

Transferring Patients with diabetes due to a Kir6.2 mutation from insulin to sulphonylureas in patients who are aged over 1 year

Andrew Hattersley (A.T.Hattersley@ex.ac.uk)

The finding that an activating mutation in the Kir6.2 subunit immediately led to the idea that sulphonylurea treatment might be successful in these patients as it binds to the same channel and would open the KATP channel by a non-ATP dependent route. In Gloyn et al (NEJM 2004) we supported this idea with functional work by showing there was no response to IV glucose in patients but there was a response to IV tolbutamide (a sulphonylurea). Since then there have been over 150 patients who have come off insulin and gone onto sulphonylureas with over 60 published (see Pearson E et al NEJM 2006 for main description and also , Sagen et al, Diabetes 2004, Zung A et al JCEM 2004, Codner E, et al Diabetes Care. 2005 Klupa T, et al Diabetologia. 2005). The hypothesis that patients could stop insulin and go onto sulphonylureas is now being tested by many clinicians – this is unpublished work which is being made available to help other clinicians make this transfer. We would hope that many people will follow previously used protocols to allow the data to be compared between patients. We also would request as much feedback as possible to help, especially if there are any problems.

Experience so far:

61 patients with Kir6.2 mutations are not on insulin, 60 transferred from insulin with the longest being 38 months to date but one has been on sulphonylureas for 46 years from diagnosis (see Gloyn et al NEJM 04).

8 Patients have not managed to transfer to sulphonylureas - 3 had DEND syndrome with Developmental delay (severe), Epilepsy as well as Neonatal Diabetes, and 2 were adults in whom the children with the same mutation have transferred (although other adults have transferred). The chances of transferring are reduced in adults especially if over 30 years where there has been poor glycaemic control.

Glycaemic control

Remarkably in a large multi-national study of the first 44 patients who discontinued insulin and went on to sulphonylureas, HbA1c improved in *all* patients (8.1% before, 6.4% after 12 weeks, $p < 10^{-11}$) without an increase in severe hypoglycaemia. (see Pearson et al NEJM 2006). This supports individual patients 24 hour glucose monitoring that shows a marked reduction in the fluctuations as well as an overall lower level of glycaemic control Sagen et al, Diabetes 2004, Zung A et al JCEM 2004). This HbA1c reduction was sustained at one year despite a reduced sulphonylurea dose. This is maintained for over 48 months and the reduction of dose with time suggests that this will be long lasting. One patient who was on sulphonylureas since diagnosis at 3 months still has excellent control aged 46 years (Gloyn et al NEJM 2004)

Neurological features

Some patients show improvement in their moderate neurological / developmental delay with sulphonylureas but in no cases has this returned to normal and motor function is more improved than higher mental function (See Slingerland A et al Diabetologia 2006). Further study of this is needed.

Doses of SU

Most have been transferred to glibenclamide where the median dose is **0.5mg/kg** (range **0.13 – 1.2 mg/kg**). After initial control is achieved glycaemic control may improve with time and the dose need to be decreased.

This is a high dose as an adult dose in type 2 diabetes for 60kg person is 5-15mg glibenclamide = **0.08 to 0.25 mg/kg**

Other sulphonylureas tried include gliclazide but this was less effective than glibenclamide in some patients.

A successful dose is likely to range from 0.1mg/kg to 1.0 mg/kg of glibenclamide (i.e. from normal adult introductory dose to up to 4 times the maximum dose). There are patients in the literature who have been treated successfully with up to 2mg/kg/day but these doses are not recommended unless there is a clear reduction of the insulin dose after 4 weeks of 1mg/kg/day glibenclamide. Any decision to go to these higher doses is a clinical decision of the local clinician after discussion with the patient and/or their parents.

Choice of sulphonylureas

Theoretically any SU should be as effective as any other in treating the diabetes. Gliclazide only binds to SUR1 (pancreas/neurons) whereas Glibenclamide binds to cardiac and muscle (SUR2A) as well. We have used glibenclamide in most cases and so have the most experience of this but other sulphonylureas have been successfully used.

Adverse reactions

The doses required exceed the maximum adult dose, and glibenclamide is not licensed in children. Reported side effects to Daonil (generic name glibenclamide) are listed on the drug information. The commonest known side effects are skin allergies (1.5%) which may resolve. GI side effects including diarrhoea in 1-2% and haematological – anaemia, leucopenia and thrombocytopenia .

To date, in the Kir6.2 patients patients, six patients have had **diarrhoea** which resolved without dose reduction, and two patients had transient mild **leukopenia** which resolved on re-test with no dose reduction. Monitoring of full blood count, and LFTs is advised. Three patients have had tooth discolouration with loss of enamel in two cases. This is expected to be a previously unreported side effect. To date it has only occurred with glibenclamide but this is the treatment used in most patients.

Inpatient protocol for the transfer of patients with Kir6.2 and SUR1 mutations from insulin to sulphonylureas in patients with PNDM

Please note these are clinical guidelines but as this is a new treatment area in diabetes – all parts of this process should be critically assessed in your patient and any final decision on treating the patient with this treatment needs to be by the patient’s physician. If you have any questions do not hesitate to contact me – my email is A.T.Hattersley@ex.ac.uk, office number +44 (0)1392 408260. Prof. Andrew Hattersley

INPATIENT TRANSFER - RAPID

Work up prior to introduction of sulphonylureas (red text essential; black text desirable). Aim to establish a baseline to establish if improvement in diabetes and other features

- **HbA1c measured**
- **General physical examination including height and weight**
- **Developmental age** – gross motor, fine motor, verbal
- Neurological examination If any developmental delay (ideally with a quantitative, repeatable method)
- IQ (age appropriate test)
- EEG if epilepsy
- MRI if neurological features

Introduction of sulphonylureas (done as inpatient)

Glibenclamide formulation.

Where the patient is able to take tablets, generic 1.75 and 5 mg glibenclamide tablets should be used. If smaller doses are needed, capsules of glibenclamide can usually be made by the local pharmacy to any strength. In infants unable to swallow tablets, a glibenclamide suspension can be used (Glibenclamide suspended in Suspension Diluent A (Xantham gum and water, Nova Laboratories) to a concentration of 2.5 mg per ml). This has a shelf life of around 4 weeks. The making of suspension in water and other diluents has also been used successfully. Discuss options with your hospital pharmacy.

1) Inpatient protocol (used in the majority of patients). The underlying principles.

The glibenclamide dose is increased daily by 0.2mg per kg per day in two divided doses up to a total daily dose of 1.0 mg per kg per day. As the dose is increased it is usually possible to reduce and then stop the insulin dose. This reduction in insulin is achieved after the first day by the use of only short acting insulin enabling rapid titration of insulin dose depending on the pre-meal glucose. The finding of a pre-meal capillary glucose value of < 7 mmol per liter either pre-breakfast, pre-lunch or pre-evening meal is taken as an indication to reduce the insulin dose (usually by 50% of the normal pre-meal insulin) and keep the glibenclamide dose unchanged. However, if subsequent pre-meal capillary blood glucose values are >7 mmol per liter then glibenclamide dose titration could be recommenced. We have found that the pre-breakfast glucose may be very slow to fall and pre-lunch or pre-evening meal glucose values fall more rapidly and are generally a better marker of response to sulphonylureas. Note the long half life of glibenclamide will mean there is only a slow increase of blood levels with this rapidly increasing regime. This means that levels will continue to rise even when the dose is kept stable. A rapid reduction in dose may be required once good control is achieved. In some patients there is initial diarrhea when the dose of SUs is increased but this settles if the dose is maintained.

Day 0 before starting sulphonylureas

- Admit patient to hospital the day before starting to introduce sulphonylureas.
- Commence regular monitoring of capillary blood glucose and blood or urine testing for ketones. If height, weight or developmental age not assessed do now
- Take normal insulin at evening/ night on Day 0 including both long and short acting insulin.

Day 1.

- **Do not take any food or insulin first thing in the morning but water may be drunk**
- Do not take insulin injections in the morning prior to fasting sample. Give long acting and short acting insulin the night/evening before but defer morning insulin doses until after fasting sample. If on pump therapy turn to the normal basal rate until after fasting sample.
- Do not take any food but water (only) may be drunk before fasting tests.
- At 08.00: take basal HbA1c, paired FASTING glucose and C peptide.. This will allow assessment of the endogenous insulin secretion prior to sulphonylureas and is an important baseline. After this take breakfast, normal fast acting insulin and also the first dose of sulphonylurea (0.1mg/kg Glibenclamide)
- Continue measuring glucose before meals and before bed daily
- Administer soluble insulin or rapid acting analogue insulin with meals as required
- Give evening sulphonylurea dose (0.1mg/kg Glibenclamide) unless capillary blood glucose <7mmol/l. Take isophane or long acting insulin as usual in the evening.

Day 2.

- **Omit isophane or long acting insulin analogue and remain off this for the period of the transfer process.** If on insulin pump reduce basal rate of insulin pump by 50 % and reduce further in accordance with capillary blood glucose measurements.
- **Throughout transfer period administer soluble insulin or rapid acting insulin analogue or insulin pump boluses with meals as required to maintain reasonable glycaemic control.**
- If capillary blood glucose > 7 mmol per liter pre-sulphonylurea (SU) then give 0.2 mg per kg glibenclamide with breakfast and evening meal (total dose 0.4 mg per kg per day)
- If capillary blood glucose < 7mmol per liter pre-SU then continue on 0.1 mg per kg (total dose 0.2 mg per kg per day) and reduce pre-meal insulin dose by 50%.

Day 3.

- If capillary blood glucose > 7 mmol per liter pre-SU then give 0.3 mg per kg glibenclamide with breakfast and evening meal (total dose 0.6 mg per kg per day)
- If capillary blood glucose < 7mmol per liter pre-SU then continue on 0.2 mg per kg (total dose 0.4 mg per kg per day) and reduce pre-meal insulin dose by 50%.

Day 4.

- If capillary blood glucose > 7 mmol per liter pre-SU then give 0.4 mg per kg glibenclamide with breakfast and evening meal (total dose 0.8 mg per kg per day)
- If capillary blood glucose < 7mmol per liter pre-SU then continue on 0.3 mg per kg (total dose 0.6 mg per kg per day) and reduce pre-meal insulin dose by 50%.

Day 5.

- If capillary blood glucose > 7 mmol per liter pre-SU then give 0.5 mg per kg glibenclamide with breakfast and evening meal (total dose 1.0mg per kg per day)
- If capillary blood glucose < 7mmol per liter pre-SU then continue on 0.4 mg per kg (total dose 0.8 mg per kg per day) and reduce pre-meal insulin dose by 50%.

Day 6 onwards.

- Maintain dose at 1.0 mg per kg per day of Glibenclamide for at least 4 weeks this may be done as an outpatient
- Doses of up to 2mg/kg/day have been successfully given without side effects and if there has been signs of some response – as shown by reduced insulin requirements then it is advisable to continue to raise the dose. Email advice will happily be given by the Exeter team.
- Frequently glucose and insulin requirements will usually continue to fall even though the patient is on a fixed dose of sulphonylureas.
- It may be that once insulin is stopped it is possible to reduce the sulphonylureas further . This should be done if the glucose values are going below 4mmol/l. (72mg/dl).

Discharge.

- Discharge when no longer requiring insulin treatment, or when stable on a combination of glibenclamide (≥ 1 mg per kg) and insulin.
- Patients should continue to monitor capillary blood glucose four times a day and at bedtime, as insulin requirements may continue to fall, or glibenclamide dose may need to be reduced.
- Weekly contact and appropriate titration of glibenclamide and/or insulin should be made.

Review as required and maintain telephone contact

Other points on SU treatment

Many patients seem to get better control with a tds regime despite the long half life of sulphonylureas

Patients may have occasional very high glucose values – ie >20 mmol/l or >360 mg/dl – these are not explained and seem to settle with the normal dose of sulphonylureas. These are rare as shown by the HbA1c.

When sick as long as not vomiting and able to take the sulphonylureas glycaemia seems to be maintained and insulin does not need to be re-introduced. If there is vomiting a fast acting insulin is appropriate

3 month review

Record HbA1c, and paired fasting glucose and insulin/Cpeptide, daily average glucose values and insulin requirements (if any). Sulphonylurea doses and how the doses are divided during the day.

Repeat height and weight.

Repeat developmental tests. If problems repeat full neurological assessment by neurologist who performed initial assessment.

If no improvement (unchanged insulin dose and similar control and if improvement in neurology) on SU then discontinue

Please email the 3 month and starting data to Prof Andrew Hattersley email A.T.Hattersley@ex.ac.uk and Prof. Sian Ellard Sian.Ellard@nhs.net . Please also tell us any problems you had with the protocol. We use this data to help improve the protocol.

Subsequent reviews

Consider reducing sulphonylureas especially if hypos or HbA1c falling markedly.

Any questions please contact Prof. Andrew Hattersley email A.T.Hattersley@ex.ac.uk Telephone +44 1392 408260

Outpatient protocol for the transfer of patients with Kir6.2 and SUR1 mutations from insulin to sulphonylureas in patients with PNDM

Work up prior to introduction of sulphonylureas (red text essential; black text desirable). Aim to establish a baseline to establish if improvement in diabetes and other features

- HbA1c measured
- General physical examination including height and weight
- Developmental age – gross motor, fine motor, verbal
- Neurological examination If any developmental delay (ideally with a quantitative, repeatable method)
- IQ (age appropriate test)
- EEG if epilepsy
- MRI if neurological features

Introduction of sulphonylureas (done as outpatient patient)

For important practical points on sulphonylurea treatment e.g formulations, side effects etc. see the inpatient protocol. The following points are important if considering outpatient treatment.

- Capillary blood glucose should be tested before all meals and at bedtime.
- Care must be made to recognise and treat hypoglycemia including the use of glucagon injection 0.5-1 mg per for emergency use if unable to take oral carbohydrate. However severe hypoglycaemia is rare in over 100 transfers done to date (1%).
- The physician, or an appropriate substitute, should see the patient every week, and be accessible by phone every day during the transfer.

Day 0 before starting sulphonylureas

- Commence regular monitoring of capillary blood glucose and blood or urine testing for ketones.
- Take normal insulin at evening/ night on Day 0 including both long and short acting insulin.

Day 1 OGTT or fasting bloods and first dose of sulphonylureas

Do not take any food or insulin first thing in the morning but water may be drunk

- Do not take insulin injections in the morning prior to OGTT / fasting sample. Give long acting and short acting insulin the night/evening before but defer morning insulin doses until after OGTT. If on pump therapy turn to the normal basal rate until after OGTT.
- Do not take any food but water (only) may be drunk before fasting tests and OGTT.
- At 08.00: take basal HbA1c, paired FASTING glucose and C peptide. If possible perform OGTT giving glucose in a dose of 1.75g/kg max 75g – see subsequent protocol at the end of this outline. This will allow assessment of the endogenous insulin secretion prior to sulphonylureas and is an important baseline.
- With lunch/ post OGTT food give fast acting insulin and first dose of sulphonylurea (0.1mg/kg Glibenclamide)
- If only fasting samples taken take fast acting insulin and first dose of sulphonylurea (0.1mg/kg Glibenclamide) with breakfast
- Continue measuring glucose before meals and before bed daily

- Administer soluble insulin or rapid acting analogue insulin with meals as required. Can be discharged to outpatient for this.
- Give evening sulphonylurea dose (0.1mg/kg Glibenclamide) unless capillary blood glucose <7mmol/l. Take isophane or long acting insulin as usual in the evening.

Protocol as out patient

Week 1.

- Continue established insulin regime initially but reduce insulin as necessary according to blood glucose values
- Give glibenclamide 0.2 mg per kg per day with 0.1mg/kg pre- breakfast (08.00 hours) and 0.1 mg / kg pre evening meal (18.00 hours). Keep the dose constant during the week.

Week 2.

- At beginning of week 2 if pre-meal capillary blood glucose values often are more than 7 mmol per liter, increase glibenclamide to 0.4 mg per kg per day (0.2mg/kg bd).
- If pre-meal capillary blood glucose values frequently are less than 7 mmol per liter, keep glibenclamide at 0.2 mg per kg per day and reduce insulin. If after reducing insulin glucose values rise then increase glibenclamide to 0.4 mg per kg per day (0.2mg/kg bd).

Week 3.

- At beginning of week 3 if pre-meal capillary blood glucose values often are more than 7 mmol per liter, increase glibenclamide to 0.6 mg per kg per day (0.3mg/kg bd).
- If pre-meal capillary blood glucose values frequently are less than 7 mmol per liter, keep glibenclamide at 0.4 mg per kg per day and reduce insulin. If after reducing insulin glucose values rise then increase glibenclamide to 0.6 mg per kg per day (0.3mg/kg bd).

Week 4.(most but not all patients can discontinue by this stage)

- At beginning of week 4 if pre-meal capillary blood glucose values often are more than 7 mmol per liter, increase glibenclamide to 0.8 mg per kg per day (0.4mg/kg bd).
- If pre-meal capillary blood glucose values frequently are less than 7 mmol per liter, keep glibenclamide at 0.6 mg per kg per day and reduce insulin. If after reducing insulin glucose values rise then increase glibenclamide to 0.8 mg per kg per day (0.4 mg/kg bd).

Week 5 and onwards.

- The vast majority of patients will now be able to discontinue insulin by the time they are on 0.8 mg/kg/day. If not, increase the glibenclamide dose to 1.0 mg per kg per day (0.5mg/kg/day). As we have seen a delayed response we would suggest at least 4 weeks and ideally 6 weeks on this dose while continuing with insulin as required.
- If at the end of this 4-6 week period there is no evidence of a response with insulin doses similar to those at starting then it is best to return to insulin alone.
- If there is a clear reduction in insulin requirement at this dose (reduction in insulin to at least 60% of pre-SU dose then it is worth continuing for longer and a higher dose of glibenclamide could be considered. Doses as high as 2mg/kg/day have been given without side effects and with full transfer off insulin.

Review as required and maintain telephone contact

Other points on SU treatment

Many patients seem to get better control with a tds regime despite the long half life of sulphonylureas

Patients may have occasional very high glucose values – ie >20 mmol/l (> 360mg/dl) – these are not explained and seem to settle with the normal dose of sulphonylureas. These are rare as shown by the HbA1c.

When sick as long as not vomiting and able to take the sulphonylureas glycaemia seems to be maintained and insulin does not need to be re-introduced. If there is vomiting a fast acting insulin is appropriate

With time the dose may be able to be reduced but this is not seen as frequently as in the inpatient rapid transfer. This should occur if the patient has glucose values below 4mmol/l (72mg/dl)

3 month review

Record HbA1c, and paired fasting glucose and insulin/C peptide, daily average glucose values and insulin requirements (if any). Sulphonylurea doses and how the doses are divided during the day. Repeat height and weight.

Repeat developmental tests. If problems repeat full neurological assessment by neurologist who performed initial assessment.

If no improvement (unchanged insulin dose and similar control and if improvement in neurology) on SU then discontinue

Please email this data and the data from before transfer to Prof Andrew Hattersley email A.T.Hattersley@ex.ac.uk and Prof. Sian Ellard Sian.Ellard@nhs.net . Please also tell us any problems you had with the protocol. We use this data to help improve the protocol

Subsequent reviews

Consider reducing sulphonylureas especially if hypos or HBA1c falling markedly.

**Any questions please contact Prof. Andrew Hattersley
email A.T.Hattersley@ex.ac.uk
Telephone +44 1392 408260**