A retrospective audit of biphasic insulin lispro

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Introduction

Diabetes presents a daily challenge to approximately 1.3 million people in the UK (DoH, 2001). As healthcare professionals we should empower people with diabetes to become the main decision makers in their diabetes care. This may lead to a more complete understanding of the importance of complying with treatment. The most serious concern that people with diabetes appear to express is regarding hypoglycaemia (Barnett, 2002). This is often more important to them than maintaining good control. Treatments that can reduce this risk should be utilised. Clatterbridge Hospital Diabetes Clinic decided to offer biphasic insulin lispro (Humalog Mix25) to interested people with diabetes when it became available. This article describes an audit that indicates the results after 1 year of use.

The discovery of insulin, approximately eight decades ago by the renowned Banting, Best, Collip and Macleod, is well documented (Bliss, 1982) and does not appear, as yet, to have been surpassed as a life-saving phenomenon. From those early beginnings biochemists have constantly strived to purify and improve on the early formulation. They have developed insulin from a soup-like preparation that led to pain and allergic reaction at the injection site, to insulin so pure that few people with diabetes today have significant adverse clinical reactions.

Although insulin is now available in many formulations (twice-daily mixtures, short-acting and intermediate-acting) which can be matched to patient lifestyle, it still cannot perfectly mimic the physiological action of endogenous insulin. This may be due in part to the many variables that control insulin absorption: site and depth of injection; systemic rather than portal delivery; factors increasing blood flow to the injection site (exercise, hot weather and hot baths); injecting into areas of lipohypertrophy (Barnett, 2001); timing of injections; and diet.

Generally, patients have been advised to inject approximately 20–40 minutes before meals to allow time for insulin appearance in the circulation. However, the evidence demonstrates that few patients follow this advice. Ahmed et al (2001) studied people with diabetes who were treated with insulin. Of the 179 participants, 27% reported having their injection 0–5 minutes before meals, and 31% reported having their injection 6–10 minutes before meals. Twenty-four percent reported an 11–20 minute interval and 18% reported following the recommendations and taking their insulin 20 minutes or more before meals. Interestingly, HbA_{1c} did not differ with pre-meal injection interval.

In an older study relevant to hypoglycaemic episodes, Lean surveyed 225 people treated with insulin (Lean, 1985). A total of 24 participants (10.6%) claimed never to have received advice about the interval between insulin injections and eating. Of the group, 67 people injected <15 minutes before their meal, 82 people injected 15–29 minutes before meals and 76 injected >30 minutes before meals. There was a significant ($p<0.01$) difference between the reported frequencies of clinical hypoglycaemia in people using different intervals.

The evidence suggests that this aspect of diabetes management may be neglected with important consequences for blood glucose control and/or hypoglycaemic episodes. It seems logical that if these variances could be overcome then improved control with the

ARTICLE POINTS

1 An audit was carried out to assess the effectiveness of biphasic insulin lispro (Humalog Mix 25) after a year of use and the degree of patient satisfaction.

2 Many formulations of insulin are available, analogue being the most recent.

3 Controlling weight is an important part of diabetes management.

4 There was a reduction in hypoglycaemic episodes after treatment with insulin lispro.

5 Coronary heart disease is the principle cause of premature mortality in people with diabetes.

KEY WORDS

- **Audit**
- **Analogues**
- **Weight control**
- **Blood glucose**
- **Cardiovascular risk**

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1 Insulin lispro differs from human insulin by the relocation of two amino acids on the B-chain of the molecule.

2 Compliance with medical advice is known to be poor in chronic disease and when treatment regimens are complex.

3 The study group consisted of 96 people with diabetes who had been treated with insulin lispro for approximately 1 year.

4 A patient questionnaire was devised to assess the satisfaction of the participants with the treatment regimen.

5 There was a significant weight gain ($p<0.05$) in the 96 participants.

possibility of less hypoglycaemia may result. It would also be more convenient for people with diabetes, allowing them more flexibility.

Development of analogues

Eli Lilly Pharmaceuticals produced the first insulin analogue, insulin lispro with this varying interval in mind. Insulin lispro differs from human insulin by the relocation of two amino acids on the B-chain of the molecule. This results in faster absorption into the blood stream. Studies showed that insulin lispro has a more physiological profile than soluble insulin (Howey et al, 1994). Insulin lispro was quickly absorbed, peaked at 30 minutes and rapidly left the circulation. It was used as a bolus in a basal bolus regimen.

In 1999, a fixed mix analogue combination of 25% insulin lispro and 75% protamine suspension was launched in the UK. One of the benefits was that a twice-daily regimen could be considered instead of a four-times daily regimen. Results were hopeful showing a reduction in postprandial hyperglycaemia, a reduced risk of hypoglycaemia but no real overall improvement in glycated haemoglobin (Vignati et al, 1997).

Hanif and Kumar (2002) illustrated that postprandial hyperglycaemia is a significant predictor of, and an independent risk factor for, coronary heart disease and mortality. The importance of reducing postprandial glucose elevation cannot be understated.

Despite the lack of evidence that documents a reduction in HbA_{1c} levels, patient choice, lifestyle and compliance must also be considered. Compliance with medical advice is known to be poor in chronic disease and when treatment regimens are complex (Dyer, 2002). The fewer the instructions required, the better for the person with diabetes.

As a consequence of these benefits insulin lispro seemed to be a step forward in improving the lifestyle of people with diabetes. The diabetes team at Clatterbridge Hospital decided to give people with diabetes the option to be commenced on insulin lispro. Those people who chose to use insulin lispro were closely monitored by the DSNs.

Aim of audit

An audit was carried out to assess whether the use of insulin lispro did deliver benefits to the daily lives of patients and what outcomes were achieved compared with previous treatments.

Participants

The study group consisted of 96 people with diabetes who had been treated with insulin lispro for approximately 1 year. Participants were individuals who had not responded to their previous treatment and a small number of newly diagnosed people with type 1 diabetes (n=5).

The age range of participants was 25–90 years with a mean age of 57 years. The groups were fairly evenly split:

- Women new to insulin therapy (n=24)
- Men new to insulin therapy (n=23)
- Women converted from other insulin therapy (n=23)
- Men converted from other insulin therapy (n=26).

Method

Weight and HbA1c were measured at the start of treatment with insulin lispro, 6 months into treatment and 12 months into treatment.

A patient questionnaire was devised with help from the clinical practice and research unit, which was used to assess the satisfaction of the participants with the treatment regimen.

Analysis

The data was analysed separately for weight and HbA_{1c} measurements using ANOVA. Using this method, data on each group of participants could be compared at the three different time points (commencement of treatment, 6 months and 12 months into treatment). Comparisons were also made on HbA_{1c} and weight between male and female participants.

Results

There was a significant weight gain ($p<0.05$) in the 96 participants. This demonstrates that people new to insulin therapy gain weight as expected (Sinha et al, 1996).

Throughout the 12 month period of the study, there was no significant difference in weight gain between male and female members of any of the groups (p=0.601). *Figure 1* demonstrates there was only a minimal change within these groups.

Controlling weight is an important part of diabetes management. Weight gain during insulin treatment is predominantly through fat mass; insulin may promote central fat deposition. This is of particular importance since visceral fat deposition correlates strongly with insulin resistance. Barnett (2001) states that women have more peripheral adipose tissue than men, but similar levels of visceral adiposity. Our audit illustrates that over a period of time, neither sex is more at risk of increasing insulin resistance due to weight gain.

There was a significant difference between the weights of people new to insulin compared with those converted from a different type of insulin (p=<0.001). *Figure 2* shows that participants who converted to insulin lispro from different insulins maintained a steady weight profile for the 12 month period. People new to insulin therapy continued to gain weight over the 12 month period. This weight gain is acceptable initially for people newly diagnosed with type 1 diabetes, as a result of reduced urinary glucose loss and general anabolic effects of insulin replacing previously lost weight. As there were only five people newly diagnosed with type 1 diabetes in this study these factors are unlikely to be the cause. It is thought that weight gain tends to plateau once insulin therapy is established (Barnett, 2001) but this did not occur in our study.

Participants who transferred from oral hypoglycaemic agents recorded a weight gain of 0.7–12.8 kg (with the exception of two participants). One of the participants was in a very poor state of health before insulin initiation, which may partly explain why no weight was gained. The other was already obese and made a very successful effort to lose weight. While weight gain is a recognised side-effect of insulin

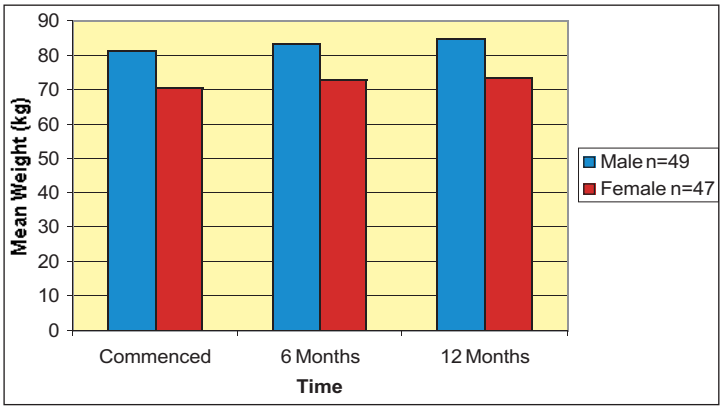

Figure 1. Comparison of weight and sex over time

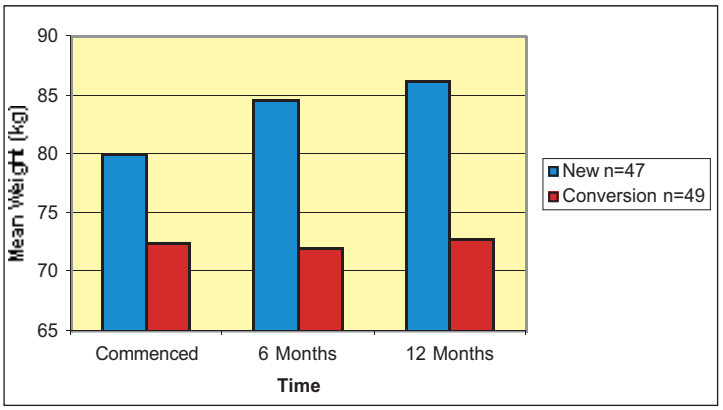

Figure 2. Comparison of weight and new/conversion groups over time

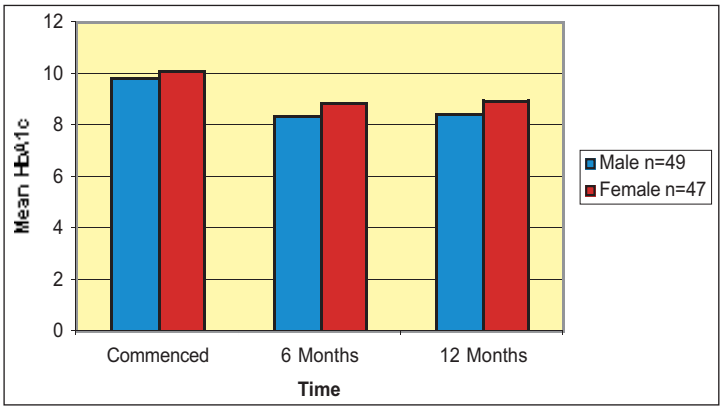

Figure 3. Comparison of HbA_{1c} and sex over time

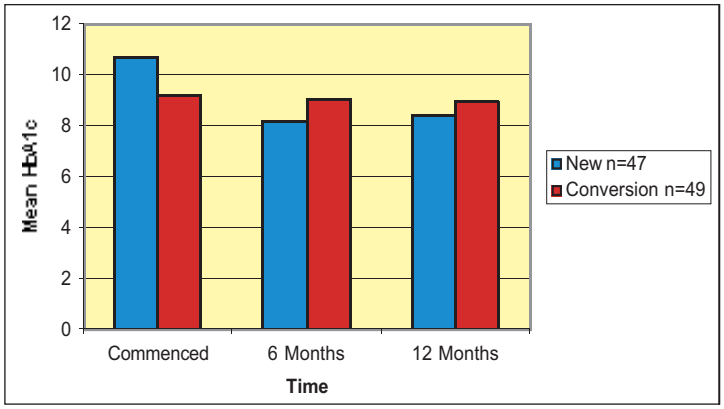

Figure 4. Comparison of HbA_{1c} and new/conversion groups over time

Table 1. Diabetes questionnaire to assess user satisfaction

1) I prefer insulin lispro because I can eat as soon as I inject

Completely agree	Agree	Not important	Disagree	Completely disagree
0%	50%	34%	14%	2%

2) I prefer insulin lispro because I can inject up to 15 minutes after I have eaten

Completely agree	Agree	Not important	Disagree	Completely disagree
11%	41%	28%	16%	4%

3) I experience fewer hypoglycaemic attacks on insulin lispro than I did on my previous treatment

Completely agree	Agree	Disagree	Completely disagree
27%	40%	31%	2%

4) How satisfied are you with insulin lispro?

Very satisfied	Satisfied	Dissatisfied	Very dissatisfied
48%	49%	3%	0%

5) Would you recommend insulin lispro to someone else with your type of diabetes?

Yes	No	Did not answer
91%	2%	7%

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1 Barnett states that mean weight gain values are highly misleading because there can be enormous differences between patients, with no reliable means of predicting who will gain weight.

2 Across the whole study group there were no substantial differences in HbA_{1c} between men and women during the 12 months of the study.

3 People who converted to insulin lispro from other insulins did not significantly improve HbA_{1c} but this was not totally unexpected.

initiation, the average amount of weight gain expected is approximately 2–4 kg and this is expected to level off with time (Barnett, 2001).

The UK Prospective Diabetes Study (1998) quotes a relatively modest weight increase due to insulin, but this should be considered in conjunction with the knowledge that baseline weight rises by about 3 kg per decade in the healthy adult population (Barnett, 2001) which also applies to people with diabetes. Barnett states that mean weight-gain values are highly misleading because there can be enormous differences between patients, with no reliable means of predicting who will gain weight. This was clearly demonstrated in our study; 0.7–12.8 kg was the range of weight gained.

Figure 3 illustrates that there was a substantial reduction in mean HbA_{1c} values between the start of treatment and at 6 months and the start of treatment and at 12 months. There is not a significant difference between 6 months and 12 months ($p=<0.05$). This clearly demonstrates that achieving an improved HbA_{1c} on a different therapy may be possible, but as there is minimal improvement between 6 and 12 months, maintaining this could present a problem. Across the whole study group there were no substantial differences in HbA_{1c} levels between men and women during the study ($p=0.79$).

There was a significant difference in HbA_{1c} between the new and conversion groups over the 12 months (*Figure 4*). This result was expected; people new to insulin showing considerably improved HbA_{1c}. The HbA_{1c} of participants new to insulin decreased from 10.7% at the start of treatment to 8.1% at 6 months. There was then a slight rise to 8.4% at 12 months. Overall, there was a decrease of 2.3% which is enough to reduce risk factors according to the UKPDS (1998). The UKPDS demonstrated that the incidence of diabetes related deaths (and any diabetes related endpoint) fell by 21% for every 1% reduction in HbA_{1c}. For microvascular complications the 1% drop in HbA_{1c} is associated with a risk reduction of 37%.

People who converted to insulin lispro from other insulins did not show significant improvements in HbA_{1c} but this was not totally unexpected. If comments and analysis from the questionnaire are to be believed then these same people did derive benefits to their lifestyle.

Patient questionnaire

Following approval from the research ethics committee, patients were sent a questionnaire with a stamped addressed envelope. The results are shown in *Table 1*. The purpose of the questionnaire was to assess user satisfaction as opposed to biochemical results.

A total of 96 questionnaires were sent and 64 returned (the response rate was 67%). Of the respondents, 24 were female, 37 were male and three did not specify their gender.

The age range varied but was predominately in the 41–80 year old bracket. Of the questionnaires returned 49 were from previous insulin users. Half of the replies agreed with the statement 'I prefer insulin lispro because I can inject up

to 15 minutes after I have eaten'. The remaining half believed that this was either not important or disagreed with the statement. Similar responses were gained when participants were questioned about the importance of being able to inject up to 15 minutes after eating.

Twice the number of participants felt that they experienced less hypoglycaemic events on insulin lispro than those who did not. Overall satisfaction with current insulin was clearly identified; 91% of users stated that they would recommend insulin lispro to others. The comments section was well used by those who responded.

Discussion

Type 2 diabetes is recognised as a risk factor for cardiovascular disease in both men and women. Coronary heart disease is the principal cause of premature mortality in people with diabetes (Krentz and Bailey, 2001). Krentz and Bailey suggest there is a linear association between HbA_{1c} levels and cardiovascular risk in people with type 2 diabetes. This supports the findings of the United Kingdom Prospective Diabetes Study (1998), that increased baseline HbA_{1c} and fasting glucose concentrations were associated with coronary heart disease.

The clinical significance of decreasing HbA_{1c} and improving diabetes control in order to reduce the risk of complications suggests that healthcare professionals must always be aware of new medications and devices that may aid in this objective.

'Designer' insulin is a progressive step forward; of the participants in our study who did not decrease their HbA_{1c}, the general feeling was that this insulin was more suited to daily living and allowed for more flexibility.

Conclusion

Healthcare professionals have clear targets for decreasing HbA_{1c} (UKPDS, 1998; DCCT, 1993) but people living daily with diabetes may not have the same agenda. It is well recognised that the most important issue to a person with diabetes is often the avoidance of hypoglycaemic episodes rather than good control of blood glucose. Without doubt the development of analogue insulin decreased the frequency of these episodes in our survey. Healthcare professionals must continue to strive to find common ground where the needs perceived by people with diabetes and the treat to target recommendations of major studies such as UKPDS and DCCT can amalgamate successfully. ■

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