Nifedipine therapy in hyperinsulinaemic hypoglycaemia due to mutations in the *PMM2* gene improves fast tolerance, stabilises blood glucose profile, and enables rationalisation of treatments for glycaemic control and hypertension: The first reported trial in 3 patients in a tertiary centre.

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Background

- Hyperinsulinaemic hypoglycaemia (HH) is the most frequent cause of severe and persistent hypoglycaemia in infancy.
- Prompt recognition and successful management are critical to ensure prevention of hypoglycaemic brain injury and neurological sequelae.
- The incidence of HH varies from 1:50,000-1:2,500, and mutations in at least 12 different genes involved in β-cell insulin release have been described (Fig. 1).[1]
- Recently, the spectrum of genetic causes for HH has been extended, with the reported co-existence of HH and congenital polycystic kidney disease (PCKD) in 17 children, caused by a promoter mutation in the phosphomannomutase 2 gene (*PMM2*).[2]
- Previous reports have documented the effectiveness of L-type calcium channel blockers, such as nifedipine, for treating different forms of HH (Fig.1).[1]

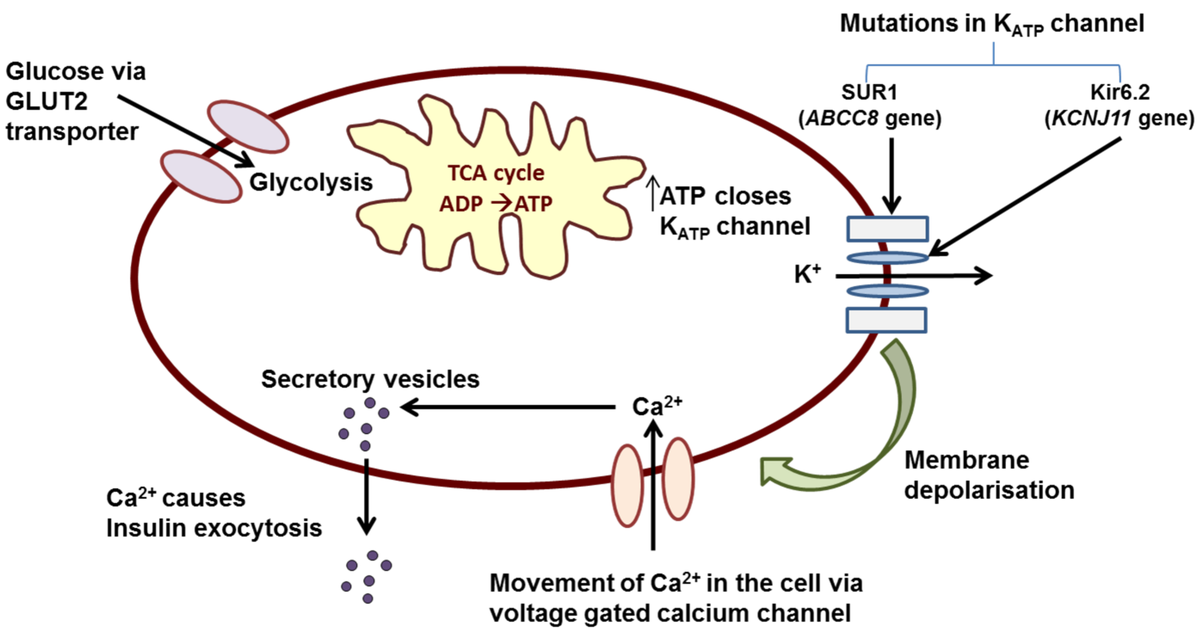

Fig. 1. Schematic cartoon of the β-cell with the genes and channels involved in insulin secretion.[1]

Objective

- To report the first trial of nifedipine therapy in 3 patients with HH due to mutations in *PMM2*.

Methods

- Nifedipine initiated at a dose of 0.5mg/kg/day and increased to 1mg/kg/day after 48 hours, with close blood pressure monitoring.
- Glycaemic response was assessed by a blood glucose profile and fast test (Table 1).

	Case1	Case 2	Case 3
Fast tolerance (hours) (Hypoglycaemia BM<3.5mmol/L)	Pre-Nifedipine 6 hours hypoglycaemia at end of fast Post-Nifedipine **16 hours** **no hypoglycaemia**	Pre-Nifedipine 13 hours with hypoglycaemia at end of fast Post-Nifedipine **16 hours** **no hypoglycaemia**	Pre-Nifedipine 17 hours hypoglycaemia at end of fast Post-Nifedipine **18 hours** **no hypoglycaemia**
Glucose profile (mmol/L)	Pre-Nifedipine **2.6**-6.2 Post-Nifedipine 4.0-11.0	Pre-Nifedipine **3.1**-10.1 Post-Nifedipine 4.4-7.8	Pre-Nifedipine 4.1-5.8 Post-Nifedipine 3.6-7.3
Medications	Pre-Nifedipine Diazoxide 10mg/kg/day Lanretotide trial Chlorthiazide Post-Nifedipine Diazoxide **8mg/kg/day** Nifedipine 1mg/Kg/day Chlorthiazide	Pre-Nifedipine Diazoxide 10mg/kg/day Chlorthiazide Post-Nifedipine Diazoxide 10mg/kg/day Nifedipine 1mg/Kg/day	Pre-Nifedipine Diazoxide 11mg/kg/day Enalapril Frusemide Spironolactone Post-Nifedipine Diazoxide **6.7mg/kg/day** Nifedipine 1mg/Kg/day Chlorthiazide
Feeds	Pre-Nifedipine 4 hourly bolus feeds overnight Post-Nifedipine **No feeds**	No feeds	No feeds

Table 1. Glycaemic response pre- and post-nifedipine therapy (n=3).

Results

Case 1: Treatment with nifedipine:

- Came off overnight feeds.
- Fasted 16 hours (6 hours prior to treatment).
- No hypoglycaemic episodes on profile.
- Diazoxide dose weaned by 20%.

Case 2: Treatment with nifedipine:

- Fasted 16 hours (13 hours prior to treatment).
- No hypoglycaemic episodes on profile.

Case 3: Treatment with nifedipine:

- Fasted 18 hours (17 hours prior to treatment).
- No hypoglycaemic episodes on profile.
- Diazoxide dose weaned by almost 40%.

Conclusions

- This is the first report of glycaemic response to nifedipine therapy in 3 patients with HH due to mutations in *PMM2*.
- Nifedipine therapy has enabled these patients to:
  1. Achieve a stable blood glucose profile with increased fast tolerance
  2. Wean diazoxide therapy
  3. Improve blood pressure control to the extent that, in one case, nifedipine is now used as monotherapy.

Nifedipine may prove useful as first line therapy in patients with HH and PCKD due to mutations in *PMM2*.

References

1. Güemes, M et al. J Clin Endocrinol Metab. 2017. 102(3): 822-830.
2. Cabezas, OR et al. J Am Soc Nephrol. 2017. 28(8): 2529-2539.

57ESPE 185--P2

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