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Article *in* QJM: An International Journal of Medicine · November 2011

DOI: 10.1093/qjmed/hcr180 · Source: PubMed

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QJM Advance Access published November 4, 2011

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doi:10.1093/qjmed/hcr180

Effects of exenatide in poorly controlled type 2 diabetes*

N. KAIMAL, J. SCHOFIELD, A. ZAKI, R. PATEL, M. SHARMA, E. MCCOURT and K.E. IMTIAZ

Department of Diabetes and Endocrinology, Lancashire Teaching hospital NHS Trust, Chorley & South Ribble Hospital, Preston Road, Chorley PR7 1PP, UK

Address correspondence to Dr Nisha Kaimal, Directorate of Medicine, Department of Diabetes & Endocrinology, Chorley & South Ribble District General Hospital, Preston Road, Chorley PR7 1PP, UK. email: nisha_kaimal@yahoo.com

*This work was first presented as two posters in the Diabetes UK meeting, March 2009 and published in the Diabetic Medicine journal; March 2009, Volume 26, Supplement 1- P348 and P365.

Received 20 May 2011 and in revised form 8 September 2011

Summary

Aim: The aim of this retrospective analysis was to assess the clinical effectiveness of exenatide in patients with type 2 diabetes in routine clinical practice.
Methods: Patients with type 2 diabetes mellitus and inadequate glycemic control were commenced on exenatide in an out-patient setting. Effects on Hba1c, weight and BMI at 3- and 6-month intervals were recorded by a retrospective review of medical records.
Results: We examined a cross-section of 61 patients. The mean weight at treatment initiation was 114 kg and baseline Hba1c was 9.8% (84 mmol/mol). Mean reduction in Hba1c at 3 months was 0.8% (10 mmol/mol, $P < 0.01$) and mean reduction at 6 months was 0.5% (6 mmol/mol, $P < 0.05$). Mean weight loss at 3 months was 4.2 kg ($P < 0.0001$) and at 6 months was 6.6 kg ($P < 0.0001$). Seventeen patients were prescribed exenatide in addition to insulin, against current guidelines. This cohort of patients showed a greater mean reduction in weight (7.4 vs 6.2 kg) as compared to the group on exenatide without insulin, but mean Hba1c increased at 6 months by 0.35% (4 mmol/mol).
Conclusions: Adjunctive exenatide treatment in patients with suboptimally controlled type 2 diabetes on oral hypoglycaemic medications, achieved reductions in Hba1c and weight, in line with published studies. However, in patients already on insulin, favourable results can be achieved by the addition of exenatide by careful patient selection and follow-up.

Introduction

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), also called incretins, are enteroendocrine cell-derived hormones that are released in the circulation in response to an ingested meal. GIP is produced and secreted by the K cells in the stomach and proximal small intestine, while GLP-1 is a product of the L cells in the distal small intestine.[1] These agents are responsible for the additional stimulus to insulin secretion that is absent with an intravenous glucose infusion.[2,3] Impairment of incretin activity plays an important part in the metabolic derangement in type 2 diabetes. GLP-1 receptor agonists represent one of the therapies currently available for the management of type 2 diabetes.

Exenatide was the first approved agent in the incretin class of medications. Exenatide is a synthetic, 39-amino acid peptide form of the exendin-4 molecule, first isolated from the salivary gland secretions of the Gila monster. It promotes

glucose-stimulated insulin secretion,[4] suppresses post-prandial glucagon levels, slows gastric emptying[5] and causes reduction of caloric intake.[6] The National Institute of Clinical Excellence (NICE) guidelines recommend exenatide as an option in patients with a body mass index (BMI) >35 kg/m^2, with specific problems arising from body weight and Hba1c > 7.5%, after a trial of metformin and sulphonylurea. We performed a retrospective analysis of patients on exenatide, in a teaching hospital, to assess the efficacy of this agent in routine clinical practice.

Patients and methods

This retrospective analysis included 61 patients with type 2 diabetes who were given exenatide in the period from July 2007 to September 2008. Patients eligible for inclusion in this analysis were those with a diagnosis of type 2 diabetes who were receiving treatment with exenatide. The list of patients was obtained from the hospital pharmacy and case notes were reviewed. The analysis and use of data from medical records were approved by the local audit department.

We recorded baseline clinical data such as weight, Hba1c and medications prior to starting exenatide. Patients were initially commenced on 5 µg by subcutaneous injection twice a day and this dose was increased to 10 µg twice daily after a month. Patients were usually seen at 1, 3 and 6 months intervals in clinic. The decision to start exenatide and alter other medications was based on the judgement of the treating physician and no standard protocol was used. We recorded subsequent BMI, weight and Hba1c measurements after 1, 3 and 6 months of exenatide therapy. We recorded lipid profile (total cholesterol, HDL, LDL, triglycerides and cholesterol/HDL ratio) and renal profile at each follow-up. Side-effects were also included in the data collection.

Results

Sixty-five patients initially fulfilled the criteria. But we could not obtain sufficient data for 4 patients and 61 patients were included in the eventual analysis. The average age was 56 years (range 37–72). The average duration of type 2 diabetes prior to commencing exenatide was 9 years. Of the total patients, 98% were Caucasian and 52% were male.

Baseline HbA1c ranged from 6.9% to 14.1% (mean 9.8%, 52–131 mmol/mol, mean 84 mmol/mol). Baseline weight varied from 64 kg to 177 kg (mean 114), while the mean BMI at baseline was 39.96 kg/m^2.

Table 1 Baseline characteristics expressed as mean ± SD

Age, mean ± SD (years)	56 ± 9
Range	37–72
Sex (%)	
Female	48
Male	52
Hba1c (%)	
Mean ± SD	9.8 ± 1.54
Range	6.9–14.1
Hba1c, mean ± SD (mmol/mol)	84 ± 16.9
Range	52–131
Weight, mean ± SD (kg)	114 ± 24.2
Range	64–177
BMI, mean ± SD (kg/m^2)	39.96 ± 7.64
Range	25–58
Duration of diabetes—9 years (mean)	
Range	1–23 years
Baseline medications for diabetes (%)	
Metformin	90.2 (n = 55)
Sulphonylurea	67.2 (n = 41)
TZD	49.2 (n = 30)
Insulin	27 (n = 17)
Intermediate and long-acting insulin	26.2
Short-acting insulin	9.8
Biphasic insulin	1.6

Of the total patients, 90.2% were on Metformin and 67.2% were on a sulphonylurea, and 49.2% were on a thiazolidinedione.

A total of 27% patients were already on insulin and were put on exenatide against current recommended guidelines. Ten patients were on basal insulin only, six patients were on basal and prandial insulin and one patient was on twice daily insulin. Many studies have shown the effects of exenatide in combination with insulin, contrary to NICE guidelines. Among the patients on insulin, 70% of the patients had body weight >100 kg (and 70% of the patients who had their BMI recorded, showed a BMI > 40). In addition, these patients had poor glycemic control and attempts to increase the insulin dose resulted in further increase in weight. Thus, a clinical decision was made to commence exenatide rather than continue to increase insulin, keeping in mind the best interests of these patients, though it was against current NICE guidelines. Summary of baseline characteristics are shown in Table 1.

After having received 5 µg twice a day for 1 month, mean reduction in weight was 2.2 kg (±2.62, P < 0.0001) with a mean reduction in

Table 2 Summary of change from baseline in clinical parameters at different time intervals

	1 month	*P*-values	3 months	*P*-values	6 months	*P*-values
Hba1c	−0.5 (1.05)	0.0191	−0.95 (1.58)	<0.01	−0.5 (1.47)	<0.05
Weight	−2.2 (2.62)	<0.0001	−4.2 (4.64)	<0.0001	−6.6 (5.62)	<0.0001
BMI	−0.69 (0.85)	<0.0001	−1.54 (1.69)	<0.0001	−2.45 (2.09)	0.0001

Data expressed as mean SD ($n = 61$).

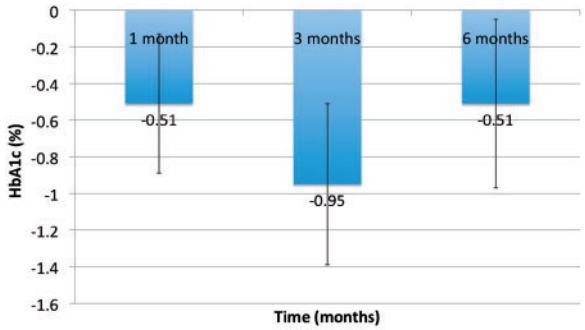

Figure 1. Mean Hba1c reduction on exenatide ($n = 61$).

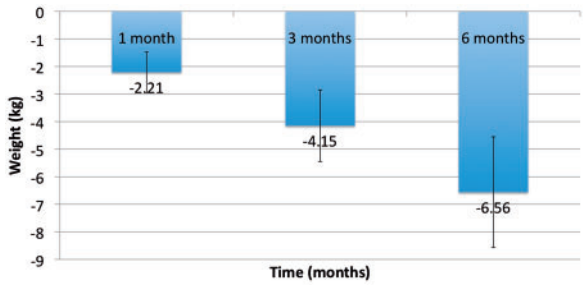

Figure 2. Mean weight reduction on exenatide ($n = 61$).

Hba1c of 0.5% (±1.05, 6 ± 12 mmol/mol, $P < 0.05$). Mean BMI at the end of a month was 39.86 kg/m^2 ± 7.09. Mean reduction in BMI in 1 month was 0.69 kg/m^2 (±0.85, $P < 0.0001$).

At 3 months mean reduction in HbA1c was 0.95% (±1.58, 10 ± 17 mmol/mol, $P < 0.01$). At 3 months, average weight loss was 4.2 ± 4.64 kg (range −16.4 to +6 kg) ($P < 0.0001$).

At 6 months, mean reduction in HbA1c was 0.5% (±1.47, 6 ± 17 mmol/mol, $P < 0.05$). Of the total patients, 26% ($n = 16$) had reductions in HbA1c >1.5%. These were not always the individuals who had lost the most weight. Average weight loss at 6 months was 6.6 kg (range −21.4 to +3.4 kg, $P < 0.0001$). A summary of the changes in these parameters are shown in Table 2, while Figures 1 and 2 show a graphical representation of the data.

Table 3 Changes in weight (kg) and Hba1c (%) at each follow-up visit for patients in the insulin and exenatide group ($n = 17$) vs the exenatide and oral agents group ($n = 44$)

	Insulin–exenatide	Exenatide alone
1 month		
Mean wt change	−2.44 (1.87)	−2.1 (2.92)
Mean Hba1c change	−0.09 (0.75)	−0.65 (1.12)
3 months		
Mean wt change	−6.98 (4.82)	−3.13 (4.18)
Mean Hba1c change	−0.27 (1.54)	−1.24 (1.53)
6 months		
Mean weight change	−7.38 (6.02)	−6.21 (5.56)
Mean Hba1c change	+0.35 (1.08)	−0.89 (1.49)

Figures in brackets indicate the standard deviation.

Exenatide and insulin

Seventeen patients were prescribed exenatide in addition to insulin. Patients on insulin at exenatide initiation achieved a better mean reduction in weight (7.4 kg) after 6 months, as against the group not on insulin (6.2 kg). This difference though, was not statistically significant ($P = 0.6403$). Mean Hba1c in the exenatide–insulin group, however, increased by 0.35% (4 mmol/mol) at 6 months. The exenatide-only group, on the other hand, showed a mean reduction in Hba1c of 0.889% (9 mmol/mol) at 6 months. Thus, intriguingly, the cohort of patients treated with exenatide only, showed a significantly greater mean Hba1c reduction as compared to the group treated with both exenatide and insulin ($P = 0.0135$). Details of the results in both the groups are as mentioned below in the Table 3.

One would have expected the group on insulin and exenatide to have a lesser degree of weight loss and a better improvement in Hba1c. But a limitation of this comparison was that the insulin–exenatide group had only 17 patients, while the exenatide-only group had 44 patients. Among these, complete data after 6 months of treatment were available for 12 patients in the exenatide–insulin group and

27 patients in the exenatide-only group. The discrepancy in numbers and the small sample size may possibly explain why the mean weight loss at 6 months was greater in the insulin–exenatide group as against the exenatide-only group.

Rates of discontinuation of exenatide in the insulin–exenatide group vs. the exenatide-only group were 17.6 vs. 15.9%. Side-effects requiring dose reduction were higher in the insulin–exenatide group (17.6 vs. 4.5%). The incidence of hypoglycemic episodes was also higher in the insulin–exenatide group (23.5 vs. 9.1%).

Side-effects

Of the total patients, 61% ($n = 37$) reported side-effects, which settled within 4 weeks, most commonly nausea. Totally, 8% ($n = 5$) patients reported gastro-intestinal side-effects requiring dose reduction, 13% ($n = 8$) patients reported hypoglycaemic episodes and 16% ($n = 10$) patients discontinued therapy (50% due to intolerance and 50% due to lack of efficacy). There were no reports of pancreatitis.

Limitations

A limitation of this analysis was that it was retrospective in nature. There was no control group in this analysis either. No fixed protocol was employed for altering doses of oral hypoglycemic agents or insulin and these changes were entirely on the discretion of the treating physician. Thus, it would be difficult to eliminate physician bias. It would also be difficult to comment on the weight loss aspect of exenatide, in view of the concomitant reduction of other agents possibly contributing to the same effect.

Discussion

The efficacy of exenatide was first demonstrated in three large, phase 3, randomized controlled trials.[7–9] These registration trials (AMIGO) had included approximately 1440 patients in total, with approximately 450 patients in the 10 μg/day study arm.[7–10] Our numbers were significantly smaller than these trials but the patient characteristics were broadly similar. Graphical representation of the comparison is shown in Figure 3.

The overall A1C reduction in our analysis (0.5%) was lesser than that compared with the clinical trials (0.78–0.86%). Weight loss was greater in our analysis (6.6 kg) compared with registration trials where weight loss varied from −1.6 to −2.8 kg. The baseline BMI in our group of patients was higher and

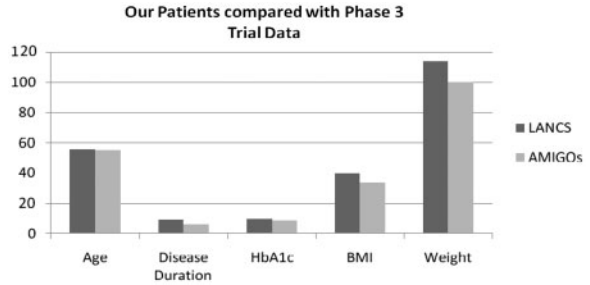

Figure 3. Comparison with clinical trials.

92% of our patients had a BMI > 30, which may explain the greater degree of weight loss.

Patients with a baseline BMI > 40 showed a mean reduction in BMI of 3.25 kg/m^2 (±1.31), while those with a baseline BMI < 40 showed a smaller reduction at 6 months of 1.45 kg/m^2 (±2.3).

Sixty-three per cent of our patients had a baseline HbA1c > 9%. Patients with a baseline HbA1c > 9% (75 mmol/mol) achieved a mean reduction in Hba1c of 0.84% (9 mmol/mol), while those with a baseline Hba1c < 9% (75 mmol/mol) paradoxically showed a mean increase in Hba1c of 0.15% (2 mmol/mol). Heterogeneity in response was observed, as in other trials, with some patients showing an increase in Hba1c or weight.

Two studies comparing insulin and exenatide have suggested that patients with longer duration of diabetes may not experience as much benefit with exenatide.[11,12]

One of these studies was a 16-week study, where exenatide was substituted for insulin in 29 patients. Of the exenatide-treated patients, 62% maintained glycemic control (defined as increase in hba1c of <0.5%), compared with 81% of the insulin-treated patients. Average duration of diabetes in this study was 11 ± 7 years. The investigators suggested that patients with longer disease duration may show deterioration in glycemic control if exenatide was substituted for insulin therapy.[11]

In a randomized, open-label, 24-week trial, subjects failing to achieve glycemic control with metformin and a sulphonylurea were randomized to receive insulin aspart or exenatide. Glycemic control achieved with insulin aspart was superior to that with exenatide. More subjects achieved HbA1c < 7% and ⩽ 6.5% in the insulin group than in the exenatide group (HbA1c ⩽ 6.5%: 25% vs. 8%, $P = 0.0004$). The investigators concluded that with the higher baseline Hba1c and longer duration of the disease, subjects may not have had sufficient β-cell function for a GLP-1 mimetic to be effective.[12]

In our group of patients, those with diabetes for <10 years achieved a mean reduction in Hba1c of 0.8% (9.3 mmol/mol), while those with diabetes

for >10 years achieved a lesser Hba1 reduction of 0.1% (1.1 mmol/mol).

Studies comparing exenatide with insulin have shown interesting results.[13–15]

When exenatide was compared with biphasic insulin aspart, Hba1c levels after 1 year were similarly reduced in both groups, with no difference in change of fasting plasma glucose. But exenatide-treated patients showed a statistically significant decline in body weight ($P<0.001$, between-group difference −5.4 kg).[13]

A 26-week, randomized trial comparing the addition of exenatide or glargine in 551 patients suboptimally controlled on metformin or sulphonylurea, again showed similar Hba1c reductions of 1.11%. But body weight decreased by 2.3 kg in the exenatide group as against an increase of 1.8 kg in the insulin group.[14]

Similarly, in the HEELA study, exenatide and glargine for 26 weeks did not demonstrate a significant difference in Hba1c improvements, but had divergent effects on body weight (−2.73 vs. +2.98, respectively, $P<0.001$).[15]

The above studies suggest that exenatide is as effective an agent as insulin in achieving glycemic control, but exenatide has the added advantage of weight loss. In our analysis, when the two drugs were combined together, patients on insulin continued to lose weight. We eagerly await large prospective studies, which would support the theory that this weight loss with exenatide translates into reduction of obesity-related cardiovascular risk.

Exenatide has also been shown to sustain improvements in β-cell function and β-cell mass in animal studies.[16] Bunck and associates compared the effects of exenatide and insulin glargine on β-cell function in 69 metformin-treated patients with type 2 diabetes who were randomized to receive exenatide or insulin glargine. Exenatide reduced body weight compared with glargine (difference −4.6 kg, $P<0.0001$). After 1 year of treatment, the two groups of patients achieved similar reductions in $HbA_{1c.}$ However, first- and second-phase glucose-induced C-peptide secretion was 2.46-fold (95% CI 2.09–2.90, $P<0.0001$) greater after a 52-week exenatide treatment compared with insulin glargine treatment.[17]

In our cohort of patients, when exenatide was combined with insulin, the results for glycemic control were not as promising as the results for weight loss. One explanation for this observation is that the insulin dose was reduced more than necessary in an attempt to prevent hypoglycemia on this combination, which led to an increase in HbA1c results. The increase in Hba1c in our patient group though, contradicts other papers, which showed an improvement in Hba1c even when combined with insulin; however, all three studies had a larger number of patients on the combination of exenatide and insulin.[18–20] Thus, solely based on the findings of our observational study, it would not be fair to say that the combination of exenatide and insulin is not beneficial.

In the study by Yoon *et al.*, 188 patients who were being treated with insulin and exenatide showed a 2.4 kg (5.1) mean reduction in weight at 6 months, with weight loss reaching a mean of 6.2 kg (9.7) at 18 months. An increase in weight was observed after 18 months, but it still remained lower than the baseline. They also showed a 0.54% (1.37%) reduction in Hba1c at 18–27 months.[18]

Sheffield *et al.*[19] reviewed 124 patients on exenatide and insulin and found a 0.87% ($P<0.001$) reduction in Hba1c at the end of 1 year with a mean weight loss of 5.2 kg ($P<0.001$), but this was offset by a 36% discontinuation rate.

In another retrospective analysis, when 38 patients were given exenatide in addition to insulin for 26 weeks, mean body weight decreased by 6.46 kg and Hba1c reduced by 0.6% ($P=0.007$).[20]

Overall, our retrospective review shows that adjuvant treatment with exenatide is associated with reductions in weight, BMI and Hba1c over a 6-month period in patients on maximum oral therapy. But prospective controlled trials are needed to ascertain the benefit of exenatide in patients already on insulin.

Conflict of interest: JDS has received an honorarium for a lecture from Eli Lilly.

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