ORIGINAL ARTICLE

Safe and Effective Dosing of Basal–Bolus Insulin in Patients Receiving High-Dose Steroids for Hyper-Cyclophosphamide, Doxorubicin, Vincristine, and Dexamethasone Chemotherapy

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Abstract

Background: Hyperglycemia occurs in cancer patients receiving high-dose steroids with cyclophosphamide, doxorubicin, vincristine, and dexamethasone (hyper-CVAD) protocol. The purpose of our study was to determine insulin requirements in patients with hyperglycemia on hyper-CVAD therapy using a systematic algorithm.

Subjects and Methods: We did a retrospective chart review of 23 leukemia inpatients with hyperglycemia (two glucose values >250 mg/dL) on hyper-CVAD chemotherapy managed by the Endocrine Diabetes Inpatient Team algorithm. We reviewed demographic and glycemic data, insulin dosages, and use of oral hypoglycemic agents. Using our algorithm, the dose of insulin for each patient was titrated daily and with each subsequent cycle of hyper-CVAD.

Results: Ninety-one percent of patients had known diabetes. The median body mass index was 32.5 (range, 21.6–40.9) kg/m², and median age was 61 (range, 40–80) years. The overall trend in glucose values across cycles showed a statistically significant decrease with each subsequent cycle of hyper-CVAD. Hyperglycemia accounted for 81% of glucose measurements in the first cycle and 60% of glucose values in the last cycle. Patients received 1–1.3 units/kg of insulin per cycle, and insulin requirements were similar across cycles. The distribution of basal versus bolus insulin for each cycle was 63–77% prandial and 23–37% basal. Nine of the 23 patients had at least one glucose value <70 mg/dL, which accounted for 1.3% of all recorded glucose values. None of the patients had severe hyperglycemia.

Conclusions: Multiple-dose insulin therapy initiated at 1–1.2 units/kg/day, distributed as 25% basal and 75% prandial, reduced hyperglycemia in patients who were receiving high-dose dexamethasone as part of hyper-CVAD.

Introduction

HYPERGLYCEMIA, DEFINED AS TWO consecutive glucose values ≥ 250 mg/dL, often occurs in patients with hematologic malignancies.¹ Although many factors contribute to hyperglycemia in cancer patients, corticosteroids, which are an essential component of various chemotherapeutic regimens, play a significant role. In addition to their inhibitory effect on the immune system and cytotoxicity to cancer

cells, steroids play an important role in cancer pain management,² prevention and treatment of chemotherapy-induced nausea and vomiting,³ appetite stimulation, and cancer cachexia.

The prevalence of hyperglycemia and its effect on remission and survival in cancer patients have been reported in many studies previously. At MD Anderson Cancer Center (Houston, TX), in patients with acute lymphocytic leukemia (ALL) treated with induction chemotherapy that included

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high-dose dexamethasone, 37% were noted to have hyperglycemia, but only 7% had a previous diagnosis of diabetes.⁴ This study also noted that patients with hyperglycemia had a shorter median survival and were more likely to develop sepsis and infections compared with their euglycemic counterparts. In another study evaluating children with ALL, overt hyperglycemia, defined as a blood glucose value of >200 mg/dL, was seen in up to 56% of children receiving induction chemotherapy.⁵ A recent international study has shown an even higher prevalence of hyperglycemia in up to 67% of patients at some time during the induction phase of chemotherapy for ALL. Of note, however, in this study, hyperglycemia was defined as a single fasting glucose value >100 mg/dL. This study also found that hyperglycemia was associated with an increased risk of complicated infections and death.⁶

These patients present a unique therapeutic challenge as they are receiving treatments that contribute to severe hyperglycemia, while their concomitant illness may affect their appetite and activity level. In addition, most of these patients have significant postprandial hyperglycemia,⁷ with lesser elevations of fasting glucose levels. Although there have been many studies discussing the use of basal-bolus insulin therapy for management of hyperglycemia in hospitalized patients, there are few studies on management of steroid hyperglycemia. In addition, there is only one study published thus far on how to manage hyperglycemia in cancer patients receiving high-dose corticosteroids. Gosmanov et al.⁸ compared the use of basal-bolus insulin with sliding-scale insulin in treatment of patients receiving high-dose dexamethasone as part of their chemotherapeutic regimen, including cyclophosphamide, doxorubicin, and vincristine (hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone [hyper-CVAD]), and found that basal and bolus insulin regimens were an effective and safe approach to management of hyperglycemia in hospitalized patients with hematological malignancies. However, there are no clear recommendations on the starting dose of insulin and the ratio for distribution of the total daily dose as basal and bolus. In this study, we discuss a management algorithm developed by the Endocrine Diabetes Inpatient Team at the University of Texas–MD Anderson Cancer Center for treatment of cancer patients receiving high-dose steroid therapy.

Subjects and Methods

As part of a quality improvement project to achieve better glycemic control in this patient population, the inpatient diabetes team reviewed the charts of 100 patients who had received high-dose steroids from our consultation census to determine the distribution of basal and bolus insulin therapy that resulted in the most improvement in glycemic control. After various meetings, we decided on 1.2 units/kg and created an algorithm that was developed and implemented (Fig. 1).

In this study, we reviewed the impact of that algorithm on glycemic control. We conducted a retrospective chart review of inpatients with hematological malignancies who received high-dose dexamethasone (40 mg) by mouth daily for four consecutive days as part of hyper-CVAD chemotherapy. Patients who were included in the study were placed on the algorithm if their blood glucose levels reached >250 mg/dL on two occasions during the same hospitalization while receiving high-dose dexamethasone with glycemic management controlled by the Endocrine Diabetes Inpatient Team at the University of Texas–MD Anderson Cancer Center for at least two cycles of treatment. Patients with and without known history of type 2 diabetes mellitus prior to steroids and chemotherapy were included. We excluded patients with type 1 diabetes mellitus or a serum creatinine level of >2.0 mg/dL. In addition to the scheduled insulin dosing, some patients received additional correctional doses of insulin when the blood glucose value was above 250 mg/dL. Dose adjustments were done on a daily basis depending on the dietary status, correctional doses of insulin given, glucose values of the patients, and clinical situation. If patients had received an additional (unplanned) dose of steroids as premedication for blood products or had more than usual carbohydrates for one meal, then we considered those factors in the decision-making process. We created a database of these patients containing individual information on demographics, blood glucose level, insulin therapy, chemotherapy, steroid use, hospital course, and use of oral or injectable antihyperglycemic agents.

At the time of initial consultation, oral and injectable antihyperglycemic medications were continued if there were no contraindications. For patients already on insulin therapy, insulin doses were increased to 1–1.2 units/kg, and basal and bolus redistribution was done as per algorithm. Once patients

FIG. 1. Algorithm developed by the Endocrine Diabetes Inpatient Team at the University of Texas–MD Anderson Cancer Center for the management of hyperglycemia in cancer patients receiving high-dose steroids.

were identified as hyperglycemic (two blood glucose values >250 mg/dL), glycemia was categorized as follows: hyperglycemia as a glucose value of ≥ 180 mg/dL, clinically acceptable glycemia as a glucose value between 71 and 179 mg/dL, and hypoglycemia as a glucose value ≤ 70 mg/dL. A patient-day was defined by the availability of at least one glucose measurement during the time period that patient received high-dose steroids. Instead of averaging the blood glucose values for each patient, we considered each individual glucose value to account for the variation within 1 day of blood glucose levels. A hyperglycemic patient-day refers to the presence of at least one blood glucose value ≥ 180 mg/dL with no values ≤ 70 mg/dL. A hypoglycemic patient-day refers to any glucose value <70 mg/dL.

Subjects were treated according to the High-Dose Steroid Algorithm (Fig. 1), created by the Endocrine Diabetes Inpatient Team. Patients received insulin detemir, insulin glargine, or NPH as basal insulin and insulin lispro, insulin aspart, or regular insulin as prandial insulin. The basal-bolus insulin therapy was titrated to reach previously defined pre-meal blood glucose goals of 100–140 mg/dL and random blood glucose values of below 180 mg/dL, as recommended for noncritically ill patients by the American Association of Clinical Endocrinologists and the American Diabetes Association.⁹ If more than 50% of glucose values were above target, then we considered dose adjustment as long as there was not an isolated incidence that could account for the elevations in blood sugar level (i.e., the patient had an unusually large meal and/or received another steroid as pre-medication for blood products).

Capillary blood glucose levels were tested with the Sure-Step[®] meter (LifeScan, Milpitas, CA) in all patients before each meal and at bedtime and in patients with signs and symptoms of hypoglycemia. Serum blood glucose levels were tested using the glucose oxidase assay. Study approval

was obtained from the University of Texas–MD Anderson's institutional review board.

Statistical analysis

All statistical analyses were done using SAS version 9.2 software (SAS Institute, Cary, NC) and R version 3.0.1 software. Descriptive statistics were used to summarize the data. Means, SDs, and medians were computed for continuous variables for each cohort. For categorical variables, frequencies and percentages were calculated. Two-sample *t* test was used to evaluate differences between patient subgroups. Longitudinal analysis was performed to evaluate the trend for the success rates of insulin management and blood glucose control, and patient heterogeneity was controlled by random effects. In Figure 2, the solid line was formed based on the statistical regression model. All tests were two-sided, and a *P* value of <0.05 was considered statistically significant.

Results

There were 23 hyperglycemic cancer patients who met the criteria above and were managed by the Endocrine Diabetes Inpatient Team. Our sample of hyperglycemic patients comprised 19 men and four women, 57% of whom were white. Ninety-one percent of the patients had a known diagnosis of diabetes prior to chemotherapy. Thirteen patients had a diffuse large B-cell lymphoma, whereas the remaining 10 patients had ALL. The median age of the group was 61 (range, 40–80) years, and the median body mass index was 32.5 (range, 21.6–40.9) kg/m². The baseline characteristics are summarized in Table 1.

All the patients who were on metformin and/or an oral secretagogue (52% and 48%, respectively) were continued

FIG. 2. Average daily blood glucose values for patients through various cycles of hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone chemotherapy.

TABLE 1. SUMMARY OF BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	Value
Age (years)	
<i>n</i>	23
Mean (SD)	59.6 (9.1)
Median	61.0
Minimum–maximum	40.0–80.0
Body mass index (kg/m ²)	
<i>n</i>	23
Mean (SD)	31.6 (5.4)
Median	32.5
Minimum–maximum	21.6–40.9
Gender [<i>n</i> (%)]	
Female	4 (17.4)
Male	19 (82.6)
Diagnosis (<i>n</i> (%))	
ALL	10 (43.5)
Lymphoma	13 (56.5)

ALL, acute lymphocytic leukemia.

on their oral regimen with the addition of insulin during steroid treatment. For patients not on oral therapy, metformin was added, if there were no specific contraindications, to improve insulin sensitivity. Each patient had blood glucose monitoring before meals and at bedtime, and at least one blood glucose measurement was available for 97% of patient-days.

Of the 278 patient-days, 85% were notable for hyperglycemia, 4% for hypoglycemia, 3% with both hyper- and hypoglycemia, and 8% with clinically acceptable glycemia. Nine of the 23 patients had at least one glucose value <70 mg/dL, which accounted for 1.3% of all recorded glucose values. No severe hypoglycemia (blood glucose level, <40 mg/dL) was observed. Hyperglycemia occurred in 80% of glucose measurements in Cycle 1 compared with 60% of Cycle 5 measurements, which was statistically significant (Fig. 2 and Table 2). Although there was no clinically meaningful intra-cycle trend in insulin requirements, the average insulin dose received by patients per cycle was 1–1.3 units/kg. Of the insulin administered to patients, the distribution of basal versus bolus insulin for each cycle was 63–77% prandial and 23–37% basal, respectively. Analysis of insulin dosage on demographic and clinical characteristics showed higher doses in patients with higher body mass index.

Patients with history of type 2 diabetes generally required higher doses of basal insulin than those without known diabetes. There was no statistically significant difference in insulin doses among whites and other races or among patients over the age of 65 years (Table 3).

Discussion

Hyperglycemia is a known complication of high-dose steroid therapy and occurs commonly in cancer patients. However, to date there are very few published studies on how to manage hyperglycemia in these patients. Although it is known that basal–bolus insulin therapy is more effective than sliding-scale insulin to control blood glucose in this patient population, there are no studies that advise the starting dose for insulin therapy or the distribution of basal or bolus insulin. To our knowledge, this is the only study to propose an algorithm to systematically manage hyperglycemia due to high-dose steroid therapy in cancer patients. This algorithm is currently used in the management of various cancer patients receiving other steroids in doses equivalent to 40 mg of dexamethasone at MD Anderson Cancer Center with similar results.

We recommend documentation of at least two glucose values above 250 mg/dL, before initiating the basal–bolus insulin algorithm. These criteria help identify patients who will require multiple-dose insulin therapy with high-dose steroids, similar to those evaluated in this study. Our study found a small increase in insulin dosage with each subsequent cycle of steroids, although this trend was not statistically significant. This may represent higher doses necessary to achieve better glycemic control or increasing insulin resistance with each cycle, although this was not a primary objective addressed by this study. With the proposed algorithm, the overall trend was a decrease in glucose values without any severe hypoglycemia. Although the number of patients who experienced hypoglycemia was slightly higher in the patients on the algorithm in comparison with the published rates of inpatient hypoglycemia,^{10,11} the numbers of patient-days spent in hypoglycemia were in accordance to other studies. And, despite using significantly higher doses of insulin, none of the patients on the algorithm had severe hypoglycemia. However, despite a decrease in glucose trends with subsequent cycles and large and increasing doses of insulin, we were unable to achieve clinically acceptable glycemia in the majority of our patients. These results reinforce the clinical management challenge that these patients can present.

TABLE 2. COMPARISON OF MEDIAN BLOOD GLUCOSE VALUES ACROSS VARIOUS CYCLES OF HYPER-CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND DEXAMETHASONE THERAPY

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	F test	P
Blood glucose measurement						32.8	<0.001
<i>n</i>	355	365	233	115	49		
Hyperglycemic values	288	231	158	67	29		
Hyperglycemia percentage	81.1%	63.3%	67.8%	58.3%	59.2%		
Daily average blood glucose						23.7	<0.001
<i>n</i>	87	91	58	30	12		
Median	266	208	217.6	207.8	205.6		
Mean (SE)	264.5 (8.0)	216.7 (6.7)	229.0 (8.7)	204.7 (12.9)	202.6 (16.0)		

Data are multilevel mixed-effects linear regression for blood glucose levels over time.

TABLE 3. COMPARISON OF INSULIN DOSE (IN UNITS) BY PATIENTS' DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Characteristic	Basal dose (units)			Prandial dose (units)			TDD (units)		
	n	Mean (SD)	P	n	Mean (SD)	P	n	Mean (SD)	P
Age (years)			0.134			0.619			0.357
<64	16	39.3 (8.2)		16	82.0 (13.2)		16	121.3 (19.5)	
≥65	7	23.8 (5.8)		7	71.4 (16.3)		7	95.1 (19.6)	
BMI (kg/m ²)			0.0037			<0.001			<0.001
21.0–25.0	4	31.0 (30.4)		4	54.0 (33.9)		4	85.0 (53.3)	
25.1–30.0	4	20.5 (25.2)		4	45.1 (34.8)		4	65.7 (55.0)	
>30.1	15	37.8 (35.9)		15	88.3 (69.4)		15	126.1 (94.8)	
Diagnosis			0.069			0.080			0.046
ALL	10	30.7 (29.3)		10	69.8 (52.1)		10	100.5 (69.4)	
Lymphoma	13	37.9 (37.1)		13	82.6 (68.4)		13	120.5 (96.3)	
Prior diabetes			0.004			0.668			0.764
No diabetes	2	19.8 (23.5)		2	72.6 (57.7)		2	92.4 (74.4)	
Type 2 DM	21	34.9 (34.4)		21	74.3 (62.5)		21	109.1 (87.0)	
Race			0.124			0.565			0.305
White	12	43.4 (9.5)		12	84.5 (17.7)		12	128.0 (26.3)	
Other	11	24.9 (6.5)		11	72.5 (10.3)		11	153.3 (51.3)	

ALL, acute lymphocytic leukemia; BMI, body mass index; DM, diabetes mellitus; TDD, total daily dose.

For patients without issues of weight loss or malnutrition, we generally place them on 1,800–2,200-calorie carbohydrate-consistent diets with no concentrated sweets so that they get a relatively equal amount of carbohydrates with each meal. We have created insulin order sets where every patient is given a supplemental scale for meals with increases in insulin doses based on patients' blood glucose level prior to the meal with incorporation of their insulin sensitivity. For patients with variable or poor appetite, the nurses are advised to give the insulin immediately after the meal if the patient consumes >50% of the meal. Every day, we review the blood glucose records from the day prior and adjust the insulin doses according to the glucose trend. For these patients who are on steroids, typically the increase is mostly in the prandial insulin, with a smaller degree of change to the basal insulin dosing. The basal insulin dosing is adjusted if the patient has a rise in blood glucose level overnight and/or hyperglycemia between meals.

Steroids are known to cause mostly postprandial hyperglycemia. Part of the mechanism of hyperglycemia involves peripheral insulin resistance, which leads to an increase in insulin requirements.¹² Better glycemic control is achieved with larger boluses of insulin with meals and relatively smaller doses of basal insulin, to avoid fasting hypoglycemia. This study supports the idea that distributing up to 75% of the total daily dose of insulin over three meals can help control the postprandial surge in blood glucose level that is observed with high-dose steroids. For each subsequent cycle of hyper-CVAD, insulin should be initiated at the total daily dose of insulin given in the previous cycle to achieve euglycemia for quicker glycemic control.

Evaluation of clinical factors that can contribute to insulin requirement showed that patients with prior diabetes and higher body mass index are more likely to require higher doses of basal insulin and total daily doses of insulin, respectively. These results are consistent with what would be expected as these two groups of patients would be more likely to have insulin resistance and further reinforce the need for higher doses of insulin in patients receiving high-dose steroids.

Caring for patients with cancer and hyperglycemia is complex as there are many factors that have to be considered prior to determining the appropriate doses of insulin. The proposed algorithm was evaluated in patients who had a good appetite and were on a regular diet. We do not recommend it for patients with nausea, vomiting, or poor appetite.

This study is limited because of its retrospective nature, and although it is the largest study of its kind, it is still a small sample size. In addition, the reported data may be biased because we only evaluated data on patients who were referred to our diabetes team, which might select for patients who are particularly insulin resistant with uncontrolled hyperglycemia, thus requiring a higher dose of insulin. As most of the patients in the study had diabetes and/or a history of steroid-induced hyperglycemia, it is unclear if the findings would apply to patients without a history of diabetes or steroid hyperglycemia. Furthermore, all of our patients were on a regular diet and allowed to make their own food choices. None of our patients was receiving tube feeds or parenteral nutrition therapy, which could also alter their insulin requirements.

In conclusion, this study suggests that high doses of insulin are needed for patients with a history of type 2 diabetes and steroid-induced hyperglycemia. In addition, it is important to consider the distribution of basal and bolus insulin as this plays a key role in management of hyperglycemia. For patients with documented hyperglycemia on high-dose dexamethasone, multiple-dose insulin therapy initiated up to 1.2 units/kg/day, distributed as 25% basal and 75% prandial, is safe and effective. However, it was difficult to achieve glycemic targets, although the overall trend for each subsequent day in the cycle was in favor of improving control without increasing the risk of hypoglycemia.

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Author Disclosure Statement

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