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Liraglutide pancreatitis: The ABCD nationwide liraglutide audit

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Abstract

Introduction: There is concern that glucagon-like peptide-1 (GLP1) receptor agonists may be associated with acute pancreatitis. The data from the ABCD nationwide liraglutide audit (November 2009–June 2013; 6010 patients) provide an opportunity to assess the extent of the problem in routine clinical practice in the UK.

Methods: At every patient visit, audit-contributors were invited to submit, via an electronic form, clinical data collected as part of routine clinical practice, including data on possible side effects of treatment. Cases of 'possible pancreatitis' were identified and we contacted the centres concerned to obtain full details.

Results: To date, the audit has monitored 3720 years of exposure to liraglutide. There were four cases of possible pancreatitis documented from the 6010 patients on liraglutide: three patients had likely causes of pancreatitis identified and one patient had no aetiological cause. This sole case represents an incidence of 0.027/100 patient-years of exposure to liraglutide.

Conclusion: In cases of acute pancreatitis of a patient on liraglutide, if another cause can be found (usually gall stones associated with obesity), the drug is not be necessarily culpable. People with Type 2 diabetes are at greater risk of acute pancreatitis (hazard ratio between 1.5 and 2.8). Thus, the possibility of liraglutide-associated pancreatitis in 'real-world' clinical practice (0.027/100 patient years) represents a very small risk.

Keywords

Diabetes; exenatide; gall stones; glucagon-like peptide-1; GLP-1 receptor agonist; incretins; liraglutide; obesity; pancreatitis; risk; side effects; Type 2 diabetes

Introduction

Recent articles in the *British Medical Journal*[1–6] and elsewhere[7,8] have resurfaced the issue of a possible association between acute pancreatitis and treatment with GLP1-based therapies in patients with Type 2 diabetes.

In 2008 the UK's diabetologists, via their association (Association of British Clinical Diabetologists (ABCD)), launched an initiative to evaluate new diabetes treatments with regard to their safety and efficacy in 'real-world' clinical practice, via an audit programme. Since 2009, the ABCD nationwide liraglutide audit has been on-going, and much is being learned;[9] data from this audit provide an ideal opportunity to assess the extent to which liraglutide may be associated with acute pancreatitis in UK patients.

Methods

In November 2009, ABCD invited diabetes physicians across the UK to submit data on their diabetes patients whom had been treated with liraglutide therapy.

Abbreviations:

ABCD	Association of British Clinical Diabetologists
BMI	body mass index
GLP-1	glucagon-like peptide-1
HbA1c	glycated haemoglobin

Anonymised data in a standardised electronic format were submitted to a central database. The requested information included:

[1]City Hospital, Birmingham, UK
[2]Rockingham General Hospital, Perth, Australia
[3]Gloucestershire Royal Hospital, UK
[4]Forth Valley Royal Hospital, Larbert, UK
[5]Southern General Hospital NHS Trust, Glasgow, UK
[6]King's College London, UK

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- Baseline data on demographics (age, gender and ethnicity);
- Disease information (duration of diabetes);
- Baseline and follow-up data on medications (diabetes and obesity drug names and doses);
- Key measurements (height, weight and blood pressure); and
- Blood tests (Hba1c, lipids, alanine aminotransferase and creatinine).

The data were provided as permitted by availability in routine clinical practice, without any extra tests being requested specifically for the audit. For the follow-up visit records, audit contributors were also prompted to provide information on adverse events, either as a reason for stopping liraglutide or as a free text comment. The data submission remains on-going.

On 1 July 2013, the data was interrogated with an electronic search, using the term 'pan' to capture all entries of 'pancreatitis'. We excluded cases where the 'pan' referred to other issues or conditions, as were cases in which pancreatitis or pancreas-related issues were mentioned at baseline only (prior to liraglutide commencing as therapy). We followed up all remaining reports of pancreatitis occurring in liraglutide-treated patients in the audit, by contacting the reporting centre. The centres involved were asked to study the patient's hospital notes and investigation reports in detail, to obtain as much information as possible about these pancreatitis cases, and to supply this information to ABCD whilst maintaining patient confidentiality.

To provide a comparison between ABCD audit patients and those in the Phase 3 clinical trials, the baseline characteristics of the patients in those trials were determined from the trial reports.[10–15]

Results

By 1 July 2013, the ongoing liraglutide audit had collected data on 6010 patients from 111 centres. Table 1 shows the baseline characteristics of patients treated with liraglutide in the UK, whom were reported in the audit.

There were 17 cases of 'pan' found in the free-text search; we excluded 11 of these cases, from further evaluation, for the following reasons: previous *pan*creatitis reported at baseline, prior to commencement of liraglutide, with no follow-up issues of concern (8 cases); *pan*ic attacks (2 cases); and *pan*hypopituitarism in a treated acromegaly patient (1 case). Of the remaining six cases identified by '*pan*', it turned out that they were actually four patients, as two of the four had the same episode of '*pan*creatitis' mentioned twice in their electronic record. Therefore, four cases of possible acute pancreatitis were further evaluated.

After local clinicians at the centres had checked the hospital records and investigation reports, three cases were found to have likely alternative explanations (gall bladder disease, gall stone pancreatitis prior to liraglutide, acute abdominal illness of uncertain cause). Table 2 has a summary description of these 'pancreatitis cases'.

Table 1. Baseline characteristics of liraglutide-treated patients reported in the ABCD UK Liraglutide Audit.

Dates of Audit	2009 – 2013
Centres	111
Contributors	455
Patients	6010
Male (%)	53.7
White Ethnicity (%)	84.2
Age (yrs)	55.6 ± 11.0
Duration of diabetes (yrs)[a]	9.0 (5.0 – 13.0)
Baseline HbA1c (%)	9.4 ± 1.7
BMI (kg/m^2)	38.8 ± 7.2
Weight (kg)	110.6 ± 22.7
Number of follow-up visits[a]	2 (2 – 3); Range: 0 – 15

[a]Reported as: % or mean ± SD or median (IQR)
ABCD: Association of British Clinical Diabetologists; IQR: interquartile range; BMI: body mass index; HbA1c: glycated hemoglobin; SD: standard deviation.

To date, this on-going audit has monitored 3720 years of exposure to liraglutide. There was only one case of acute pancreatitis, in whom we identified no other causes for pancreatitis. This case might therefore be related to liraglutide therapy, representing an incidence of 0.027/100 patient-years of exposure to liraglutide. The total incidence of pancreatitis (ie: $n = 4$, including the three cases with another cause or who probably did not have pancreatitis) was 0.108/100 patient-years of exposure to liraglutide.

Combining the data from the Phase 3 clinical trials of liraglutide[10–15] showed that patients had a mean HbA1c of 8.5% and BMI of 31 kg/m^2, respectively. By contrast, our cohort of patients had a markedly higher baseline HbA1c and they were considerably heavier (mean ± SD: HbA1c 9.4 ± 1.7%; BMI 38.8 ± 7.2 kg/m^2) (Table 1).

Discussion

This analysis of the ABCD nationwide liraglutide audit data evaluated the cases of pancreatitis reported in UK patients on liraglutide therapy. In the same way as for the ABCD nationwide exenatide audit (2007–2009),[16] a strength of this audit was the ability to follow up, in detail, on reported cases of pancreatitis to establish the history, investigation results, disease severity and likely cause. By investigating the 'possible pancreatitis' cases further with the local clinicians, we were able to accurately attribute the most

Table 2. Reports of pancreatitis in the ABCD nationwide liraglutide audit.

Pancreatitis?	Summary
Possible liraglutide pancreatitis	Male, 59 years, BMI 36.7 kg/m^2. Admitted with abdominal pain and vomiting ***28 days after starting liraglutide.*** Amylase raised at 1095 U/L (normal range 28 – 100 U/L), thin-walled gallbladder with no gallstones on ultrasound scan, CT scan suggestive of acute pancreatitis. No history of excessive alcohol consumption. Triglycerides not measured.
Liraglutide pancreatitis unlikely	Male, 68 years, BMI 34.9 kg/m^2. Gallstone pancreatitis and pancreatic pseudocyst prior to liraglutide. Had abdominal pains (not investigated) ***6 days after starting liragltutide***: concerned regarding possiblity of pancreatitis (was warned regarding risks) and therefore stopped treatment, as a precaution.
Acute on chronic pancreatitis with gallbladder disease and history of increased alcohol intake	Male, 52 years, BMI 34.4 kg/m^2. Increased alcohol intake in the past. Admitted ***5 months after starting liraglutide*** *(exenatide for 2 years prior)* with abdominal pain, raised bilirubin (40 µmol/L) and normal amylase. CT/USS scans compatible with acute (no necrosis) on chronic pancreatitis (asymptomatic for the latter); there was biliary sludge and the common bile duct was at upper limit of normal. Post discharge, had 'biliary colic' until cholecystectomy 7 months later.
Not a convincing case of pancreatitis	Male, 44 years, BMI 43.7 kg/m^2. Abdominal pain, fever, raised white blood cell count and vomiting ***15 weeks after starting liraglutide***. Initially left iliac fossa pain treated as diverticulitis, but failed to respond to oral antibiotics. Later, right hypochondrial pain and positive Murphy's sign responded to parenteral antibiotics. USS normal gallbladder. CT scan result: 'possible recent acute pancreatitis'. Five normal amylase measurements during the 8-day illness.

ABCD: Association of British Clinical Diabetologists; BMI: body mass index; CT: computerised tomography; USS: ultrasound scan.

likely underlying cause in each case. In doing so, we found alternative causes for the 'pancreatitis' in three out of four patients (Table 2) whom, in a less rigorous audit, might have been taken as true liraglutide-induced pancreatitis cases.

Limitations of this liraglutide audit included the possibility of reporting bias. Given the notoriety of GLP-1-related therapies as possible causes of pancreatitis, we find it hard to imagine contributors to the audit would not report possible cases. More likely as an issue is the need for the contributors to have knowledge of all pancreatitis episodes, in order to be able to report them. As the data were collected in routine clinical practice by busy clinical staff, it may well be that some cases were not reported, because of a lack of awareness that such an event had occurred. Furthermore, there was no specific question during the follow-up questionnaires as to whether the patient had an episode of pancreatitis while on liraglutide. Instead, the free-text comment allowed for any adverse events to be reported, which is important to the integrity of the adverse events data in general; as otherwise, we may miss other important adverse events. Nevertheless, we believe that the occurrence of pancreatitis would have, in most cases, led to discontinuation of liraglutide and that would have alerted clinical staff looking for a cause for cessation of the therapy.

People with diabetes are more likely to develop acute pancreatitis than people without diabetes: reports are of hazard ratios of 1.5,[17] 2.1[18] and 2.8.[19] Gallstones or alcohol are the most frequent causes of acute pancreatitis, with other causes including drugs, infectious agents, hypertriglyceridemia, trauma and pancreatic ductal obstruction.[20–22] Approximately 10% to 25% of cases of acute pancreatitis have no readily identifiable cause and are termed 'idiopathic'. Many of these cases are eventually shown to be caused by microlithiasis.[20–22] When considering pancreatic cases without any obvious alternative cause, it is worthwhile to remember that because 'idiopathic' acute pancreatitis is so common, liraglutide may not necessarily be the aetiological factor, even if no other cause is found.

The ABCD exenatide[16] and liraglutide (Table 2) audits showed that in most cases of pancreatitis in patients taking liraglutide or exenatide, another cause for the pancreatitis can be found, such that these drugs do not need to be implicated. The patients in the ABCD liraglutide audit were considerably heavier and had considerably worse glycaemic control (Table 1) than the patients in the Phase 3 clinical trials with these agents.[10–15] The same was true for the exenatide audit.[16,23] Obesity is associated with gall bladder disease and hypertriglyceridaemia, both of which are risk factors for acute pancreatitis.[20-22,24,25] Hence, not surprisingly, most of the reported cases of pancreatitis in both audits had causes related to obesity, especially gall bladder disease.

It is important that when alternative causes, such as gall stones, are identified as the causative agent, a balanced view is taken. For instance, it may not be necessary in all cases to stop liraglutide treatment long-term and implicate it as the root cause, if another more likely reason is present. If the actual root cause of the acute pancreatitis is not identified, there will be a missed opportunity to provide targeted treatment to expedite

Table 3. Acute pancreatitis and GLP-1 receptor agonists.

	N	Exposure (Years)	All cases of pancreatitis	Unexplained cases of pancreatitis
ABCD nationwide liraglutide audit	6010	3720	0.108	0.027
Combined clinical trials of liraglutide	7043	5006	0.160	0.040
Patients on active comparators in the combined clinical trials of liraglutide	1901	1418	0.071	0.071
ABCD nationwide exenatide audit	6717	3336	0.120	0.030

Comparison between the reported rates of acute pancreatitis (cases/100 patient-years of exposure) in the ABCD Nationwide Liraglutide Audit and those in the combined clinical trials of liraglutide,[30] including the rates of those on active comparators in those trials.[30] We also show, for comparative purposes, the results from the ABCD Nationwide Exenatide Audit.[32] The 'all cases' rates are within the predicted range for rates of acute pancreatitis in patients with Type 2 diabetes (0.05 – 0.56 cases/100 patient years of exposure).[17-19,31] Cases of otherwise unexplained acute pancreatitis in patients on liraglutide (or exenatide) might be related to the liraglutide (or the exenatide), or they might be simply 'idiopathic' acute pancreatitis cases, such cases being common.[20-22]

ABCD: Association of British Clinical Diabetologists; GLP-1: glucagon-like peptide 1.

recovery, bearing in mind that acute pancreatitis is a condition known for its considerable morbidity and mortality (the latter may be as high as 5%).[26] Furthermore, the patient in question may miss out on the possible benefit from the GLP-1 receptor agonists in the future, if the latter are erroneously implicated as a cause of harmful effects. This is true not only for possible liraglutide-associated pancreatitis cases, but for any condition in which a drug, which may confer benefit to a patient, is erroneously listed on record as an 'allergy', e.g. such as with incorrectly labelled penicillin allergies in septicaemic patients or incorrectly labelled 'statin intolerance'.

The suggestion that GLP1-related therapies cause pancreatitis[1–8] was recently challenged.[27–29] In keeping with this, our 'real world' audit found that the incidence of unexplained acute pancreatitis was low, at 0.027/100 patient-years of exposure to liraglutide. Taking all the cases, including the ones unlikely to be related to liraglutide, the incidence was only 0.108 cases/100 patient-years of exposure. Combining the data from the clinical trials of liraglutide, there were 7043 patients with 5005.7 years of exposure to liraglutide, and eight reported patients whom might have had acute pancreatitis, making a total incidence of 0.160 cases/100 patient-years of exposure.[30] After examination of the patients' histories, six of the eight patients had illness deemed unlikely to be linked to liraglutide treatment, leaving two possible liraglutide cases remaining (0.040 cases/100 patient-years of exposure).[30] Amongst the patients on active comparators in these studies (1901 patients, with 1418.4 years of exposure) there was a single case of acute pancreatitis in which the cause was unclear (0.071 cases per hundred patient-years of exposure).[30] Comparisons between the results from the ABCD nationwide audit and those from the combined clinical trials are shown in Table 3. The 'all cases' rates are low and within the predicted range for rates of acute pancreatitis in patients with Type 2 diabetes (0.05 – 0.56 cases/100 patient-years of exposure).[17–19,31]

The rates of acute pancreatitis found in the ABCD nationwide liraglutide audit are similar to those found in the ABCD nationwide exenatide (2007 – 2009) audit[32] (Table 3). It has been well argued that the benefits of GLP-1-related therapies far outweigh the potential risks.[27] It is clear that clinicians in the UK who are treating patients with exenatide and liraglutide, see considerable benefits in terms of reductions in weight and Hba1c; and reduction in other therapies, including insulin.[23,33,34] This audit is in keeping with the everyday experience of clinicians who treat 'real-world' Type 2 diabetes patients on a daily basis and who see benefits with these agents. Those same clinicians hardly ever find their exenatide and liraglutide-treated patients experiencing acute pancreatitis, and when they do,

Key messages

The key messages obtained in this audit:

- The overall incidence of acute pancreatitis in this audit was 0.108/100 patient years of exposure to liraglutide. This is low and within the predicted range for rates of acute pancreatitis in patients with type 2 diabetes (0.05–0.56 cases/100 patient years of exposure).
- The incidence of unexplained pancreatitis was 0.027/100 patient-years of exposure to liraglutide which is extremely low. It should be remembered that in day-to-day practice many cases of acute pancreatitis cases are 'idiopathic', reducing the need to implicate liraglutide even in otherwise unexplained cases.
- In most cases of pancreatitis in patients taking either liraglutide or exenatide, another cause can be found, usually obesity-associated gall bladder disease.

there is usually another cause: in particular, gall stones. We await the long-term cardiovascular outcome study with liraglutide,[35] to understand more fully the true balance of risks and benefits in this agent.

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Declaration of conflicting interest

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CJGK received speaker fees, consultancy fees and/or educational sponsorship from a number of companies, including Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Novo Nordisk and Takeda.

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CS and MLC declare they have no conflicts.

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Appendix: ABCD nationwide liraglutide audit contributors

The following are those whom we know about.

ABCD nationwide liraglutide audit – initial setup, maintenance and nationwide analysis: Ryder REJ, Walton C, Thong KY, Sen Gupta P, Cull ML, Mills AP. Statistician: Blann A.

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