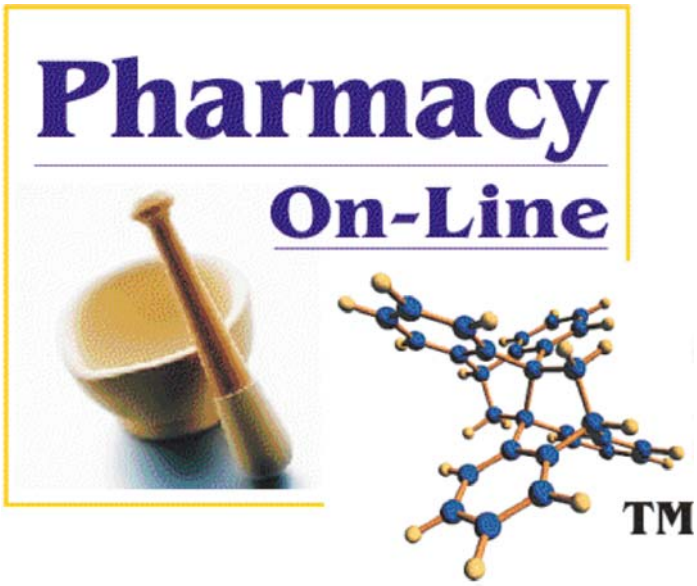

Multiple-dose insulin injection therapy in patients with type 2 diabetes using a basal-bolus regimen, team management, and nutrition education

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Abstract

We determined the efficacy of basal-bolus insulin therapy delivered through team education and nutrition counseling for management of type 2 diabetes in 17 patients treated with a regimen of once-daily insulin glargine and either insulin aspart or lispro three times a day. They received written instructions and specific education about ‘basal-bolus’ insulin administration, use of a ‘forced-titration’ schedule for glargine dose adjustment, and calculation of rapid-acting pre-meal bolus insulin. The average hemoglobin A1c level decreased from 8.7 ± 2.06% to 7.0 ± 1.07%, a significant reduction of 1.7% ($p<0.05$) over 3 months or more. 7 patients (41%) reported improvement in hypoglycemic events. In conclusion, an intensive multidose basal-bolus insulin treatment using self-titration and flexibility through carbohydrate counting confers beneficial effects in patients with type 2 diabetes, including better glycemic control and reduced hypoglycemia. These results are best achieved through multi-disciplinary patient care involving the nurse educator and dietician as part of a diabetes care team.

Key words: type 2 diabetes, insulin treatment, basal-bolus therapy, carbohydrate counting, team management, nutrition education

Introduction

Communities nationally and globally are confronting an epidemic of type 2 diabetes due to changes in lifestyle (1,2). Aggressive therapy is becoming the standard of care to prevent long-term complications. Many treatment options exist for type 2 diabetes, including dietary changes, physical activity, oral agents, and insulin. However, according to recent reports, overall glycemic control remains unsatisfactory (3,4).

Early use of insulin in the setting of progressive deterioration of metabolic control is being advocated in type 2 diabetes for attaining optimal recommended glycemic targets (5,6). Studies have demonstrated the benefits of basal as well as mealtime short acting insulin (6,7). However, little data exists regarding the practical implementation of a simultaneous basal and bolus insulin combination on glycemic control and other treatment-related end-points in patients with type 2 diabetes. There is a dearth of multiple-dose insulin regimens that are effective, target-oriented, and easy to employ in routine medical practice. In addition, the importance of formal diabetes self-management and nutrition education in this area has not been clearly delineated. We report the observational results of using a combination of long- and rapid-acting insulin in a 'physiologic' basal-bolus fashion on glycemic control, hypoglycemia, and treatment satisfaction in patients with type 2 diabetes taught by diabetes educators and managed in an academic endocrinology practice setting.

Methods

Patients were seen in an ambulatory clinical endocrinology practice. They had type 2 diabetes and were considered for intensive multiple-dose insulin injection therapy if their current treatment failed to achieve the desired glycemic targets, was associated with frequent, severe, or unacceptable hypoglycemia, or both. The rationale behind use of the combination short- and long-acting insulin therapy was explained to all patients, who then received diabetes and nutrition education at a hospital-based, ADA (American Diabetes Education) - recognized education program (Palmetto Health Richland, Columbia, South Carolina). They underwent three formal diabetes education classes of three hours each encompassing diabetes self-management skills and nutritional aspects. They were educated in the basal-bolus concept (8), proper use, injection technique, and timing of insulin administration, and given written instructions (table 1). Treatment consisted of a multiple-dose insulin regimen of once-daily insulin glargine and either pre-meal insulin aspart or lispro three times a day dispensed by pen or syringe. Patients were required to monitor and record their glucose readings several times a day, including premeal, 2-hour postprandial, bedtime, and 3 a.m. values. They were encouraged to maintain regular and close communication with the office by phone or fax regarding their glucose readings and treatment-related issues.

Advice about the optimal caloric and carbohydrate content of the diet was given to all patients. They were given preliminary instructions in the office by the physician-nurse team, and then educated by registered dieticians on methods of assessing carbohydrate content of food by either counting in grams or choices (one carbohydrate choice or

portion equaling 15 grams) (9). Instructional materials and carbohydrate counting booklets were distributed to the patients (10).

Glargine was used as the basal insulin and the physician determined the once-daily starting dose. Thereafter, patients were able to self-titrate the dose based on the fasting or prebreakfast reading. A forced-titration schedule was used by patients to increase the glargine dose based on their fasting pre-breakfast glucose level (11). The dose was increased by 1-3 units every 3 days by the patient if the fasting value remained above target (usually 120 mg/dl). A rapid-acting insulin analog, either lispro or aspart, was utilized as the "bolus" insulin for prandial coverage. Patients were taught to calculate these bolus insulin doses by calculating the 1) "correction dose" for pre-meal glucose readings 2) food coverage for carbohydrate content of the meal. The correction was derived from the sensitivity factor, also known as supplemental factor. This was calculated using the "1800 rule" (1800 divided by the total daily insulin dose) (12). Food coverage was based on carbohydrate counting. The insulin-to-carbohydrate ratio was employed using one unit of insulin to cover 15 grams of carbohydrate (1:10 in more insulin-resistant individuals), and adjusted based on subsequent glycemic profile (12). The total dose was determined by adding the "correction" derived from the sensitivity factor, and food coverage for carbohydrate ingestion. Patients were encouraged to check two-hour postprandial glucose readings in order to verify the carbohydrate ratio and supplemental factor (13). If necessary, modifications were made in these parameters and the bolus insulin doses were fine-tuned. Patients were seen in the office every 3-4 weeks on average during this titration phase.

The effectiveness of management was assessed by comparing glycemic control, frequency and severity of hypoglycemic events, and subjective treatment satisfaction before and after at least 3 months of combination basal-bolus insulin therapy. The analysis was retrospective, and reflected the customary, individualized therapeutic decision-making encountered in “real-life” clinical practice situations. Concomitant treatments including oral-antidiabetic medications were continued, stopped, or their dosage modified as deemed necessary.

The level of glycemic control was determined by self-monitored blood glucose values and hemoglobin A1c (HbA1c) at baseline and at least 3 months after implementation of the basal-bolus regimen (range 3 to 8 months). For statistical analysis, HbA1c levels were expressed as mean values ± standard error. A statistically significant difference in HbA1c was indicated by a *P* value of less than 0.05 as judged by the student’s *t* test. Evaluation of hypoglycemia was patient-based. Patients were asked whether the frequency and degree of low blood sugars had improved or worsened on the new treatment regimen. The patients’ responses were corroborated with a review of their self-monitored blood glucose (SMBG) readings and evaluation of hypoglycemia (SMBG < 70 mg/dl) before and after initiating the new insulin regimen. In addition, the patients' subjective feelings were explored by evaluating their responses when asked about their quality of life and satisfaction with their current diabetes management, and if it was better or worse compared with their previous treatment. Answers pertaining to both hypoglycemia and quality of life were obtained as *yes* (improved or better), *no* (worse), or *unchanged.*

Results

Baseline Characteristics

Of the 22 patients whose records were reviewed, five patients were excluded. Two patients discontinued rapid-acting insulin because of the frequency of injections, another required corticosteroid therapy for polymyalgia rheumatica, a fourth had intercurrent hospitalization for a lower extremity revascularization procedure, and a fifth patient was lost to follow up.

Therefore, data on 17 patients (10 female and 7 male) were included in the final analysis. They ranged in age from 30 to 76 years with a mean age of 57.8 years (see table 2). Five patients were on oral agents, 8 patients on insulin, and 4 on a combination of oral medications and insulin combination. Patients underwent formal education as described above, and followed on the basal-bolus insulin therapy for a mean period of 5.5 months. Oral agent therapy was individualized; they were continued initially in all patients and they were subsequently modified or stopped as transition to the new insulin regimen and improved glycemic control was achieved.

Outcomes

Treatment results after institution of the new insulin regimen are displayed in table 2. The average HbA1c level decreased from 8.7 ± 2.06% to 7.0 ± 1.07%, a statistically significant reduction of 1.7% ($p<0.05$). All patients except one showed a reduction in HbA1c. 16 out of the 17 patients reported either improvement in hypoglycemia (7 patients, 41%), or no worsening (9 patients, 56%). Thus, patients previously on insulin or oral agents who were experiencing hypoglycemia generally showed amelioration. 13

(76%) of patients had increased treatment satisfaction on the new regimen. There was no significant change in body weight (data not shown). With frequent provider-patient communication, most patients were able to follow the self-titration, carbohydrate counting, and bolus calculations without significant problems. A minority of patients (2/17) felt uncomfortable in attempting insulin self-titration and preferred that the clinician adjust the dose. Some patients (4/17) preferred the use of carbohydrate exchanges rather than carbohydrate counting to cover meals.

Discussion

The traditional and largely prevalent approach to treatment of type 2 diabetes is that of oral agent monotherapy, often in a sequential manner, slowly progressing to combination treatment and eventually insulin (14). In contrast to type 1 diabetes, the latter is not considered an essential component of therapy, and its role in type 2 diabetes is not clearly defined. It is commonly relegated to a “last-ditch” or “last resort” use when all other avenues have been exhausted (15). Providers are reluctant to initiate insulin therapy due to “clinical inertia´(16), while the well-known aversion of most patients to injections compounds the delay in its implementation. Indeed, numerous studies have shown that insulin therapy is started too late in the course of this disease due to factors related to provider and patient resistance, as well as lack of awareness about potential benefits (17,18). Clinicians worry about hypoglycemia, weight gain, and increased cardiovascular risk. In reality, these concerns have been shown to be unfounded misconceptions (19). Early insulin therapy is now being advocated for improving glycemic control and reducing the risk of diabetic complications in type 2 diabetes (6).

The optimal type and regimen of insulin is another hurdle that is often overlooked or not properly addressed. Insulin therapy is commonly employed in improper dosage, frequency, or timing, and is associated with glycemic variations and increased risk of hypoglycemia. The goal with insulin treatment is to mimic normal physiology by employing it in a basal-bolus fashion, with an emphasis on duplicating the natural release of insulin when normal pancreatic function is present (20). This approach consists of discrete amounts of continuous 'basal' insulin required to maintain euglycemia in the fasting state, and 'bolus' insulin during times of hyperglycemia (for example, in the postprandial state). Ideally, doses of bolus insulin should be calculated at each meal by taking into account the blood glucose level and the amount of food (grams of carbohydrates) to be consumed. This philosophy is widely recognized and accepted in the management of type 1 diabetes, and requires precise insulin timing and calculations. However, with emphasis on aggressive therapy and early insulin use, the basal-bolus approach is being increasingly advocated in type 2 diabetes as well (21,22). However, the advantages offered by formal teaching through diabetes educators (nurses and dieticians) is often not fully utilized during this process.

In addition to inherent pharmacokinetic insulin properties, the ambient glucose levels, carbohydrate intake, and physical activity are variables that determine the dose and pattern of insulin requirements in a particular individual. The current study, although limited by size and short follow-up time, provides thought for several points regarding the treatment of type 2 diabetes. Multiple-dose combination of basal and bolus insulin, when instituted in the context of a multidisciplinary diabetes education and close ongoing communication and supervision, can be effective in achieving treatment goals. It is not

enough to start a patient on insulin – a critical element is its proper, physiologic use. As evidenced in our analysis, many patients were already on insulin; however, it was not being utilized in the optimal fashion. The complexity of a multi-dose insulin regimen may appear daunting and formidable, yet with patience and persistence, is amenable to implementation by most providers. The report reaffirms the advantages of the newer insulin analogs that have certain superior pharmacologic characteristics, making them better suited for use in a basal-bolus fashion. Insulin aspart and lispro are rapid-acting preparations that have been shown to control post-prandial glycemic excursions, while glargine is a relatively peakless, long-acting insulin, which duplicates basal pancreatic function when given by once-daily injection. The availability of insulins with desirable profiles should make it easier to implement insulin therapy in type 2 diabetes.

Perhaps the most significant point derived from our study is the crucial role of patient-centered team management that includes, at its core, physician-diabetologists, nurse educators, and nutritionists in putting the patient on “the right footing” at the outset of initiation of multi-dose insulin regimen to achieve short-term, and hopefully long-term, success. Setting unambiguous glycemic targets and empowering patients to titrate their basal insulin dose by following a logical guideline is likely to enhance their participation in therapeutic decision-making. Meal-directed doses of rapid-acting insulin based on insulin sensitivity factor and carbohydrate counting can be satisfactorily taught to patients by trained professionals in educational sessions and do not necessarily require a high degree of patient sophistication. Most patients are able to use this method without major problems and find it preferable to the ‘sliding scale’ regimen. The latter is often prescribed in a rigid, ‘one-size fits all’ manner, does not take into account individual

sensitivity to insulin, nor is it flexible to account for variations in carbohydrate intake of meals (23). As such, it is often unsuccessful and leads to wide excursions in glycemia. Another common approach is in the form of an inflexible regimen without an understanding of basal and bolus requirements (for example, a fixed ‘split-mix’ insulin prescription or a premixed insulin that may lead to undesirable peaks). A built-in flexibility in an insulin regimen with some degree of patient empowerment and autonomy is, therefore, key to efficacious therapy. The above-mentioned aims are best obtained by seeking the expertise of clinical specialists and skilled diabetes educators familiar with nutritional principles and the art and science of insulin use.

Some limitations of this retrospective analysis need to be acknowledged. The small sample size and limited follow up time hamper generalizability, but the promising results can serve as an impetus for larger-scale studies. Access to an ADA-recognized diabetes education program may not be available in all areas, especially rural communities. It may also be argued that a substantial contribution to glycemic control was merely the result of initiation of insulin therapy alone. However, most patients were already on insulin, but showed a significant improvement in treatment parameters by intensifying and fine-tuning the insulin regimen through proper education. The success of long-term adherence to multiple-dose insulin injections cannot be fully ascertained due to the short period of follow-up. Most patients, though, displayed a high level of enthusiasm and compliance. Lastly, comparison with a control arm using a ‘conventional care’ approach would have allowed a better evaluation of an intensive insulin regimen and the value of focused education by diabetes educators. However, this would necessitate a prospective study,

with the conventional care patients unlikely to achieve the currently-emphasized standards of care in diabetes.

Conclusions

A big hurdle in improving glycemic control in the primary care setting is the lack of availability of insulin regimens that have the necessary complexity to be effective, yet are flexible and non-intimidating to both patients and providers. In addition, fear of hypoglycemia is the main limiting factor in escalating and intensifying insulin treatment (24). Our analysis suggests that a combination of once-daily long-acting insulin analog (glargine) and multiple daily doses of a preprandial rapid-acting insulin analog (aspart or lispro) used in a true basal-bolus manner is a successful and viable management strategy in patients with type 2 diabetes. A forced titration-modification schedule and carbohydrate counting achieved through a multidisciplinary patient education and written instructions can confer beneficial effects in patients who are unable to achieve treatment goals with conventional therapy. These changes included better glycemic control without increased hypoglycemic events, and enhanced patient satisfaction with their therapeutic regimen. In this respect, the leadership and participation of interested clinicians, diabetes educators, and dieticians in working collaboratively to implement optimal insulin therapy is critical to improved outcomes, patient satisfaction, and adherence to the individual treatment regimen. For diabetes professionals, the effort put forth in stepping up the level of care and acquainting themselves with the teaching skills required to impart practical education to their patients is likely to pay dividends. On the basis of these observations, it is hoped that the wider use of a basal-bolus treatment philosophy employing a team

approach will be helpful in overcoming obstacles to the management of diabetes. Over the long-term, attainment of treatment goals could potentially translate into reduced morbidity, complications, and cost.

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Table 1. Written Instructions for patients starting on Basal-Bolus Multi-Dose Insulin Injection Therapy for Type 2 Diabetes.

Division of Endocrinology, Diabetes, and Metabolism
University of South Carolina School of Medicine
Tel: --- --- ---- *Fax:* --- --- ----

Insulin Regimen

date _____

for (patient's name) _____

1. BASAL INSULIN *Glargine (Lantus)* units

If the pre-breakfast reading is greater than _____, increase insulin dose by ___ units every _____ days. If the total _____ insulin dose reaches _____ units, do not increase any more - call us at 803-540-1000.

2. BOLUS INSULIN *Lispro (Humalog)* or *Aspart (Novolog)* **calculation before meals:**

1. *Food coverage* using carb ratio of _____

$$\frac{\text{grams (number) of carbs}}{\text{carb ratio}} = \text{grams of carbs} = \text{___ units}$$

2. *Correction* (Supplement) for pre-meal glucose reading, using Sensitivity factor of ____

$$\frac{\text{pre-meal glucose} - 100}{\text{Sensitivity factor}} = \frac{\text{pre-meal glucose} - 100}{} = \text{_____ units}$$

3. *Total pre-meal bolus* = food coverage + correction = ____ units

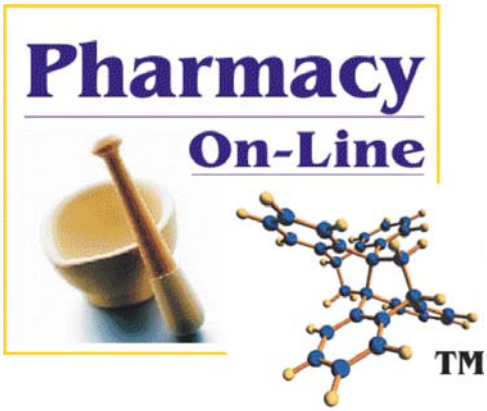
CHECK GLUCOSE FINGERSTICK READINGS :

Before meals _____
2 hours after meals _____
Bedtime _____
3 a.m. _____
Other times _____

Call or fax glucose readings every _____ days

Table 2 – Data on patients with diabetes treated with basal-bolus insulin injection therapy.

No	Age	M / F	Prior Therapy	Glargine dose (units)		Bolus Insulin	HbA1c		Hypo-glycemia	Subjective patient treatment satisfaction
				start	titrated		base line	F/U		
1	73	M	Glipizide XL, Rosiglitazone, Acarbose	10	46	Lispro	8.9	6.9	improved	better
2	71	F	NPH, Aspart	50	55	Aspart	8.1	7.3	same	better
3	53	F	Glargine, Regular	14	15	Lispro	7.6	7.5	worse	same
4	65	M	Glargine, Metformin, Rosiglitazone	40	60	Aspart	8.6	7.4	same	better
5	38	F	Regular, Metformin	20	60	Lispro	12.3	8.4	same	same
6	72	M	NPH, Regular	20	40	Lispro	7.9	7.5	same	better
7	76	M	NPH, Lispro	15	18	Lispro	6.9	6.8	improved	better
8	70	F	75/25 Humalog Mix	20	14	Aspart	15.0	5.6	improved	better
9	54	M	Glyburide-metformin, Rosiglitazone	20	42	Lispro	8.7	9.8	same	worse
10	45	F	NPH, Regular	30	48	Aspart	9.5	7.3	improved	better
11	60	M	Novolog Mix 70/30, Pioglitazone	40	40	Aspart	7.0	6.1	improved	better
12	30	F	Metformin, Glipizide, NPH, Regular	34	42	Aspart	9.9	9.2	same	better
13	58	F	Metformin, Glipizide, Pioglitazone	20	64	Aspart	10.8	8.6	same	better
14	57	F	Metformin, Pioglitazone	20	25	Aspart	9.7	7.3	same	same
15	29	M	Metformin, Pioglitazone	20	50	Aspart	10.0	8.1	same	better
16	59	F	Glargine, Lispro	50	70	Lispro	7.1	6.5	improved	better
17	72	F	NPH, Regular	40	60	Aspart	8.9	8.0	improved	better



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