Exenatide therapy in insulin-treated type 2 diabetes and obesity

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Summary

Background: Exenatide, a GLP-1 analogue, is used in combination with oral anti-diabetic agents in type 2 diabetes and obesity, and promotes weight loss. Exenatide use in combination with insulin in insulin-treated type 2 diabetes and obesity is unlicensed in the UK and outcomes are unclear.

Aims: To assess the effectiveness of exenatide in insulin-treated type 2 diabetes with obesity.

Design and Methods: This prospective study included 174 consecutive patients with insulin-treated type 2 diabetes and obesity initiated on exenatide in our out-patient, between October 2007 and November 2008. Weight, BMI, HbA1c, serum fructosamine, total cholesterol, HDL-cholesterol and insulin doses were recorded at baseline, 3, 6 and 12 months. Side effect profiles were recorded.

Results: Fourteen patients discontinued exenatide before 3 months of initiation, because of side effects, and were excluded. Data were analysed on remaining 160 people all of whom completed 6 months and 57 completed 12 months treatment. Mean weight loss was 10.7±5.6 kg and 12.8±7.5 kg (P < 0.001) at 6 and 12 months. Insulin doses dropped significantly (mean 144±90 U/day at baseline to 51±55 U/day and 55±53 U/day at 6 and 12 months). At 3 months, 25% came off insulin. There was little change in HbA1c.

Conclusions: Exenatide therapy in insulin-treated type 2 diabetes and obesity was associated with very significant reductions in weight and insulin doses. Exenatide should be considered in people with type 2 diabetes on insulin and have obesity, weight gain and poor glycaemic control.

Introduction

People with type 2 diabetes and obesity who are on insulin therapy present challenging clinical problems, especially so if glycaemic control is poor. Progressive weight gain after the establishment of insulin therapy is well recognized as indeed it is with various oral hypoglycaemic agents. In those patients with obesity and type 2 diabetes, intensifying insulin therapy to achieve target HbA1c outcomes is associated with yet further weight gain. For the person with diabetes, weight gain is one of the key anxieties of insulin therapy.

In the UK, NICE have issued guidance for the management of obesity which emphasizes diet and lifestyle but also supports drug therapy and obesity surgery. Drug therapies, at best, yield marginal weight outcomes. Whilst obesity surgery is increasingly recognized as being effective in those with diabetes, it carries significant risks. A variety of new therapeutic agents have become available for the management of glycaemia in type 2 diabetes that are either weight neutral or indeed promote weight loss. The NICE have recently updated glycaemic management guidance in type 2 diabetes to recognize this. Crucially, this introduces a notion...
of tailoring therapies in relationship to the risk of obesity. Of greatest interest in this regard are the GLP-1 analogues. There are now a number of reports of their favourable impact in type 2 diabetes on glycaemic control and weight outcomes, both early and later following diagnosis and in conjunction with variety of oral hypoglycaemic agents.\textsuperscript{10–12}

However, there have been no randomized controlled trials of the use of GLP-1 analogues in conjunction with insulin. Such use is not incorporated in the new NICE guidance and it remains outside product license in the UK. When presented with type 2 diabetes patients on insulin therapy, poor glycaemic control and degrees of obesity that present significant morbidity and mortality risk, UK specialist clinicians are increasingly exploring the use GLP-1 analogues in combination with insulin.\textsuperscript{13} In the absence of evidence, it is unclear how this combination should be initiated and what the expected outcomes might be.

We have established a protocol to structure the use of a GLP-1 analogue (exenatide) in combination with insulin in those type 2 diabetes patients already well established on insulin therapy who have obesity, weight gain and poor glycaemic control and in whom progressive up-titration of insulin was felt likely to promote weight gain, worsen obesity-related co-morbidity and not necessarily improving glycaemic control. The objective of the protocol, described here in detail, was to promote weight loss, spare insulin utilization and through weight loss attain glycaemic control. This article reports on our early audit outcomes.

Methods

This study was undertaken in the out-patient setting of the Wolverhampton Diabetes Centre over a 12-month period between October 2007 and November 2008. It was a prospective audit of our local intended clinical protocol for the use of exenatide amongst people with type 2 diabetes with both obesity and progressive weight gain on insulin therapy.

A set protocol was followed and is detailed in Table 1. The essential objective was to foster weight loss by maximizing metformin use, introducing exenatide and down titrating insulin dosages so long as glycaemic control was safe and did not deteriorate from base line. Where metformin was not previously used, it was started and up titrated to maximal dose in 4 weeks before exenatide initiation. The expectation over the short and intermediate term (0–6 months) was that progressive weight loss, consequent upon insulin dose reduction, together with the introduction of exenatide therapy, would subsequently improve glycaemic control. As such moderate glycaemic control was tolerated pending weight loss. At 6–12 months, the process of review shifted to ensuring that any weight loss achieved was maintained and that any residual poor glycaemic control was corrected.

All decisions to use exenatide in combination with insulin were made by consultant medical staff who were the only practitioners authorized to prescribe exenatide by the local hospital and Primary Care Trust prescribing committees. It was made clear to patients that the use of exenatide in combination with insulin therapy was outside the UK product licence. All patients were asked to give their verbal consent to this therapy, as they would do for any new therapeutic change, and this was documented in the formal clinic correspondence. As an audit of an intended clinical intervention driven by the pressing clinical need of individual patients, ethical committee approval was not deemed necessary.

All patients had received previous repetitive nurse educator and dietetic input in relationship to their insulin therapy (including diet, exercise, self blood-glucose monitoring and insulin dose adjustment) and further routine non-intensive input was offered as requested. The individual educational and induction sessions into the practicalities of exenatide therapy were brief, were undertaken by nurse educators and supported by a patient information leaflet. Following initiation, patients were reviewed by our diabetes specialist nurses at regular intervals over the initial 3-month start up phase and then with diminishing frequency as indicated by patient need over 3–6 months and subsequently over 6–12 months only as deemed necessary by the diabetes team (e.g. to support insulin dose titration) or as requested by the patient or their primary care team. Medical review occurred at 3 months, 6 months and 12 months at which point management plans were reviewed and set according to the protocol outlined.

The standard diabetes service clinic parameters were evaluated at baseline, 3, 6 and 12 months including weight, BMI, blood pressure, insulin doses, Hba\textsubscript{1c}, serum fructosamine, total cholesterol, HDL-cholesterol. A record was kept of the side effects and tolerability of exenatide therapy.

Audit data were subsequently analysed on SPSS (version 16). The difference between any two means was tested by Student’s \textit{t}-test for unpaired and paired samples as appropriate. In the multiple related samples at the 0, 3, 6 and 12 month time points, analyses were by the Friedman test.
Differences between proportions were sought by the chi-squared test. Results were considered significant at a level of >5% probability. Results are presented as the mean ± standard deviation unless otherwise indicated.

**Results**

The baseline clinical characteristics of the 160 patients audited are shown in Table 2 and their other key outcomes in Table 3.
Over the 1-year period, 174 patients with type 2 diabetes were initiated on exenatide in combination with insulin according to the protocol. Of these, 14 (8%) withdrew early because of intolerable gastrointestinal side effects. We thus present the results of remaining 160 that attained a minimum of 3 months follow-up, all of whom completed 6 months follow-up. Since the majority of patients were recruited as the year progressed, only 57 patients had completed 12 months follow-up at the time of analysis. Data on this entire cohort of 160 patients are presented on an intention to treat basis so that the data of any patient that subsequently discontinued exenatide therapy after 3 months are included.

Clinical characteristics

All patients had a BMI of >30 kg/m² and 105 patients (66%) had a BMI of >40 kg/m². All patients had been on insulin therapy for >1 year. Their glycaemic control was generally poor. Otherwise their complications profile was as might be expected for a cohort of this type. Of note, we made a specific decision to use exenatide combination therapy in one patient with a serum creatinine of >200 μmol/l. This patient (male, aged 39 years, initial weight 110 kg and BMI 32.6 kg/m²) was peritoneal dialysis-dependent following renal failure due to adult polycystic renal disease and his progression on a renal transplant list was impeded by his obesity.

Oral hypoglycaemic agents

The majority of patients were already established on maximum dose metformin and it was commenced in nine further patients in whom it was not contraindicated. It is not local practice to use other oral agents in combination with insulin and these were discontinued in the only two patients taking them (both Sulphonylureas, no patient was using a Glitazone). In the remaining 15 patients, metformin was either not previously tolerated (including modified release formulations) or was relatively contraindicated.

Body weight

The cohort were initially significantly clinically obese with the majority meeting the definition of morbid obesity with a BMI of >40 kg/m². Rapid weight loss occurred in 3 months and further weight loss by 6 months. At 6 months, three patients had gained weight (+0.6, 1.8 and 4.5 kg) but the remainder all lost weight (range: -0.1 to 25.8 kg). All told, percentage weight attained at 6 months compared to baseline was 91.5% (range 75–104%) with 166 (73%), 51 (43%), 37 (23%) and 7 (6%) achieving 5, 10, 15 and 20% body weight reduction, respectively. In the group attaining 12 month follow-up further weight loss that occurred after 6 months was smaller but still significant [6 vs. 12 months: 113.7 ± 2.3 vs. 111.8 ± 2.4 kg (P < 0.01), Δ1.9 ± 4.3 kg]. In multivariate regression, baseline total insulin dose (+ve), HbA1c (−ve) and weight (+ve) but not age, duration of diabetes or BMI were significantly but weakly correlated with weight loss at 6 months (r = 0.33, r² = 0.11, F = 5.62, P < 0.01) such that only 11% of the variance in weight loss could be explained.

Insulin—doses, regimes and discontinuation

The baseline mean insulin dose was large with 103 (65%) patients on >100 U/day. This equated to 1.2 ± 0.7 U/kg/day with 89 (56%) and 21 (13%) on >1 and >2 U/kg/day, respectively. Large falls in insulin dosages occurred in the first 3 months but little thereafter. This pattern was reflected when assessing continued insulin users separately to the combined whole group—inclusive of those continuing or discontinuing insulin therapies. The intensity
of insulin regimes shifted with greater numbers moving to once daily insulin. Insulin discontinuation was achieved largely in the early phase (up to 3 months) with little subsequent proportional change. The net group outcomes masked individual outcomes. Thus, 7 of 39 who had stopped insulin at 3 months had restarted by 6 months whereas another 6 on insulin at 3 months had stopped at 6 months. Only baseline HbA1c (8.1 ± 1.6 vs. 9.0 ± 1.7, \(P < 0.01\)) and insulin dose [161 ± 90 (range 28–550) vs. 88 ± 62 (18–136) U/day, \(P < 0.01\) and 0.75 ± 0.45 vs. 1.32 ± 0.71 U/kg/day, \(P < 0.001\)] were significantly different between those stopping and continuing insulin at 6 months but not age, duration of diabetes, duration of insulin therapy, weight and BMI. At 6 months, those discontinuing insulin had a lower weight (105.2 ± 20.7 vs. 113 ± 20.2 kg, \(P < 0.05\)), BMI (37.3 ± 5.8 vs. 40.3 ± 6.5 m²/kg², \(P < 0.05\)), tended to have lost more weight although not significantly so (12.0 ± 5.9 vs. 10.4 ± 5.6 kg, NS) and had a lower HbA1c (7.8 ± 2.0 vs. 8.8 ± 1.8, \(P < 0.05\)). In analysis of factors related to insulin discontinuation, three components emerged: the first included any static measure of obesity (weight or BMI) whether at baseline or 6 months as the major significant factors; the second included measures of baseline insulin dosage and weight loss at 6 months; and the third HbA1c whether at baseline or 6 months. In multivariate analysis, utilizing baseline BMI \(t = -1.449, \text{NS}\), baseline total insulin dose \(t = -3.796, P < 0.001\), baseline HbA1c \(t = -1.743, \text{NS}\) and weight loss at 6 months \(t = 2.095, P < 0.05\), the association was significant \((F = 7.6, \tau = 0.43, P < 0.001)\) but explained very little of the variance \((\tau^2 = 0.185)\) and was of no practical clinical utility in making predictions regarding insulin. At 12 months, 14 out of 57 patients had stopped insulin, representing a net of two who had stopped and four who had restarted from the 6-month review point. The proportion of insulin therapy was static. No further significant shifts had occurred in the intensity of insulin regimes and there had been no significant increase in the total dose of insulin in continued insulin users over that time period.

**Glycaemic control**

Whilst HbA1c showed a minor but significant fall at 3 months \((\rho = 0.001)\), there was essentially no meaningful change in the HbA1c at 6 or 12 months.
Other outcomes

There was a significant fall in systolic blood pressure. Diastolic blood pressure rose slightly but not significantly compared to baseline in the 6-month group and this trend was significant in the smaller 12-month cohort. Such minor variation in diastolic blood pressure has been reported in a systematic review of weight loss studies and probably reflects chance variation. Total cholesterol levels did not change.

Side effects and tolerability

Putting aside the early phase discontinuation as discussed above, of the 160 people entered a further eight (5%) discontinued exenatide between 3 and 6 months—gastrointestinal side effects were the reason for these discontinuations. Between 6 and 12 months, four (of 57) discontinued the treatment: one person died after 6 months after exenatide initiation due to cardiac events; exenatide was discontinued at 10 months in a patient with deterioration in glycaemic control following initiation of long-term steroids for temporal arteritis; two patients discontinued exenatide (after insulin discontinuation) because they had excellent glycaemic control following substantial weight loss. No episodes of major hypoglycaemia were reported.

Discussion

We report the preliminary outcomes of our local protocol designed to use exenatide therapy in combination with insulin in type 2 diabetes patients with obesity, weight gain on insulin therapy and, typically, poor glycaemic control and large insulin dosages. The logic of the protocol was based on the known mechanisms of action of GLP-1 analogue, their reported impact on glycaemic control and weight in type 2 diabetes and the negative impact of insulin therapy. The objectives of the protocol were to utilize exenatide to promote weight loss and impact on glycaemic control sufficiently to permit simultaneous reduction in insulin use. The reduction in insulin dosage was planned to further enable weight reduction. Ultimately, it was intended that exenatide therapy and weight loss would offset the impact of insulin dose reduction on glycaemic control and, indeed, the intermediate term aim was to ensure that improved glycaemic control was also achieved.

Without doubt, the weight loss outcomes were highly satisfying. The magnitude of weight loss can be considered in comparison to that attained following bariatric surgery. The percentage of excess weight loss (%EWL) achieved after bariatric surgery in people with diabetes is less than those without diabetes (59–67% vs. 77–83%). Furthermore insulin treatment in type 2 diabetes has been shown to reduce the attained %EWL post surgery. Kadara et al. reported a mean %EWL of 59% at 12 months post-Roux-en-Y gastric bypass (RYNGB) in insulin-treated type 2 diabetes. In our study, the %EWL was 23% and 26% at 6 and 12 months, respectively.

In the early and intermediate phase following exenatide start up, we were able to reduce insulin doses and number of insulin injections significantly without any worsening of glycaemic control or any other significant risk, most especially hypoglycaemia. Substantial numbers of patients became free of insulin therapy. It was not possible to predict insulin cessation; it had to be arrived through repetitive review and assessment. Zeni et al. looked at insulin cessation rates after RYGB and noted 44% (11 of 25) no longer required insulin therapy after the surgery. In those who remained on insulin post-operatively, the mean daily insulin doses reduced from 99 ± 48 to 26 ± 18 U (75% reduction). In our cohort with combined insulin exenatide use, insulin cessation rates were 25% and mean insulin dose reduction 62%.

In our cohort with poor control, glycaemic control did not worsen but we failed in delivering improved glycaemia outcomes. This failure essentially related to a reluctance to up titrate insulin between 6 and 12 months. That reluctance was based on an apprehension by patients and professionals alike that insulin up titration would either inhibit further weight loss or indeed promote regain of weight. Despite the stipulation of the protocol and inertia developed with the adoption of ‘wait and see’ approach.

There is little or no evidence to inform the diabetes community of how best to approach insulin exenatide combination therapy. Others have published retrospective observational data on the use of exenatide in combination with insulin in type 2 diabetes. Viswanathan et al. have reported data on 38 patients who completed 26-weeks treatment, Sheffield et al. on 134 patients out of whom 76 completed 1-year treatment and Yoon et al., on 188 patients out of whom 35 had completed 2 years of exenatide treatment. Mean HbA1c reduction in these studies were also small, being 0.6, 0.87 and 0.54%. Mean weight loss was 6.4, 5.2 and 5.5 kg, respectively, which is less than what was achieved in our cohort. These studies did not have a set protocol for insulin dose reduction on exenatide start up although generally there were reductions in rapid acting insulin dose. There were no significant changes in the total daily insulin doses.
in the latter two studies. Insulin discontinuation rates were lower than in our study group.

In light of our outcomes, our approach will be to further focus on glycaemia outcomes at 6 months. This will essentially require insulin up-titration in those patients with persistent poor control. We must therefore emphasize that the preliminary 12-month outcomes might be predicted to shift to weight gain and HbA1c reduction but the magnitude of such movements is uncertain. They will be subject to further reports.

We conclude that exenatide insulin combination therapy should be considered in a certain category of patients with type 2 diabetes who are established on insulin treatment and have obesity, weight gain and poor glycaemic control. Such use can be associated with significant gains in weight loss and reduced insulin use. Attainment of glycaemic control requires particular focus after the start up phase has been completed, especially from 6 months onwards, and patients and professionals should understand that outcomes will not improve without active intervention. All parties must respect that this combination therapy is an outside of licence use. We strongly advise that local clinical governance frameworks must be in place to permit this therapeutic strategy. Until such time that there is a greater body of evidence, such a strategy should be under specialist supervision only.

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References


