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Better Glycemic Control with Lesser Hypoglycemia on Transition of Insulin Glargine Administration at Bed time to Morning in Type 2 Diabetes Mellitus

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Abstract

Background: Insulin glargine either U 100 (Lantus) or U 300 (Toujeo) is approved to be used once daily at the same time. However, most providers recommend administration at bedtime (HS) as initially approved as comparative data about outcomes between administration HS and morning (AM) is lacking.

Objective: Assessment of glycemic control, body weight, daily dose and hypoglycemic events on transition to AM administration of insulin Lantus in subjects with Type 2 diabetes mellitus experiencing recurrent nocturnal hypo glycaemia while receiving Lantus HS.

Methods: 32 subjects with Type 2 diabetes (age, 60±4 years) and duration, 12±3 years were seen in endocrine clinic from 1/1/2008 to 6/30/2008 for recurrent nocturnal hypo glycaemia with at least 1 visit to emergency room during 2 weeks before referral. Lantus administration was changed from HS to AM while metformin 2000 mg and glimepiride 8 mg or glipizide 40 mg daily were continued. Subjects were instructed to check AM blood sugar and increase Lantusevery 3 days until AM blood sugar ≤ 7mM/l was attained. The dose was continued for 3 months. Subjects were requested to check blood sugar with onset of hypoglycemic symptoms and ingest 2 glucose tabs or 4 oz. orange juice. Fasting plasma glucose (FPG), HbA1c, body weight, daily dose of insulin and number of hypoglycemic events during 4 weeks prior to transition (HS) and at 3 months on stable AM Lantus were assessed.

Results: FPG (7.6±0.4mM/l), HbA1c (7.4 ± 0.04%) and Hypo (3.7 ± 0.32) on Lantus HS declined on transition to AM (6.5 ± 0.4mM/l, 6.9 ± 0.03%, 0.51 ± 0.13; p <0.01) without weight change despite increase in daily dose (63 ± 4 to 70 ± 4units; p< 0.01). Subjects expressed greater convenience of prompt AM dose titration after blood sugar determination rather than waiting till HS. More subjects attained HbA1c ≤ 7% with AM (60%) when compared with HS (30%) as well as ≤7.5% (AM 88% vs. HS 57%)

Conclusion: In subjects with type 2 DM, AM Lanus administration results in better glycemic control, lesser hypoglycemia, weight neutrality and therefore may be a preferred option when compared with HS administration.

Introduction

Both insulins,glargine U100 (Lantus) and U300 (Toujeo) are approved to be administered subcutaneously (SC) at the same time, once daily in subjects with diabetes mellitus. However, most providers recommend administration at bedtime as was initially approved following clinical trials which were conducted with administration of both insulin Lantus and more recently insulin Toujeoat bed time [1-6]. Alternative reason for continued use of administration of both insulin's at bedtime is likely to be the lack of adequate comparative data regarding outcomes,e.g. glycemic control, hypoglycemic events, change in body weight etc. between administration at bedtime and in the morning.Therefore, glycemic control as expressed by fasting plasma glucose and HbA1c, body weight, daily insulin dose and number of hypoglycemic events were assessed on transition from insulin Lantus administered at bedtime to morning while being used in combination with oral agents in subjects with type 2 diabetes who experienced recurrent nocturnal hypoglycemia while receivingInsulin Lantusat bedtime.

Subjects and Methods

32 subjects with Type 2 DM with age, 60±4 years and duration, 12±3 years were referred to endocrine clinic at Veterans Affairs Medical Center in Des Moines, Iowa, USA between 1/1/2008 and 6/30/2008 because they experienced recurrent nocturnal hypoglycemia requiring at least 1 visit to emergency room during 2 weeks prior to the day of referral. Subjects were receivingmetformin 1000 mg twice daily and glimepiride 8 mg once daily in the morning or glipizide 20 mg twice daily prior to breakfast and dinner. Insulin Lantus administration was changed from bedtime to morning to be injected at the same time daily. Oral agents were continued in the same daily dose. Subjects were instructed to check blood sugar with the glucose meter in the morning prior to administration of insulinLantus and increase the dose at interval of 3 days until the morning blood sugar ≤ 7mM/l was attained. The same daily dose was continued for 3 months. Subjects were requested to check blood sugar with symptoms of hypo glycaemia e.g. profuse drenching sweating, tremulousness; palpitations etc. and ingest 2 glucose tabs or 4 oz. orange juice. Subjects and their caregivers were also advised to obtain assistance from paramedical personnel by contacting emergency telephone number or by a visit to emergency room at the local medical center if subject was unable to consume sugar in any form orally because of confusion, seizure or change in state of consciousness. Fasting plasma glucose, HbA1c, body weight and the daily insulin Lantus dose were determined prior to transition from administration at bedtime and again at 3 months on a stable daily dose of insulinLantus administered in the morning. Number of hypoglycemic events during 4 weeks prior to transition while receiving insulin Lantus at bedtime and again during 4 weeks prior to end of the study while insulin Lantus was administered in the morning were documented. Finally, the subjects were surveyed for convenience of titration based on the scale, 1-5 between administration of insulin Lantus in the morning and the bedtime injection. Statistical analyses for comparisons between all the above mentioned outcomes with administration of insulin Lantus in the morning on one hand and bedtime on the other were conducted using Student's 't' test and analysis of variance.

Results

On transition of administration of insulin Lantus from bedtime to morning, glycemic control improved markedly as evidenced by a significant lowering of fasting plasma glucose and HbA1c levels (Table 1). More subjects attained HbA1c ≤ 7% while insulin Lantus was administered in the morning (60%) when compared with its administration at bedtime (30%). Moreover, 88% of subjects achieved HbA1c ≤7.5% following administration ofinsulin Lantus in the morning compared to 57% with bedtime administration ($p < 0.01$.for both comparisons). Number of hypoglycemic events reported during the last 4 weeks while receiving insulinLantus in the morning were significantly fewer when compared with events during 4 weeks prior to transition while insulin Lantus was administered at bedtime (Table 1).Nocturnal hypoglycemia was almost completely abolished on changeover to administration of insulin Lantus in the morning. Body weights were not significantly altered from the time of transition from bedtime administration to the end of study period while subjects received insulin Lantus in the morning (Table 1).The daily dose was significantly higher when insulin Lantus was administered in the morning in comparison to the dose injected at bedtime (Table 1). Subjects also expressed a greater satisfaction for the convenience of a prompt titration of the morning dose after blood sugar determination rather than waiting for titrationat bedtime according to blood sugar assessed in the morning (4.1±0.6 for morning vs 2.2±0.3 for bedtime, $p < 0.01$).

Table1: Fasting Plasma Glucose (FPG), HbA1c, Body Weight, Daily Dose of Insulin and Number of Hypoglycemic(hypo) Events in Subjects with Type 2 Diabetes while being Administration of Insulin Glargine at Bedtime(HS) or in the Morning(AM)

	HS Glargine	AM Glargine	p
FPG (mM/L)	7.6 ± 0.4	6.5 ± 0.4	<0.01
HbAc (%)	7.4 ± 0.04	6.9 ± 0.03	<0.01
Body Weight (kg)	95± 4	93 ± 4	>0.05
Daily Dose (units)	63 ± 4	70 ± 4	< 0.01
Number Hypo	3.7 ± 0.32	0.51 ± 0.13	<0.001

Discussion

Several pre and most marketing studies have examined the efficacy and adverse events with SC administration of both glargine insulin's namely Lantus and Toujeo at bedtime in subjects with both type 1 and type 2 diabetes [1-9]. Similarly, almost all comparative clinical trials are conductedbetweenother ' basal' insulinsand insulin Lantus being administered only at bedtime [10-28]. In contrast, the data regarding outcomes following use of glargineinsulins, namely Lantus and Toujeo in the morning in subjects with either type1 or type 2 diabetes is sparse.

In a recent clinical trial in subjects with type 1 diabetes examining the efficacy of both insulins, Lantus and Toujeo administered either in the morning or evening, a relatively lower HbA1c concentrations with less number of severe hypoglycemic events were noted in subjects following administration of Toujeo in the morning as compared to those receiving Toujeo in the evening [6]. Moreover, in subjects administered insulin Lantus, no difference in HbA1c level was evident between groups with morning or evening injections although subjects administered insulin Lantus in the morning experienced less number of severe as well as confirmed nocturnal hypoglycemic episodes. However, these differences were not statistically significant because the results may have been influenced by simultaneous premeal administration of rapid acting insulin required for attaining desirable postprandial glycemic control. In contrast, in recent comparative trials between insulin Toujeo and Lantus in type 2 diabetes, both insulins were administered only at bedtime [3-5].

This study demonstrates several therapeutic advantages including better glycemic control with lesser overall as well as nocturnal hypoglycemic events and weight neutrality on transition of insulin Lantus administration from bedtime to morning. The data is consistent with isolated reports in the literature [29,30]. Better glycemic control may be attributed to the increase in the daily dose being safely administered in the morning because of an almost a total decline in nocturnal hypoglycemic events probably induced by lower serum insulin concentrations during later 10-12 hours on its administration [31]. Alternatively, greater insulin concentrations documented in the initial 12 hours after administration in the same study [31] may render its administration in the morning more effective in lowering day time blood sugars between meals as documented in a previous report [29].Moreover, timely release of stored endogenous insulin induced by the meal and the insulin secretagogue,either glimepiride or glipizide may be a major contributor to achieving adequate control of postprandial glycemia. Finally, administration of metformin with its well established efficacy in enhancing sensitivity of both exogenous and endogenous insulins thus acting synergistically with secretagogues and insulin Lantus administered in the morning may have facilitatedimprovement in overall glycemic control as evident by lower HbA1c concentrations.

Lowering of nocturnal hypoglycemia to almost negligible level may be attributed to lower insulin concentrations during the night after administration of insulin Lantus in the morning as documented in the study mentioned earlier [31]. The decline in day time hypoglycemic events may secondary to higher serum concentrations of counter regulatory hormones, e.g. glucagon, human growth hormone, cortisol and catecholamine's, induced by subjects being awake,alert and active as well as by consumption of meals. Lack of significant weight gain on transition from administration of insulin Lantus at bedtime to morning may be explained by the reduction in intake of calories following discontinuation of a snack consumed by subjects at bedtime in order to prevent or overcome nocturnal hypoglycemia.

Therefore,in conclusion, in subjects with type 2 diabetes, subcutaneous administration of insulin Lantus in the morning results in a better glycemic control with a lesser hypoglycemia and weight neutrality despite a higher daily dose when compared with bedtime administration and may be a preferred option. Moreover, our comparative studies have demonstrated several distinct benefits of insulin Lantus administered in the morning once daily over insulin detemir either administered as one or 2 daily injections [32-34]. The advantages include better glycemic control without an increase in hypoglycemic events, a lack of a significant gain in body weight probably secondary to a lesser daily dose injected once daily and may be attributed to the differences in pharmacokinetic and pharmacodynamics properties of these insulins injected SC in the same dose at the same time in subjects with both type 1 and type 2 diabetes [35,36]. These studies documented a more basal peakless profile of insulin Lantus lasting almost 24 hours in comparison to the profile with a peak for insulin detemir with a significantly shorter duration [35,36] while another euglycemic clamp study showed a progressively higher peak and longer duration with increase dose of insulin detemir [37]. Additionally, the subjects administered insulin Lantus expressed a better quality of life probably secondary to once daily injection, once daily convenient and easy titration following once daily blood sugar monitoring rather than conducting all these procedures twice daily required for insulin detemir in most subjects in our studies [32-34]. Finally, administration of insulin Lantus once daily was determined to be more cost effective than therapy with insulin detemir because of the lesser expenses incurred for the equipment's and the labor required for conducting the aforementioned procedures. Therefore, in the light of the data in this and our other studies [32-34], comparative clinical trials between insulin Lantus or Toujeo administered in the morning and other ' basal' insulin's injected as approved by the regulatory agencies need to be conducted to validate earlier results since insulin Lantus was administered exclusively at bedtime in these previous studies [10-28].

The study was presented at World Diabetes Congress of the International Diabetes Federation in Vancouver, Canada in 2015, Abstract No.VA - 1668.

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