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Outpatient management of steroid-induced hyperglycaemia and steroid-induced diabetes in people with lymphoproliferative disorders treated with intermittent high dose steroids

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ABSTRACT

High dose steroids (HDS) are used in the treatment of haematological malignancies. The reported risk of steroid-induced diabetes (SID) is high. However, screening is not consistently performed. We implemented a protocol for detection and management of SID and steroid-induced hyperglycamia (SIH) in haematology outpatients receiving HDS.

Eighty-three people were diagnosed with a lymphoproliferative disorder, of whom 6 had known Type 2 diabetes. Fifty-three people without known diabetes were screened by HbA1c and random venous plasma glucose. All patients (n = 34) subsequently prescribed HDS checked capillary blood glucose (CBG) pre-breakfast and pre-evening meal. Treatment algorithms used initiation and/or dose titration of gliclazide or human NPH insulin, aiming for pre-meal CBG 5–11 mmol/l. Type 2 diabetes was identified in 4/53 people screened (7.5%). Of 34 people treated with HDS, 17 (44%) developed SIH/SID. All 7 people with Type 2 diabetes developed SIH and 3 required insulin. Of 27 people without known diabetes, 8 (30%) developed SID and 1 required insulin. Pre-treatment HbA1c was higher in people who developed SID compared to those that did not (p = 0.002). This is the first report of a SID/SIH detection and treatment protocol for use in people with lymphoproliferative disorders receiving intermittent HDS, demonstrating its feasibility and safety.

Introduction

High dose steroids (HDS) are commonly used in the treatment of haematological disorders. Steroid-induced diabetes (SID), in people without pre-existing diabetes, and steroid-induced hyperglycaemia (SIH), in people with diabetes, are recognised as important complications of steroid treatment [1–3]. The incidence of SID in people with haematological malignancies is likely to be underestimated, however, case series suggests the incidence is as high as 40% [4,5]. We designed and piloted a protocol for the detection and management of SIH/SID in haematology outpatients.

Methods

The full protocol is available in supplementary data and was piloted between November 2013 and November 2014. Patients diagnosed with a lymphoproliferative disorder, and not known to have diabetes, were screened for diabetes using the WHO diagnostic criteria [6].

In people requiring HDS, the protocol recommended referral to the diabetes team prior to commencement for those with: Type 1 diabetes, ketosis prone Type 2 diabetes, new diagnosis of diabetes, known diabetes with HbA1c ≥ 8.0% (64 mmol/mol), or on basal bolus insulin regimen, GLP-1 receptor agonist, or pioglitazone or an eGFR <45 ml/min. People without known diabetes and people with known Type 2 diabetes not meeting the criteria above were managed by the haematology team using a series of algorithms.

For those not on a sulphonylurea or insulin, treatment algorithms were based on starting gliclazide or human NPH insulin (Humulin I). People with capillary blood glucose (CBG) > 18 mmol/l, and those already on gliclazide 160 mg bd, were started on insulin. Doses were titrated with a target CBG 5–11 mmol/l. At the end of the HDS the gliclazide and/or insulin was stopped and people were advised to continue monitoring. The algorithm for those already on gliclazide used similar parameters, but titration rather than commencement of gliclazide.

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Patient feedback was sought. A student's *t*-test was used to compare parameters. A p value <0.05 was considered statistically significant.

Results

Eighty-three people were diagnosed with a lymphoproliferative disorder during the pilot and 59 (71%) had an HbA1c measured. Six (7%) had pre-existing diabetes (all Type 2 diabetes). Four of 53 (7.5%) people without known diabetes were found to have Type 2 diabetes (Fig. 1).

Thirty-four patients received treatment with HDS as part of their chemotherapy regimen. Patient characteristics are given in Table 1. Fifteen (44%) developed SIH/SID requiring treatment.

Of the 34 patients treated with HDS, 7 (20%) had Type 2 diabetes, one identified by screening. Prior to HDS, all were treated with diet or oral agents, including 3 people on gliclazide. The mean HbA1c was 7.1% (54 mmol/mol), range 6.1–8.2% (43–66 mmol/l). All those with pre-existing diabetes developed SIH requiring a change of treatment. Of 2 people on diet alone, 1 required gliclazide and 1 declined treatment for hyperglycaemia. Of 2 people on non-sulphonylurea oral hypoglycaemic agents (OHAs), 1 required gliclazide and the other was initially managed with gliclazide and then required insulin on a later course. Of 3 people on OHAs including gliclazide, 1 was managed with dose titration and 2 required insulin (see Fig. 2).

Twenty-seven of the 34 people treated with HDS did not have known diabetes and 8 (30%) developed SID. Two of 8 did not have SID during their first HDS course and developed it on subsequent courses. The mean HbA1c prior to HDS in those that developed SID was significantly higher than those who did not (p = 0.002). There was no significant difference in BMI. Four of 9 (44%) patients of African/Caribbean descent developed SID. Seven of 8 patients were managed with gliclazide. One patient receiving high doses of methylprednisolone (1 mg/kg/day) required insulin.

There were no hyperglycaemia-related hospital admissions and no episodes of hypoglycaemia reported.

Seven patients completed a feedback questionnaire. Their overall confidence in the protocol and testing CBG was scored as an 8/10 (with 0 being not confident at all and 10 being most confident).

Table 1
Patient characteristics.

Patients	N = 34 (%)
Mean age (yrs)	58.6 (22–87)
Men	21 (62)
Ethnicity	
White	23 (68)
Black african/caribbean	9 (26)
Other	2
Mean HbA1c in patients without diabetes (n = 21) mmol/mol; % (range)	41; 5.9 (30–66)
HbA1c in patients with diabetes (n = 6) mmol/mol;% (range)	54; 7.1 (43–66)
Mean BMI	27.7 (19–43.6)
Known Type 2 diabetes	6 (18)
Non-diabetic	27 (79)
Screen-detected diabetes	1
Diagnosis	
B-cell lymphoma	25
Acute lymphoblastic leukaemia	4
Hodgkin lymphoma	4
T-cell lymphoma	1
Steroid regimen as part of the chemotherapy, once daily	
Prednisolone 100 mg daily for 5 days repeated every 21 days	20
Prednisolone 60 mg/m^2 daily for 15 days and repeated every 28 days	3
Dexamethasone 6 mg/m^2 for 4 days repeated every 2 weeks	3
Prednisolone 1 mg/kg for 2 weeks	5
Dexamethasone 8 mg, then reducing dose	1
Methylprednisolone 1 mg/kg for 5 days repeated every 28 days	1
Prednisolone 40 mg, then reducing by 10 mg weekly	1
Mean steroid dose, prednisolone equivalent in mg	155 (30–2500)

Discussion

In this pilot in people with lymphoproliferative disorders requiring short courses of HDS we found an overall incidence of SID/SIH of 44%. All people with known Type 2 diabetes developed SIH requiring medication change. The finding of a progressive impact on glycaemia with successive steroid courses has previously been reported, highlighting the importance of continued monitoring [7]. In people without diabetes, 30% developed SID. Our population may have been at increased risk with 26% being of Black African or Caribbean ethnicity, a mean age of 58.6 years and a mean BMI of 27.7 kg/m^2. In addition, the steroid doses were high, a factor directly correlated with risk of SID [8,9]. However this is similar to the incidence of SID in people with haematological malignancies reported previously [4,5,9,10].

We identified undiagnosed Type 2 diabetes in 7.5% of those screened. Given that all people with pre-existing diabetes treated with HDS developed SIH requiring treatment, we suggest screening for undiagnosed diabetes in patients starting HDS.

Our protocol aligns with the JBDS-IP guidelines recommending treatment if CBG $\geq$ 11.1 mmol with a target of 5-11 mmol/l compared to the JBDS-IP of recommending treatment if CBG > 12 mmol/l with a desired target of 6–10 mmol/l and the use of gliclazide or human NPH insulin [1]. However, we initiated gliclazide at 80 mg (rather than the 40 mg) and recommended starting insulin directly at CBG above 18 mmol/l. Our protocol

Fig. 1. Flowchart showing patient selection for pilot study.

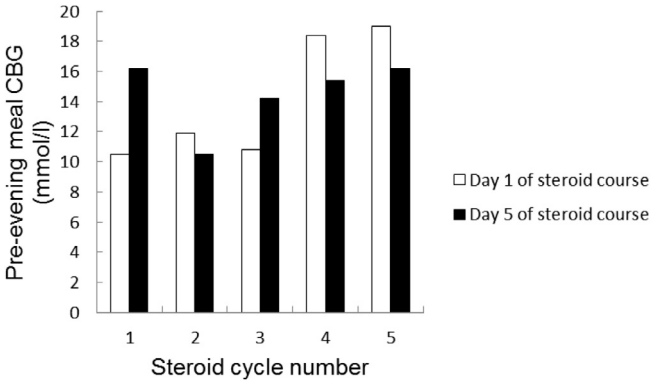

Fig. 2. Capillary blood glucose before breakfast (A) and before evening meal (B) for one person over five cycles of HDS. We have chosen to present this patient because he had good glycaemic control before HDS and required gliclazide and then insulin. Prior to HDS he had Type 2 diabetes treated with sitagliptin 100 mg od only with HbA1c 43 mmol/mol (6.1%) and was not monitoring CBG. He received prednisolone 100 mg om for 5 days every 21 days for 5 cycles. Cycle 1: no change in glucose lowering therapy (team not informed of CBG readings); cycle 2: gliclazide 80 mg om started on day 1; cycle 3: gliclazide 80 mg om started on day 1, increased to 160 mg om and 80 mg pm by day 5; cycle 4: used gliclazide regimen from previous cycle; cycle 5: started bd humulin I on day 1. Although target CBG were not achieved, the protocol attenuated the marked increase in CBG from day 1 to day 5 seen in cycle 1, he did not require hospital admission and there was no hypoglycaemia.

appears to be safe with no episodes of hypoglycaemia and no hospital admissions.

The adverse consequences of SIH/SID are increasingly being recognised in both the inpatient and outpatient setting. These include adverse effects on cardiovascular health, increase in infectious complications, increase in length of hospital stay and a negative impact on outcomes following solid organ transplantation [11]. Consequently, there are published recommendations for the early detection and prevention of SIH/SID. Most management algorithms are similar to our protocol although there are alternative oral agents that may provide similar efficacy to gliclazide for those with mild to moderate elevations in blood glucose [11,12].

The importance of interventions to manage symptomatic SID/SIH and prevent hospital admissions seems self-evident. However, whether short episodes of asymptomatic SID/SIH in patients with haematological malignancies are clinically relevant is not known. A large review of patients requiring treatment for myeloma reported that patients with diabetes or SID had a significantly lower overall survival [4]. A study of SID in patients with acute lymphoblastic leukaemia found that those that developed hyperglycaemia had a shorter survival and an increase in infective complications [10]. Whether intervention impacts outcome is not known.

This is the first report of a SID/SIH detection and treatment protocol for use by haematology staff specifically for people with lymphoproliferative disorders receiving intermittent high doses of steroids and demonstrates its feasibility and safety.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcte.2017.06.003.

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