THERAPEUTICS

Glucagon-like peptide-1 analogues for type 2 diabetes

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Mabel Chew discusses this paper with one of its authors

This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com.

What are glucagon-like peptide-1 analogues?

Glucagon-like peptide-1 (GLP-1) is a naturally occurring peptide hormone, released from the gut after eating. GLP-1 stimulates insulin release (the incretin effect), suppresses glucagon release (thus reducing hepatic gluconeogenesis), delays gastric emptying, and promotes satiety. Natural GLP-1 has a short half life of a few minutes as a result of breakdown by endopeptidases such as dipeptidyl peptidase-4. GLP-1 analogues, also known as incretin mimetics (exenatide and liraglutide), are modified GLP-1-like peptides that are resistant to degradation by dipeptidyl peptidase-4, with elimination half lives of 2.4 hours and 13 hours respectively. GLP-1 analogues are indicated as an adjunct to other treatments in the management of type 2 diabetes and are given once daily (liraglutide) or twice daily (exenatide) by subcutaneous injection.

How well do GLP-1 analogues work?

Exenatide

Exenatide has been studied in several randomised controlled trials in which either exenatide or placebo was added for up to six months to existing treatment with sulphonylurea or metformin monotherapy, dual therapy with metformin plus sulphonylurea, or a thiazolidinedione with or without metformin.[1-5] In these studies exenatide was associated with a consistently lowered HbA_{1c} concentration compared with the placebo (an average 0.9% fall in HbA_{1c} concentration). The number needed to treat to achieve an HbA_{1c} concentration of <7% observed in these studies ranged from three to six. Body weight also fell significantly, by an average of 1.3 kg, in the group taking exenatide, compared with the group taking placebo. Some patients in these trials continued in longer term "open label" extensions for up to three years; during these extension trials the effect on HbA_{1c} concentration seemed to be sustained and weight loss continued.[6 7]

Exenatide has also been compared with the alternative options of adding either basal or premixed insulin in randomised open label trials of up to one year's duration. In these studies the effect on HbA_{1c} concentration was shown to be no better than insulin (a reduction of HbA_{1c} concentration of about 1% in both arms). However, patients treated with exenatide were more likely to lose weight (average of 2-3 kg), whereas those treated with insulin were more likely to gain weight (average of 2-3 kg).[8 9]

The current joint guidelines from the American Diabetes Association and the European Association for the Study of Diabetes support the use of exenatide as an alternative third line treatment in overweight and obese patients,[10] but more established options such as insulin treatment, for which outcomes data are available, are the preferred option. The guidelines from the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom are more specific and recommend considering exenatide in addition to sulphonylurea and metformin for patients with a body mass index of >35 if they are of European descent, and for patients with a body mass index of <35 if *(a)* they are South Asian or from another ethnic group in which metabolic risk is greater at a lower body mass index, *(b)* weight loss might benefit other comorbidities, or *(c)* insulin treatment is unacceptable. NICE also defines criteria for stopping exenatide and recommends that it should be continued only if, after six months of treatment, the HbA_{1c} concentration has fallen by at least 1% and the body weight by 3%.[11]

CASE SCENARIO

A 58 year old woman attends a diabetes clinic with type 2 diabetes of seven years' duration and no history of macrovascular disease. She is obese (body mass index 37), but says she eats a healthy diet and describes this. Her blood pressure is 134/78 mm Hg, and she has microalbuminuria, but normal renal function and a lipid profile within target levels ranges. She is taking simvastatin 40 mg daily and perindopril 4 mg daily. Glycated haemoglobin (HbA_{1c}) is 8.3% despite treatment with metformin 850 mg three times a day and gliclazide 160 mg twice a day. How would you best manage her hyperglycaemia? (The table shows the drug treatment options.)

After discussion with the patient of the benefits and risks of the available treatment options (including the "do nothing" option, risks of hypoglycaemia, and effects on body weight), you agree on a glucagon-like peptide-1 (GLP-1) analogue (exenatide or liraglutide).

Drug treatment options

Drug class	Advantages	Disadvantages
Pioglitazone	Long term safety and availability of outcomes data; low risk of hypoglycaemia	Weight gain likely; peripheral oedema (risk of heart failure); risk of fracture
Insulin	Long term safety and availability of outcomes data; flexible dosing is possible to meet patients' needs	Weight gain likely; risk of hypoglycaemia; administered by subcutaneous injection only
Acarbose	Weight neutral; low risk of hypoglycaemia	Gastrointestinal side effects; modest efficacy
Dipeptidyl peptidase-4 inhibitors*	Weight neutral; low risk of hypoglycaemia	No data from long term trials; possible risk of pancreatitis
Glucagon-like peptide-1 analogues† (exenatide and liraglutide)	Weight loss; low risk of hypoglycaemia, except when used with sulphonylurea	No data from long term trials; nausea; possible risk of pancreatitis; administered by subcutaneous injection only

*Also known as gliptins.

†Also known as incretin mimetics.

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Data on long term effects of GLP-1 analogues on vascular complications are not yet available from current trials.

Liraglutide

Clinical trials evaluating liraglutide included a monotherapy active comparator trial versus glimepiride[12] and placebo controlled trials in patients taking metformin or sulphonylurea, with or without a thiazolidinedione.[13-15] The number needed to treat to achieve an HbA_{1c} concentration of <7% compared with placebo when added to metformin was three.[13] Add-on trials have compared liraglutide with placebo or insulin in patients poorly controlled with dual therapy of metformin plus a sulphonylurea[16]; some trials have also compared liraglutide to the dipeptidyl peptidase-4 inhibitor sitagliptin.[17] These trials also show that liraglutide significantly improved glycaemic control.

One published randomised controlled trial compares exenatide with liraglutide over six months of treatment. This used the highest dose of liraglutide and showed at six months that liraglutide was better at lowering the HbA_{1c} concentration (by 1.12% *v* 0.79%; estimated treatment difference −0.33 (95% confidence interval for difference, −0.47 to −0.18), had similar effects on body weight (about 3 kg weight loss), and was associated with fewer reports of nausea (in 3% of patients *v* 9%).[18] A longer term follow-up of that trial, in which patients taking exenatide were switched to liraglutide for a further six months, showed further improvement in glycaemic control (mean falls in HbA_{1c} concentration (0.32%), body weight (0.9 kg), and systolic blood pressure (3.8 mm Hg)).[19]

Liraglutide has been available in Europe since 2009 and has only just been approved for use in the United States. A recent NICE technology appraisal recommended the use of the 1.2 mg dose, with the same stopping criteria as described for exenatide.[20]

How safe are GLP-1 analogues?

Gastrointestinal tolerability is the main concern with both drugs as nausea or vomiting, or both, affect 30-50% of patients (number needed to harm two to three), although only 5% of patients taking exenatide and 4.3% taking liraglutide discontinued clinical trials as a result of these adverse effects (number needed to harm, 20). As these gastrointestinal side effects are dose related and tend to diminish with long term treatment, this provides the rationale for the dose titration regimens used with both agents and probably explains why few of these events led to withdrawal in clinical trials. Liraglutide (perhaps because of its slower onset of action and longer half life) may be slightly less problematic in this respect.

Reactions at the injection site such as itching and rashes have also been reported but are uncommon. Thirty eight per cent of patients will develop antibodies with exenatide treatment. Most of these are of low titre and do not seem to influence the therapeutic effect, but about 6% of patients will have higher titres of antibodies, and of these about half (3% overall) do not show an improvement in HbA_{1c} concentration (number needed to harm, 33).

The frequency of hypoglycaemia is similar in patients treated with GLP-1 analogues alone and those taking placebo. However, among patients taking metformin and/or a thiazolidinedione, hypoglycaemia may occur at higher frequency in patients taking sulphonylurea, which may require a dose reduction in the sulphonylurea when starting treatment.

Currently no data are available for long term cardiovascular safety of treatments incorporating GLP-1 analogues, although such trials are being undertaken with liraglutide, and longer acting agents are being developed.

What are the precautions?

- Do not use GLP-1 analogues in patients with:
  - -An estimated glomerular filtration rate of <30 mL/min as their use has not been extensively studied in patients with renal impairment. Liraglutide is also not recommended for patients with moderate renal impairment (estimated glomerular filtration rate <60 mL/min), but exenatide can be used with caution in patients with moderate renal impairment (estimated glomerular filtration rate 30-50 mL/min)
  - -A history of pancreatitis or a high risk of pancreatitis (for example, severe hypertriglyceridaemia) as acute pancreatitis has been reported in patients taking these drugs (296 cases in 800 000 patient years of exposure, [21] although a causal link has not been proved; these rates are similar to rates seen in patients taking other glucose lowering drugs, but in some cases researchers found a clear temporal relation to GLP-1 analogue use and a positive response to rechallenge
  - -Inflammatory bowel disease or gastroparesis, which may affect drug absorption or exacerbate adverse effects.
- Neither exenatide nor liraglutide has been formally studied with, or has a licence for use in combination with, insulin; however, exenatide is sometimes used with insulin in clinical practice.[22]
- GLP-1 analogues should not be used in patients who are severely insulinopenic (for example, those who are losing weight rapidly with poor glycaemic control, particularly if ketosis is present) or who have type 1 diabetes as these patients are unlikely to respond.

How are GLP-1 analogues taken and monitored?

Both exenatide and liraglutide are given by subcutaneous injection via prefilled pen injector devices. Exenatide is given twice daily, with doses given up to an hour before meals and at least six hours apart. Liraglutide is given once daily, and at any time, but at about the same time each day. Dose titration is required to help minimise initial nausea; for exenatide half the maximal dose is given for one month before titrating up to the full dose. Liraglutide titration is at weekly intervals, with most patients only requiring titration to the second highest of the three doses available.

Regular home glucose monitoring is recommended when GLP-1 analogues are used in combination with sulphonylurea because of the risk of hypoglycaemia.

Monitor HbA_{1c} (every three months), body weight, blood pressure, and lipids, as in any patient with diabetes. Some

TIPS FOR PATIENTS

Exenatide [or liraglutide] is a relatively new medicine for diabetes that is given by injection. It may also lead to some weight loss. You will be given the drug for a trial period, and it will only be continued after six months if it improves your glucose control and lowers your body weight (according to national guidelines for diabetes (NICE)). We will agree the target figures for your glucose and body weight when you are given your first injection.

Nausea and sometimes vomiting are known side effects with the drug but usually improve after a few doses. About 1 in 20 people find they are unable to continue. If this happens, you will be offered a different treatment.

The chances of hypoglycaemia (low blood sugar) are low, but if you are taking a sulphonylurea (such as gliclazide or similar medicine) then it is important to monitor blood glucose more frequently; it may be necessary to reduce the dose of the sulphonylurea.

A few patients develop a reaction (such as redness or itching) at the injection site. If this is persistent or troublesome, you should discuss it with your doctor.

A few patients taking these medications have developed a potentially serious condition called pancreatitis (inflamed pancreas), although this hasn't been proved to be caused by the medications. However, if you develop abdominal pain, nausea, or vomiting, seek medical help at once.

evidence suggests slight improvements in lipids and blood pressure with these agents, which may be related to weight loss.

How cost effective are GLP-1 analogues?

These new treatments are much more expensive than older, well established drugs such as metformin, to which they are usually added when control is inadequate. The NHS cost for 30 days' supply is £68.24 for exenatide 10 µg dose and £78.48 for liraglutide 1.2 mg dose but only £1.33 for metformin 850 mg (twice daily) and £1.45 for gliclazide 80 mg (twice daily). The 30 day cost for pioglitazone (30 mg/day) is £33.25 and for sitagliptin £33.26 (100 mg/day).

Although GLP-1 analogues are relatively expensive, for many patients the alternative is often insulin therapy. For a patient who requires 25 units of insulin glargine a day (the mean dose in one of the trials with exenatide),[8] the cost for insulin would be £20.18 a month. For obese, insulin resistant patients, insulin doses and costs can be very high—for example, £80.72 a month for a patient taking 100 units a day. One cost effectiveness study with exenatide has been published,[23] and cost effectiveness was also considered as part of the NICE guideline appraisal process.

In the model considered by NICE, the incremental cost effectiveness ratio (ICER) for liraglutide 1.2 mg or exenatide 10 µg twice daily as part of a triple therapy regimen (liraglutide or exenatide, plus two oral hypoglycaemic agents) compared favourably with that for insulin glargine (ICERs were in the range £9000-£11 000); the ICERs for exenatide versus glargine were lower (£1600 for men and £7000 for women) when patients with a body mass index of at least 35 were entered into the model. Liraglutide also compared favourably with exenatide in the head to head comparison (ICER £10 000), but liraglutide was deemed not to be cost effective in dual therapy regimens. Liraglutide 1.8 mg was not cost effective when compared with a 1.2 mg dose.

These costs do not include the additional costs of education and glucose monitoring required for patients treated with insulin. In summary, it is difficult to draw firm conclusions with regard to cost effectiveness from the limited information available, but NICE considers that exenatide and liraglutide are probably cost effective if used within their licensed indications with the caveats and stopping rules suggested in the NICE guideline document.[11 20]

How do GLP-1 analogues compare with other drugs

The future potential of glucagon-like peptide-1 analogues will depend on three main factors:

- Evidence of cardiovascular safety and of long term benefits compared with other agents for microvascular and macrovascular complications of diabetes
- Whether GLP-1 analogues can alter the natural course of type 2 diabetes by preserving β cell function
- The development of even longer acting analogues that can be given weekly or less frequently.

Current clinical trials with exenatide, liraglutide, and several new analogues in development are trying to clarify these important topics.

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EASILY MISSED?

Type 1 diabetes in children

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at easilymissed@bmj.com.

Type 1 diabetes in childhood is one of the commoner long term conditions of childhood. It is treated by specialist teams in secondary care using increasingly intensive insulin regimens, but the onset is generally diagnosed by primary care physicians, sometimes later than is ideal.

Why is it missed?

About 30% of children with newly diagnosed diabetes have had at least one related medical visit before the diagnosis, suggesting that medical practitioners are missing the diagnosis.[5] Drinking a lot and passing a lot of urine may not be mentioned by parents, even when children start bed wetting after having been dry. Other early symptoms of diabetes in young children (headache, constipation, oral and vulval thrush, abdominal pain, vomiting) may be non-specific. In older children and adolescents, polyuria and polydipsia usually predominate, but these symptoms can be misinterpreted by parents and schools or ignored by adolescents. Doctors may not consider the diagnosis as a cause of the initial symptoms; they may fail to ask about polyuria and polydipsia in children with other suggestive symptoms or may fail to carry out the appropriate investigation. Incorrect diagnoses in children with newly presenting diabetes include respiratory infection, simple candidiasis, gastroenteritis, urinary tract infection, stomatitis, and appendicitis.[6]

Why does this matter?

Children can develop dehydration and acidosis within 24 hours of first presentation, and children aged under 2 years are most at risk. In a recent UK study, a higher proportion of children with delayed diagnosis presented in diabetic ketoacidosis than did those with no delay (52% *v* 21%).[7] Diabetic ketoacidosis is the leading cause of mortality and morbidity in children with type 1 diabetes mellitus; 10 children a year die from diabetic ketoacidosis in the UK. Most diabetes related deaths are due to cerebral oedema, which is more common when diabetic ketoacidosis occurs at onset of diabetes.[8]

KEY POINTS

- Secondary nocturnal enuresis is the commonest symptom of new diabetes in children
- Ask about polyuria and polydipsia in toddlers with constipation, thrush, vomiting, weight loss, or any acute illness
- Investigate children with polyuria, polydipsia, and weight loss for diabetes
- Investigation for diabetes requires only a single immediate capillary blood glucose test; values above 11.1 mmol/L indicate diabetes
- Refer children with a raised blood glucose concentration to secondary care the same day
- Do not wait for a fasting blood glucose test or urine sample as this may allow diabetic ketoacidosis to intervene

How is type 1 diabetes diagnosed in children?

Clinical features

Clinical features can be non-specific in children under 2 years, and a high index of suspicion is important. Polyuria

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CASE SCENARIO

A 7 year old boy with acute abdominal pain and vomiting is brought to see his general practitioner by his mother. He was being bullied at school, and because his mother attributed his recent onset of bed wetting to stress she did not mention this symptom to the GP. The GP considers appendicitis a possibility but first decides to rule out a urinary tract infection. A urine dipstick test is positive for glucose and ketones. She refers the child at once to the paediatric team for immediate management of his diabetic ketoacidosis.

and polydipsia are the main symptoms of diabetes in all age groups, occurring in up to three quarters of school age children.[9] However, these symptoms are not always mentioned initially and must be elicited by a proper history taking. Nocturnal enuresis in a previously "dry" child is the earliest symptom of diabetes in 89% of children over the age of 4 years.[9 10] Weight loss occurs in half those aged 10-14 years but in only 5% of children under 2 years. Lethargy occurs in 10-20% of children of all ages. Constipation is an important symptom in the under 5s, occurring in around 10%, secondary to chronic dehydration.[9] Recurrent infections are uncommon as a presentation, occurring in only 2%, although oral and vulval thrush has been reported. Positive predictive values of these symptoms are not known as the appropriate research has not been carried out.

If ketoacidosis has already supervened, then the symptoms can include vomiting, deep sighing respiration, reduced conscious level, and abdominal pain. Because of these, diabetic ketoacidosis can be misdiagnosed as acute abdomen, possible gastroenteritis, acute asthma, or pneumonia if the parents are not asked about a history of polyuria and polydipsia.

Investigations

Diabetes can be diagnosed with a single capillary blood glucose test if a proper technique has been followed—that is, the child's hands have been washed and dried thoroughly. The diagnostic criteria for diabetes are the same in children as in adults: a random blood glucose concentration >11.1 mmol/L. Any delay obtaining a urine sample or a glucose measurement may allow diabetic ketoacidosis to supervene. If symptoms suggest diabetes, the consultation should not finish until a diagnosis has been made or diabetes ruled out. Children should not wait for a fasting blood glucose test. The capillary blood glucose results will be confirmed with a laboratory testing of blood glucose when the child arrives in hospital.

How is it managed?

Refer a child or young person with a high capillary blood glucose concentration promptly (same day) to secondary care for further management.

Children with type 1 diabetes require insulin, which is given in various regimens and is started on the day of referral. The management, education, and support are carried out by a multidisciplinary team based in secondary care, consisting of doctors, diabetes specialist nurses, and dietitians. Many centres are starting to use multiple injection regimens in most age groups (using basal and rapid insulin four to six times daily). Other possible regimens are two or three injections

HOW COMMON IS IT?

In England diabetes occurs in 1 in 450 children, of whom 97% have type 1 diabetes mellitus[1]

The current incidence is around 26/100 000 per year

In a large UK general practice, a child with new diabetes will be seen about every two years

Incidence is increasing by around 4% a year in the UK, in common with other northern European countries[2]

The prevalence of diabetic ketoacidosis at diagnosis over the past 20 years has remained unchanged, at around 25% of newly diagnosed children of all ages and 35% in children under 5 years[3 4]

per day of various combinations of insulin types. Educating the child and family is the keystone of management, as families will need rapidly to learn all of the practical techniques required to give insulin injections, measure blood glucose, and treat mild hypoglycaemia. Most centres admit children to hospital for up to 48 hours, but some have the resources to send children home on the first night, with follow-up and education at home.

An aggressive and relatively inexpensive campaign of information aimed at health professionals and the public on the early symptoms of diabetes dramatically reduced the incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in children in Italy.[10] A similar campaign should be tried in the UK.

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10-MINUTE CONSULTATION

Hypoglycaemia

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This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.

A 58 year old white man who has had type 2 diabetes for 10 years is concerned about increasingly frequent hypoglycaemic episodes, usually in the late afternoon. He has been taking a stable, once daily dose of basal insulin glargine 14 units for two years, as well as twice daily gliclazide 160 mg and metformin 1000 mg. His body mass index is 23 (weight (kg)/ (height(m)^2)) and his weight is stable. He works in finance and has recently divorced.

What you should cover

Hypoglycaemia can occur in diabetic patients treated with insulin or sulphonylureas. Most cases are caused by an imbalance between carbohydrate intake and hypoglycaemic treatment. Mild hypoglycaemia is common, although rarely problematic in people with tight glycaemic control, and can occur in people with poor glycaemic control owing to wide fluctuations in glucose concentrations. It is important to identify the underlying cause, as recurrent or severe hypoglycaemia can have serious consequences, such as injury to the patient or others, or serious cognitive dysfunction.

To confirm hypoglycaemia a clear history is vital. The differential diagnosis should be considered, but diagnosing hypoglycaemia is straightforward if the three Whipple's criteria are met:

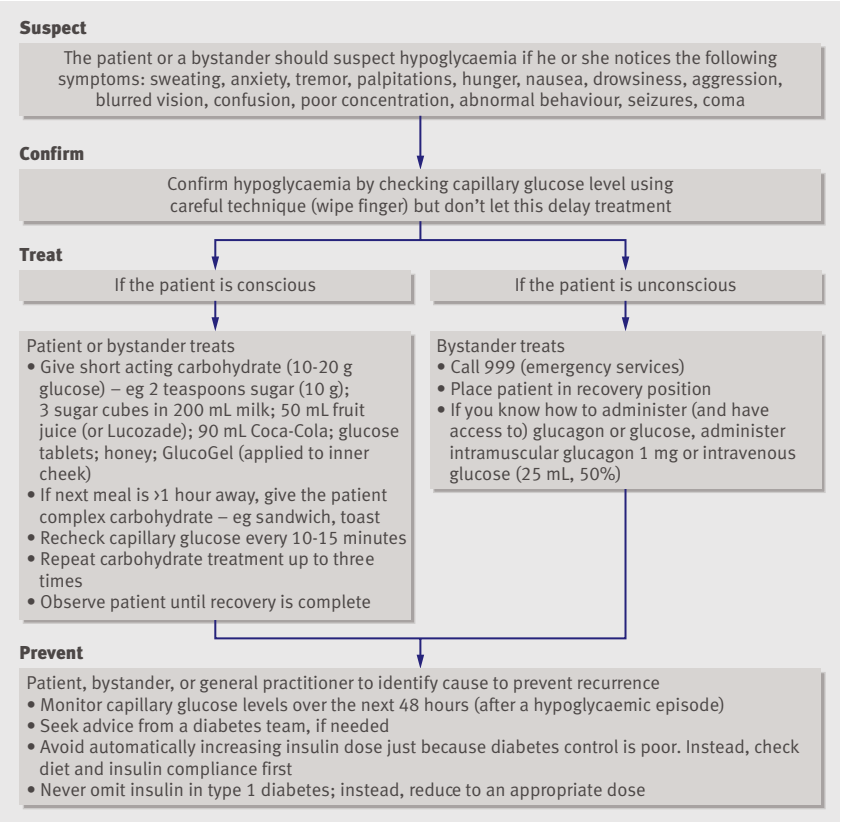
- Warning symptoms of altered mental status, sympathetic nervous system stimulation or gastrointestinal symptoms (see the first box in the figure)
- Blood glucose concentrations ≤3.1 mmol/L when symptoms are present. Patients with poor glycaemic control may experience hypoglycaemic symptoms with normal glucose concentrations. This "false hypoglycaemia" does not require emergency treatment, and symptoms will tend to be short lived if glycaemic control improves
- Symptom reversibility with administration of glucose.

Explore the patient's understanding of hypoglycaemia and the consequences of these episodes. How frequent are they? Is he alone during episodes or are others available to help? Has he needed hospital, paramedic, or other third party help? Has he sustained any injuries, or is there any evidence of depression or anxiety as a consequence?

Look for the cause of hypoglycaemia—changes in the patient's physical condition or lifestyle that may have occurred recently. In this case, his moderate lunchtime alcohol consumption, coupled with eating less since his divorce, may be contributory factors. A detailed history covering the following areas will identify most causes:

- Diet: content, portion, recent changes, vomiting
- Insulin regimen: type, dose, frequency, recent changes (can be checked against the patient's primary care record)
- Exercise: amount
- Alcohol: amount
- Timing: establish events in the hours preceding a hypoglycaemic episode
- Job and lifestyle factors
- Change in weight.

Otherwise, consider symptoms and causes (including new medications) of renal or liver failure (reduced clearance of drugs or metabolites) and adrenal failure (reduced cortisol leading to hypoglycaemia).



Management of a hypoglycaemic episode in the community. Based on information drawn from the Patient UK and Diabetes UK websites

What you should do

Examination and investigations

Check his glycaemic control—Examine his primary care record for previous glycated haemoglobin (HbA_{1c}) concentrations, complications, and hospital admissions with problems related to diabetes.

Examine his home diary readings for any pattern—If previously well controlled, he may not be testing frequently, in which case you should encourage more frequent tests while hypoglycaemia is a problem. Check that:

- He performs quality control checks on his glucometer regularly

FURTHER READING

Diabetes UK (www.diabetes.org.uk/Guide-to-diabetes/Complications/)

Patient UK (www.patient.co.uk/doctor/hypoglycaemia.htm)

Driver and Vehicle Licensing Agency (www.dft.gov.uk/dvla/medical/ataglance.aspx)

- He does most of his measurements at relevant times of the day (fasting, before meals, before bedtime, and occasionally at night (if hypoglycaemia at night is a problem). These regular measurements will help define his level of hypoglycaemic unawareness if he is obtaining regular low glucometer readings despite no symptoms
- He knows not to substantially delay treatment of hypoglycaemia by checking a capillary glucose level if he is convinced that his symptoms indicate hypoglycaemia.

Examine injection sites—Lipohypertrophy may cause erratic insulin absorption. Any sites showing lipohypertrophy should be avoided in favour of rotation elsewhere (for example, abdomen, thighs, and buttocks). It may be appropriate to reduce the insulin dose slightly (by about 10%) if his injection sites show lipohypertrophy, as absorption of insulin may change with use of other sites.

Check renal and liver function and HbA_{1c} concentration—Random glucose measurement is rarely helpful as it depends on the timing of carbohydrate ingestion.

Treatment and advice

- Check the patient's knowledge of how to treat hypoglycaemia, and re-educate him about the appropriate treatment if necessary (figure).
- Deal with the underlying cause. Consider reducing his insulin or sulphonylurea dosage if appropriate, and educate him on how to adjust his medication himself. Cessation of medications is usually unnecessary. His regular intake of lunchtime alcohol may be responsible for hypoglycaemia later in the day: he should be encouraged to reduce alcohol intake and ensure he eats carbohydrate when drinking alcohol.
- The HbA_{1c} concentration may aid decision making on how to adjust medication: if it is low (<7.0% (0.07)), consider reducing his medications for hypoglycaemia; if it is high (>8.0%), reflecting labile blood glucose concentrations and perhaps overtreatment of hypoglycaemia, management should focus on preventing hypoglycaemic episodes.
- Advise him to avoid high risk situations (swimming, use of heavy machinery, heights) until control improves.
- Advise him to check capillary glucose concentration before and after exercising.
- Encourage him to wear a medical identification bracelet or necklace and to explain to work colleagues, family, and friends how to treat hypoglycaemia.
- Encourage easy access to carbohydrates—store at home and/or in the office, car, gym bag, pocket.
- Driving—ensure the patient knows that according to the DVLA (Driver and Vehicle Licensing Agency) guidance, he:
  - -Must inform the agency if he has more than one episode of disabling hypoglycaemia in one year; disabling hypoglycaemia while driving; or hypoglycaemic unawareness
  - -Should monitor capillary glucose concentration at times relevant to driving—for example, before driving and regularly during long journeys (taking a break every two hours)
  - -Must stop safely and treat hypoglycaemia immediately if it occurs while he is driving, and not restart driving until his symptoms resolve.
- To avoid recurrent hypoglycaemia, a temporary period of mild hyperglycaemia may be necessary.

Follow-up

Hypoglycaemia can usually be managed in the primary care setting. Arrange follow-up with frequent home monitoring and meal recordings to establish a glycaemic pattern. If hypoglycaemia responds to changes in diet or treatment, no further evaluation is needed, but consider referral to a specialist for structured education. Arrange specialist assessment if he has severe hypoglycaemia or frequent or recurrent hypoglycaemia without a clear cause or warning symptoms, or if he cannot manage his own treatment (for example, he lives alone or has been unable to treat himself during a hypoglycaemic episode and needed the help of others).

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- Chalazion (*BMJ* 2010;341:4044)
- Vitamin B-12 deficiency (*BMJ* 2010;340:2305)

ANSWERS TO ENDGAMES, p 447. For long answers go to the Education channel on bmj.com

STATISTICAL QUESTION

Meta-analyses VI

Statements *a* and *b* are true, whereas *c* is false.

ON EXAMINATION QUIZ

Developmental dysplasia of the hip

A is false, whereas B, C, D, and E are true.

CASE REPORT **A boy with a painful arm**

1. The most likely diagnosis is an acute compartment syndrome.
2. After tissue insult, oedema and haematoma lead to an increase in interstitial pressure within a rigid osteofacial compartment.
3. Patients should be monitored by close observation. An essential key clinical feature is severe pain, which is out of proportion to the nature of the injury and has an increasing analgesic requirement.
4. If a compartment syndrome is clinically apparent, open fasciotomy should be performed immediately.
5. Possible complications are irreversible muscle and nerve damage and Volkmann's ischaemic contracture.