Effectiveness of Calcium channel blocker Nifedipine in children with Hyperinsulinaemic Hypoglycaemia due to genetically proven mutations in *ABCC8* gene

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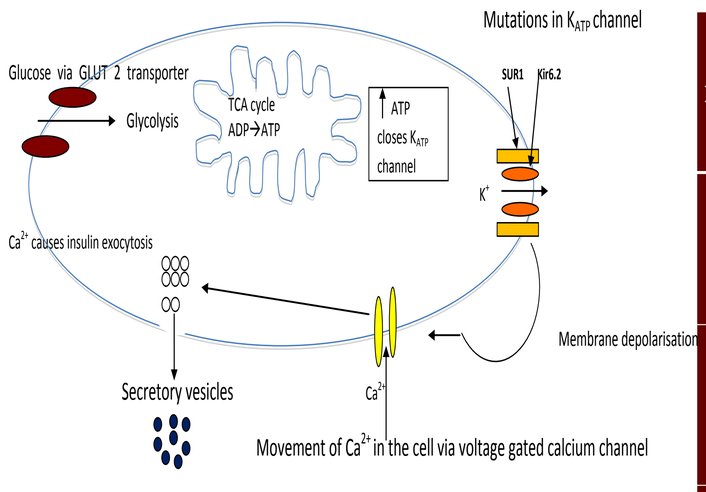
INTRODUCTION

Hyperinsulinaemic hypoglycaemia (HI) is the most common cause of severe and persistent hypoglycemia during infancy. The first line medical therapy for HI is diazoxide. Other medical therapies used in patients with HH include short and long acting octreotide preparations and mTOR inhibitors such as sirolimus. Several previous publications have documented the usefulness of Nifedipine for treating HI. These reports include transient and persistent forms of HI, with and without known genetics, used in monotherapy or in combination with other drugs, and demonstrate various outcomes (**See Table1**).

PUBLICATIONS, year	Number of patients, age	HI type/ genetics	Previous pancreatectomy	Dose of nifedipine (mg/kg/day)	Glycemic control on discharge.
Lindley et al. 1996	1 infant 5m	B-cell hyperplasia + ducto-insular endocrine cell proliferation	Yes (95%)	0.7	Yes, monotherapy
Eichmann et al 1999	2 Infants: Pt 1: 6m. Pt 2: 15m	-Pt 1: Not specified -Pt 2: maternal members with HI (unknown genetics)	-Pt 1: No -Pt 2: No	-Pt 1: 0.7 -Pt 2: 2	-Pt 1: Yes, in with Diazoxide -Pt 2: Yes, monotherapy
Bas et al. 1999	3 infants, 8-12 days of age	-Pt 1: islet cell hyperplasia and epithelial proliferation around ectatic ducts. -Pt 2 & 3: Not specified	-Pt 1: Yes near-total -Pt 2: No. Pt 3: No	-Pt 1: 0.7 -Pt 2: 0.5. Pt 3: 0.8	Yes, monotherapy in all three
Suprasongsin et al 1999	2 Infants: Pt1:14 m. Pt2: 21 m	-Pt 1: Pathology "compatible with the diagnosis of nesidioblastosis" -Pt 2: Not specified	-Pt 1: Yes, two resections (95%) -Pt 2: No	-Pt 1: 0.5 -Pt 2: 0.7	Yes, both patients +corn-starch + frequent feeds.
Gussinyé et al 2000.	1child, 13 y	Focal suspected by PET, not confirmed in pathology	Yes	0.7-2	Yes but only when lanreotide introduced
Darendeliler et al. 2002	8 infants, ages between 8d-5.5m	-Pt #4: Pathology: diffuse. Pt #5: Pathology: diffuse. Compound heterozygous *ABCC8* . Pt #9: Compound heterozygous *ABCC8* mutation. Rest: not specified	Yes, 95% in pts #4 & #5	range 0.5-0.8	Yes, in monotherapy in 6 cases. No response in 2 cases
Shanbag et al. 2002	A 30d old infant	Not specified	No	0.5	Yes, monotherapy
Müller et al. 2004	A 5y old	Not specified	No	0.9	Yes, monotherapy
Kortoglu et al. 2005	A 9d old	Transient (mother taking Ritodrine)	No	0.25	Yes, monotherapy
Loechner et al. 2011	A neonate	Homozygous *KCNJ11* mutation	No	0.1 (amlodipine)	Yes, in combination with amlodipine
Liberatore et al. 2012	2 children, age not specified	Not specified	-Pt 1: No. Pt 2: No	-Pt 1: 1.5. Pt 2: 1.0	Yes, in Pt 2 with octreotide + diazoxide
Koklu et al. 2013	An infant	Diffuse in histology	Yes, two resections (95%)	2	Yes
Neylon et al. 2013	A child, 9 m	Paternal mosaic recessive *ABCC8* mutation (PET: Diffuse. Intraop: focal)	Yes, two resections (95%)	Not specified	No
Durmaz et al. 2014	An infant, 2 m	Homozygous nonsense *ABCC8* mutation (diffuse histology)	Yes	0.75	Yes, with octreotide
Khawash et al. 2015	An infant	Compound heterozygote *ABCC8* (diffuse histology)	Yes	0.8	Yes, monotherpay

When the L-type calcium channel in the β-cell is activated, there is an increase insulin release after a depolarising stimulus. Nifedipine and other L-type calcium channel blockers have shown to inhibit the secretion of insulin in rodent islets *in vitro* (Szollosi et al. 2010).



OBJECTIVE

To systematically trial Nifedipine in children with known HI mutations and diazoxide unresponsive, assessing glycaemic control.

METHODS

Nifedipine was administered according to our hospital's protocol for HI management. Maximum dose administered was 2.5mg/kg/day. 2 hourly blood glucose determinations were performed whilst on this medication. The dose of Nifedipine was withheld should the systolic blood pressure be under the 5th percentile for gender and age.

RESULTS (See table 2)

None of the patients had any syndromic features. The median gestational age was 39 weeks (range 35+3 to 42 weeks) and the median birth weight was 4.035kg (3.13 - 4.74kg) or +1.7 SDS (range: 1.07 - 3.05). The age when Nifedipine was trialled was at a median of 0.42 years (0.14 – 3.77) and the median time it was tried for was 6 days (3-23).

ID	Gender	Genetics	Form of HI	Age at Presentation	Age when NFD tried (years)	Number of days tried for	Feeds	Iv dextrose (glucose load)	Other meds used concomitantly	Max dose NFD (mg/kg/day)	Glycaemic Response to NFD	Meds & dose child responded to	Pancreatectomy
1	F	Paternally inherited heterozygous missense *ABCC8* mutation	Diffuse*	6 h of life	0.71	23	Oral, on demand	no ivs	Octeotide inj. 5mcg/kg/day, Amikacin, piptazobactam	2.8	No	Lanreotide 60mg 4 weekly + octreotide 12mcg/kg/day	No
2	F	Compound heterozygous *ABCC8* mutation	Diffuse*	2 days of life	1.2	3	PEG Continuous feeds (Peptijunior + maxijoule)	no ivs	Lactulose, Lansoprazole, Ranitidine	2.5	No	Unresponsive to diazoxide, octreotide or lanreotide, so on continuous feeds	No
3	F	Heterozygous paternal *ABCC8* mutation	Expected diffuse	2h of life	0.42	8	Continuous feeds 95ml/kg/day	no ivs	Octreotide inf. 2mcg/kg/h	2	No	Lanreotide 30mg 4 weekly + sirolimus 2.5mg/m2/day	No
4	M	Compound heterozygous *ABCC8* mutation	Expected diffuse	2 days of life	0.12	7	203ml/kg/day: demand feeding cow and gate &EBM	15% dextrose 15ml/kg/day (2.7 mg/kg/min)	Glucagon 5mcg/kg/h Octreotide 30mcg/kg/day Vancomycin, Ranitidine Lansoprazole	2.5	No	Octreotide 45mcg/kg/day + sirolimus 8mg/m2/day.	No
5	F	Homozygous *ABCC8* gene mutation	Diffuse*	Day 1 of life	2.02	3	Cont Feeds Nutrini via PEG = 3 mg.kg.min glucose	20% dextrose (2.3 mg/kg/min)	Octreotide inj. 40mcg/kg/day, clindamycin, ranitidine, lansoprazole	2.44	No	Continuous feeds + octreotide 39mcg/kg/day	Subtotal prior to this trial
6	M	Compound Heterozygous *ABCC8* mutation	Expected diffuse	46 h of life	0.14	6	150mls/kg/day (Aptamil demand feeds)	no ivs	Diazoxide 8.67 mg/kg/day, Octreotide inj. 25 mcg/kg/day, Furosemide, Spironolactone, Lansoprazole, Ranitidine	2.5	No	sirolimus 6mg/m2/day + octreotide 30mcg/kg/day	No
7	F	Homozygous *ABCC8* mutation	Expected diffuse	2h of life	0.11	8	oral sma HE (110 ml/Kg/day)	20% dextrose (4.2 mg/kg/min)	Glucagon inf. 5 mcg/kg/hr IV Octreotide inf. 35 mcg/kg/d s/c	2.5	No	Octreotide 40mcg/kg/day + sirolimus 2.5mg/m2/day	No
8	M	Paternal heterozygous *ABCC8* mutation	Focal in the neck*	First hours of life	0.23	14	oral SMA1 (80ml/kg/day)	no ivs	Octreotide 35 mcg/kg/day, ranitidine, lansoprazole, lactulose	2.5	No	octreotide 35mcg/kg/day injection + sirolimus 5mg/m2/day	No
9	F	Autosomal dominant *ABCC8* mutation	Expected diffuse	2 days of life	3.77	4	oral. Continuous o/n with Vitajul	no ivs	Cornstarch am and pm, Iron, Colecalciferol	2 (as hypo--tension)	No	sirolimus 1mg/m2/day	No
10	M	Paternal heterozygous *ABCC8* missense mutation	Focal in the tail*	5 months of life	0.46	6	oral on demand	no ivs	Octreotide inj. 35mcg/kg/day	2.5	No	Lesionectomy	Yes, after nifedipi-ne trial
11	M	Compound Heterozygous *ABCC8* mutation	Expected diffuse	First hours of life	0.41	6	oral on demand	iv 30%dex 15ml/h (9.8 mg/kg/min)	octreotide 37mcg/kg/day, lansoprazole, ursodeoxycholic	2.5	No	sirolimus 4mg/m2/day + octreotide 35mcg/kg/day	No

CONCLUSIONS

Children with HI due to mutations in *ABCC8* gene do not respond to therapy with Nifedipine. The underlying molecular basis of Nifedipine ineffectiveness is not clear but might involve abnormalities of the L-type calcium channel secondary to the defect in the K_{ATP} channel.

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