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Biphasic Insulin Aspart 70/30 Three Times a Day in Older Patients With Type 2 Diabetes Not Achieving Optimal Glycemic Control on a Twice-Daily Regimen: A Retrospective Case Series Analysis From Clinical Practice

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ABSTRACT

This retrospective study was conducted to determine whether the addition of a third injection of biphasic insulin aspart 70/30 (BIAsp 30) just before lunch in older patients with type 2 diabetes who did not achieve goals with a twice-daily (BID) regimen would optimize glycemic control in a clinical practice setting. A retrospective chart analysis was conducted. In 12 patients aged 52 to 80 y with type 2 diabetes that had been diagnosed between 5 and 24 y earlier and who remained on oral antidiabetes agents, a third injection of BIAsp 30 was added because optimal glycemic control (glycosylated hemoglobin [HbA_{1c}] <7%) was not achieved on a BID regimen. Changes in HbA_{1c}, body weight, total insulin dose, and frequency of hypoglycemia were analyzed after 6 mo of three times daily (TID) treatment. Mean HbA_{1c} decreased from 8.4% to 7.2%. An HbA_{1c} goal of <7% was attained by 58% of patients. Although the total insulin dose increased by 11% with the TID regimen, pre-breakfast and pre-dinner doses decreased by 15%. No patient experienced major hypoglycemia on BID or TID dosing. With the TID regimen, no minor hypoglycemic events were reported by patients and mean body weight decreased by 2.25 lb. The addition of a third injection of BIAsp 30 substantially improved HbA_{1c} and

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decreased body weight and the incidence of hypoglycemia in 12 patients with type 2 diabetes who did not achieve optimal glycemic control on a BID regimen.

Keywords: premixed insulin analog; BIAsp 30; HbA_{1c}; hypoglycemia; dosing

INTRODUCTION

Insulin therapy is usually started after combination therapy with oral antidiabetic drugs (OADs), such as secretagogues, metformin, and thiazolidinediones (TZDs), is no longer effective.[1] Although there is no standard way to initiate and intensify insulin therapy, most physicians use neutral protamine Hagedorn insulin, a long-acting insulin analog, or a premixed formulation once (QD) or twice daily (BID) in combination with 1 or several OADs. Guidelines acknowledge that because of further β cell decline, regimens have to be intensified, and more insulin and additional injections are needed to achieve glycemic goals as recommended by the American Diabetes Association (ADA) and the American College of Endocrinology (ACE).[2,3] Despite landmark trials showing that intense glycemic control reduces microvascular complications, only 42% of individuals in the 1999 to 2002 National Health and Nutrition Examination Survey had a glycosylated hemoglobin (HbA_{1c}) level <7%.[4]

Oral agents and incretin mimetics can lower HbA_{1c} by 1% to 2%, and the glucose-lowering capacity of insulin is limited only by its potential for hypoglycemia.[5] Many of the inadequacies of older human insulin formulations have been overcome by insulin analogs and by premixed insulin analogs with more physiologic time–action profiles and more convenient dosing options.[6-8] Insulin delivery systems have also improved. Several studies have shown that most patients prefer to inject insulin with a pen device rather than a vial and syringe.[9-11]

ACE guidelines recommend premixed insulin analogs or basal-bolus therapy when HbA_{1c} is above 8.5%.[3] Basal-bolus therapy with multiple daily injections or an insulin pump is the most physiologic approach to insulin replacement therapy. Few studies have focused on intensive glycemic control in patients older than 60 y,[12] however, and less stringent glycemic targets may be reasonable for older patients with comorbid conditions.[13] In the author's experience, many older patients with type 2 diabetes resist basal-bolus therapy because of its perceived complexity, confusion regarding 2 different insulins, and the need for carbohydrate counting. Furthermore, elderly individuals are more susceptible to hypoglycemia.[14] It is crucial that safe and effective insulin regimens are developed for the elderly because the prevalence of diabetes in individuals older than 65 y is nearly 2-fold higher than in those between 45 and 64 y of age.[15]

Premixed insulin analogs offer an alternative to basal-bolus therapy and provide basal and prandial coverage with a single injection. These preparations are suitable for patients who desire a simple and convenient regimen and who are not willing to use traditional basal-bolus therapy.[7,8] Premixed insulin analogs are available in a pen device that is more convenient than a vial and syringe, particularly for patients with problems with cognition, vision, or dexterity.[16] Although premixed insulin analogs are usually administered BID, a QD regimen at dinnertime can be effective in many

patients; for those using a BID regimen, an additional injection can be given to cover lunch, if necessary.[17]

This report describes the impact on glycemic control of three times daily (TID) dosing with biphasic insulin aspart 70/30 (BIAsp 30) in a predominantly older group of 12 patients who chose to add the third injection rather than switch to basal-bolus therapy when glycemic control was no longer maintained with BIAsp 30 given BID.

METHODS

Patients

Charts from all patients on a premixed insulin analog (BIAsp 30) BID regimen between January and August 2005 were reviewed; 12 patients who had added a third lunchtime injection within the past 3 y were identified. All patients had been taking BIAsp 30 BID for at least a year before they moved to TID dosing. These patients were offered the choice of changing to basal-bolus therapy or adding the third injection of BIAsp 30. For 5 of the 12 patients, recurrent minor hypoglycemia (n=3) or increased risk of hypoglycemia (n=2) precluded an increase in dose while they were on the BID regimen. Two other patients using vial and syringe who wished to use an insulin pen had to take an additional injection because no further dose increase was possible after the maximal dose of 60 units had been reached with the pen delivery device via morning and dinner injections. For all injections, BIAsp 30 was administered just before the meal was taken.

Treatment and BIAsp 30 Titration

To use TID dosing, patients had to leave at least 4 h between meals to avoid insulin stacking. When hypoglycemia limited dose increases with the BID regimen, 15% to 20% of the total daily dose was subtracted and was added as a third (lunchtime) injection. If the maximum dose (<60 units) of the pen device had been reached at breakfast or at dinner, 16 units was added at lunch at first. On the basis of a pre-dinner fasting glucose target of <120 mg/dL, the lunch dose was titrated in 2-unit increments every 3 d. When pre-dinner glucose had reached goal levels, pre-dinner insulin was titrated according to the same criteria on which pre-breakfast fasting glucose was based. Finally, pre-breakfast insulin was titrated by measurement of pre-lunch glucose. An HbA_{1c} goal of <7%, as opposed to a more aggressive target, was chosen because most patients were elderly, lacked strong motivation, and were not counting carbohydrates.

Reporting of Results

Initial HbA_{1c} was reported as the value achieved on BID dosing with BIAsp 30 before the TID regimen was begun. Final HbA_{1c} was taken at 6 mo unless patients had been given drugs such as corticosteroids (n=1), or unless they had discontinued the 3 shots (n=1); 2 others did not have their first follow-up visit for 9 and 13 mo, respectively.

RESULTS

Patient Characteristics

The main demographic characteristics of study patients are shown in Table 1. Overall, this was an older group of 11 white patients and 1 African American patient; 8 were male and all were overweight. When treatment with BIAsp 30 BID was first initiated, secretagogues were discontinued but patients remained on metformin 1000 to 2000 mg/d unless it was contraindicated. Patients who were unable to take metformin used a TZD, and 2 patients continued on both metformin and a TZD. No changes in the OAD regimen were made when the third injection was added.

Table 1. Demographic Characteristics of Patients

Patient No.	Age, y	Sex	BMI	Metformin	TZD	Years With T2DM	Years Using Insulin
1	76	F	27.5	Yes	No	7	6
2	79	M	25.2	Yes	No	13	6
3	80	M	29.7	Yes	Yes	11	6
4	77	F	27.0	Yes	No	20	13
5	75	F	30.2	No	Yes	24	18
6	76	M	31.9	Yes	No	16	5
7	69	M	37.7	Yes	No	24	10
8	61	M	38.6	Yes	Yes	7	2
9	53	M	39.5	Yes	No	5	2
10	65	M	38.0	No	Yes	16	7
11	58	M	43.4	Yes	Yes	21	14
12	52	F	56.6	No	Yes	11	9
Mean	68.4		35.4			14.58	8.16
SD	10.3		8.8			6.65	4.86

SD=standard deviation; T2DM=type 2 diabetes mellitus; TZD=thiazolidinedione.

Change in HbA_{1c}

After 6 mo of TID treatment with BIAsp 30, HbA_{1c} was decreased in each patient, with a range from 0.4% to 2.6% (Fig 1). Mean HbA_{1c} decreased from 8.4% with BID to 7.2% after TID dosing (Table 2). Seven patients reached or maintained an HbA_{1c} <7%, and only 1 patient's HbA_{1c} remained above 8%.

Body Weight

Body weight decreased by at least 1 lb in 10 of 12 patients when the change was made from a BID to a TID regimen (Fig 2). The mean decrease was about 2 lb (Table 2).

Fig 1. Individual changes in HbA_{1c} when patients went from BID to TID dosing of BIAsp 30.

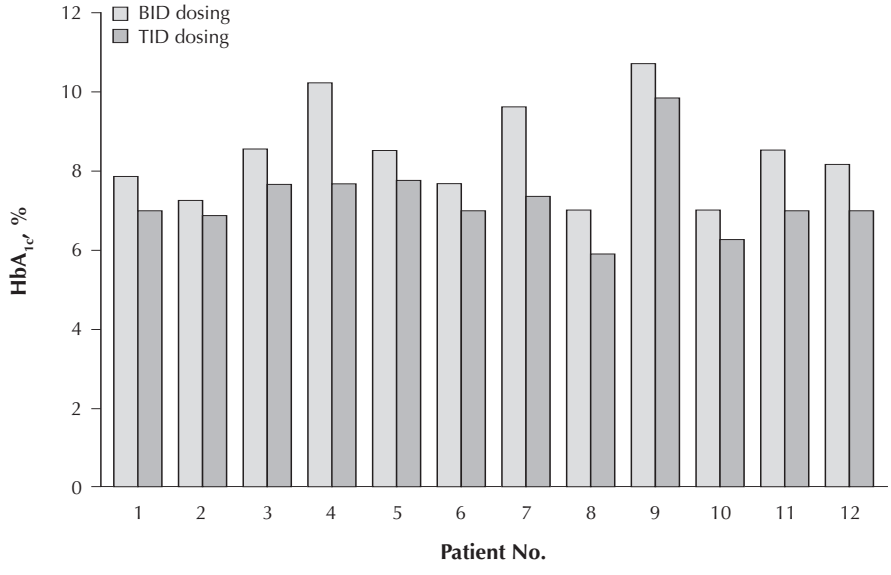


Table 2. HbA_{1c} and Body Weight With BID and TID Dosing of BIAsp 30

Variable	BID Dosing	TID Dosing	Change
HbA_{1c}, %*	8.4±1.2	7.2±1.0	–1.1±0.7
HbA_{1c} <7%, n	2/12	7/12	
Body weight, lb*	235.75±65.0	233.5±65.90	–2.25±1.60

*Mean±SD.

Hypoglycemia

Although 3 patients had experienced recurrent minor hypoglycemia on BID dosing and 2 others were at high risk for hypoglycemia, no patient reported a major or minor hypoglycemic episode on the TID regimen.

BIAsp 30 Dose

Despite the addition of a third injection of BIAsp 30, overall dose increased by only 11% because of redistribution of insulin over 3 rather than 2 injections (Fig 3). In 4 patients, the total daily dose remained the same or decreased slightly. Overall, pre-breakfast and pre-dinner doses were observed to decrease by ~15% (Fig 3).

Fig 2. Individual changes in body weight when patients went from BID to TID dosing of BIAsp 30.

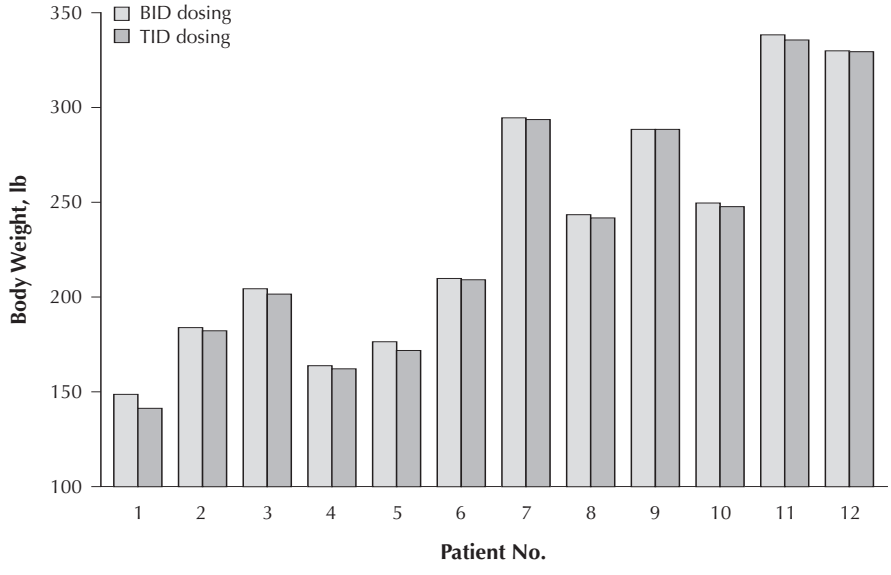
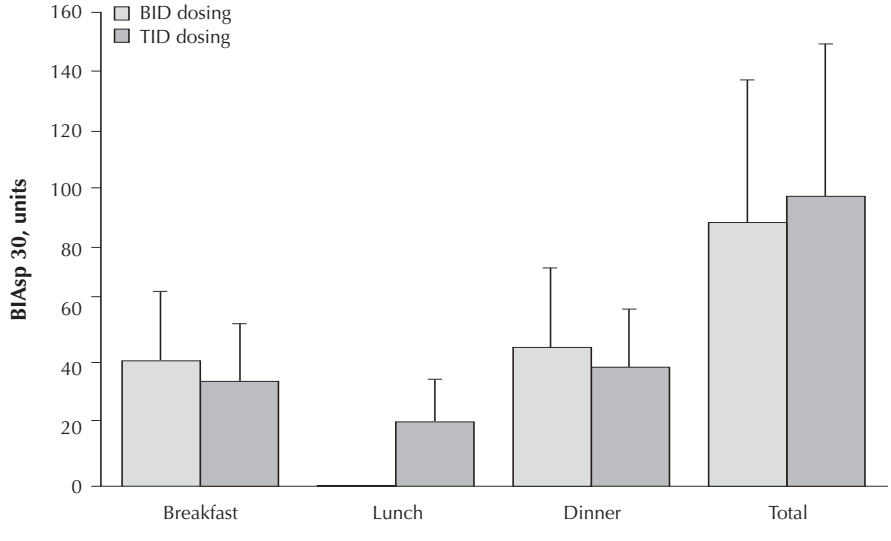


Fig 3. Change in BIAsp 30 dosing seen when patients went from BID to TID dosing.



Data are expressed as means±SD.

For 3 patients with a body mass index (BMI) <30 who were prone to minor hypoglycemic events before beginning the TID regimen, only 6 to 9 units were administered at lunch. As of February 2006, most patients were still using the TID regimen with BIAsp 30.

DISCUSSION

This series of case studies shows that for all 12 patients, addition of a third injection of BIAsp 30 after glycemic goals were not met on a BID regimen achieved a notable decrease in HbA_{1c}; 58% of patients attained the ADA goal of <7%. Addition of a third injection also reduced the frequency of reported hypoglycemic episodes and resulted in decreased body weight. This may have been due to redistribution of the insulin over 3 rather than 2 injections. These results are consistent with those reported in a recent study of 100 patients with type 2 diabetes that showed cumulatively that BIAsp 30 given QD, BID, or TID enabled 77% of patients to attain an HbA_{1c} of <7% and 60% to reach an HbA_{1c} of ≤6.5%.[17] Further, as occurred with patients in the present study, the frequency of hypoglycemia decreased when the third injection was added.[17]

Improvements in HbA_{1c} may be due to improved postprandial glucose (PPG) control. Although PPG excursions are a substantial contributor to overall hyperglycemia, most diabetes therapies have focused on control of fasting plasma glucose (FPG).[18] As patients get closer to their target HbA_{1c} levels, elevations in PPG have a much greater role in glycemic control than is attributed to FPG.[19] Premixed insulin formulations offer a convenient approach to covering basal and prandial insulin requirements. They reduce by 40% to 60% the magnitude of postprandial glucose excursions as compared with human insulin 70/30.[20-22] When compared with patients on a QD basal insulin regimen, patients who remained on metformin and who used a premixed insulin analog regimen BID had lower postprandial glucose excursions and were more likely to reach HbA_{1c} goals, despite an increased risk of minor hypoglycemia.[23-25]

Because human insulin 70/30 has to be administered at least 30 min before a meal, and because it exhibits broad overlapping peaks of basal and prandial insulin components, its use is impractical in a TID regimen. In contrast, these pharmacokinetic limitations have been overcome by premixed insulin analogs; consequently, BIAsp 30 can be used TID. Studies in healthy subjects[26] and those with type 2[27] diabetes have shown that time to peak absorption is 30% to 40% faster and maximum serum concentration of insulin is 50% to 75% higher with BIAsp 30 or insulin lispro 75/25 than with human insulin 70/30.

Poor adherence to the use of OADs and insulin and low levels of persistence occur in many patients with diabetes[28] and are worsened in patients given multiple doses and taking multiple medications. Because poor adherence and persistence can compromise treatment outcomes, potential barriers should be identified. Insulin pens are more accurate and convenient and are preferred by most patients over use of the vial and syringe[9-11]; therefore, patients should be encouraged to use these devices as long as they are not cost prohibitive.

This study involved 12 patients in a single practice who were followed for 6 mo. Its limitations include the following: (1) it was not a randomized prospective study; (2) the investigators relied on self-reporting of hypoglycemic events; (3) some patients

did not follow up every 3 mo; (4) 1 patient required corticosteroids; and (5) 1 patient chose to try exenatide. An HbA_{1c} goal of ≤6.5% was not pursued because study patients were elderly, were not well motivated, and were not counting carbohydrates; therefore, the risk of hypoglycemia was too great. Few published studies on insulin therapy in a practice setting, particularly with elderly patients, have been conducted. As was done with these patients, recommendations based on the results of clinical trials or put forth by professional societies must often be customized for the heterogeneous patient population encountered in clinical practice.

In conclusion, addition of a third injection at lunchtime for patients with type 2 diabetes who are using a premixed insulin analog BID is an alternative to switching to basal-bolus therapy, particularly in older patients. Convenience and accuracy of the delivery device should be considered when insulin regimens are implemented or changed.

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