Sandwell and West Birmingham Hospitals NHS Trust

Liraglutide and acute pancreatitis in the Association of British Clinical Diabetologists (ABCD) nationwide liraglutide audit

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Introduction

- During the first quarter of 2013, concerns have again been expressed that glucagon-like peptide-1 (GLP-1) therapies may be associated with an increased incidence of acute pancreatitis.[1–3] ABCD's previous nationwide exenatide audit obtained data on 6717 patients (2007–2009) from 126 centres across the UK.[4] The audit revealed only one mild unexplained case of acute pancreatitis in these exenatide-treated patients.[5]
- Since 2009, ABCD has been running a nationwide liraglutide audit to gather data on the safety and efficacy of liraglutide in real clinical practice in the UK.[6] The data from this audit provide an ideal opportunity to assess the extent to which liraglutide may be associated with acute pancreatitis. By 23 March 2013 the ongoing liraglutide audit had collected data on 5948 patients from 89 centres. At every visit contributors to the audit were invited to submit data on possible side effects from liraglutide.

Methods

- ABCD has access to anonymised data on the 5948 patients so far submitted to the audit. Reported cases of possible pancreatitis were identified in the database and the centres reporting these 'possible pancreatitis' cases were contacted to obtain full details.

Results

- The patients treated with liraglutide and reported in the audit were found to have much more poorly controlled diabetes and be heavier (mean±SD HbA_{1c} 9.4±1.7%; BMI 38.8±7.3 kg/m^2) than patients in the combined clinical trials of liraglutide (mean HbA_{1c} 8.5%, BMI 31 kg/m^2). There were four cases of possible acute pancreatitis reported but three of these had likely alternative explanations (gall bladder disease, pancreatitis prior to liraglutide, acute abdominal illness of uncertain cause). To date the audit has monitored 3713 years of exposure to liraglutide. There was thus only one case of acute pancreatitis that we identified in which there were no other causes for pancreatitis found. This case might therefore be related to liraglutide therapy, representing an incidence of 0.027/100 patient-years of exposure to liraglutide.

Table 1. Audit characteristics

Dates of audit	**2009–2013**	
Centres	89	
Contributors	500	
Patients	5948	
Male (%)	53.9	
White ethnicity (%)	89.6	**vs. Combined Clinical Trials Liraglutide**
Age (years)	55.6±11.0	
Duration of diabetes (years)*	9.0 (6.0–13.0)	
Baseline HbA_{1c} (%)	9.4±1.7	8.5
Baseline BMI (kg/m^2)	38.8±7.2	31
Baseline weight (kg)	110.6±22.8	
Number of follow-up visits*	2 (2–3); Range: 0–16	

BMI, body mass index.
Reported as: % or mean±SD or median (IQR)*

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Table 2. The reported four cases of possible acute 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, 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 (had been warned regarding risks) and therefore stopped 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 necosis) 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 convincing case of pancreatitis	Male, 44 years, BMI 43.7 kg/m^2. Abdominal pain, fever, raised white blood cell count and vomiting. 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 "possible recent acute pancreatitis". Five normal amylase measurements during 8-day illness.

CT, computerised tomography; USS, ultrasound scan.

Conclusion

- In most cases of pancreatitis in patients taking either liraglutide or exenatide, another cause for the pancreatitis can be found such that the drug does not need to be implicated.
- Overall, the incidence of unexplained pancreatitis with liraglutide (0.027/100 patient-years of exposure to liraglutide in this audit) seems to be very 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 if no other cause is found.[7,8]
- Considering the benefits of GLP-1 receptor agonists in terms of weight loss, improved glycaemic control and reduction in other diabetes therapies, including insulin, the possibility of pancreatitis in real clinical practice seems to represent a very small risk in comparison to the potential benefit gained from its use.
- We await the results of the ongoing cardiovascular outcome studies with these agents to give us hard endpoints with regard to risks and benefits.[9]

References

1. Gale EA. *BMJ* 2013;346:f1263.
2. Cohen D. *BMJ* 2013;346:f1304.
3. Singh S, Chang HY, Richards TM *et al*. *JAMA Intern Med* 2013;173(7):534–9.
4. The Association of British Clinical Diabetologists (ABCD). ABCD nationwide exenatide audit – papers, presentations, posters, abstracts. www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsExenatide.htm. Accessed 16 April 2013.
5. Ryder REJ, Thong KY, Cull ML, *et al*. on behalf of the ABCD nationwide exenatide audit contributors. *Practical Diabetes International* 2010;27(8):352–357.
6. The Association of British Clinical Diabetologists (ABCD). ABCD nationwide liraglutide audit – papers, presentations, posters, abstracts. www.diabetologists.org.uk/GLP1_Audits/PresentationsPostersAbstractsLiraglutide.htm. Accessed 16 April 2013.
7. Venneman NG, van Brummelen SE, van Berge-Henegouwen GP *et al*. *Ann Hepatol* 2003;2(1):30–5.
8. Sekimoto M, Takada T, Kawarada Y *et al*. *J Hepatobiliary Pancreat Surg* 2006;13(1):10–24.
9. Novo Nordisk. Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation (LEADER®). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2013 Apr 16]. Available from: http://clinicaltrials.gov/show/NCT01179048M. NLM Identifier: NCT01179048

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