Novel Insulin & Better Glycemic Control in Type 2 Diabetics

MMJ 2009; 8:8-13

Hazim A. Abdulwahab

CABM, Ass. Professor of Internal Medicine & Endocrinology, Al-Mustansiriya College of Medicine

Background: Recently a new premixed insulin analogue has been introduced with good results achieved in different parts of the world particularly regarding good glycemic control and safety.

Objective: This clinical study was conducted to evaluate the effectiveness and safety of introducing new insulin (biphasic insulin aspart 70/30)for the treatment of type 2 diabetic patients.

Methods: This prospective follow up study included 68 type 2 diabetic patients who has been randomly selected from those attending the National Diabetes Centre (NDC)of Almustansiria University during the period between 1st of oct.2004 to 31st of march 2005.Each patient had been followed for an average period of 6 months. Detailed history had been recorded and thorough physical examination has been performed for each patient. Readings of fasting and postprandial plasma glucose (FPG,PPPG), HbA1c,body mass index (BMI), and the frequency of hypoglycemic attacks had been recorded at the baseline ,interim, and the final visit which had been separated by 3 months between each other. At the baseline visit , each patient has been instructed how to use insulin pen properly and biphasic insulin aspart 70/30 had been supplied to the patients included in this study freely. Statistical analysis using students t-test had been used to assess the difference between different means using a p value of less than 0.05 as the level of statistical significance.

Results: This study showed that there was significant difference between the mean human insulin dose used before the study(48.3u/day) and the mean premixed insulin Aspart (36.88u/day) P value less than 0.05.The use of insulin analogue was associated with significant reduction in FPG (130.5mg/Dl in the last visit ,compared with 216mg/Dl in the 1st visit)P value less than 0.001,and the PPPG (160.2mg/Dl compared with 280mg/Dl in the 1st and last visit respectively)P value less than 0.001, and the mean HbA1c (7.1% compared with 9.41%)P value less than 0.001.There was no significant difference between the 1st and last visit recordings of BMI (27.9Kg/m2 compared with 28.1Kg/m2 respectively)P value more than 0.05 ,and in the average incidence of mild hypoglycemic episodes (1.01 compared with 0.42 episode respectively)P value more than 0.05.

Conclusion: This study showed that the use of this type of insulin analogue for type2DM lead to marked and statistically significant improvement in the glycemic control ,mainly in the PPPG. In addition the use of this type of insulin was associated with only mild elevation in the BMI and slight lowering in the incidence of hypoglycemic episodes ,both non-significant statistically.

Key words: biphasic insulin aspart , type2 DM, glycemic control

Introduction:

Type 2 diabetes produces or is a contributor to a considerable morbidity in the form of metabolic complications and long term complications of diabetes ,like vision disorder, neuropathy, and kidney disease , the associated mortality has been estimated at 5.5 % annually , moreover the disease reduces life expectancy by 5-10 years (1) .

Although there is no cure for diabetes mellitus (DM) , but the United Kingdom Prospective Diabetes Study (UKPDS) have pointed to the importance of intensive blood glucose (b.gl) control in reducing its associated morbidity (2).To maintain blood glucose at accepted levels more aggressive therapy has to be introduced at the proper time when oral antidiabetic agents (ODA) and human insulin are no more effective .

The introduction of newer insulin analogues is a great advent in the management of DM. Of these is the premixed insulin aspart which is composed of 30% insulin aspart and 70% protaminated insulin aspart , this combination has been shown to result in improved postprandial glycemic control and reduced risk of delayed postprandial hypoglycemia (3) ,both criteria are required for better glycemic control and to achieve a high degree of compliance. Also the premixed insulin offer patients the convenience of not having to self mix their insulin preparation and therefore reduces dosing error and improve patients compliance(3) .This study was conducted to evaluate the efficiency and safety of introducing biphasic insulin aspart 30/70 for the treatment of type 2 diabetic patients who were beyond optimal control on different regimens (ODA, human insulin, or both).

Patients & Methods:

This prospective follow-up study had enrolled 68 type 2 diabetic patients who had been randomly selected from those who were attending the National Diabetes Center (NDC) at Al-Mustansiriya University during the period between the 1st of October 2004, to the 31st of March 2005. At the baseline visit, a registration record had been opened for each patient including the personal information and other information about the history of other illnesses associated with diabetes, and the frequency of hypoglycemic attacks prior to inclusion in this study. In addition, it included baseline readings of body mass index, FPG, postprandial plasma glucose and HbA_{1c} levels. Each patient had been instructed about how to use insulin and receive the biphasic insulin aspart 30/70. Each patient had been instructed to consult us about any problem he might face with this type of insulin. The readings of fasting and postprandial plasma glucose, the HbA_{1c} levels, the frequency of hypoglycemic attacks and body mass index had been recorded in the baseline, interim and final visits with 3 months separating each from the other visit. Each patients signed a written consent for the use of biphasic insulin aspart and participating in this study.

The collected data had been assessed using Microsoft Excel 2003 software program and statistical analysis was done using the student's t-test. P value of less than 0.05 had been selected as the value of significant association or difference between different means.

This study included 68 patients with type 2 diabetes mellitus, including 36 male and 32 females. Their age ranged between 31-79 year-old (56.3 ± 11.5 years). In regard to the duration of diabetes, it ranged between 1-31 years (12.32 ± 7.6 years). 70.6% of the sample (48 patients) was diabetics for 5-19.9 years.

Thirty six out of 68 patients (52.9% of the sample) had used human insulin either alone (22 patients, 32.3% of the sample) or in combination with ODA(14 patients, 20.6% of the sample). The mean total daily dose of human insulin used by them was 48.3 ± 15.2 U/day. By reaching the end of this study the mean total daily dose of biphasic insulin aspart used by the patients included in this study was 36.88 ± 16.8 U/day. Twenty four out of 68 (35.3% of the sample) used biphasic insulin aspart alone and 44 patients (64.7% of the sample) used it in combination with metformin. 41 patients (60.3% of the sample) used biphasic insulin aspart in a dose of less than 40 U/day. Statistical analysis testing the difference between the mean total daily dose of biphasic insulin aspart and the mean total daily dose of human insulin revealed statistically significant difference between the two means (calculated t = 3.56, p value < 0.05). The dose of metformin used by the 44 patients in combination with the biphasic insulin aspart had ranged between 1000-2550 mg/day (1753.4 ± 544.6).

The mean FPG at the baseline visit was 216 ± 54.86 mg/dl (range 125-369 mg/dl), which became 130.5 ± 14.5 mg/dl (range 95-199 mg/dl) at the final visit after six months of treatment with biphasic insulin aspart. Statistical analysis revealed a significant reduction in the mean FPG (FPG) over the period of study (calculated t = 12.57, p value < 0.001). Furthermore, no one of the patients had FPG of less than 120 mg/dl at the baseline visit, while this FPG level had been achieved by 16 patients
(23.5% of the sample) by the final visit (Table-1).

The FPG measured at the baseline visit had been observed to be reduced in average by 36.4% ± 15.1% (range 5.5% - 64.8%) by reaching the final visit. Statistical analysis revealed that there was no significant difference between the mean reduction observed in patients who had used biphasic insulin aspart only (36.6% ± 14.4%) and those used combination therapy (36.3% ± 15.6%) (p value > 0.05).

Postprandial plasma glucose (PPPG) concentrations had a mean of 280 ± 58.58 mg/dl (range 160-392 mg/dl) at the baseline visit and had a mean of 160.2 ± 17.9 mg/dl (range 94-201 mg/dl) at the final visit. Statistical analysis revealed a highly significant reduction in the PPPG in the final visit after 6 months of biphasic insulin aspart use compared to the mean of PPPG observed at the baseline visit (calculated T =13.7,P less than 0.001). 8 patients (11.8% of the sample) reached a PPPG level of less than 140 mg/dl. (Table-2).

The observed reduction in the PPPG between the baseline reading and the final reading was in average 40.4% ± 13.5% (range 4.6-60.1%). 20 patients (29.4% of the sample) showed 50% and more reduction in their PPPG level at the final visit reading compared to that estimated at the baseline visit. Statistical analysis revealed no significant difference in the mean of reduction between those used biphasic insulin aspart only (41.6 ± 15.01%) and those used it in combination with metformin (39.7 ± 12.7%) P> 0.05. The mean concentration of glycated hemoglobin (HbA1c) was 9.41 ± 1.48% (range 7-14.3%) at the baseline visit, and it was 7.1 ± 0.43% (range 6.3 – 8.3%) at the final visit, this difference was statistically significant (calculated t = 12.8, p value<0.001). 22 patients (32.4% of the sample) had reached HbA1c level of less than 7% (Table-3).

The mean reduction in HbA_{1c} level observed at the final visit after 6 months with biphasic insulin aspart therapy was 22.37 ± 10.1% (range 2.8-44.1). Statistical analysis revealed no significant difference between the mean reductions observed in patients using biphasic insulin aspart only from that in the combination therapy group, P>0.05 (table 4).

Table-1: Patients' distribution according to their Fasting blood glucose (FBG), postprandial plasma glucose (PPPG), and glycated hemoglobine (HbA_{1c}) levels

		Baseline visit (n=68)		*Interim visit (n=68)*		*Final visit (n=68)*	
		No.	**%**	**No.**	**%**	**No.**	**%**
FBG (mg/dl)	**<120**	0	0	11	16.2	16	23.5
	120-159	10	14.7	51	75	51	75
	160-199	18	26.5	6	8.8	1	1.5
	200-239	21	30.9	0	0	0	0
	≥ 240	19	27.9	0	0	0	0
	Range	*125-369*		*105-215*		*95-199*	
	Mean ± SD	*216 ± 54.86*		*138.05 ± 20.3*		*130.5 ± 14.5*	
PPPG (mg/dl)	**< 140**	0	0	1	1.5	8	11.8
	140-179	3	4.4	43	63.2	58	85.3
	180-219	11	16.2	20	29.4	2	2.9
	220-259	11	16.2	4	5.9	0	0
	≥ 260	43	63.2	0	0	0	0
	Range	*160-392*		*130-265*		*94-201*	
	Mean ± SD	*280 ± 58.58*		*178.3 ± 24.8*		*160.2 ± 17.9*	
HbA_{1c} (%)	**<7%**	0	0	4	5.9	22	32.4
	7-7.9%	7	10.3	41	60.3	43	63.2
	8-8.9%	26	38.2	19	27.9	3	4.4
	9-9.9%	15	22.1	4	5.9	0	0
	≥ 10%	20	29.4	0	0	0	0
	Range	*7-14.3*		*6.9-9.1*		*6.3-8.3*	
	Mean ± SD	*9.41 ± 1.48*		*7.7 ± 0.57*		*7.1 ± 0.43*	

Table-2: Patients' distribution according to the observed reduction in their HbA1c concentration between the baseline visit and final visit readings in the two different regimen groups

Reduction in HbA1c (%)	***Biphasic insulin aspart only***		***Biphasic Insulin aspart + ODA***		***Total***	
	No.	**%**	**No.**	**%**	**No.**	**%**
<25	15	62.5	31	70.5	46	67.6
25-49.9	9	37.5	13	29.5	22	32.4
Total	***24***	***100***	***44***	***100***	***68***	***100***
Range	*2.8-44.1*		*6.7-43.4*		*2.8-44.1*	
Mean ± SD	*23.8 ± 11.25*		*21.6 ± 9.4*		*22.37 ± 10.1*	

Ten patients (14.7% of the sample) had more than 2 minor hypoglycemic attacks at baseline while none had more than 2 minor attacks at final visit. The average of the frequency of hypoglycemic attacks identified at the baseline visit was 1.01 ± 2.2 minor hypoglycemic attacks compared to 0.42 ± 0.6 minor hypoglycemic attacks observed at the final visit. Statistical analysis indicated that there was no significant difference between the mean

frequency of hypoglycemic attacks detected at the baseline and final visits (calculated t = 2.18, p value > 0.05) (Table-5) .
The mean of the body mass index (BMI) was 27.9 ± 4.8 (range 19.4 – 44.7 kg/m^2) at baseline compared to 28.1 ± 4.1 kg/m^2 estimated at the final visit. No significant increase in the body mass index had been detected using the student's t-test for statistical analysis (calculated t = 0.26, p value > 0.05)(Table-6).

Discussion:

In assessing any drug therapy, one has to choose his markers of efficacy and markers of safety of the studied drug. The best efficacy markers to be discussed here are the levels of FPG, PPPG, and HbA_{1c}. On the other hand, the best safety markers to be selected in evaluating insulin therapy are the risk of hypoglycemia and the possible rise in BMI and the risk of any possible adverse effects.
The mean daily dose of biphasic insulin aspart used in this study (36.88 ± 16.8 U/day) was significantly lower than the dose of conventional insulin used by 36 patients (52.9% of the sample) prior to inclusion in this study (48.3 ± 15.2 U/day), (calculated t = 3.56, p value < 0.05), . In a study of patients with type 2 diabetes with combination of different types of insulin and metformin by Kilo et al (2003)[4], the total daily dose of biphasic insulin aspart was less than the dose of other types of conventional insulin and it was even lower than the dose used in this study (26 ± 13.6 U/day in Kilo et al study, versus 36.04 ± 18.6 U/day used in this study by patients on combination therapy). The low dose of insulin in this study is probably due to the use of metformin in about 2/3 of the patients as adjuvant drug and may be the pharmacodynamic properties of the drug.

Table-3: Patients' distribution according to the frequency of hypoglycemic attacks during the study period and their body mass index (BMI)

		Baseline visit		***Interim visit***		***Final visit***	
		No.	**%**	**No.**	**%**	**No.**	**%**
Hypoglycemia	**0**	53	77.9	45	66.2	43	63.2
	1-2	5	7.4	23	33.8	25	36.8
	3-4	2	2.9	0	0	0	0
	5-6	5	7.4	0	0	0	0
	7-8	3	4.4	0	0	0	0
	Total	68	100	68	100	68	100
	Range	*0-8*		*0-2*		*0-2*	
	Mean ± SD	*1.01 ± 2.2*		*0.47 ± 0.72*		*0.42 ± 0.6*	
BMI (kg/m^2)	**< 20**	1	1.5	0	0	0	0
	20-24.9	24	35.3	17	25	16	23.5
	25-29.9	22	32.4	29	42.6	30	44.1
	≥ 30	21	30.8	22	32.4	22	32.4
	Total	68	100	68	100	68	100
	Range	*19.4-44.7*		*20.6-41.5*		*20.7-44.3*	
	Mean ± SD	*27.9 ± 4.8*		*28.1 ± 4.3*		*28.1 ± 4.1*	

This study showed that the use of biphasic insulin aspart is associated with marked reduction in the FPG (216 ± 54.86 mg/dl at the baseline visit reduced to 130.5 ± 14.5 mg/dl at the final visit), this reduction was statistically significant (calculated t = 12.57, p value < 0.001). In addition, 22.1% of the sample (15 patients) had reduction in their FPG by 50% or more in comparison between the baseline and the final visit readings . The improved FPG during this study obviously due to the effect of basal insulin coverage provided by the protaminated insulin aspart. It is important to ask a vital question on discussing the targeting of plasma glucose, that, is it enough to say that this patient reached a good or strict glycemic control by only having a fasting plasma glucose which lie within the goal range? Data from the Third National Health and Nutrition Examination Survey suggest that in about 10% of type 2 diabetic patients, the 2-hour value was > 200 mg/dl, when the fasting plasma glucose was < 126 mg/dl[5,6]. Erlinger and Brancati[5] , in agreement with Monier et al[7], showed that postprandial plasma glucose elevations (> 200 mg/dl) occurred generally in 39% of patients whose HbA_{1c} was optimal (< 7%). Thus postprandial plasma glucose elevation is a frequent finding when "optimal" control is achieved[6]. Fortunately, the maximum reduction and the most statistically significant effect of the introduction of biphasic insulin aspart had been observed in the postprandial plasma glucose of the patients included in this study. The mean of postprandial plasma glucose was 280 ± 58.5 mg/dl at the baseline visit compared to 160.2 ± 17.9 mg/dl at the final visit (calculated t = 13.7, p value < 0.001). Furthermore, 20 out of the 68 patients included in this study (29.4%) had a reduction rate in their postprandial plasma glucose concentration of 50% or more . Gallagher concluded that insulin aspart resulted in improved postprandial glycemic control in type 2 diabetic patients, even to a lower level than the mean observed in this study (142.2 ± 7.2 mg/dl) compared to (160.2 ± 17.9 mg/dl) which had been observed in our study [8]. The improved PPPG was expected due to the effect of insulin aspart on post-prandial hyperglycemia and to a lesser extent due to the effect of long acting protaminated insulin aspart.

Although there was statistically significant difference in the mean of HbA_{1c} between the baseline and final visit (9.41% ± 1.48% versus 7.1% ± 0.43%, respectively; calculated t = 12.8, p value < 0.001), but the rate of reduction in the HbA_{1c} was the least marked (22.37% ± 10.1%) compared with the reduction rate in both the fasting plasma glucose (36.4% ± 15.1%) and the postprandial plasma glucose (40.4% ± 13.5%). This finding can be explained by that the patient want to please his doctor so he will be more compliant before attending the clinic . Much less reduction had been observed by Kilo et al in their study which had extended for 12 weeks only (this study extended for 26 weeks), they showed 1.1-1.3% reduction from the baseline after 12 weeks of treatment with biphasic insulin aspart and metformin. But it must be mentioned that patients, who had been included in Kilo et al study, had mean HbA_{1c} of about 7.6 at the baseline evaluation reduced to 7.04% by the end of the 12 weeks [9].

In this study, statistically significant reduction in the mean of the rate of hypoglycemic attacks between the baseline visit and the final visit is not observed (calculated t = 2.18, p value > 0.05). However, no one of the patients included in this study developed any major hypoglycemic attacks (attack that require help from a relative or a medical personnel). In addition, the frequency of the minor hypoglycemic attacks observed in this study was 1-2 times only and observed in 36.8% of the sample (see table-12). These findings are comparable to that observed in Kumamoto study and UKPDS[9,10].The decreased incidence of hypoglycemic attacks support the hypothesis that the improved pharmacokinetic profile of

biphasic insulin aspart may favorably affect the balance between hypoglycemia and hyperglycemia in insulin treated type 2 diabetics. Boehm et al, in their study which continued for 2 years, showed that in the end of the study no one of the patients treated with biphasic insulin aspart developed major hypoglycemic attack, but they showed that 63% of patients treated with insulin aspart develop one hypoglycemic attack during the 2 year period [11]. The latter finding is similar to the finding of our study in relation to the frequency of minor hypoglycemic attacks.

The use of insulin has been associated with weight gain[12]. This study revealed that there was negligible, if present, weight gain associated with the use of biphasic insulin aspart for 6 months. Boehm et al showed in their study that patients treated with biphasic insulin aspart changed weight by 0.05 ± 0.81 kg, which is comparable with the finding in this study.

This minor weight gain might be explained by the use of metformin [13] by 44 patients (64.7% of the sample) in combination with biphasic insulin aspart and the lower insulin doses. In addition, the patients appeared to be more motivated and stick to the instructions given to them regarding diet and exercise.

In the first 3 months of the study, only one patient had been withdrawn from the study because of having allergic reaction and lipodystrophy at the injection sites. Surprisingly this patient tolerated well the premixed human insulin (mixtard) without any adverse effects.

So in conclusion this study indicated that:

1-The use of biphasic insulin aspart is associated with better glycemic control in term of lower levels of fasting and postprandial plasma glucose and HbA_{1c} concentrations.

2-The most pronounced beneficial effect had been observed on the postprandial plasma glucose level.

3-The use of biphasic insulin aspart had been associated with less frequent minor hypoglycemic effect, but this association was not statistically significant.

4-The increase in body mass index after the use of biphasic insulin aspart was small and insignificant statistically.

References:

1. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR,Wiedmeyer H-M, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes Care 1998 21:518–524
2. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes: prospective observational study. BMJ 2000; 321:405–12
3. Boehm B, Home PD,Bott U, Behrend C, Kamp NM, Lindholm A .Premixed insulin aspart 30/70 versus premixed human insulin 30/70 twice daily : a randomized trial in type 1 and type 2 diabetic patients. Diabetic Medicine,19,2002; 393-399.
4. Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once daily injection of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. Journal of Diabetes and Its Complications 2003; 17: 307-13.

5. Erlinger T, Brancati F: Postchallenge hyperglycemia in a national sample of U.S. adults with type 2 diabetes. Diabetes Care 2001; 24:1734–1738.
6. Schort RJ. Targeting plasma glucose: preprandial versus postprandial. Clinical Diabetes 2004; 22: 169-72.
7. Monnier L, Lapinski H, Colette C: Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetes patients. Diabetes Care 2003; 26: 881–885.
8. Gallagher A. The effect of postprandial blood glucose control on postprandial metabolism and markers of vascular risk in people with type 2 diabetes. Diabetes Res Clin Pract 2005; 67: 196-203.
9. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995; 28:103–117.
10. U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; 353:837–53.
11. Boehm BO, Vas JA, Brondsted L, Home PD. Long term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. Europ J Int Med 2004; 15: 496-502.
12. White JR, Davis SN, Cooppan R, et al. Clarifying the role of insulin in type 2 diabetes management. Clinical Diabetes 2003; 21: 14-21.
13. Kilo C. Metformin: a safe and effective treatment in the management of NIDDM. Missouri Medicine ,1997 ,94(3); 114-122.