Guidance for transferring patients with a disease-causing variant in the *ABCC8* or *KCNJ11* gene causing transient neonatal diabetes (TNDM) and/or later adult-onset diabetes from insulin to a sulphonylurea

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

Pathogenic variants in the potassium channel (K_{ATP}) genes *ABCC8* and *KCNJ11* can lead to transient neonatal diabetes (TNDM) and/or later adult onset diabetes but also cause permanent neonatal diabetes (PNDM). There is usually a close relationship between the genetic variant and the clinical presentation, so specific pathogenic variants found in patients with TNDM are also likely to result in TNDM in other patients.

In K_{ATP} gene variants that result in TNDM, the typical pattern is of:

- diabetes being diagnosed in early infancy, typically 4 weeks (range 0-16 weeks);
- and then going into remission in early childhood – typically at 8 months (range 0.5-48 months;
- and then relapse with diabetes again typically at around 15 years (range 2 – 45 years).

These different stages should be anticipated – we would recommend at least yearly HbA1c after remission to detect relapse early.

Interestingly K_{ATP} channel TNDM can present in ketoacidosis but still remit and not require any treatment. Mild developmental features maybe seen in some children with K_{ATP} channel TNDM (more frequently *ABCC8* variants) but these are not well characterised.

We know that some patients with a genetic variant that causes K_{ATP} channel TNDM can present later in life – typically around 30 years (range 5 – 50 years) without having diabetes as a neonate (Flanagan *et al* 2007 PMID: 17446535). We found that the characteristics of the diabetes in these patients were similar to those who had relapsed having presented in infancy and then remitted. It is as if the patients who presented in adulthood did not have the initial neonatal phase but went straight to the "relapse" phase.

Patients with K_{ATP} channel TNDM variants have significant endogenous insulin secretion and can usually be treated with sulfonylureas

The identification of an activating *KCNJ11* or *ABCC8* variant means that a trial of sulfonylureas is usually appropriate.

TNDM patients, unlike those with PNDM, are likely to have significant endogenous insulin production; regardless of whether in the initial neonatal phase, in the relapse phase or whether diagnosed in childhood/ adulthood only. This is shown by C peptide being clearly measurable and patients getting good glucose control with less than a replacement dose of insulin (often <0.5U/kg/day). As these patients with TNDM have significant endogenous insulin, they are much more responsive to sulfonylureas (than patients with PNDM) and may need very low doses (unlike patients with PNDM that need a very high dose of sulfonylurea).

If the patient is on insulin, it is best to confirm first that they are making their own insulin by measuring a non-fasting post meal C-peptide (typically >200pmol/l). When this is confirmed a trial of low dose sulfonylurea and discontinuing insulin is appropriate.

Switching from insulin before remission in infancy or very early childhood (<2 years)

Once a molecular genetic diagnosis establishes that a patient has a TNDM causing variant in one of the K_{ATP} genes then most patients can switch from insulin to sulfonylureas. Patients with TNDM only need hypoglycaemic agents (insulin or sulfonylurea) for the first few weeks to months post-diagnosis until they go into remission. The aim of a switch to a sulfonylurea is to prevent the need to inject the infant with insulin. It is also likely to allow improved glycaemic control before the diabetes remits but hypoglycaemia can easily occur as the diabetes remits so glucose should be carefully monitored.

We recommend a starting total daily dose of 0.05mg/kg/day glibenclamide divided into two doses. This is usually easiest to give as a solution which can be made from water for injections (https://www.lifescienceglobal.com/pms/index.php/jnt/article/view/618). Rarely patients have become hypoglycaemic on this low dose, so close monitoring and adjustment of the dose is necessary. At first the dose may need to be slowly adjusted upwards to ensure glycaemic control. However, weeks to months after initial transfer, glycaemic control will improve, the diabetes will remit and the dose will need to be decreased and stopped.

Switching from insulin to a sulfonylurea after relapse or first presentation in later childhood or early adulthood

Patients whose TNDM relapses or those that just present for the first time typically develop diabetes between the ages of 10 and 40 years. They are often thought to have Type 1 diabetes and hence treated with insulin. The dominant inheritance of diabetes in early adulthood can also mean they can be classified as having MODY (Bowman *et al* 2012 PMID: 21989597 and Bonnefond *et al* 2012 PMID: 21049026).

These patients can be very sensitive to sulfonylureas so we would recommend starting at low doses. In children we would recommend starting at total daily dose of 0.05mg/kg/day glibenclamide divided into two doses. In adults we recommend starting at 0.0625-1.25mg glibenclamide 1/4-1/2 tablet) or gliclazide and 20-40mg gliclazide (1/4-1/2 tablet)– as in HNF1A MODY (see http://www.diabetesgenes.org/content/guidance-transferring-hnf1a-or-hnf4a-patients-insulin-sulphonylureas).

In the relapsed/adult onset patients, after initial success with sulfonylurea treatment the response to sulfonylureas may reduce. The sulfonylurea should be increased up to the usual adult dose (with next option being adding in background insulin or considering other oral agents.

Choice of sulfonylurea

Theoretically any sulfonylurea 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 of TNDM/PNDM and so have the most experience of this but it has been harder to obtain recently. Other sulfonylureas have been successfully used. As patients only require a low dose the fact that it is less effective than glibenclamide in some patients is not critical.

Adverse reactions

The doses of sulfonylureas required are below the normal maximum adult dose (if you allow for the weight difference) however, no sulfonylureas are licensed for use in children although they are widely used. Reported side effects from glibenclamide are listed on the drug information.

The commonest known side effects are: skin allergies (1-5%) which may resolve and gastrointestinal including diarrhea (1-2%). Blood disorders – anaemia, leucopoenia and thrombocytopenia – are very rare. Sulfonylureas can occasionally cause a disturbance in liver function.

Further information

For specific advice regarding individual patients please contact Prof Andrew Hattersley **a.t.hattersley@exeter.ac.uk** or Prof Maggie Shepherd on 01392 408261 **m.h.shepherd@exeter.ac.uk.**

References

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