Case Series: Premixed Insulin Dosing in Actual Practice: Two-Thirds in AM, One-Third in PM, or Half and Half?

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Initiation of insulin in type 2 diabetic patients failing to meet glycemic targets may include addition of either intermediate- or long-acting basal insulin or a biphasic premixed insulin that incorporates both basal and bolus insulins. Dual-acting basal/bolus insulin preparations are administered before meals to improve postprandial glucose levels and provide sustained glucose control throughout the dosing interval. Premixed insulins increase the convenience and acceptability of insulin use by type 2 diabetic patients who are not willing to take on or are not yet candidates for intensive basal/bolus insulin therapy.[1,2]

The conventional initial approach to dosing premixed insulins (biphasic insulin aspart 70/30, biphasic insulin lispro 75/25, or regular/NPH 70/30) still cited in medical texts and used in general practice is to prescribe a ratio of two-thirds of the total daily insulin dose in the morning before breakfast and one-third in the evening before dinner.[3–5] Health care providers in nonspecialty settings may be less likely to use ratios other than two-thirds/one-third because of concerns regarding the safety and effectiveness of a regimen that does not follow this conventional approach. Yet, it is difficult to find practical evidence to guide providers in using a different premixed insulin regimen.

After an extensive literature search of published clinical trials of premixed insulins, the authors were unable to reliably determine the ratios used in studies of type 2 diabetic patients in which premixed insulins were compared to each other or compared to basal or bolus insulins alone. No studies examined the actual prescribing patterns of the premixed insulins when used in a realistic clinical specialty practice setting in which endocrinologists use more treat-to-target approaches for rapid dose titration of insulin.

This retrospective, observational, descriptive study was designed to examine the use of premixed insulins in a community-based endocrinology practice and to analyze the ratio, hereafter referred to as the "dosing ratio," for morning and evening doses of premixed insulin. The primary objective was to determine the dosing ratio of evening doses to total daily doses (TDDs) of insulin and compare it to the "standard" dosing ratio of 0.33. Secondary objectives were to determine the correlation between dosing ratios and A1C and between TDD and A1C.

PATIENTS AND METHODS

Study subjects. The study sample was selected from a population of adult patients (> 18 years of age) who received their diabetes care from a specialty endocrinology private group practice office and who were currently prescribed premixed insulins. During the data collection period, the practice employed five endocrinologists, three mid-level practitioners, two diabetes educators, and adequate nursing and support staff. It currently manages > 5,000 patients with diabetes, about two-thirds of whom have type 2 diabetes.

Patient records were included for review if the patients were followed in the endocrinology practice regularly for diabetes management, received any type of premixed insulin, and had been receiving premixed insulin twice daily for at least 3 months. Patient records were excluded from the study if the patients received only once-daily dosing of premixed insulin, received premixed insulin three times daily, administered premixed insulin for less than 3 months, or had no recorded A1C during the past year from the date of the electronic medical record (EMR) review.

Study procedures. The study used a retrospective, observational, descriptive design. All data were extracted from the EMR using an inquiry of the patient database applying the criteria listed above. Patient data were collected for the 1-year period before the date of the EMR review. The study was approved by the Mercy Medical Center Institutional Review Committee and Des Moines University Institutional Review Board. Data were collected during a 2-week period from the last week of November to the first week of December 2006.

Information gathered included age, sex, type of diabetes, duration of diabetes, weight, BMI, last two

A1C results, date of current and initial dosing of premixed insulin, type of device used for insulin delivery, types and doses of premixed insulin (current and initial), category of other diabetes medicines concomitantly prescribed, and severe hypoglycemia resulting in transport to the emergency department or hospitalization.

The individual providers used their own algorithms for starting insulin but later titrated the morning or evening dose based on blood glucose trends. Decisions were clinically driven based on blood glucose levels. The practice did not employ any standard predefined algorithm for initiating or titrating premixed insulin doses.

Height was measured by nursing staff using an Accustat Genetech Stadiometer (San Francisco, Calif.), and weight was obtained on a Detecto scale (Webb City, Mo.). All results were recorded in the EMR. BMI was obtained from a calculated field within the EMR based on height and weight entered. A1C was measured using results from either a fingerstick or brachial artery sample analyzed on a CLIA-waived DCA-2000+ machine (Siemens, Tarrytown, N.Y.). All other information was extracted from the EMR flow sheet and the providers' progress notes written on the day of the most recent office visit.

Statistical analysis. Standard descriptive statistics (mean and standard deviation) or simple counts were calculated where appropriate. The ratio of evening dose to TDD (dosing ratio) of premixed insulin was calculated for all patients. Means, standard deviations, and 95% CIs for the dosing ratio were calculated for: *1*) all patients, *2*) patients with A1C levels ≤ 7%, and *3*) patients with A1C levels > 7%. Student's *t* tests for all these groups were calculated to determine whether the actual dosing ratio significantly differed from the "standard" dosing ratio (0.33). Correlation coefficients were calculated to examine the relationship between dosing ratio and A1C, as well as TDD and A1C. The latter relationship was also examined after covariate analysis for BMI. For all tests, $\alpha = 0.05$.

RESULTS

A summary of demographic characteristics is shown in Table 1. The study sample consisted of 70 patients who were mainly older obese men with type 2 diabetes. The mean duration of diabetes was 12 years. Two patients with type 1 diabetes received premixed insulin and were included in the analysis.

A review of concurrent diabetes medications is shown in Table 2. Approximately one-third of patients received premixed insulin alone for glucose control, one-third received monotherapy with an oral antidiabetic agent in addition to their premixed insulin, and one-third received combination oral therapies in addition to their premixed insulin.

Descriptive characteristics of the study subjects are provided in Table 3. The majority of patients were prescribed aspart 70/30. One-half of patients used a pen delivery system, and the remaining half used insulin vials and syringes. Only one patient experienced a severe hypoglycemic event that was recorded in the EMR. The mean A1C was 8% for both the most recent measurement and a previous measurement.

The mean overall dosing ratio of premixed insulin was 0.47 ± 0.07 (95% CI 0.45–0.49). This ratio was similar to the ratio calculated for the subset of patients with an A1C ≤ 7% (ratio: 0.48 ± 0.05, 95% CI 0.46–0.50)

Table 1. Subject Demographics (*n* = 70)

Characteristic	Mean or Number
Age (years)	62.6 ± 13.82
Male	39 (56%)
Female	31 (44%)
BMI (kg/m^2)	36 (range 19.2–53.5)
Type 1 diabetes	2
Type 2 diabetes	68
Duration of diabetes (years)	12

Table 2. Concomitant Medication by Class

Medication Class	Number (%)
Monotherapy: • Sulfonylurea • Metformin • Thiazolidenedione • Meglitinide • α-Glucosidase inhibitor • Sitagliptin • Exenatide • Pramlintide	25 (35.7%) 0 16 9 0 0 0 0 0
Combination oral therapies	22 (31.4)
Premixed insulin monotherapy	23 (32.9)

Table 3. Descriptive Characteristics of Subjects	
Characteristic	**Mean ± SD or *n* (%)***
Type of premixed insulin: Aspart 70/30 Regular/NPH 70/30 Lispro 75/25	 63 (90) 4 (5.7) 3 (4.3)
TDD of insulin (units)**	76.4 ± 43
Insulin administration device used: Pen/flex pen Vial and syringe	 33 (47) 33 (47)
A1C (%):*** Most recent Previous	 7.7 ± 1.6 8.1 ± 1.8
Patients with A1C: ≤ 7% > 7%	 22 (31.4) 48 (68.6)
Ratio of evening dose to TDD: A1C ≤ 7% A1C > 7%	0.47 ± 0.07 (95% CI 0.45–0.49) 0.48 ± 0.05 (95% CI 0.46–0.50) 0.47 ± 0.08 (95% CI 0.44–0.49)
**Patient numbers may not add up to 70 if data were missing; **Based on* n *of 68, where complete datasets were available; ***Based on* n *of 65, where complete datasets were available.*	

and A1C > 7% (ratio: 0.47 ± 0.08, 95% CI 0.44–0.49). The dosing ratios differed significantly from the standard ratio of 0.33 for the subjects as a whole ($t = 16.0$, $P < 0.0001$), those with A1C levels ≤ 7% ($t = 11.6$, $P < 0.0001$), and those with A1C levels > 7% ($t = 13.8$, $P < 0.0001$). There were no significant ($P > 0.05$) correlations between A1C and dosing ratio for any group (all $R < 0.03$). In addition, there were no significant ($P > 0.05$) correlations between TDD and A1C for any group (all $R < 0.05$).

DISCUSSION

The primary findings of this study in the practice environment analyzed are: *1*) the premixed insulin dosing ratio of evening dose to TDD significantly differs from the standard value of 0.33 and is on average close to 0.5 or 50%, and *2*) there was no significant relationship between dosing ratio and glycemic control as assessed by A1C.

The importance of addressing postprandial glucose control in insulin regimens has been highlighted by Monnier et al.[6] They determined that 70% of overall glycemic control as represented by A1C relates to postprandial glucose when A1C values are < 7.3%, and 50% of overall glycemic control relates to postprandial glucose when A1C values are 7.3–8.4%. Although Riddle et al.[7] found that adding daily basal insulin assists many patients with type 2 diabetes to achieve the American Diabetes Association (ADA) A1C target of < 7%, Monnier et al. concluded that adding bolus insulin to a regimen of basal insulin monotherapy would result in improved ability to reach the A1C target.

Raskin et al.[8] published results of the 28-week treat-to-target INITIATE study that dosed aspart 70/30 twice daily in a 1:1 ratio and compared results to bedtime dosing of insulin glargine alone. The aspart 70/30 was more effective than daily glargine in achieving an A1C target of ≤ 6.5% (42% vs. 28%, respectively, achieved A1 ≤ 6.5%) and an A1C target of < 7% (66% vs. 40%, respectively, achieved A1C < 7%). Episodes of major hypoglycemia were comparable, although episodes of minor hypoglycemia were more frequent in the aspart 70/30 group compared to the glargine group (3.4 episodes/year compared with 0.7 episodes/year, respectively). Our study found that 31% of patients were able to achieve a target A1C of ≤ 7%, a proportion lower than the 66% reported in the clinical trial conducted by Raskin et al.

Garber et al.[9] published results of the 1-2-3 Study that examined the effects of aspart 70/30 on achievement of American Association of Clinical Endocrinologists (AACE) and ADA targets when added to oral antidiabetic drugs sequentially in a once-, twice-, and thrice-daily regimen. Ratios of aspart 70/30 used were only cited for the three times daily regimen, with 38%, 16%, and 46% of the TDD being administered before breakfast, lunch, and dinner, respectively. The rates of self-reported minor hypoglycemic episodes were 15.4, 22.4, and 12 events/patient-year in the once-, twice-, and thrice-daily regimens, respectively. Reporting of these episodes was widely variable, however, and only 7 of 100 patients reported a major hypoglycemic event: 3 each in the once- and twice-daily regimens, and 1 in the thrice-daily regimen.

Two studies using three times daily dosing of aspart 70/30 divided doses as 40% breakfast/20% lunch/40% dinner or 30% breakfast/20% lunch/50% dinner.[10,11] However, it is not possible to compare them to our study because their design either compared twice- to three times daily dosing or compared three times daily dosing of aspart 70/30 to NPH and soluble aspart. Sun et al.[12] conducted a retrospective review of basal to premixed insulin but did

not specify the ratios used. Tibaldi[13] conducted a retrospective study of aspart 70/30 dosed twice daily in 12 patients in a case series. He did not specify ratios used, although a figure suggests a dosing ratio of 0.5.

Patients in the specialty endocrinology office of the current study ended up receiving about equal amounts of insulin at breakfast and dinner after titrations. A review of published clinical trials did not consistently provide complete information on ratios of premixed insulins used or correlations of A1C with ratios studied. This is problematic for practitioners who need the type of practical clinical guidance that our study provides. Our study results suggest that patients should be started on equal amounts of premixed insulin twice daily and then titrated based on blood glucose response.

Our patients did not experience significant problems with major hypoglycemia, indicating that the treat-to-target approach taken by our specialists did not expose patients to undue risk. Alternatively, only about one-third of our patients were able to achieve a target A1C of ≤ 7% using premixed insulin in a treat-to-target approach. This could be due to a number of reasons, including: the observation period was not long enough to see a greater proportion of patients achieve target A1C; dosing titration was not aggressive enough; or patients may have actually needed a more intensive basal/bolus insulin regimen. One interesting observation noted in the current study was that the mean TDD of premixed insulin was 76 ± 43 units/day (median = 70), or on a weight basis, 0.7 ± 0.4 units/kg of body weight/day.

This type of observational retrospective study has some limitations. Our sample was taken from a population of adults seen in an endocrinology practice, thus limiting generalizability to other types of practice settings or patients. Given the retrospective nature of the study, the authors were not able to control for many factors, including the effects of exercise, concurrent medications, changes in medications, dietary influences, adherence to the care plan, or accurate assessment of hypoglycemia. Patients were not randomized to premixed insulin, but rather selected it on the basis of the individual clinical judgment of their physician, creating a potential sample bias in the population selected. It is not possible to draw any conclusions about the incidence of hypoglycemia in the current study because of its dependence on patient self-reports during office visits and the resulting potential for underreporting. Despite these limitations, this study demonstrated that the dosing of premixed insulin in practical clinical use in an endocrinology group was close to a 1:1 ratio of morning and evening premixed insulin doses.

CONCLUSION

The ratio of evening insulin doses to TDD of premixed insulin in this practice was ~ 0.5 and was significantly different from the standard dosing ratio of 0.33 still recommended in various tertiary references and used in general practice. Based on these results and the authors' clinical experience, premixed insulin should be initiated in a 1:1 ratio for twice-daily dosing rather than in the conventional approach of two-thirds in the morning and one-third in the evening. Large prospective, randomized, controlled trials will be needed to confirm these findings.

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