LESSON OF THE WEEK

Artificially low HbA_{1c} associated with ribavirin

Michael Robertson

Marcham Road Health Centre, Abingdon OX14 1DB

Michael.robertson@gp-k84041.nhs.uk

BMJ 2008;336:505
doi:10.1136/bmj.39457.828287.47

Ribavirin treatment for hepatitis C may artificially lower HbA_{1c} and give misleading information about glycaemic control

Introduction

Glycated haemoglobin (HbA_{1c}) is widely used to assess glycaemic control in diabetes. Reynolds et al recently pointed out that anaemia with reduced red cell life can cause misleadingly low HbA_{1c} values.[1] In the case presented here, ribavirin treatment for coexisting hepatitis C infection was associated with suppression of HbA_{1c} in a patient with diabetes mellitus.

Case report

A 55 year old man presented to his general practitioner with dark urine and concern about possible liver disease. Liver function tests showed that alkaline phosphatase was normal but alanine aminotranferase was raised (259 U/l; normal range 10-45 U/l), as was γ-glutamyltransferase (237 U/l; normal range 15-40 U/l). Hepatitis serology was positive for hepatitis C infection and the patient was referred for specialist advice.

A liver biopsy confirmed established cirrhosis consistent with chronic hepatitis C infection, and he was recommended to start treatment with peginterferon alfa and ribavirin and given an estimated chance of virological cure of 45-50% after one year of treatment.

Before starting this treatment he presented in primary care with a three week history of polyuria and polydypsia, and recent 7 kg weight loss, heavy glycosuria, and a random blood glucose concentration of 17.6 mmol/l. This is diagnostic of diabetes, and at this time HbA_{1c} was 11% (normal non-diabetes range 4.5-6.2%).

We tried to manage his diabetes with metformin; as there were concerns about using this agent in a patient with cirrhosis, this was discussed with his liver specialist. On review a few days later he had uncontrolled blood sugars of between 12 and 25 mmol/l and 2+ ketonuria, and he had lost more weight. He was therefore started on insulin, using a twice daily mixed insulin regime with appropriate support from the primary care diabetes team. Within six weeks his blood sugar had normalised; he felt better and was beginning to gain weight. At this point his treatment with peginterferon and ribavirin was started by the liver unit.

Three months after starting insulin his reported control was excellent, with home blood glucose readings of 4-9mmol/l, and because of hypoglycaemic episodes his initially high daily requirement of 80 units of insulin was reduced to 40 units. Even so, it was a surprise to receive an HbA_{1c} result of 4.9%. His haemoglobin was marginally low at 113 g/l but the importance of this was not realised immediately.

Almost a year after the patient started insulin his home blood glucose results were consistently 4-7 mmol/l, but his HbA_{1c}—at 4.4%—was the lowest seen in a clinic of more than 300 patients with diabetes and below the usually quoted reference range for people without diabetes. At about this time Reynolds et al published an article on misleading HbA_{1c} levels in conditions such as haemolytic anaemia,[1] and it was noticed that his haemoglobin, which had been 164 g/l before antiviral treatment, was consistently running at 115 g/l during monitoring. The *British National Formulary* mentions haemolytic anaemia as a side effect for ribavirin.[2] A web search using PubMed clinical queries (accessed via nelh.nhs.uk > pubmed > pubmed resource > clinical queries) found a study showing that ribavirin treatment dramatically reduces red cell life, from 120 days to 40 days on average.[3] Since glycosylation of haemoglobin continues during the life of the red cell, this dramatically shortened survival is the likely mechanism for the lowering of the HbA_{1c}. A check of fructosamine was requested, and the result of 317 μmol/l (normal range 202-285 μmol/l) confirmed that glycaemic control was at that time only average.

After one year of antiviral treatment, virological cure had not been achieved and the ribavirin and peginterferon were stopped. Three months later his haemoglobin concentration had recovered to 155 g/l and fructosamine had dropped slightly to 296 μmol/l, but measured HbA_{1c} had increased from 4.4% to a more credible 6.5%. Home blood glucose readings were unchanged. It is likely, but unproved, that the suppression of both haemoglobin and HbA_{1c} were caused by haemolysis due to ribavirin treatment.

Conclusions

The National Institute for Health and Clinical Excellence has now recommended that treatment with interferon and ribavirin be extended to patients positive for hepatitis C even in the absence of established cirrhosis,[4] and it estimates that as many as 500 000 patients may be eligible. Of these, 3-4% may have diabetes and therefore this interaction will occur again. If it is not recognised it may lead to inappropriate advice on diabetes management based on misleading HbA_{1c} concentrations.

Competing interests: None declared.

1 Reynolds TM, Smellie WSA, Twomey PJ. Glycated haemoglobin (HbA1c) monitoring. *BMJ* 2006;333:586-8.
2 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British national formulary.* London: BMA, RPS, 2006:335. (No 52.)
3 Virtue MA, Furne JK, Ho SB, Levitt MD. Use of alveolar carbon monoxide to measure the effect of ribavirin on red blood cell survival. *Am J Haematol* 2004;76:107-13.
4 National Institute for Health and Clinical Excellence. Peginterferon alfa and ribavirin for the treatment of mild hepatitis C. 2006. www.nice.org.uk/guidance/TA106.

Accepted: 5 April 2007