Hypo review

Melissa P Ford considers a review of hypos by Stephanie Amiel and David Kerr

This session took place at the 64th Scientific Sessions and Annual Meeting of the American Diabetes Association, Orlando, Florida, on Monday 7 June 2004.

Recognizing and Reversing Hypoglycaemia Unawareness: Clinical Implications

Monday 7 June 2004, 8am-10am

Chair: William Clarke, MD (University of Virginia)

Stephanie Amiel, BS, FRCP, MD (University of London - Guy's/King's/St. Thomas's)

David Kerr, MD (Bournemouth/University of Southampton)

(The session was crowded, but not absolutely packed)

I. **Stephanie Amiel: Recognizing and Reversing Hypoglycaemia Unawareness: Clinical Implications**

1. We usually think in terms of Whipple's Triad when we identify hypoglycaemia
    a. Symptoms of low blood sugar
    b. Measurably low blood sugar
    c. Relief of symptoms by administration of glucose
        i. Whipple was a surgeon whose work focused on insulin-secreting tumours
2. What do we do when the patient cannot sense the hypoglycaemia?
    a. At a blood glucose of 4.0 mmol/L, epinephrine and a sympathetic nervous system response should be present
    b. At 3.0 mmol/L, acute symptoms and cognitive impairment arise
    c. At 2.0 mmol/L, EEG changes occur
    d. At 1.0 mmol/L, the patient can fall into a coma
        i. If you do not have an automatic reduction in insulin secretion in hypoglycaemia, the liver does not release glucagon
        ii. As many as 25% of long-term diabetes patients may be hypoglycaemia unaware, whether type 1 or insulin-requiring type 2.
        iii. Exogenous insulin is the problem (sulfonylureas to a lesser extent)
3. Hypoglycaemia unawareness comes from too much insulin, lack of counterregulation, and possibly a genetic predisposition.
    a. Counterregulatory hormone deficiencies can also arise from hypothyroidism, Addison's disease, hypopituitarism, and growth hormone deficiency.
    b. Insulin excess and failure of glucose absorption are the other two main causes
    c. Hypoglycaemic unaware people have less of an epinephrine response in hypoglycaemia
        i. It's not difficult to induce counterregulatory failure through frequent hypoglycaemia
4. Cranston et al. published in the Lancet (1994), that it is possible to restore hypoglycaemia awareness by keeping blood glucose levels >3.0 mmol/L
    a. 3.0 mmol/L is the blood glucose level that triggers epinephrine
5. How do you recognize/identify hypoglycaemic unawareness?
    a. Ask patients about both severe and mild low blood sugars
        i. Ask parents, children, or spouses (as appropriate) if the patient had low blood sugars that he/she did not detect personally
    b. When patients have frequent low blood glucose levels, ask how often they're below 3.0 mmol/L
    c. Quantify the hypoglycaemic burden: are there any patterns to it so it may be stopped?
6. In Diabetes (2003), Ryan et al. published a hypoglycaemia score, used as a criterion for islet cell transplant. The greater the hypoglycaemia, the higher the score and the more likely the

individual is to receive islets

7. Patients with frequent hypoglycaemia should be investigated on the bases of diet, exercise, alcohol, hormones, any coeliac disease – both historically and on the day of interview
    a. Patient-reported causes of hypoglycaemia at emergency rooms in the UK:
        i. 12% exercise
        ii. 20% alcohol
        iii. 17% insulin
        iv. 51% thought they had not eaten properly
    b. Fanelli et al. (Ann. Intern. Med.) showed that moving pre-dinner NPH (isophane) insulin to bedtime is really successful for preventing nocturnal hypoglycaemia
    c. Eliminating hypoglycaemia cuts down the amount that patients snack, which is better for weight control and increases patients' satisfaction with treatment
8. The German Dusseldorf program reduces HbA1c and hypoglycaemia in comparison to the DCCT protocol, which lowers A1c but increases hypoglycaemia. The Dusseldorf program was translated into English as DAFNE (Dose Adjustment for Normal Eating)
    a. DAFNE is a 5-day, outpatient curriculum that teaches flexible basal-bolus insulin replacement.
    b. DAFNE reduces HbA1c and increases patients' quality of life
9. Patients can also be taught how to manage exercise
    a. Eat before sports, take less insulin at the time (reduce insulin pump basal rate), take 20% less NPH insulin at the next dose after exercise
10. Alcohol: patients should take more fast-acting insulin while drinking and reduce overnight basal dose by 20%
11. Patients need to learn not to overtreat hypoglycaemia to avoid giving themselves rebound hyperglycemia
12. Hypoglycaemia-prone patients can benefit from analogues (analogue insulins act more predictably than conventional insulins)
    a. Ashwell et al. published in *Diabetes* (2003) that HbA1c and hypoglycaemia could both be reduced – though low blood sugars not completely eliminated – on an analogue-only insulin regimen
13. We need to ask about hypoglycaemia, we need to help patients avoid hypoglycaemia, and we need to consider CSII (insulin pump therapy) if longer-acting insulins are causing or exacerbating hypoglycaemia.
    a. We need to consider islet cell transplants for the perhaps c.10% of patients whose hypoglycaemia is truly unmanageable.

II. David Kerr: Recognizing and Reversing Hypoglycaemia Unawareness: Clinical Implications

1. Causes of hypoglycaemia: in 13-17% of cases, too much insulin; in 26-70% of cases, patient error; in 19-38%, who knows??
2. Possible causes of hypoglycaemia: intensive insulin therapy, sleep, long duration of diabetes, alcohol/lifestyle, extremes of age, pregnancy
    a. Kerr takes a Sherlock Holmes approach: when you have eliminated the impossible, whatever remains, however improbable, must be the truth
    b. Self-reported symptoms may differ from those reported by bystanders
        i. Hypoglycaemic individuals may not realise that they are acting strangely
    c. Lifestyle, HbA1c, or iatrogenic factors may give clues to the cause of hypoglycaemia
        i. Shift workers, time-zone travellers, and heavy drinkers may be prone to hypoglycaemia
        ii. When HbA1c >10%, hypoglycaemia avoidance behaviours may be present
3. There are 3 different types of hypoglycaemic unawareness:
    a. No symptoms
    b. Symptoms but no idea what is going on
    c. Symptoms and cognition, but **inaction** (cf. locked-in syndrome); neuroglycopenia
4. Kerr thinks that looking at the patient's blood sugar and medication logbook shows physician's interest in the patient's self-care
    a. But keep in mind that lots of people lie in their logbooks. The blood glucose meter's memory, however, will not have the same rate of error
5. Kerr knows the lag times and poor detection of hypoglycaemia that make the CGMS less than fantastic, but he decided to do a study with it anyway.

    a. He discovered that his type 2 diabetic neighbour was hypoglycaemic almost all night long
    b. CGMS has helped Kerr's clinic figure out what is happening during night-time seizures
        i. Diabetologists almost always assume night-time hypoglycaemia when they hear the word *seizure*, but neurologists think *epilepsy* when they hear someone has had a seizure
    c. CGMS can also show both doctor and patient if a change to therapy is generally working - before and after glucose profiles can be compelling
    d. Kerr believes that implantable pumps with glucose sensors - closed loops - and disposable micropumps (like Starbridge Systems' project) are next on the horizon
6. Kerr summarized the National Institute for Clinical Excellence (NICE) guidance (no. 57) on insulin pump therapy, the rules for getting an insulin pump funded by the UK National Health Service
    a. HbA1c still >7.5 after a 3-month trial of insulin glargine (Lantus) or frequent hypoglycaemia requiring third-party assistance if A1c <7.5
7. Kerr has overseen 3 Disetronic Dia-Port implantations, which have not been uncomplicated. Recurrent infections are a problem
8. Kerr introduced the concept of sin: in diabetes, enjoyment of pleasurable foods, sex, alcohol, and caffeine can have profound physical effects. Many patients feel guilty a lot of the time
    a. Quotation from Richard Asher: It is easier to treat disease than to eliminate sin
9. Alcohol can cause reactive hypoglycaemia in susceptible individuals
    a. Alcohol interferes with hypoglycaemia detection and may diminish counterregulatory response
    b. After a night of heavy drinking, a diabetic patient is likely to experience a delayed hypoglycaemic reaction between 10 a.m. and 12 noon the following day - anticipation is key
10. Coffee can improve hypoglycaemia detection
    a. Caffeine reduces blood flow to the brain, creating a demand for glucose because caffeine interacts with adenosine. With caffeine on-board, an individual will have better hypoglycaemic symptoms - and a reduced risk of hypoglycaemia unawareness (See 2004 ADA abstract 379-PD)
    b. Caffeine may also be good for the heart: it reduces variances in heart rate, decreasing risk for arrhythmia

III. Discussion

1. How do we deal with hypoglycaemia in older people on insulin, especially type 2s? Amiel says to do what you would for a type 1 in the situation, and if you cannot get to a low end of the target range without unacceptable hypoglycaemia, revise the target range upwards. Kerr agrees.
2. Charles Fox from the UK asked if sometimes doctors and patients did not collude to explain addiction to hypoglycaemia by blaming unknown variables. Kerr suggested getting the significant other or a parent into the room, and if there's an argument when you ask about hypoglycaemia, that's an answer. Amiel pointed out that some people really do fear complications so much that they risk dangerously low blood sugars - those patients need more realistic education about risks and benefits of good control. On the other hand, she noted that there are people who really do enjoy the altered mental state of hypoglycaemia. They need liaison psychiatrists. (A liaison psychiatrist at King's, Amiel's hospital, views addiction to hypoglycaemia just as she sees any other addiction)
3. An anonymous person asked when physicians should just give up. Amiel and Kerr agreed that sometimes you don't achieve what you want with a patient, but it is not right just to give up trying.
4. Some people with non-diabetic hypoglycaemia insist on adhering to weird diets that make them ill - in them, acarbose may be helpful
5. In Denmark, there's work going on to determine an ACE-genotype cause of hypoglycaemia. Amiel thinks there are a few people who have a genetic predisposition to hypoglycaemia unawareness.
6. Question for the chair, William Clarke: What has become of BGAT (blood glucose awareness training)? Clarke says it will be on-line in the next 6 months at http://www.bgathome.com
7. Good anonymous point: lipohypertrophy can cause variable insulin absorption, making hypoglycaemia more likely. Kerr says you have to ask patients to undress and have a good

look at their injection sites

8. Anonymous question: Has anyone thought to study hypoglycaemic but not diabetic people and see what happens years down the road? Is it possible that hypoglycaemia can be a precursor to diabetes? Amiel says that would be difficult to do in real life, but yes, a lot of patients do have a history of symptoms when they are diagnosed. In the UK, ME [(Myalgic Encephalomyelitis (ME) - also known as Chronic Fatigue Syndrome (CFS)]; in Germany hypotension, and in the US hypoglycaemia are often pre-existing when people are diagnosed with diabetes. (Our cultures assess our symptoms and create our diseases in this example.)
9. An American questioner pointed out that in the UK, the slogan Make 4 the Floor was created to encourage people with diabetes not to run their blood sugars lower than 4 mmol/L - why did Amiel talk about 3? Amiel responded that 4 is indeed a better level than 3 for patient health, but in clinical studies 3.0 mmol/L is the threshold. Amiel tells her own medical students that 3.5 mmol/L is definite hypoglycaemia. Clarke added that 1 3.9 mmol/L blood glucose level doubles the risk of a repeat hypoglycaemic event in the next 24 hours
10. Another audience question: should patients have a bedtime snack? Amiel says that patients are often confused about why they are supposed to have a snack. A snack is supposed to prevent early-sleep-stage/first few hours of sleep hypoglycaemia, not to keep their glucose levels up through the night. Acarbose or cornstarch is a different tactic. There does not seem to be any study data comparing bedtime snack vs. no bedtime snack. Data showing that analogue insulins are better does not mention whether or not patients snacked
11. Amiel offered a caveat on analogues: while we're still learning how to use them, we should be careful about prescribing them. She wants to see how a new drug acts in a population for which it is specifically indicated before prescribing it to people who may or may not get any specific benefit from it.
12. Lastly, it is possible that the antibiotic quinolone can cause hypoglycaemia

Author: Melissa P Ford <mford@hotmail.com>. Melissa P Ford is not a medical professional. She has Type 1 diabetes and uses an insulin pump. The information given here is based on her own personal experience. More about Melissa P Ford...

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