ABCss: A is for A_{1c}

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This, the first in a series of case studies focusing on the ABCss of diabetes care (A_{1c}, blood pressure, cholesterol, smoking, salicylates), discusses how to get glycosylated haemoglobin (A_{1c}) closer to target and keep it there.

Case scenario

Arnold is 67 years old and has had type 2 diabetes for the past eight years. He has a strong family history of diabetes (both parents and one sister) and, with a weight of 91 kg and a height of 1.82 m, is overweight (BMI, 27.5 kg/m^2). Following the rough guide formula, healthy weight = height (cm) – 100, a healthy weight for Arnold would be about 82 kg.

Arnold is taking glimepiride 4 mg/day and metformin 1 g twice daily. His plasma creatinine of 0.11 mmol/L gives him a calculated creatinine clearance of 68 mL/min (creatinine clearance = 1.25[(140 – age) x healthy weight] ÷ plasma creatinine in μmol/L; for Arnold, 1.25 x [(140-67) x 82] ÷ 110). This is greater than the glomerular filtration rate (GFR) value below which metformin dosage should generally be limited (i.e. a calculated GFR <60 mL/min) or probably stopped (a calculated GFR <30 mL/min).

He has had hypertension for the past 15 years, and this is currently moderately controlled (systolic blood pressure, 135 to 145 mmHg; target, <130 mmHg) on an ACE inhibitor/hydrochlorothiazide preparation. He has been taking prophylactic aspirin since the age of 60 years.

There is evidence of microvascular disease (background retinopathy and pins and needles in his feet and legs, especially at night), but no history of a cardiovascular event.

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Arnold's glycosylated haemoglobin (A_{1c}) has been climbing over the past 18 months and is now 8.7% (ideal, <7%), and many of his capillary blood glucose values exceed 10 mmol/L.

Questions

- Regarding Arnold's hyperglycaemia, what else do you need to find out?
- What options are there to control Arnold's hyperglycaemia?
- How would you choose between these options?
- Four years later, the chosen combination of oral hypoglycaemic agents is not controlling his blood glucose. How will you suggest Arnold start insulin?

Before changing medication

Before changing Arnold's medication to better control his hyperglycaemia, it is worth finding out more about his medication and lifestyle, and also other medical conditions he may have that may be contributing to his hyperglycaemia.

Medication

Is Arnold taking his oral hypoglycaemic agents? In randomised controlled trials, ongoing participation requires adherence rates generally exceeding 80%. In the real world, adherence rates may be closer to 30%.

Is he taking other prescription or nonprescription medications that could cause hyperglycaemia? We know that patients often see more than one GP and take more nonprescription and/or complementary medications than prescription medications. Table 1 lists common medications likely to cause hyperglycaemia.

Table 1. Medications and medical conditions causing hyperglycaemia*

Medications
Oral contraceptive pill
Oral corticosteroids
Thiazides†
Beta blockers
Phenytoin
Glucosamine
Medical conditions
Urinary tract infection‡
Hyperthyroidism
Occult malignancy

* Not an exhaustive list.
† Equivalent to 50 mg hydrochlorothiazide.
‡ May be more common and asymptomatic in individuals with neuropathy.

Lifestyle

Is Arnold trying to 'Eat less, walk more', and is he succeeding? Has his weight/waist been growing or shrinking over the past two years?

It is unlikely that Arnold would be willing or able to make the sort of lifestyle changes that could bring his A_{1c} into the target range but the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes has shown that modest achievable lifestyle changes can bring the A_{1c} down by 0.5 to 1%.[1]

Medical matters

Has Arnold developed some secondary cause of hyperglycaemia? This may not be obvious but its treatment could help in the control of his glycaemia (Table 1).

Options for controlling hyperglycaemia

Apart from lifestyle changes, acarbose, glitazones and/or insulin might be useful in controlling Arnold's hyperglycaemia.

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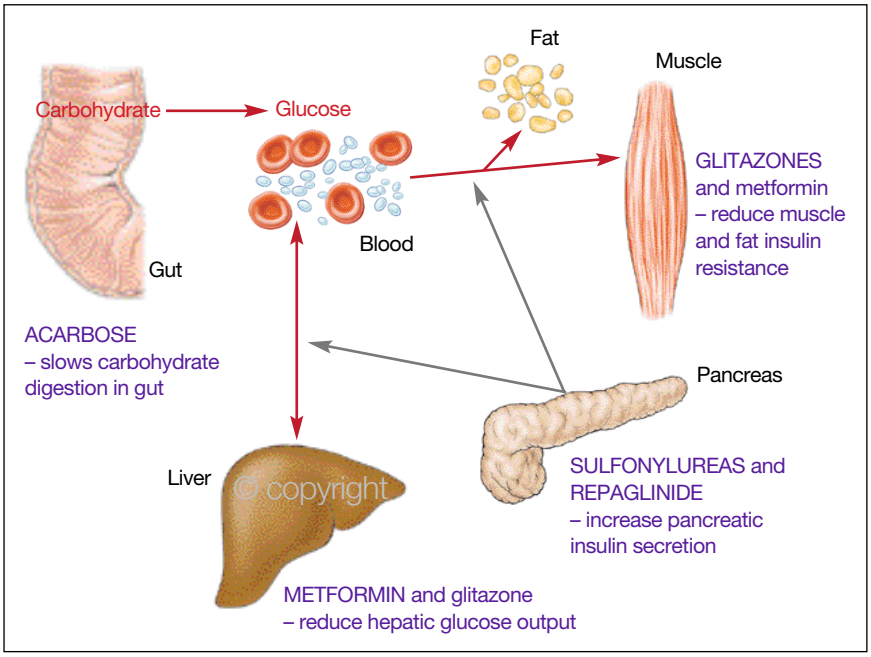

Figure. Sites of action of oral hypoglycaemic agents.

There are five classes of oral hypoglycaemic agents, and they have different mechanisms of action (Figure):[2]

- acarbose (Glucobay) – slows carbohydrate digestion
- glitazones – reduce muscle and fat insulin resistance, and also reduce hepatic glucose output (but to a lesser degree than metformin)
- metformin – reduces hepatic glucose output, and also reduces muscle and fat insulin resistance (but to a lesser degree than glitazones)
- repaglinide (NovoNorm), a glitinide – is a short acting insulin secretagogue
- sulfonylureas – are long acting insulin secretagogues.

Each class can be added to the others with additive effects, with the exception of combining repaglinide and a sulfonylurea as they are both insulin secretagogues. Generally, metformin is tried first, followed by a sulfonylurea and then a glitazone.[3] Both acarbose and repaglinide may be useful to control postprandial glcaemia early in the course of diabetes.

On average, each class of oral hypoglycaemic agent will decrease A_{1c} by about 0.5 to 1.5%. Some patients may experience more or less effect because of the differing contributions of increased insulin resistance and decreased capacity for insulin secretion.

The use of basal and/or bolus insulin is a treatment option at any stage of type 2 diabetes but is usually resisted by both the patient and the doctor until all other agents have been tried. This psychological resistance to use therapeutic insulin and the patient's pathological insulin resistance both contribute to hyperglycaemia.

Choosing between options

The pros and cons of each class of oral hypoglycaemic agent are listed in Table 2.

Adding repaglinide to Arnold's medications will not help as he is already taking the sulfonylurea glimepiride (Amaryl, Aylide, Diapride, Dimirel).

We do not know Arnold's blood glucose profile but if his blood glucose values before meals were not far off the target value of 4 to 6 mmol/L and the problem was caused by postprandial glycaemia, adding acarbose could help. It would be started low, e.g. 25 mg before meals, and then increased slowly towards 50 or 100 mg before meals if tolerated. Arnold's A_{1c} of 8.7% suggests that his average blood glucose level exceeds 10 mmol/L (as a rough guide, blood glucose level = $2A_{1c} - 6$; for Arnold, 11.4 mmol/L) so it is unlikely that any of his blood glucose values, before or after meals, are on target. Thus, acarbose is not likely to improve control.

For Arnold, therefore, the main choice lies between using a glitazone or insulin.

In the UKPDS, 50% of participants required insulin within six years to maintain $A_{1c} \leq 7\%$.[4] In practice, however, patients and doctors usually delay longer than this. Arnold has had diabetes for almost nine years and his capacity to secrete insulin is likely to have decreased considerably since diagnosis. Insulin may well prove necessary in the short to medium term and it may be worth discussing this now so that Arnold is not disappointed or resistant when insulin is needed.

The choice of glitazone is largely driven by the prescribing indications. Compared to each other, rosiglitazone (Avandia) has less potential for medication interactions and pioglitazone (Actos) may have more beneficial effects on the lipid profile. However, rosiglitazone can be prescribed as ongoing triple therapy (with metformin and a sulfonylurea) whereas, at present, the PBS indication for pioglitazone is more limited.

It will take two to three months for either rosiglitazone or pioglitazone to have maximal therapeutic effect. However, if the glitazone is going to work, some effect is usually seen in the first few weeks.

The major risk with both glitazones is the accumulation of extracellular fluid. Arnold has no history of cardiovascular events but should be advised to seek medical attention if he develops oedema. He should also be made aware that NSAIDs

Table 2. Pros and cons of oral hypoglycaemic agents

Oral hypoglycaemic agent or class	Pros	Cons	Overall usage*
Acarbose	No hypoglycaemia† Weight neutral	Gastrointestinal side effects Less A_{1c} reduction	1%
Glitazones	Increase insulin sensitivity No hypoglycaemia†	Increased subcutaneous fat or fluid	–
Glitinides	Increase meal time insulin secretion	Hypoglycaemia risk	–
Metformin	Increase insulin sensitivity No hypoglycaemia† Weight loss or neutral	Gastrointestinal side effects Lactic acidosis risk	76%
Sulfonylureas	Increase insulin secretion	Hypoglycaemia risk Weight gain	47%

* Overall usage (mono and combination therapy) in the 2005 National Prescribing Service clinical audit of 1733 GPs and 34,576 patients with type 2 diabetes (personal communication).
† Unless insulin or an insulin secretagogue is coadministered.

(prescription and over-the-counter) or a high sodium intake (e.g. Chinese food) could precipitate dangerous fluid accumulation.

Starting insulin

The 'keep it safe and simple' (KISS) principle will apply when it comes to the time for Arnold to start using insulin.

Reassure Arnold that insulin therapy is safe and simple, that the injections do not hurt and that all patients with diabetes feel better once they have started insulin and control of their glycaemia has improved (in fact, many patients say they wish they had taken the step much earlier). The new insulin injection devices make the process of injecting insulin much easier and the practice nurse or diabetes nurse educator could show Arnold the range of devices available and how to use them. The nurse could also stress to Arnold the importance of continuing the 'Eat less, walk more' program to prevent the weight gain associated with better glycaemic control due to the decreased loss of glucose in the urine.

Arnold should continue taking the oral hypoglycaemic agents while insulin is initiated. If he stops taking one or more of them, his blood glucose control will get worse, not better.

Insulin therapy should be started with a 10 U night time (bed time) basal dose of the intermediate acting insulin isophane insulin (human), also known as NPH insulin (Humulin NPH, Protaphane).[3] The long acting insulin analogue insulin glargine [Lantus] has recently become listed on the PBS for type 2 diabetes and may be used as the basal insulin instead. A dose of 10 U is a small dose and will probably not make much difference to the blood glucose level; on the other hand,

Table 3. Insulin titration*

Start with 10 units of isophane insulin at bedtime.
Adjust the dose twice weekly, to reach the target fasting blood glucose of <6 mmol/L, using the regimen below:

Mean fasting glucose over preceding 2 days (mmol/L)	Insulin increase (U/day)
>10	8
8 to 10.0	6
7 to 7.9	4
6 to 6.9	2

- Do not increase insulin dosage if the blood glucose level is <4 mmol/L at any time in the preceding week.
- The insulin dose may be decreased (small decreases of 2 to 4 units) if there is severe hypoglycaemia (requiring assistance) or the blood glucose level is <3.0 mmol/L in the preceding week.

*Derived from reference 5 (*Diabetes Care* 2003; 26: 3080-3086).

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it is not going to cause hypoglycaemia. Having reassured Arnold that insulin is safe, the last thing you want is a hypo on day one or two.

Although premixed insulins are widely used to start insulin therapy in patients with type 2 diabetes, the main requirement is for basal insulin replacement. The quick acting component is usually not necessary at this stage, and may cause hypoglycaemia and/or weight gain.

Initially, follow a patient's blood glucose level before breakfast and review the insulin dose every two to three days. This can be done either by phone or in conjunction with the practice nurse or diabetes nurse educator using an agreed protocol, such as the insulin titration given in Table 3.[5]

When the before breakfast blood glucose is at the desired target (e.g. 80% between 4 and 6 mmol/L), change to reviewing the blood glucose before the evening meal. If this is on target, the other blood glucose values through the day are also likely to be on target. Measuring the A_{1c} will confirm this. If the evening blood glucose is not on target, add morning basal insulin (10 U) before breakfast and repeat the titration process.

Once the before breakfast and evening blood glucose values are on target, consider stopping one or more of the oral hypoglycaemic agents. If blood glucose levels were to increase, the oral agent could be restarted or the insulin therapy increased. With regard to Arnold stopping taking these agents:

- Arnold's beta cells are probably not making much insulin and he is already being given exogenous insulin, so stopping the sulfonylurea may not make much difference to his blood glucose control
- if fluid retention and increased extracellular fluid are a concern, the glitazone could be phased out as these effects are caused by both the glitazones and insulin
- Arnold's renal function will deteriorate as he gets older (GFR decreases by about 1 mL/min/year), and a metformin dose that was appropriate 10 to 15 years ago will become excessive; starting insulin may provide the opportunity of proactively reducing the metformin dose (e.g. from 1 g to 850 mg or 500 mg tablets) or simplifying the schedule (e.g. from a thrice daily to a twice daily schedule).

In the more distant future, Arnold may need a rapid or short acting bolus insulin before one or more meals to control postprandial glycaemia. However, ensure that the basal blood glucose levels before breakfast and before the evening meal are on

target, and always adjust the basal insulin before adding or adjusting the bolus insulin.

Key points

- Before changing a patient's oral hypoglycaemic agent therapy, review his or her medication, lifestyle and medical issues that can affect blood glucose control.
- Each of the five classes of oral hypoglycaemic agent have pros and cons. Generally, the sequence of prescribing these is metformin, sulfonylurea, glitazone. Acarbose and repaglinide may be useful to control postprandial glycaemia early in the course of diabetes.
- The KISS principle makes starting insulin more acceptable to the patient and practical for the doctor. First get the fasting glucose on target using bed time basal insulin, then review evening glycaemia and, if necessary, add morning basal insulin.
- Once the patient's blood glucose is on target, consider stopping one or more of the oral hypoglycaemic agents.
- When adjusting insulin, always adjust the basal insulin to get the fasting and evening glucose on target before adding or changing preprandial bolus (rapid or short acting acting) insulin. MT

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