Diabetes & Metabolism

Lam et al., J Diabetes Metab 2014, 5:8
http://dx.doi.org/10.4172/2155-6156.1000422

Case Report Open Access

Diabetic Ketoacidosis Secondary to L-Asparaginase and Dexamethasone during Treatment for Acute Lymphoblastic Leukaemia

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Abstract

Diabetic ketoacidosis is an unusual adverse event following chemotherapy for acute lymphoblastic leukaemia. Treatment of haematological malignancies with L-asparaginase has been associated with hyperglycaemia in 1-2% of patients. The concomitant use of glucocorticoids has an additional deleterious effect. We describe a case of diabetic ketoacidosis occurring in a 25 year old male following treatment with L-asparaginase and high dose dexamethasone. Insulin therapy was required only for the duration of treatment. Greater awareness of this adverse effect may reduce the significant morbidity associated with treatment for leukaemia.

Background

Glucocorticoids are commonly used to treat a variety of illnesses, and are a vital part of many chemotherapy regimens. However, their use is accompanied by side effects including hyperglycaemia. The mechanisms are multifactorial, and include opposition of insulin action, augmentation of hepatic gluconeogenesis and inhibition of glucose uptake in adipose tissue [1,2]. L-asparaginase is an agent used to treat Acute Lymphoblastic Leukaemia (ALL) which is reported to cause hyperglycaemia in approximately 10% of patients [3]. However, this has mostly been described in the paediatric population. We present a case of Diabetic Ketoacidosis (DKA) in a 25 year old patient without previously known diabetes who had leukaemia treated with glucocorticoids and L-asparaginase.

Case Presentation

We describe a case of a 25 year old Chinese male who was diagnosed with T-cell Acute Lymphoblastic Leukaemia (ALL) in December 2010. Baseline fasting Blood Glucose Level (BGL) was normal at 5.4 mmol/L (97.2 mg/dL). The patient commenced chemotherapy based on the AIEOP-BMF ALL 2009 protocol, consisting of daunorubicin, vincristine, colaspase, cyclophosphamide, intrathecal methotrexate and dexamethasone. As part of the induction phase, he was treated with prednisolone 105 mg (60 mg/m^2/day) daily for 28 days. Following this, he received high dose dexamethasone 36 mg (20 mg/m^2/day) with each treatment cycle for 3 cycles followed by a re-intensification phase, which included vincristine, doxorubicin, L-asparaginase and dexamethasone 18 mg for 14 days. After commencement of chemotherapy, he had random capillary BGLs performed which ranged between 4.6 to 11.3 mmol/L (82.8 to 203.4 mg/dL). In August 2011, 8 months after the diagnosis of ALL and 2 weeks after commencing L-asparaginase, on a weaning dose of dexamethasone 2 mg twice daily, the patient became acutely unwell with significant polyuria and polydipsia for 3 days prior to admission. He did not have a family history of diabetes mellitus or autoimmunity.

On physical examination, he was dehydrated and afebrile. He had no clinical evidence of acute pancreatitis. Laboratory investigations showed a blood glucose level of 41.7 mmol/L (751 mg/dl) and capillary blood ketones 6.0 mmol/L. An arterial blood gas analysis showed a pH 7.24, bicarbonate 11.0 mmol/L, base excess -15.0 mmol/L, anion gap 25 mEq/L and lactate 1.9 mmol/L, confirming the diagnosis of a high anion gap metabolic acidosis consistent with DKA. Due to recent chemotherapy, other parameters were also deranged, with a leukocyte count of 0.8x10^9/L (3.7-9.5x10^9/L) including significant neutropaenia, and platelet count of 35x10^9/L (150-400x10^9/L). Blood and urine cultures were negative and CRP (C-reactive protein) was normal (<5 mg/L). HbA1c was elevated at 62 mmol/mol (7.7%), reflecting a period of hyperglycaemia prior to presentation. His haemoglobin was normal at 142 g/L (130-180 g/L) having had a blood transfusion 3 months prior to presentation. Islet cell antibodies were not detected. Dexamethasone was ceased, an insulin infusion commenced, and he was discharged on a basal bolus regimen of insulin aspart and glargine.

Over the next 4 months, the patient completed re-intensification phase chemotherapy with high dose dexamethasone. His glycaemic control remained stable on insulin with BGLs between 4-10 mmol/L (72-180 mg/dl). In December 2011, maintenance chemotherapy was commenced, consisting of methotrexate and 6-mercaptopurine for the ensuing 15 months. Despite withdrawal of glucocorticoids , the patient continued to require insulin therapy for the next 6 months. In August 2012, 8 months after glucocorticoids were stopped, he ceased insulin therapy. His HbA1c was 4.8% (29 mmol/mol).

Twelve months after cessation of insulin, his fasting C-peptide was in the upper normal range at 0.59 nmol/L. Anti-GAD antibodies was negative. A 75 gram oral glucose tolerance test was normal with fasting glucose of 4.6 mmol/L (83 mg/dl), and 2 hour glucose of 5.3 mmol/L (95 mg/dL). To date, the patient remains euglycaemic and in remission from leukaemia.

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Received May 19, 2014; **Accepted** August 27, 2014; **Published** September 06, 2014

Citation: Lam T, Chipps D, Gunton JE (2014) Diabetic Ketoacidosis Secondary to L-Asparaginase and Dexamethasone during Treatment for Acute Lymphoblastic Leukaemia. J Diabetes Metab 5: 422 doi:10.4172/2155-6156.1000422

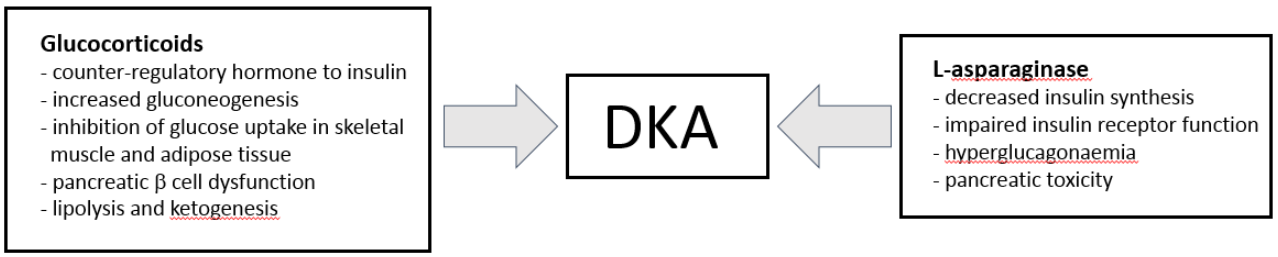

Figure 1: Interaction between L-asparaginase and glucocorticoids in DKA.

Discussion

Glucocorticoids have a variety of effects that can cause hyperglycaemia or exacerbate pre-existing diabetes. The development of ketoacidosis in the setting of glucocorticoids is uncommon but has been previously described [2,4,5]. Alavi et al. [2] described the onset of glucocorticoid-induced DKA in 5 patients receiving glucocorticoids for collagen vascular disease. The reported doses of prednisone ranged between 30 to 120 mg daily. Çagdaş et al. [4] reported a case occurring in a 15 year old girl receiving methylprednisolone for acute rheumatic fever. Auto-antibodies were not detected. Insulin was required transiently while the patient was receiving glucocorticoid therapy. In our patient, ketoacidosis occurred 3 months after being treated with high dose dexamethasone at doses up to 36 mg per day.

Ketoacidosis occurs when there is insufficient insulin for carbohydrate metabolism, with the net effect being a release of Free Fatty Acids (FFAs) from adipose tissue which is converted into ketone bodies [2]. Insulin and glucocorticoids play opposing roles in the mobilisation of FFA. Many hormones promote FFA release from adipose tissue but the full lipolytic effect is not achieved in the absence of the adrenal cortex. Glucocorticoids stimulate lipolysis and ketogenesis and contribute to hyperglycaemia by directly promoting hepatic gluconeogenesis and inhibiting glucose uptake into muscles. They are also known to cause pancreatic β-cell dysfunction [6,7]. Thus, important hormonal factors for ketosis are insulin deficiency and glucocorticoid excess.

In addition to glucocorticoids, our patient received concurrent treatment with L-asparaginase (Figure 1). Robertson et al. [8] reported six cases of DKA in 797 paediatric patients treated for ALL who all responded to insulin treatment without the need for long term therapy. Age greater than 10 years was identified as the only risk factor. Alves et al. [9] also described a case of DKA occurring in a 13 year-old girl treated with L-asparaginase and dexamethasone. L-asparaginase hydrolyses L-asparagine to L-aspartic acid and ammonia. Asparagine is necessary for cell survival, and most cells have the enzyme L-asparagine synthetase, allowing synthesis of asparagine. Lymphoblasts in ALL lack L-asparagine synthetase, and therefore cannot survive asparagine depletion caused by L-asparaginase. Administration of L-asparaginase as chemotherapy preferentially limits L-asparagine to leukaemic cells during the G1 phase of mitosis [3]. L-asparaginase induces hyperglycaemia via depletion of L-asparagine resulting in decreased insulin synthesis, as pancreatic -cells require three L-asparagine molecules to generate each insulin molecule [3]. In addition, there is impaired insulin receptor function and hyperglucagonaemia [10]. Pancreatic toxicity has also been described in up to 8.5% of children receiving L-asparaginase, which can result in hyperglycaemia and diabetes mellitus in 2.5-23% of patients [10]. Our patient had no clinical evidence of acute pancreatitis, and recovered quickly after an insulin infusion was commenced.

Furthermore, our patient also received doxorubicin as part of his chemotherapy regimen for ALL. Although it is not well studied in humans, the use of doxorubicin in rodent models results in elevated triglyceride and BGLs. Doxorubicin inhibits adipogenesis through down-regulation of PPARγ, which then inhibits blood glucose and lipid clearance causing hyperglycaemia, and hyperlipidaemia resulting in lipotoxicity, glucotoxicity, and inflammation and insulin resistance [11]. These effects could also have contributed to the severe hyperglycaemia observed in our patient.

Conclusion

The long-term outcome of ALL has improved dramatically during the last few decades because of the development of well-designed and effective treatment protocols. Both L-asparaginase and glucocorticoids form part of the cornerstone treatment for ALL. Although DKA is rare during treatment with ALL, it carries significant morbidity and mortality. Recognition of the potential effects of L-asparaginase and glucocorticoids on glucose metabolism is critical in preventing life-threatening DKA. Furthermore, as these patients are treated in an out-patient setting, monitoring of BGLs should be encouraged during the use of these agents, with blood ketone levels checked if hyperglycaemia develops.

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