Transferring patients with permanent neonatal diabetes (PNDM) subtypes *KCNJ11* or *ABCC8* from insulin to sulfonylureas

What is a pathogenic PNDM causing variant and how does diabetes present in these patients?

Pathogenic variants in the ATP-sensitive potassium (K<sub>ATP</sub>) channel genes *KCNJ11* and *ABCC8* can cause permanent neonatal diabetes (PNDM) or transient neonatal diabetes (TNDM) or later onset diabetes. There is usually a close relationship between the genetic change and the clinical presentation, so specific pathogenic variants found in patients with PNDM are also likely to result in PNDM in other patients. This information sheet is for patients who have a variant in *KCNJ11* or *ABCC8* that results in PNDM.

In K<sub>ATP</sub> gene variants that result in K<sub>ATP</sub> channel-related PNDM, the diabetes is usually diagnosed in early infancy, typically 4-8 weeks (range 0-26). Patients usually present with severe hyperglycaemia, and ketoacidosis is frequent. Patients will initially be treated with insulin. K<sub>ATP</sub> channels are also present in the brain, nerves and muscle, and a range of neurodevelopmental features may be present in children with K<sub>ATP</sub> channel-related PNDM. These are more likely with specific variants. (See appendix 1 “*KCNJ11* or *ABCC8* Neonatal Diabetes and the brain” at the end of this protocol).

Sulfonylureas are excellent treatment for K<sub>ATP</sub> channel- PNDM

Sulfonylureas can overcome the genetic defect in K<sub>ATP</sub> channel-related PNDM by binding and closing pancreatic K<sub>ATP</sub> channels independently of ATP. Transfer to high dose sulfonylurea therapy has been successful in the majority of patients with K<sub>ATP</sub> channel pathogenic variants and results in improved glycaemic control (Pearson *et al* 2006 PMID: 16885550 and Rafiq *et al* 2008 PMID: 18025408). This excellent glycaemic control is maintained long-term (Bowman *et al* 2018 PMID: 29880308 and Bowman *et al* 2021 PMID: 33184150). Sulfonylureas can also lead to some improvement in neurological features; the benefit is greater if treatment is started at a younger age (de Gouveia Buff Passone *et al* 2022 PMID: 35657808) and higher doses are used.

It is important to recognise that the response to SU treatment is different compared to Type 2 diabetes. The doses required are 2-4x higher and have a different mechanism of action. In PNDM the sulfonylureas depolarise the unresponsive hyperpolarised beta-cell and allow it to respond to incretins such as GLP-1 (Pearson *et al* 2006 PMID: 16885550) but not glucose while in Type 2 diabetes the hyperglycaemia mediated closure of the channel is augmented. Doses of glibenclamide should not be adjusted according to food or premeal glucose unlike insulin.

Experience of transferring K<sub>ATP</sub> channel- PNDM patients from insulin to sulfonylureas

A high proportion (85-90%) of patients with K<sub>ATP</sub>-related PNDM can successfully transfer from insulin to sulfonylureas (Pearson *et al* 2006 PMID: 16885550 and Rafiq *et al* 2008 PMID: 18025408). From 2004-2023 over 2500 patients worldwide have successfully transferred. The chance of successful transfer relates to the specific genetic variant as well as the age of the patient (with higher likelihood in children vs adults) (Babiker *et al* 2016 PMID: 27033559, Thurber *et al* 2015 PMID: 25877689 and Garcin *et al* 2020 PMID: 32418263).
Treatment with high dose sulfonylureas results in improvement in HbA1c which is maintained at 10 years and is likely to be lifelong (Bowman et al 2018 PMID: 29880308 and Bowman et al 2021 PMID: 33184150). Despite high doses, severe hypoglycaemia is extremely rare (no cases in 700 patient years follow-up (Bowman et al 2018 PMID: 29880308 and Garcin et al 2020 PMID: 32418263)). In those with neurological features, some improvement in these features is seen in approximately half on starting sulfonylureas (Bowman et al 2018 PMID: 29880308). Neurological improvement is more marked in patients treated as infants (de Gouveia Buff Passone et al 2022 PMID: 35657808).

**Choice of sulphonylurea**

The vast majority of our experience and that in the literature of treating PNDM is with the sulfonylurea glibenclamide (also known as Glyburide). This was originally selected as it was widely available and non-selective and so could help in all tissues where the channel is present and it was the most potent. Theoretically any sulfonylurea should be as effective as any other in treating the diabetes. Other sulfonylureas tried include gliclazide and glimepiride but these can be less effective than glibenclamide in some patients, and are not reported to benefit the neurological features in the way that glibenclamide does. To calculate comparable doses for other sulfonylureas for the glibenclamide doses in our protocols use the maximum dose of the SU suggested in adults and compare that to 10mg glibenclamide.

Recently there has been difficulty in some counties including the UK in getting hold of glibenclamide. If you search for “UK Access To Glibenclamide“ on our website www.diabetesgenes.org potential suppliers can be identified.

**Solutions of glibenclamide to help administration to infants**

Dosing and administration of glibenclamide to infants is helped by making a solution of glibenclamide. Stable glibenclamide solutions can be made by hospital pharmacies. Glibenclamide can be suspended in Suspension Diluent A (Xanthan gum and water, Nova Laboratories) or similar to a concentration of 2.5 mg/ml. This has a shelf life of 90 days (Estevez et al 2016 PMID: 31156851) Suspension in water and other diluents has also been used successfully with a similar stability (https://www.lifescienceglobal.com/pms/index.php/jnt/article/view/618/pdf). Alternatively, tablets can be crushed and given with food. Discuss options with your hospital pharmacy.

While it is possible to purchase a ready formulated solution from a French firm this is extremely expensive and the results reported in the literature was from making up solutions or using crushed tablets.

**Doses of sulfonylureas**

Our experience in Exeter is that most patients have been transferred to glibenclamide where the median maintenance dose is ~0.3mg/kg/day (range ~0.1 – 1.2mg/kg/day). This is a high dose compared to Type 2 diabetes where the dose for an adult with type 2 diabetes is typically 0.07mg/kg/day (range 0.03–0.20mg/kg/day) glibenclamide.

In KATP-related PNDM doses up to 2.8mg/kg/day have been reported on in the literature (Garcin et al 2020 PMID: 32418263). Very high doses (> 1mg/kg/day) have been used in unresponsive mutations with marked neurological features with some improvement reported in some cases. No side effects of going to these higher doses has been reported. 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.

Titrating of dose in the first 4 weeks can usually achieve excellent glucose control. As there is not the same risk of severe hypoglycaemia in these patients as there is with insulin treatment it is not necessary to keep the glucose above 4mmol/l and doses rarely need to be reduced to avoid hypoglycaemia. As the child grows doses should be increased in line with weight increase so the dose/kg/day is constant.

**Adverse reactions**

Reported side effects are listed on the drug information leaflet but the doses required exceed the maximum recommended adult dose and so previously unrecognised side effects could be encountered. In our >10 year term follow up of 81 patients with KCNJ11 PNDM, 11 (14%) had side-effects, but no patients had to stop the sulfonylurea treatment as a result. The most common (9/11) side effects were
GI disturbance typically transitory diarrhoea, or transitory nausea when glibenclamide was first initiated or the dose increased. One patient had initial hepatic steatosis and one had tooth discolouration (we know of 2 other cases of this). Although haematological side effects are reported we only know of 2 patients have with transient mild leukopenia which resolved on re-test with no dose reduction.

Transfer as in-patient or out-patient?
We provide information below on a rapid transfer as an inpatient or a slower transfer as an outpatient. Both have worked well. The outpatient transfer is more controlled and the longer time taken to increase the dose allows the response to a dose of glibenclamide to be fully observed and adjusted to. However, the transfer as an outpatient protocol takes longer and it does rely on excellent communication with the parents and them being confident to cope with a changing situation. The use of CGM has helped this communication.

In infants (< 1 year) the response to starting the glibenclamide is sluggish and the slower titration of the outpatient regime can help if the home situation is appropriate.
Inpatient protocol for the transfer of patients with permanent neonatal diabetes, subtypes KCNJ11 and ABCC8 from insulin to sulfonylureas.

Please note these are clinical guidelines that have only been trialled in relatively few patients. 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 taken by the patient’s physician. If you have any questions do not hesitate to contact Prof. Andrew Hattersley (A.T.Hattersley@exeter.ac.uk, office number +44 (0)1392 408260 and mobile number +44 (0)7973165924).

**Introduction of sulfonylureas (done as inpatient)**

**Glibenclamide formulation**

Since infants are unable to swallow tablets, a glibenclamide suspension can be used (see section above). Where the patient is able to take tablets, generic 2.5mg and 5mg glibenclamide tablets should be used. If smaller doses are needed, capsules of glibenclamide can usually be made by the local pharmacy to any strength.

**Inpatient protocol: the underlying principles.**

The glibenclamide dose is increased by 0.2mg/kg/day in two divided doses up to a total daily dose of 1.0 mg/kg/day although 0.3-0.6mg/kg/day is usually sufficient to allow insulin to be discontinued. As the dose is increased it is usually possible to reduce and then stop insulin. This reduction in insulin is achieved after the first day when normal insulin doses are given by the use of only short acting insulin enabling rapid titration of insulin dose. Evidence of response as shown by the pre-meal glucose values being lowered 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 raised, then glibenclamide dose up-titration could be recommenced. When there is clear evidence of a response to the sulfonylurea the dose can usually be maintained and insulin stopped over 1-3 days. Usually within 5-7 days it is possible to discontinue insulin completely. The scheme proposed below is an outline of one way to reduce the insulin as the sulfonylurea dose increases it should be interpreted flexibly rather than rigidly.

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 sulfonylureas. 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 glibenclamide levels will continue to rise even when the dose is kept stable.

In some patients there is initial diarrhea when the dose of sulfonylureas is increased but this settles if the dose is maintained.

**Work up prior to introduction of sulfonylureas:**

1. **1. How likely is the mutation in your patient likely to transfer and are CNS features expected?**
   - Obtain information from diagnostic lab or one of these publications (Babiker et al 2016 PMID: 27033559 and Garcin et al 2020 PMID: 32418263) about how likely it is that the mutation found in your patient is likely to transfer. When >95% of patients with this mutation have successfully transferred then a glibenclamide dose of 0.6mg/kg/day is usually sufficient and you will rarely need to go above this dose although this may need 2-3 days at this higher dose before insulin can be fully stopped. If no patients have transferred then a dose of at least 1mg/kg/day is needed and usually insulin will need to be continued in normal replacement doses rather than being reduced.
   - Also identify if mutation is known to be associated with marked neurological features (see appendix 1) known as DEND (Developmental delay, Epilepsy, and Neonatal diabetes) syndrome or the less severe intermediate DEND (iDEND) where epilepsy is not an early feature. This information will alter the doses of SU advised see appendix 1.
2. Establish a baseline to identify improvements in diabetes and other features
   - HbA1c and C peptide (this can be a non-fasting random) measured (results not needed to proceed). If using CGM record time in target.
   - General physical examination including height and weight.
   - Developmental assessment age appropriate – gross motor, fine motor, verbal.
   - Neurological examination and investigation (EEG/MRI) if appropriate).

Admission to start sulfonylurea and titrate down insulin

Day 0 before starting sulfonylureas
   - Admit patient to hospital the day before starting to introduce sulfonylureas.
   - Commence regular monitoring of capillary blood glucose or CGM and blood or urine testing for ketones.

Day 1.
   - Continue established insulin regime (short and long acting insulin or insulin pump).
   - Give 0.1mg/kg glibenclamide before breakfast (approx. 08.00 hours).
   - Prior to evening meal administer 0.1mg per kg glibenclamide with evening meal (approx. 18.00 hours).
   - Take overnight long acting insulin.

Day 2.
   - Omit long acting insulin 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.
   - Administer rapid acting insulin analogue or insulin pump boluses with meals as required depending on blood glucose values to keep good glycaemic control.
   - If capillary blood glucose >7mmol per liter pre-sulfonylurea (SU) then give 0.2mg per kg glibenclamide with breakfast and evening meal (total dose 0.4mg per kg per day).
   - If capillary blood glucose <7mmol per liter pre-SU then continue on 0.1mg per kg (total dose 0.2mg per kg per day) and reduce pre-meal insulin dose by 50%.

Day 3.
   - If capillary blood glucose >7mmol per liter pre-SU then give 0.3 mg per kg glibenclamide with breakfast and evening meal (total dose 0.6mg per kg per day).
   - If capillary blood glucose <7mmol per liter pre-SU then continue on 0.2mg per kg (total dose 0.4mg per kg per day) and reduce pre-meal insulin dose by 50%.

Day 4.
   - If evidence of mutation being able to transfer in >95% of cases consider keeping Glibenclamide at 0.3mg per kg/day bd so 0.6mg per kg/day for 2 days and see if response that allows insulin doses to be reduced or stopped.
     Alternatively:
     - If capillary blood glucose >7mmol per liter pre-SU then give 0.4mg per kg glibenclamide with breakfast and evening meal (total dose 0.8mg per kg per day).
     - If capillary blood glucose <7mmol per liter pre-SU then continue on present SU dose and reduce pre-meal insulin dose by 50%.

Day 5.
   - Continue to titrate the sulfonylurea and insulin doses.
   - If no evidence of response to glibenclamide then increase both the breakfast and evening meal doses by 0.1mg/kg/day up to maximum 0.5mg per kg glibenclamide (total dose 1.0mg per kg per day).
• If good response (capillary blood glucose <7mmol per liter pre-SU) then continue on present dose of glibenclamide and reduce pre-meal insulin dose by 50% or stop.

Day 6 onwards.
• Continue to titrate the sulfonylurea and insulin doses.
• If no evidence of response to glibenclamide then increase both the breakfast and evening meal doses by 0.1mg/kg/day up to maximum 0.5mg per kg glibenclamide (total dose 1.0mg per kg per day).
• Once on a dose of 1.0mg per kg per day of Glibenclamide for at least one week. Frequently glucose and insulin requirements will continue to fall even though the patient is on a fixed dose. The patient can usually be discharged at this point.

Discharge.
Discharge at any point when the physician is happy that parents will be able to cope at home. This will depend on the response to glibenclamide, the home situation and the monitoring that is available. It may be when no longer requiring insulin treatment, or when stable on a combination of glibenclamide and insulin. Patients should continue to monitor blood glucose at least four times a day and at bedtime, as insulin requirements may continue to fall, or glibenclamide dose may need to be reduced.

Follow-up
Initially at least weekly contact and appropriate titration of glibenclamide and/or insulin should be made as an outpatient

Other points on SU treatment.
• Many patients seem to get better control with a tds regime rather than bd.
• Patients may have occasional very high glucose values – i.e. >20mmol/l (360mg/dl) – these are not explained and seem to settle with the normal dose of sulfonylureas. These are rare as shown by the HbA1c/mean glucose on CGM.
• When sick, as long as not vomiting and able to take the sulfonylureas, glycaemia seems to be maintained and insulin does not need to be re-introduced. If there is vomiting and hyperglycaemia, a fast-acting insulin is appropriate.
• Doses of glibenclamide should be fixed and unlike insulin not adjusted according to food or pre-meal glucose.
• As there is not the same risk of severe hypoglycaemia in these patients as there is with insulin treatment it is not necessary to keep the glucose above 4mmol/l and doses rarely need to be reduced to avoid hypoglycaemia.
• As the child grows doses should be increased in line with weight increase so the dose/kg/day is constant.

3-month review
• Record HbA1c, a non-fasting random C-peptide if possible, Time in range (3.5-10mmol/l) or daily average glucose values, insulin requirements (if any), and 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 on high dose sulfonylurea (1mg/kg/day) with no improvement (unchanged insulin dose with similar control and if improvement in neurology) then either discontinue or consider increasing dose further.

Subsequent reviews
If good control of insulin HbA1c <6.5% without problematic hypoglycaemia raise dose in line with the weight increase of patients to keep dose /kg/day stable. Consider reducing sulfonylureas especially if hypos.
Outpatient protocol for the transfer of patients with permanent neonatal diabetes, subtypes KCNJ11 and ABCC8 from insulin to sulfonylureas

In patients aged under 12 months at transfer there is often a delayed glucose response to starting sulfonylureas mean doses of SU rapidly increase using the inpatient regime and may be higher than is needed by the time insulin is discontinued. This probably relates to altered renal clearance of sulfonylurea in infants resulting in an increase in the half-life of the sulfonylurea. One approach to this is to not immediately increase above a dose of 0.6mg/kg/day in the inpatient transfer regime when the mutation is likely to respond (see above) or, alternatively, if the home circumstances are appropriate, the infant patient is slowly introduced to sulfonylureas over a period of weeks as an outpatient using the following regime.

Please note these are clinical guidelines that have only been trialled in relatively few patients; 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 taken by the patient’s physician. If you have any questions do not hesitate to contact Prof. Andrew Hattersley (A.T.Hattersley@exeter.ac.uk, office number +44 (0)1392 408260 and mobile number +44 (0)7973165924).

**Introduction of sulfonylureas (done as inpatient)**

**Glibenclamide formulation**

Since infants are unable to swallow tablets, a glibenclamide suspension can be used (see section above). Where the patient is able to take tablets, generic 2.5mg and 5mg glibenclamide tablets should be used. If smaller doses are needed, capsules of glibenclamide can usually be made by the local pharmacy to any strength.

**Outpatient protocol: the underlying principles.**

Glibenclamide is started at 0.2mg/kg/day in two divided doses and glucose control assessed at the end of each week. If there is sufficient response of pre-meal glucose values the glibenclamide dose is kept unchanged and the insulin can be reduced or stopped. If there is not good glucose control then the dose is increased by 0.2mg/kg/day in two divided doses and again glucose control assessed. In the absence of good glucose control the dose is increased by a further 0.2mg/kg/day in two divided doses up to a total daily dose of 1.0mg/kg/day. As the dose is increased slowly it allows the glibenclamide to have its full effect by the end of the 1 week period. This means the glucose improvement leading to a reduction in insulin is slow over a period of days after increasing the sulfonylurea dose. This makes the reduction of the insulin and its final discontinuation depending on the pre-meal glucose values easier to manage compared to when the glibenclamide is rapidly increased. With this regime, a marked reduction of the sulfonylurea dose is rarely needed. 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 sulfonylureas.

In some patients there is initial diarrhea when the dose of sulfonylurea is increased but this settles if the dose is maintained.

The scheme proposed below is an outline of one way to reduce the insulin as the sulfonylurea dose increases it should be interpreted flexibly rather than rigidly.

**Work up prior to introduction of sulfonylureas:**

1. How likely is the mutation in your patient likely to transfer and are CNS features expected?
   - Obtain information from diagnostic lab or one of these publications (Babiker et al 2016 PMID: 27033559, Garcin et al 2020 PMID: 32418263) about how likely it is that the mutation found in your patient is likely to transfer.
   - When >95% of patients with this mutation have successfully transferred then a glibenclamide of 0.6mg/kg/day is usually sufficient and you will rarely need to go above this dose although this may need 2-3 days at this higher dose before insulin can be fully stopped). If no patients have
transferred then a dose of at least 1mg/kg/day is needed and usually insulin will need to be continued in normal replacement doses rather than being reduced.

- Also identify if mutation is known to be associated with marked neurological features (see appendix 1) known as DEND (Developmental delay, Epilepsy, and Neonatal diabetes) syndrome or the less severe intermediate DEND (iDEND) where epilepsy is not an early feature. This information will alter the doses of SU advised see appendix 1

2. Establish a baseline to identify improvements in diabetes and other features

- HbA1c and C peptide (this can be a non-fasting random) measured (results not needed to proceed). If using CGM record time in target.
- General physical examination including height and weight.
- Developmental assessment age appropriate – gross motor, fine motor, verbal.
- Neurological examination and investigation (EEG/MRI) if appropriate.

Week 1 - outpatient.

- Ensure their blood glucose will be measured at least 4 x day (ideally CGM), and it is known how to test for blood ketones and treat hypoglycaemia if needed.
- Give glibenclamide 0.2mg/kg/day with 0.1mg/kg pre-breakfast (08.00 hours) and 0.1mg/kg pre-evening meal (18.00 hours). Keep the dose constant during the week.
- Continue established insulin regime initially (at least day 1) but reduce insulin dose as necessary according to blood glucose values. Initially mainly reduce long acting insulin (or basal doses if on a pump) and then reduce fast acting insulin bolus doses.

Week 2. – outpatient.

- At beginning of week 2 if pre-meal capillary blood glucose values are often >7mmol/L, increase glibenclamide to 0.4mg/kg/day (0.2mg/kg bd).
- If pre-meal capillary blood glucose values are frequently <7mmol/L, keep glibenclamide at 0.2mg/kg/day and continue to reduce insulin. Initially mainly reduce long acting insulin (or basal doses if on a pump) and then reduce fast acting insulin bolus doses.

Week 3. – outpatient.

- At beginning of week 3 if pre-meal capillary blood glucose values are often >7mmol/L, increase glibenclamide by a further 0.1mg/kg/ bd so an increase of 0.2 mg/kg/day.
- If pre-meal capillary blood glucose values are frequently less <7mmol/L, keep glibenclamide dose constant and reduce insulin. If after reducing insulin, glucose values rise, then increase glibenclamide to 0.6mg/kg/day (0.3mg/kg bd).

Week 4. – outpatient.

- Most but not all patients can discontinue insulin by this stage.
- At beginning of week 4 if pre-meal capillary blood glucose values are often >7mmol/L, increase glibenclamide by a further 0.1mg/kg/ bd so an increase of 0.2mg/kg/day.
- If pre-meal capillary blood glucose values are frequently <7mmol/L, keep glibenclamide unchanged and reduce insulin.

Week 5 and onwards – outpatient.

- If pre-meal capillary blood glucose values are often >7mmol/L, increase glibenclamide by a further 0.1mg/kg/ bd so an increase of 0.2mg/kg/day per week up to a dose of 1.0mg/kg/day.
- If pre-meal capillary blood glucose values are frequently <7mmol/L, keep glibenclamide unchanged and reduce insulin. There can now be fine tuning of the glibenclamide dose including moving to a tds regime with an aim to stop insulin completely.
- The vast majority of patients are able to discontinue insulin by the time they are on 0.8mg/kg/day. If not, increase the glibenclamide dose to 1.0mg/kg/day (0.5mg/kg bd). 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. An exception to this would be if there are significant neurological features (DEND syndrome see appendix 1), in which case consideration can be given to continuing sulfonylurea alongside insulin.

• If there is a clear reduction in insulin requirement at dose 1.0mg/kg/day (0.5mg/kg bd) reduction in insulin to at least 60% of pre-sulfonylurea 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.

Follow-up
Patients should continue Once a stable dose of SU initially at least weekly contact and appropriate titration of glibenclamide and/or insulin should be made as an outpatient

Other points on SU treatment.
• Many patients seem to get better control with a tds regime rather than bd.
• Patients may have occasional very high glucose values – i.e. >20mmol/l (360mg/dl) – these are not explained and seem to settle with the normal dose of sulfonylureas. These are rare as shown by the HbA1c. / mean glucose on CGM.
• When sick, as long as not vomiting and able to take the sulfonylureas, glycaemia seems to be maintained and insulin does not need to be re-introduced. If there is vomiting and hyperglycaemia, a fast-acting insulin is appropriate.
• Doses of glibenclamide should be fixed and unlike insulin not adjusted according to food or pre-meal glucose.
• As there is not the same risk of severe hypoglycaemia in these patients as there is with insulin treatment it is not necessary to keep the glucose above 4mmol/l and doses rarely need to be reduced to avoid hypoglycaemia.
• As the child grows doses should be increased in line with weight increase so the dose/kg/day is constant.

3-month review
• Record HbA1c, a non-fasting random C-peptide if possible, Time in range (3.5-10mmol/l) or daily average glucose values, insulin requirements (if any), and 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 on high dose sulfonylurea (1mg/kg/day) with no improvement (unchanged insulin dose with similar control and if improvement in neurology) then either discontinue or consider increasing dose further

Subsequent reviews
If good control of insulin HbA1c <6.5% without problematic hypoglycaemia raise dose in line with the weight increase of patients to keep dose /kg/day stable. Consider reducing sulfonylureas especially if hypos.
References


Appendix 1: KCNJ11 and ABCC8 Neonatal Diabetes: Effects on the brain

Background
Around 20% of patients with KCNJ11 or ABCC8 Neonatal Diabetes will have delayed development as well as diabetes. In these people the KCNJ11 and ABCC8 genetic change affects the potassium channels in the brain in addition to the channels in the pancreas which control insulin release. This is known as DEND syndrome as the key features are: Developmental delay, Epilepsy and Neonatal Diabetes. When it is less marked epilepsy is rare and it is called intermediate DEND syndrome (iDEND).

Who is likely to have developmental delay?
The specific genetic change determines whether the brain is likely to be affected and if it is how severe the affect is. The more severe the genetic change affecting the potassium channel the more likely developmental problems are and the more severe they are if they occur. The commonest genetic change causing developmental problems in KCNJ11 is p.(Val59Met) where most patients have moderate to severe difficulties. There is some variability between children with the same genetic change so it is not possible to predict exactly how severely a child will be affected.

What type of developmental delay is seen?
The developmental delay varies from children who are very mildly affected and attend normal schools to severe effects where individuals are unable to walk or talk. Some of the difficulties that have been identified include the following:

- Being slow to walk or being ‘clumsy’.
- Being slow to talk.
- Having difficulty concentrating which may be diagnosed as attention deficit disorder or hyperactivity.
- Doing less well at school, especially with numeracy/maths.
- Difficulty in social situations which may be diagnosed as Asperger’s syndrome or Autism.
- Epilepsy – this may be present in the first year of life when patients have severe genetic changes causing DEND syndrome. With iDEND due to the KCNJ11 p.(Val59Met) they may develop epilepsy later, typically between 3-10 years of age, these are usually ‘absence’ seizures that do not require prolonged treatment.

Can sulfonylureas help delayed development as well as the diabetes?
Some improvement has been noted in most children with developmental delay when they are treated with high doses of glibenclamide (we recommend a minimum 0.5mg/kg/day, many patients require 1mg/kg/day and some take up to 2mg/kg/day). In patients with established learning problems this will result in small improvements in areas such as concentration and speech but their development will still be delayed compared to other children of the same age. There is clear evidence suggesting there are considerable benefits in treating the child with glibenclamide immediately the diagnosis of a potassium channel mutation is made. The best outcome is if they are treated with sulfonylureas in the first 6 months of life. Early treatment is likely to help the brain develop correctly in the crucial first months of life.

Summary
Developmental delay affects approximately 20% of children with KCNJ11 or ABCC8 neonatal diabetes. It is important to identify those patients whose genetic change means they are at high risk of developmental delay since early treatment with high dose sulfonylureas (around 1mg/kg/day) is likely to achieve the best outcome.