 67-year-old South Asian male with type 2 diabetes mellitus, hypertension and ischemic heart disease was admitted with dry gangrene of right leg second toe. Angiography of right lower limb revealed peripheral vascular disease. He received pentoxifylline 400mg twice a day and cilostazol 100mg twice a day for 6 days following disarticulation. During this period, there was a marked elevation of blood sugar requiring higher dosage of insulin. On withholding the offending drugs there was a definite fall in blood sugar indicating a positive dechallenge. An erroneous exposure of pentoxifylline occurred following which the glycemic control further deteriorated, suggestive of a positive rechallenge though it was unintentional. Pentoxifylline and Cilostazol might have induced hyperglycemia by favoring intestinal glucose absorption through increased cAMP levels and GLUT2 expression necessitating management with higher dosage of insulin.

Keywords: Cilostazol, Diabetes mellitus, Hyperglycemia, Pentoxifylline

INTRODUCTION

Pentoxifylline is a non-selective phosphodiesterase inhibitor and cilostazol a selective phosphodiesterase-III inhibitor. In peripheral vascular disease, the therapeutic dose is pentoxifylline 400mg b.i.d. and cilostazol 50 – 100mg b.i.d. The frequent adverse events (AE) reported with pentoxifylline are nausea, anemia, fatigue and hypotension. The frequent AEs with cilostazol are pyrexia, anemia, pneumonia and diarrhea. As per FDA adverse event reporting system, the incidence of increased blood glucose with pentoxifylline is 0.41% and cilostazol is 0.27%.^{1,2,3,4} Drug induced hyperglycemia is mentioned for cilostazol by pharmaceutical companies in their summary of product characteristics.

CASE DESCRIPTION

This is patient with known case of type 2 diabetes mellitus for the past 20 years and ischemic heart disease. He was treated with glyclazide 80mg + metformin 500mg (1 ½ b.i.d), voglibose 0.3mg (1 t.i.d), insulin 70/30, aspirin 75mg + atorvastatin 10mg, metoprolol 50mg and telmisartan 40mg + amlodipine 5mg, and Insulin had been stopped a few days ago before admission due to an episode of hypoglycemia.

He presented with swelling of right lower limb with discharge, pain, fever and blackish discoloration following thorn injury to the second toe 20 days ago. He was treated elsewhere with linezolid. His general and systemic examination was normal. Local examination revealed dry gangrene of the second toe of the right lower limb with cellulites of the plantar aspect of the sole.

Investigations revealed random blood glucose 66mg/dl (70 – 140mg/dl), glycosylated hemoglobin 9.8% (3.8 - 6.3%), haemoglobin 8.9g/dl (13-17g/dl), serum creatinine 1.8mg/dl (0.8-1.44 mg/dl), serum potassium 7.32meq/l (3.5 - 4.5 meq/l). Urine for ketones was negative. Angiography of right lower limb was suggestive of peripheral vascular disease. He underwent a minor surgery for disarticulation of the toe on day 2.

The patient had a mean glycemic level of 276mg/dl prior to therapy with phosphodiesterase inhibitors (day 3 to day 6) requiring an average of 18.5 Units insulin per day. On day 7 to day 12, during treatment with pentoxifylline 400mg (1 b.i.d) and cilostazol 100mg (1 b.i.d), the mean blood glucose level was 351mg/dl, requiring higher dosage of insulin, a range of 28 to 95 Units of insulin. So, pentoxifylline 400mg (1 b.i.d) and cilostazol 100mg (1 b.i.d) were withheld. A significant fall in blood glucose with a mean blood glucose of 191mg/dl was then recorded, which was in-turn managed with an average of 69 Units insulin per day. An unintentional rechallenge with a single dose of 400mg pentoxifylline occurred on day 16 due to an administration error causing a

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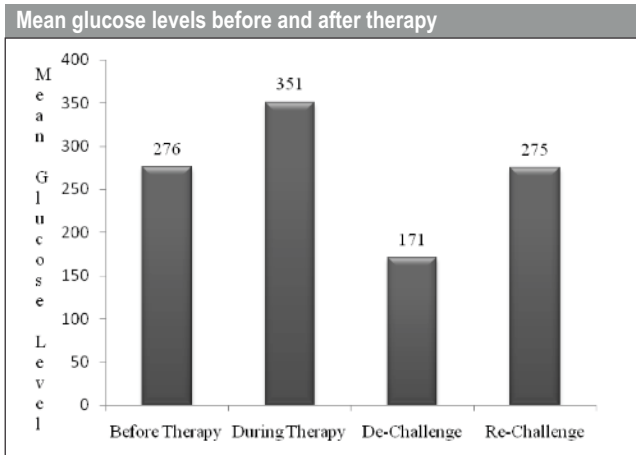
rise in the mean blood glucose to 275mg/dl requiring 84Units insulin. This was followed by a positive dechallenge again on stopping the drugs. The glycemic level was brought under control with an average of 35.6 Units insulin per day. He was treated with glyclazide 80mg + metformin 500 mg (1 ½ b.i.d), voglibose 0.3 mg (1 t.i.d), insulin (30/70) 20 Units – 0 –10 Units, aspirin 75 mg + atorvastatin 10 mg (1 HS), metoprolol 50 mg (once daily) and telmisartan 40 mg + amlodipine 5 mg (1 HS), pentoxifylline 400mg (1 b.i.d) and cilostazol 100mg (1 b.i.d). The patient was suspected to have drug induced hyperkalemia due to telmisartan, which was later withheld and serum potassium was brought to 3.96 meq/l with calcium polystyrene sulfonate.

DISCUSSION

Drug induced hyperglycemia can have perpetual effects on the body, particularly in patients with diabetes. The present case is remarkable for the early diagnosis, aggressive management, twice positive dechallenge and a positive rechallenge. Following intake of pentoxifylline 400 mg b.i.d and cilostazol 100 mg b.i.d, there was a marked rise in the mean blood glucose level to 351 mg/dl which is about 1.3% increase in the baseline value. The patient at baseline had a high blood glucose value (276 mg/dl) which could have been contributed by the focal dry gangrene, sepsis and uncontrolled diabetes. However following disarticulation, he had a healthy wound and diet was strictly monitored as part of the in-patient care. Despite this, the patient's blood sugar continued to increase and the insulin requirement hiked progressively. The clinical situation raised the probability of drug induced hyperglycemia by phosphodiesterase inhibitors, i.e. pentoxifylline and cilostazol. None of the concomitant medications are known to cause hyperglycemia.

In the present case, there is a reasonable time relationship displayed by a marked elevation of glycemic levels on intake of the offending drugs. The twice positive de challenge and a positive rechallenge are suggestive of a causal relationship of the drugs with the event. According to the Naranjo scale for causality assessment, the association of pentoxifylline and cilostazol with hyperglycemia was probable (score of 6) [5]. The WHO – UMC causality assessment qualified the event as possible [6].

The underlying mechanism of hyperglycemia could be due to significantly enhanced expression of GLUT2 on jejunal enterocytes, thus leading to the highest rate of intestinal glucose absorption in presence of pentoxifylline [7]. While some of the absorbed glucose is used for cellular metabolism, the remaining crosses the basolateral membrane into circulation via GLUT2 [7]. Another mechanism contributory to the effect could be the activation of high-affinity, low capacity transporter SGLT-1, also involved in intestinal glucose



absorption, by cAMP. This is supported with the finding that both pentoxifylline and cilostazol increase cAMP by inhibition of phosphodiesterases. Our hypothesis is that phosphodiesterase inhibitors i.e. pentoxifylline and cilostazol could favour intestinal glucose absorption through a direct pathway involving increased cAMP levels and another mechanism requiring enhanced GLUT2 expression [7]. Hence, we propose a combined effect of pentoxifylline and cilostazol causing drug induced hyperglycemia in this patient.

CONCLUSION

Thus the case study of this patient has revealed that the phosphodiesterase inhibitors, pentoxifylline and cilostazol could be causally related to the hyperglycemic event. Although, the precise mechanism is unclear, we hypothesize that increased intestinal glucose absorption leading to altered glucose homeostasis could have precipitated the adverse event. Therefore it is strongly recommended that monitoring the glycemic levels of all the patients being prescribed pentoxifylline and cilostazol is imperative, especially if the patient is also a diabetic.

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