Sustained release metformin where standard metformin is not tolerated

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Article points

1. Few people will continue taking medication while experiencing side effects.
2. Hypoglycaemia does not usually occur with metformin when used as monotherapy.
3. In the UKPDS metformin reduced macrovascular complications and mortality in type 2 diabetes.
4. The DARTS study showed that simple regimens lead to significantly better adherence.
5. If medication is not tolerated we must not assume that the patient is doing something wrong.

Key words

- Type 2 diabetes
- Sustained release metformin
- Once-daily dosing

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Research has found that few people will put up with unwanted side effects from a prescribed medication for more than a month (ICM Research, 2004). The most common side effects of metformin tablets are gastrointestinal (GI) and although the literature states that these can easily be managed in most people by cautious dose titration, administration after meals or dose reduction, many people with diabetes discontinue taking the drug. Sustained release metformin (Glucophage SR, Merck, West Drayton) is a slow release formulation that promises fewer GI side effects and allows once-daily dosing, both of which should provide better concordance (Davidson and Howlett, 2004). This article looks at whether people with type 2 diabetes who could not tolerate standard metformin followed advice on administration and titration and if they could tolerate sustained release metformin. The effect this had on HbA_{1c}, weight and insulin or oral hypoglycaemic agents was also examined.

Metformin is the only drug available in the biguanide class. Its positive effects are mainly caused by decreasing gluconeogenesis and increasing the peripheral utilisation of glucose. Metformin is the first choice drug in overweight people (BMI >25 kg/m^2) in whom strict lifestyle intervention has failed to control their diabetes (NICE, 2002). It is the drug of first choice in overweight patients and is also used when diabetes is inadequately controlled with sulphonylureas (SU) and now with increased frequency in combination with insulin (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2006).

Hypoglycaemia does not usually occur with metformin when used as monotherapy, but can occur if used in conjunction with other oral hypoglycaemic agents (OHAs) or insulin. Metformin is associated with lactic acidosis but is most likely to occur in people with renal impairment and thus should not be used even in mild renal impairment (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2006).

In addition to its glucose lowering effects,

metformin appears to have beneficial effects on other cardiovascvular risk factors including dyslipidaemia, plasminogen activator inhibitor-1 levels, monocyte adhesion to endothelial cells, insulin resitance and hyperinsulinaemia (Cusi and Defronzo, 1998; Nagi and Yudkin, 1993; Uehara et al, 2001; Mamputu et al, 2003). The UK Prospective Diabetes Study (UKPDS) has also demonstrated that metformin reduced macrovascular complications and mortality in people with type 2 diabetes (UKPDS, 1998).

Concordance

The Diabetes Audit and Research in Tayside Scotland (DARTS) study showed that only one-third of people with diabetes who are prescribed one type of tablet collected their medication as recommended (Donnan et al, 2002). People on combination therapy with two types of tablets found it even harder, with only one-tenth collecting their prescriptions as recommended. The findings also reveal potential solutions, with those on simple regimens such as once-daily treatment showing significantly better adherence.

Consumer research into attitudes towards long-term medication for conditions such as type 2 diabetes found that 11 % would put up with unwanted side effects from a prescribed medication for a month and only 2 % would tolerate them for three months. Headaches were cited as the side effect with the most negative impact on life, closely followed by diarrhoea and then nausea (ICM Research, 2004).

It is well known that the principal side effects of standard immediate release (IR) metformin tablets are gastrointestinal (GI) in nature (Howlett and Bailey, 1999). A double blind, parallel group dose–response trial in a total of 451 people with type 2 diabetes showed that the incidence of GI side effects was approximately 20–30 % in participants randomised to receive IR metformin 500–2500 mg/day. The incidence of such side effects with IR metformin is highest in the period immediately after the initiation of treatment and tends to diminish over time (Garber et al, 1997). Generally, GI side effects can be easily managed in most people by cautious dose titration, administration after meals or by reducing the total daily dosage (Fujioka et al, 2005).

Blonde et al (2004) retrospectively reviewed patient records to compare the frequency of adverse GI events in groups taking either IR metformin (n=158) or sustained release (SR) metformin (n=310). They concluded that the frequency of any GI adverse event during the first year of treatment was not significantly different between the two groups (11.94 % versus 11.39 %; *P*=not significant).

The SR metformin formulation promises fewer GI side effects (Davidson and Howlett, 2004), thereby providing better concordance and improved diabetes control as well as the potential cardiovascular risk reducing effects of metformin. Data from previous studies confirms that the antihyperglycaemic efficacy of SR metformin is comparable to that of IR metformin given in divided doses (Fujioka et al, 2003; Fujioka et al, 2005). This work also demonstrated that SR metformin exerted little effect on body weight, with mean changes in body weight being small (reductions of up to 1 kg).

Methods

The aim of this study was to investigate whether people unable to tolerate IR metformin:

- had been taking IR metformin appropriately
- could tolerate SR metformin
- the effect SR metformin had on their:
  - HbA_{1c}
  - weight
  - insulin or SU dose.

Twenty-two participants were recruited through the general diabetes clinic within a large teaching hospital in Liverpool. Any person not on metformin without contraindications were asked whether they

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1. Metformin was shown to reduce macrovascular complications and mortality in people with type 2 diabetes.
2. A low percentage of people will put up with the long-term GI side effects of immediate release (IR) metformin.
3. Sustained release (SR) metformin promises fewer gastrointestinal side effects, thus improving concordance and diabetes control.
4. This study of 22 people aimed to investigate whether people unable to tolerate IR metformin had been taking their medication appropriates, whether they could tolerate SR metformin, and the effects SR metformin had on their: HbA_{1c}, weight and insulin or SU dose.

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1. All participants were found to have been taking IR metformin according to guideline recommendations when intolerance occurred.
2. Mean HbA_{1c} was significantly lower after 12 weeks in the twelve participants (55 %) who could tolerate 1–1.5 g of SR metformin.
3. There was a significant weight gain observed, on average 1 kg per participant.

had previously been taking IR metformin. Any person who had previously been taking IR metformin and had stopped due to side effects were questioned on the following points:

- initial dosage (in comparison to administration advice by the British Medical Association and Royal Pharmaceutical Society of Great Britain, 2006)
- speed of titration (in comparison to administration advice by the British Medical Association and Royal Pharmaceutical Society of Great Britain, 2006)
- when the metformin was taken (i.e. pre-meal, with meal or post-meal)
- maximum tolerated dose
- side effects (if any).

If the person with diabetes was administering IR metformin correctly and had to stop due to side effects at a dose of 2 g or less they were prescribed SR metformin and included in the study. There were no other exclusion criteria and individuals on any anti-diabetic medication, be it insulin or other OHAs, were included.

Biomedical variables were measured on the individuals' usual diabetes clinic attendances and nurse-led follow-up clinics.

Measures

All measures were obtained in the clinic environment on commencement of SR metformin and at 12 weeks. The following variables were measured:

- HbA_{1c}
- weight
- insulin or OHA dose.

Tolerance was measured by assessing side effects. This also determined the dose titration as the participants were maintained on the highest dose tolerated (up to 2 g) without unwanted side effects.

Other information was also noted: maximum tolerated dose of immediate release metformin, maximum tolerated dose of SR metformin, age, gender and type of diabetes.

Results

All patients, when questioned, had been prescribed and were taking metformin according to the British National Formulary guidance when intolerance occurred. This was to start on 500 mg with breakfast for at least one week, increasing to 500 mgs at breakfast and evening meal for at least another week, then 500 mgs at breakfast, lunch and evening meal increasing as tolerated to 2–3 g daily in divided doses (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2006).

Thirteen participants (59 %) could not tolerate any IR metformin, and nine (41 %) could tolerate 1 g of IR metformin.

Upon completion 10 participants (45 %) could tolerate 2 g of SR metformin and 12 (55 %) could tolerate 1–1.5 g of SR metformin.

Mean HbA_{1c} was 9.0 % at commencement of SR metformin and was significantly lower at 12 weeks: 8.3 % (P=0.008). A significant reduction in mean insulin dose was also noted, from 65 to 59 units per day (P=0.041). There was a significant increase in mean weight from 90.8 kg to 91.8 kg (P=0.041). On comparison of insulin or OHA dose and HbA_{1c}, 10 participants (45 %) were able to reduce their doses without increasing their HbA_{1c} (*Table 1*).

Increased weight was recorded in 10 people (45 %) who commenced on SR metformin. Four (18 %) lost weight, 8 (36 %) maintained weight. Comparisons between changes in weight and changes in OHA or insulin levels are shown in *Table 2*, and between weight and HbA_{1c} in *Table 3*.

Discussion

One may surmise that improvements in blood glucose levels could potentially lead to a gain in weight, as glucose is removed from the blood and is stored by the body. One may also surmise that improved blood glucose levels accompanied by a reduction in OHA or insulin dose would be associated with weight reduction or maintenance.

In this study there was significant weight gain, be it only an average of 1 kg. A weight gain of 1 kg may not appear to be a great deal but literature suggests that it may increase cardiovascular risk by 3.1 % and diabetes risk by 4.5 % to 9 % (Willet et al, 1995; Ford et al, 1997; Mokdad et al, 2000). The weight gain demonstrated in this study may well have been significantly greater if the same improvements in HbA_{1c} had been achieved with an increase in the participants' insulin or OHA doses rather than with the addition of SR Metformin.

On further analysis of weight compared with OHA or insulin dose all participants who lost weight had a reduction in their insulin or OHA doses, but an equal number of people had a reduction in OHA or insulin and gained weight. However, those who lost weight showed the greatest reduction in insulin or OHA at 12 weeks, ranging from a 19 % reduction to a 100 % reduction. The individual who had a 100 % reduction had been taking an SU and was able to cease administering the SU after 8 weeks due to hypoglycaemia. While it is tempting to attribute this change to the SR metformin, it may also be due to other variables not examined by this study, for example changes in diet or activity levels.

In this study, those who could not tolerate 2 g of SR metformin after the evening meal had their dose split into 1 g twice daily. Even on dividing the dose, 55 % of participants could not tolerate 2 g per day, but all patients could tolerate at least 1 g of SR metformin per day. This study demonstrated that SR metformin was tolerated well by 10 people (45 %) who took the maximum 2 g dose and 12 people (55 %) tolerated 1–1.5 g, with significant reductions in HbA_{1c}, and insulin or OHA dose. Also demonstrated was a significant weight gain, of an average 1 kg: but this ranged between weight loss of 1.9 kgs to a gain of 6.3 kgs.

Some bodies, including the Scottish Medicines Consortium and a number of PCTs, do not recommend the use of SR metformin as they feel that it has similar short-term efficacy to IR metformin and are not convinced on its improved GI tolerability and are conscious of the increased cost issues. There have been several studies looking at GI tolerability, many of which show improved tolerability with SR metformin, but the above bodies argue that these were either retrospective, not powered to detect differences in tolerability or that key assumptions were made for which the clinical evidence base was not convincing (Scottish Medicines Consortium, 2005).

In the author's experience people who were previously unable to tolerate IR metformin have been able to take SR metformin with improved HbA_{1c}, along with the added cardiovascular benefits of metformin, very

Table 1. Comparison of number of participants with changes in HbA_{1c} and with changes in OHA or insulin doses.

	Reduced OHA or insulin	Maintained OHA or insulin	Increased OHA or insulin
Reduced HbA_{1c}	9	4	3
Maintained HbA_{1c}	1	1	0
Increased HbA_{1c}	0	3	1

Table 2. Comparison of number of participants with changes in weight and with changes in OHA or insulin doses.

	Weight reduction	Weight maintained	Weight increased
Reduced OHA or insulin	4	2	4
Maintained OHA or insulin	0	5	3
Increased OHA or insulin	0	1	3

Table 3. Comparison of number of participants with changes in HbA_{1c}.

	Weight reduction	Weight maintained	Weight increased
Reduced HbA_{1c}	4	3	8
Maintained HbA_{1c}	0	1	1
Increased HbA_{1c}	0	4	1

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1. Even on dividing the dose to 1 g twice daily, 55 % of participants could not tolerate 2 g per day, but all patients could tolerate at least 1 g of SR metformin per day.
2. Some professional bodies do not recommend the use of SR metformin, but in the author's experience people unable to tolerate IR metformin have been able to take SR metformin with improved HbA_{1c} and often a reduction in insulin or OHA dose.

little weight gain, and often a reduction in insulin or OHA dose. Local PCTs in the author's district support the use of SR metformin if used appropriately along the same published guidelines as this study.

Conclusion

Education in relation to timing, administration and dose adjustment of IR metformin is essential. This study has highlighted the importance of healthcare professionals not assuming that the person with diabetes is not following administration advice if IR metformin is not tolerated. Changing to SR metformin may well improve tolerability and concordance, enabling most people to improve their diabetes control and possibly reduce their insulin or OHA dose. ■

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