LETTER TO THE EDITOR

Senders:
John Walsh, P.A., C.D.E.,
and Ruth Roberts, M.A.

In two articles in the January issue of this journal,[1,2] Allen King, M.D., and Dana Armstrong, R.D., presented evidence from a study that glucose control can be achieved in 31 type 1 patients who follow a controlled diet and use an insulin pump that is programmed with lower daytime basal rates and higher bolus insulin doses than are typically used.

Although determination of ideal basal and bolus doses was the primary focus of the study, the more relevant clinical interventions may be frequent clinical follow-up and introduction of an isocaloric diet. The diet contained a controlled number of carbohydrates with fewer calories that produced an average weight loss of 1.3 kg over 11.6 days. The weight loss and A1c improvements may have derived more from dietary improvements than from specific changes in basal or bolus doses. A retrospective continuous glucose monitoring system (CGMS) was used at each clinic visit to make changes in basal and bolus doses, but the authors provided no insight into the decision tree and circumstances under which changes were made regarding basal and bolus doses.

On average, clinicians and patients select a basal/bolus balance that contains just under 50% of the total daily dose (TDD) for basal insulin delivery, whereas the other 50% is utilized for both carbohydrate and correction boluses.[3,4] Once correction boluses are removed, daily basal insulin doses are generally larger than the total carbohydrate bolus doses for the day. In studies of patients using multiple daily injections, rapid and long-acting insulins are also found to average about 50% each relative to the TDD.[5] These findings contrast with the King–Armstrong study where 38.4% of the TDD was used for basal and 61.6% for boluses.[1]

Years of clinical experience have shown that selection of a proper basal and bolus balance must always address variations in an individual's physiology, diet, and activity. Young children and thin adults are often sensitive to insulin and may benefit from lower basal rates when they consume a high carbohydrate diet or are involved in physical activity. During puberty or with a strong dawn phenomenon, pump users often do better with relatively high basal rates. Type 1s who acquire insulin resistance as a result of weight gain and many insulin resistant type 2s fare better with relatively high basal rates, sometimes above 65% of the TDD. Although low carbohydrate diets are not advised, those who eat them find that their basal rates may make up 80% or more of their TDD. Basal insulin need also changes significantly with age.[6] Given the controlled environment in which the King and Armstrong study was conducted, recommending a one-size-fits-all approach to basal and bolus doses is equivalent to fitting everyone's feet into size 9 shoes.

Much of the authors' drive to reduce basal insulin doses in their study came after the controlled diet was introduced and subjects began to experience hypoglycemia. King and Armstrong elected to have subjects skip the evening meal to begin basal testing, a time of day when it is difficult to separate basal effect from prior boluses because of the long tailing action of rapid insulins. The subjects' basal doses at the start of the study were already low at 42.1% of the TDD (14.9 of 35.4 U). King and Armstrong decided for reasons that are not stated to eliminate the hypoglycemia by lowering basal insulin delivery further rather than reducing the size of the bolus given for the previous meal.

In *Pumping Insulin*, we suggest waiting at least 5 hours after the last bolus at dinner and testing the overnight basal rates first as an easy way to eliminate bolus effects during the test.[7] This ensures that most, but probably not all, of the tailing insulin action from the dinner bolus is eliminated. Next we suggest users skip breakfast to test basal rates

during the first part of the day when basal insulin will again be acting independently of bolus doses. Basal tests are conducted over a 6- to 8-hour period to ensure that the glucose stays flat when only basal insulin is acting. Although not as convenient as skipping a single meal to conduct a basal test as in the King and Armstrong study, we believe it is a more accurate basal testing method.

The authors provided no convincing evidence that the glucose-lowering activity of previous boluses had cleared when the evening meal was skipped to show that basal insulin activity was responsible for the hypoglycemia that was encountered. The CGMS method used by the authors cannot independently differentiate tailing bolus activity from basal insulin effect. The consistent eating times and carbohydrate intakes in this study permit insulin to be shifted between basal and bolus delivery over a wide range of basal percentages relative to the TDD because of the long physiodynamic action of today's insulins. Given a more rigorous effort to identify the source of the hypoglycemia encountered by the subjects, other clinicians might choose alternative interventions that could be equally effective in the diet-controlled environment in which the study was conducted.

One unusual finding in the study was that the subjects' peak basal need occurred between 11 P.M. and 2 A.M. The authors attributed this rise in nighttime basal need to a new "dusk to dawn phenomenon." [1] This finding contradicts well-documented studies of basal insulin requirements[5,8,9] and is likely an artifact following the tailing off in activity of the large dinner bolus, followed by the need for a large increase in the basal rates around bedtime to catch up to the low daytime basal rates that can no longer suppress hepatic gluconeogenesis.

In Figure 4 on page 39 of the study, basal rates throughout the day appear to double or triple between minimum and maximum basal rates for most participants. This degree of basal variability contrasts with numerous glargine and detemir studies and with numerous well-conducted basal studies, including those that measure basal requirements through the night where both minimal and maximal basal needs are typically encountered.[6,9] One study found that overnight basal requirements varied by only 40% between the low and the high rates in young patients in whom the dawn phenomenon is typically strongest.[9] Given the intended role of basal insulin to keep the glucose flat when meals are skipped, it is not clear why older patients' basal rates would vary to the degree seen in the King and Armstrong study.

Table 1 compares basal and bolus doses used by Davidson *et al*. and those from Tables 10.6, 10.4, and 10.7 in the 4th edition of *Pumping Insulin*, which provides carbohydrate and correction factors for someone using 40, 50, and 60% of the TDD for basal delivery, respectively, with recommendations in the King and Armstrong study. **Table 1** provides basal and bolus doses for the average participant in the study who weighs 163 lbs. (74.1 kg) and is in excellent control with a TDD of 35.4 units.

Table 1.
Basals, Carbohydrates, and Correction Factors for a TDD of 35.4 Units from Three Sources

	Daily basal total (U)	Daily bolus total (U)	Carbohydrate factor (g/U)	Correction factor (mg/dl per unit)
King and Armstrong	13.6 (38.4%)	21.8	9.13	42.4
Davidson *et al.*[a]	17.0 (48%)	18.4	12.9	48.0
Walsh and Roberts 40% basal table[b]	14.2 (40%)	21.2	12.7	50.8
Walsh and Roberts 50% basal table[b]	17.7 (50%)	17.7	14.1	56.5
Walsh and Roberts 60% basal table[b]	21.2 (40%)	14.2	15.5	62.1

[a] Davidson PC, Hebblewhite H, Steed R, Bode B. A deductive framework to aid in understanding CSII parameters: carbohydrate-to-insulin ratio (CIR) and correction factor (CF). ADA Annual Meeting abstract; 2003. p. 443.
[b] Tables 10.6, 10.4, and 10.7 in Walsh and Roberts[7] provide different carbohydrate and correction factors for 40, 50, and 60% of the TDD as basal.

Note the large difference in carbohydrate factors in the gray-highlighted area of **Table 1**. We are concerned that the carbohydrate factor recommended by King and Armstrong may induce hypoglycemia when patients in ordinary life consume meals that contain more carbohydrates. To illustrate this, let us take the average individual in the study (163 lbs. with 35.4 U/day) who has a prebreakfast glucose reading at target and plans to eat 150 grams of carbohydrates for breakfast at a local pancake house. The gray area in **Table 2** shows differences in the carbohydrate bolus recommendations among the three methods.

Table 2.
Differences in Carbohydrate Boluses for a Meal Containing 150 Grams

	Average bolus for a meal (U)	Carbohydrates in average meal (g)	Bolus for a 150-g meal (U)	% of average TDD
King and Armstrong	7.3	66.6	16.4	46.3
Davidson *et al.*	6.1	78.6	11.6	32.8
Walsh and Roberts (40% basal)	7.1	90.1	11.8	33.3

To cover this single meal with 150 grams of carbohydrates, our method and that of Davidson and colleagues suggest giving smaller bolus doses, equal to 33.3 and 32.8% of the average daily TDD, respectively. In contrast, King and Armstrong suggest a bolus equal to 46.3%, or nearly half of the average TDD for the same high carbohydrate meal.

Their recommended bolus gives 4.6 extra units to cover these carbohydrates compared to the other two methods. Although Davidson's method does provide 3.4 additional units of basal insulin per day compared to King and Armstrong, this basal delivery is spread over 24 hours and would be substantially less than the extra 4.6 units spread over a 5- to 7-hour period following the pancake breakfast.

The aggressive carbohydrate factors and relatively aggressive correction factors from King and Armstrong will work only as long as the excess bolus insulin evenly replaces relatively low basal rates over the next 5 to 7 hours. Their formulas for carbohydrate and correction factors were derived in a clinical setting in which the carbohydrate intake was controlled. When the same carbohydrate factor is used to cover a high carbohydrate meal, the resulting bolus begins to exceed the amount needed to replace the reduced basal insulin delivery.

The source for this error, we believe, can be seen in Figure 1 on page 44. This graph, which is used to determine the author's carbohydrate factor formula, shows more outlying values than Figure 2 from which their correction factor formula was derived. Statistically, it appears a least-squares approach was used to determine the carbohydrate factor formula. This approach gives more influence to the outlying values in Figure 1. A larger data set or use of different statistical tools would likely result in a different carbohydrate formula than the one given.

Another cause for their use of a stronger carbohydrate factor at lower TDDs may be the need for lower basal percentages in those who use less insulin per day. A clinical decision to use relatively lower basal rates in those who have lower TDDs may have clinical merit. If the authors provide a graph of TDD versus basal percentages, this may provide some explanation that could be explored in a future clinical study.

The King and Armstrong carbohydrate formula (217/TDD +3) gives relatively larger boluses to those who are more sensitive to insulin. For example, someone on a lower TDD of 20 units a day would require 7.2 units for 100 grams of carbohydrate using the King and Armstrong method, compared to only 4.4 units for the other two methods. This represents a 63% increase in the bolus dose for someone who requires less insulin per day compared to a 41% increase in the pancake example given earlier.

Our approach in *Pumping Insulin* is significantly different from those offered by King and Armstrong and by Davidson and colleagues. We believe that as the average basal percentage relative to the TDD changes, the carbohydrate and correction factors must change also. Once one finds a correct TDD for an individual, based on A1c and frequency of highs and lows, the carbohydrate and correction factor numbers must change in proportion to the change in basal

percentage. No single formula can be used for the carbohydrate and correction factors because they need to change in relation to the different basal percentages required by different individuals.

Summary

This nonrandomized, preliminary study provides one formula for basal and bolus percentages of the TDD for all clients. Unfortunately, it did not test whether alternate basal and bolus approaches might provide an equal level of control, nor did it fully demonstrate that the therapeutic outcomes were derived primarily from the basal and bolus adjustments that were made. Additional information is needed to evaluate this approach, including the DIA<AU: Please spell out> used, the time intervals between prior meal boluses and start of the basal test, the average basal rate profile over a 24-hour period, how long after the previous bolus hypoglycemia began when a meal was skipped, and whether hypoglycemia occurred in the morning hours when breakfast was skipped. Although reduced rates for hypoglycemia and hyperglycemia are shown based on CGMS measurements, no confirmation with actual finger stick BG results is provided to evaluate the possibility of false negatives.[10]

Varied clients and lifestyles necessitate a variety of basal and bolus percentages relative to the TDD, and clinicians are able to achieve good control in different patients through appropriate utilization of a wide range of these. More research in this important area is needed with real-time continuous glucose monitors, confirmed with finger stick readings, and with basal testing intervals that accommodate the relatively long physiodynamic action of today's insulins. Despite the authors suggestion that their "results can be generalized to a broad population of adult patients with type 1 diabetes,"[2] their dose recommendations require testing in less controlled environments before they are implemented.

References:

1. King A, Armstrong D. A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: basal dosing. J Diabetes Sci Technol. 2007;1(1):36-41.
2. King A, Armstrong D. A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: bolus dosing. J Diabetes Sci Technol. 2007;1(1):42-6.
3. Analysis of 541 insulin pumps used across the U.S., to be published by J Walsh, D Wroblewski, and T Bailey.
4. Table 3 in Apidra product handout, Rev. April 2004a.
5. Garg SK, Rosenstock J, Ways K. Optimized basal-bolus regimens in type 1 diabetes: insuin glulisine versus regular human insulin in combination with basal insulin glargine. Endocr Pract. 2005;11(1):11-7.
6. Scheiner G, Boyer BA. Characteristics of basal insulin requirement by age and gender in Type-1 diabetes patients using insulin pump therapy. Diabetes Res Clin Pract. 2005;69:14-21.
7. Walsh J, Roberts R. Pumping insulin. 4th ed. San Diego: Torrey Pines Press; 2006. p. 132.
8. De Feo P, Perriello G, Ventura MM, Calcinaro F, Basta G, Lolli C, Cruciani C, Dell'Olio A, Santeusanio F, Brunetti P, *et al*. Studies on overnight insulin requirements and metabolic clearance rate of insulin in normal and diabetic man: relevance of the dawn phenomenon. Diabetologia. 1986;29(8):475-80.
9. Garg S, Chen Y, Souhami E. Reduction in insulin dose and body weight with pre- and post-meal insulin glulisine (GLU) versus human regular insulin (RHI) in patients with type 1 diabetes. Diabetes. 2004;53(2):A119.
10. Diabetes Research in Children Network (DIRECNET) Study Group. The accuracy of the CGMS in children with type 1 diabetes: results of the Diabetes Research in Children Network (DirecNet). Diabetes Technol Ther. 2003;5:781-9.

Corresponding Author: John Walsh, P.A., C.D.E., 1030 West Upas Street, San Diego, CA 92103; email address *jwalsh@diabetesnet.com*