

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006;355:467-77.

Details of Protocols used for the transfer of patients with Kir6.2 mutations from insulin to sulfonylurea treatment

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 eight days.

1) Inpatient protocol (used in the majority of patients)

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 values are < 7 mmol per liter either pre-breakfast and or before the evening meal is taken as an indication to reduce the insulin dose (usually by 50% of the normal pre-meal insulin dose) 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.

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

Day 1.

- Continue established insulin regime.
- Give 0.1 mg per kg glibenclamide with breakfast (08.00 hours)
- If capillary blood glucose >7 mmol per liter prior to evening meal administer 0.1 mg per kg glibenclamide with evening meal (18.00 hours)

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.
- Administer soluble insulin or 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 > 7 mmol per liter pre-sulfonylurea (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 < 7 mmol 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 < 7 mmol 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 < 7 mmol 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 < 7 mmol 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 one week. Frequently glucose and insulin requirements will continue to fall even though the patient is on a fixed dose.

Discharge.

- Discharge when no longer requiring insulin treatment, or when stable on a combination of glibenclamide (>0.8 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.

2) Outpatient protocol

- 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.
- The physician should see the patient every week, and be accessible by phone every day during the transfer.

Supplementary information: Pearson et al: Successful Transfer of Patients with Diabetes due to Mutant Kir6.2 from Insulin to Oral Sulfonylureas

Week 1.

- Continue established insulin regime
- Give glibenclamide 0.05 mg per kg per day with breakfast (08.00 hours) and evening meal (18.00 hours). Start the medication the following morning and keep the dose constant during the week. The morning dose should be equal to or larger than the evening dose.
- If pre-meal capillary blood glucose values are 4-7 mmol per liter, reduce bolus rapid-acting insulin dose by 25 %, and if values are less than 4 mmol per liter, reduce bolus rapid-acting insulin dose by 50 %.

Week 2.

- If pre-meal capillary blood glucose values often are more than 7 mmol per liter, increase glibenclamide to 0.2 mg per kg per day.
- If pre-meal capillary blood glucose values frequently are less than 7 mmol per liter, reduce intermediary- or long-acting insulin dose (or basal rapid-acting insulin if on insulin pump) by 25-50 %.

Week 3.

- If pre-meal capillary blood glucose values often are more than 7 mmol per liter, increase glibenclamide to by 0.3 mg per kg per day.
- If pre-meal capillary blood glucose values are 4-7 mmol per liter, reduce bolus rapid-acting insulin dose by 25 %, and if values are less than 4 mmol per liter, reduce bolus rapid-acting insulin dose by 50 %.

Week 4.

- 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.
- If pre-meal capillary blood glucose values frequently are less than 7 mmol per liter, reduce intermediary- or long-acting insulin dose (or basal rapid-acting insulin if on insulin pump) by 25-50 %.

Week 5 and onwards.

- Many patients will now be able to discontinue insulin. If not, continue as described above until the glibenclamide dose is 1.0 mg per kg per day.
- If there still is an insulin requirement at this dose, discontinuation of insulin is unlikely. A higher dose of glibenclamide could be considered or glibenclamide should be ceased and insulin used as before the transfer attempt..
- Patients should continue to monitor pre-meal capillary blood glucose four times a day and at bed-time, as insulin requirements may continue to fall, or the glibenclamide dose may need to be reduced.
Visits every month are recommended first six months, then every three months or as frequent as needed.

Details of protocols for Physiological Studies

Intravenous glucose tolerance test.

Following an overnight fast and basal sampling, 0.3 g per kg glucose was given over one minute and plasma was collected at 2, 3, 4, 6, 8, 10 minutes for glucose and insulin assay. Insulin was not administered to those normally treated with insulin on the morning of the day of plasma collection. The insulin increment above base line was taken as the largest increment in the first ten minutes.

Oral glucose tolerance test

Following an overnight fast and basal - sampling 1.75 g per kg oral glucose (maximum 75 g) was ingested over two minutes at time zero and plasma was collected at 15, 30, 45, 60, 90 and 120 minutes for assay of glucose, insulin and the incretins- glucagon like peptide-1 (GLP-1) and gastro-intestinal peptide (GIP). Insulin was not administered to those normally treated with insulin on the morning of the day of plasma collection.

Mixed Meal test

The mixed meal test followed an overnight fast and basal sampling, and consisted of 7 milliliter per kg (maximum 360 milliliter) of Boost HP (Mead-Johnson) containing 0.14 g carbohydrate per ml and 0.06 g protein per ml ingested over two minutes, beginning at time zero. Plasma was collected at 15, 30, 45, 60, 90 and 120 minutes for assay of glucose, insulin, GLP-1 and GIP.

Glucagon stimulation test.

Before and after successful introduction of sulfonylureas, one mg glucagon was given intravenously in five patients at time zero, and samples for insulin measurement were collected at 0, 5, 10 and 15 minutes. Insulin was not administered to those normally treated with insulin on the morning of the day of plasma collection.

Subgroups 1	Subgroup 2	Mutations	% Male	Birth weight (g)	Birth weight SDS	Age at Diagnosis (months)	Age at transfer (years)	Insulin dose (U/kg)	HbA1c (%)	Equivalent glibenclamide dose mg/kg/day
Study group who successfully transferred to sulfonylureas (n=44)		F35V, H46Y, R50Q, G53N, G53R, V59M(6), K170T, R201C (5), R201H (23), R201L, E322K, Y330S, F333I	55	2740 (2420 to 3115)	-1.0 (-2.2 to -0.5)	1.5 (0.6 to 3)	6 (3 to 12.5)	0.7 (0.6 to 0.9)	7.9 (7.1 to 9.4)	0.45 (0.3 to 0.8) Min 0.05 Max 1.5
No physiological studies (n=23)		F35V, G53R, V59M, R201C (2), R201H (11), E322K, Y330S, F333I	48	2700 (2360 to 3100)	-1.6 (-2.2 to -0.7)	1.5 (0.3 to 3.0)	5 (3 to 11)	0.7 (0.6 to 0.9)	8.0 (7.1 to 9.4)	0.55 (0.4 to 0.9)
Paired IVGTT study (n=16)		G53N, R50Q, V59M, K170T, R201C (3) R201H (8), R201L	63	2770 (2693 to 3039)	-0.9 (-1.7 to - 0.3)	2 (0.75 to 3)	8.5 (2 to 13.8)	0.7 (0.55 to 0.81)	7.5 (6.7 to 8.8)	0.4 (0.2 to 0.9)
Plus MMT and OGTT (n=7)		V59M, K170T, R201H (4), R201L	71	2700 (2120 to 3005)	-1.7 (-2.4 to - 1.0)	1.5 (0.75 to 3)	10 (5 to 13)	0.7 (0.6 to 0.93)	7.3 (6.7 to 9.5)	0.7 (0.4 to 1.0)
Paired OGTT study (n=5)		H46Y, R201H (4)	60	3180 (2160 to 3400)	-0.5 (-3.0 to -1.4)	1.5 (0.75 to 2.1)	9 (2.5 to 20.5)	0.77 (0.67 to 0.9)	8.8 (7.8 to 11.5)	0.8 (0.3 to 1.0)
With GLP-1 measured (n=4)		H46Y, R201H (3)	75	2875 (2015 to 3450)	-1.44 (-3.4 to 0.3)	2.5 (0.63 to 3.0)	10 (3.8 to 25.3)	0.8 (0.4 to 1.0)	9.3 (7.5 to 12.3)	0.8 (0.4 to 1.0)
P value across subgroup 1			0.42	0.32	0.43	0.5	0.96	0.43	0.29	0.38

Supplementary Table 1. Details of the subgroups involved in physiological studies. IVGTT = intravenous glucose tolerance test. MMT = mixed meal test. OGTT = oral glucose tolerance test. Comparison across subgroup 1 was by Kruskal-Wallis test.