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CASE REPORT

**Diazoxide use for neonatal hyperinsulinaemic hypoglycaemia
in a low-resource setting: A Case Report****Adekoya AO*, Adekanye TE, Abolurin OO, Adebawojo OO, Ajayi FG,
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Summary

The management of neonatal hyperinsulinaemic hypoglycaemia remains a major challenge in hospitalized newborns globally. Diazoxide is one of the recommended therapeutic options.

We report a late preterm, male infant of a diabetic mother who suffered severe perinatal asphyxia and had persistent hypoglycaemia requiring progressively increasing intravenous glucose concentrations to as high as 12.5 mg/kg/minute along with intravenous hydrocortisone administration. A critical sample revealed inappropriately high serum insulin, inappropriately low serum cortisol and growth hormone responses. Urinalysis was negative for ketones. With the persistence of hypoglycaemia, oral diazoxide at 5 mg/kg/day with oral hydrochlorothiazide was administered. The infant was diazoxide-responsive with complete resolution of hypoglycaemia. Diazoxide therapy was discontinued after 14 days and he was discharged after one month of admission. This report emphasizes the importance of diazoxide in the management of neonatal transient hyperinsulinaemic hypoglycaemia. The availability and cost of diazoxide, as well as the endocrine and metabolic tests, are major concerns in resource-poor settings.

Keywords: *Critical sample, Diazoxide, Hyperinsulinaemic hypoglycaemia, Maternal diabetes, Newborn.*

Introduction

Neonatal hypoglycaemia (NH) is a common condition among hospitalized newborns, with the prevalence rates ranging from 11.0 to 32.7% in Nigerian newborns. [1,2] Globally, there is no consensus on the definition of NH. In fact, within the United States of America, divergent views exist between the guidelines of the American Association of Paediatrics (AAP) and the Paediatric Endocrinology Society (PES) on the definition and management of neonatal

hypoglycaemia, within and beyond the first 48 hours of life. [3-5] The AAP recommends the administration of intravenous glucose in a symptomatic neonate with blood glucose <40mg/dl within the first 24 hours of life while the target glucose concentration afterwards, should be >45 mg/dl. [4] On the other hand, the PES suggests a target of >50mg/dl for high-risk neonates in the first 48 hours of life. [5] The diagnosis of hypoglycaemia in the new-born requires a high index of suspicion as the clinical

presentations may be mimicked or masked by other conditions.

Hyperinsulinaemic hypoglycaemia (HH) is defined as inappropriately raised plasma insulin concentration (>1.6 mU/l) during a hypoglycaemic episode in infants receiving glucose infusion rate >8 mg/kg/minute. Other parameters include reduced blood ketones (<0.6 mmol/l) and serum free fatty acids (<0.5 mmol/l) and an increased glycaemic response to parenteral glucagon administration, resulting from a dysfunction in ATP-sensitive potassium channel of the pancreatic β -cells. [6,7] It can be classified as transient (when it resolves within days), prolonged (when the resolution takes several weeks or months) or persistent, in increasing order of severity. [8] Managing HH may be quite challenging, especially in low-resource settings.

The use of buccal dextrose gel is gaining grounds in the management of asymptomatic hypoglycaemia while the symptomatic form is managed with dextrose-containing intravenous fluids. [9] In some cases, intravenous dextrose-containing fluids may be ineffective in correcting hypoglycaemia. In such instances, the recommended options include medications such as glucagon, diazoxide, nifedipine and octreotide. [10] Diazoxide is an ATP-sensitive potassium (K_{ATP}) channel agonist which acts on K_{ATP} receptors on the pancreatic β -cells to inhibit insulin release by preventing calcium influx into the cells. [11] Diazoxide is administered orally at a dose of 5-20 mg/kg/day, in two or three divided doses, [12] or at higher doses depending on the course and response to treatment. [13] Its onset of action is within one hour of administration with a duration of action of about eight hours in patients with normal renal function. [14]

Established long-term neurologic complications of NH include neurodevelopmental delay,

mental subnormality as well as epilepsy. [15] Therefore, NH should be promptly and appropriately diagnosed and managed. In Nigeria and indeed Africa, there is a paucity of documentation on the use of diazoxide in the management of HH. This report describes the use of diazoxide in an infant of a diabetic mother with HH in a tertiary level of care in South-western Nigeria.

Case Description

A male infant delivered at 35 weeks gestational age to a 32-year old Para 2⁺⁰ (2 alive) diabetic mother via emergency caesarean section on account of severe pre-eclampsia at a secondary health facility was referred to Babcock University Teaching Hospital, Ilishan-Remo, Nigeria at 61 hours post-delivery. He reportedly had severe perinatal asphyxia with a low first minute Apgar score. The mother had a history of foetal macrosomia in her previous babies.

At admission, the infant was acutely ill-looking, in respiratory distress and was hypoglycaemic with random blood glucose (RBG) of 29 mg/dl. The weight, occipitofrontal circumference and length were 2.44 kg, 33 cm and 45 cm respectively and were all appropriate for the gestational age. The stretched penile length was 2.20 cm. There were no dysmorphic features or midline defects.

The infant had recurrent episodes of hypoglycaemia. The frequency of RBG monitoring varied from every 30 minutes to hourly to 2 hourly and later 4 hourly, depending on RBG values obtained. However, the recurrence of hypoglycaemia warranted progressively increasing intravenous glucose concentrations to as high as 12.5 mg/kg/minute administered via a central line, along with intravenous hydrocortisone administration at the dose of 4mg/kg/dose 12 hourly. The target

glucose value recommended by the AAP was followed for the management of hypoglycaemia. Enteric feeding was introduced at the age of three days. Glucagon was not available hence oral nifedipine was commenced at 1 mg/kg/day with an insignificant effect on the blood glucose levels. The infant also received albumin and fresh frozen plasma infusions for hypoproteinaemia (Total - 4.8 g/dl [reference values 6.0 - 8.0g/dl], albumin - 2.7g/dl [reference values 3.5 - 5.2g/dl]).

A critical sample, which is a blood sample taken during a hypoglycaemic episode for relevant hormonal assays (to determine the aetiology), revealed low serum cortisol [108 nmol/l (reference values 240-618nmol/l)], high insulin level (7.1 μ IU/ml [reference >1.6 μ IU/ml]), low growth hormone response [2.66 μ g/l (reference values <5.4 μ g/l)] and β -hydroxybutyrate of <0.10 mmol/l (reference values 0.03 - 0.30mmol/l). Serum free fatty acids, serum lactate and pyruvate, urinary reducing sugars and organic acids were not measured due to financial constraints. A diagnosis of congenital hypopituitarism was considered given the inappropriate growth hormone and cortisol response, but further investigations were unaffordable. Serial urinalyses were negative for ketones. Transfontanelle ultrasound scan was reported normal while an abdominal ultrasound scan also revealed no abnormality.

Due to the persistence of hypoglycaemia despite the interventions, oral diazoxide, which was not readily available, was commenced at 5 mg/kg/day in two divided doses, ten days into the management of the child. Oral hydrochlorothiazide at 2mg/kg/dose 12 hourly was administered simultaneously, but it was discontinued after two days when the infant developed acute kidney injury. The infant was diazoxide-responsive with the normalization of the blood glucose values within an hour of commencement, and this was sustained

thereafter. There was no consequent hyperglycaemic episode. Following the commencement of diazoxide, mild weight gain was noticed which reverted by the fifth day. Diazoxide was reduced to 2.5 mg/kg/day after 5 days of commencement and was discontinued following a therapeutic period of 14 days, a week before discharge from the hospital.

The infant was discharged after one month of admission and he is currently being followed up in the Paediatric Endocrinology Clinic to exclude pituitary abnormality. At the age of 20 months, he has a neurodevelopmental delay, the length (74 cm) and weight (8 kg) were both below the 3rd centile for age and sex, and have been persistently so since infancy. At the last clinic visit, thyroid function was normal [Serum Thyroid Stimulating Hormone: 2.3mIU/l (reference values 0.7 - 5.8 mIU/l), serum Free T3 was 6.8pmol/l (reference values 4.4 - 7.3 pmol/l, serum Free T4 was 14.5pmol/l (reference values 7.2 -16.4 pmol/l)], and fasting serum cortisol was 358.2nmol/l (reference values 240 - 618 nmol/l)].

Discussion

Neonatal hypoglycaemia is a potentially harmful condition. In the index child, all the criteria for the definition of HH were met except for free fatty acids which could not be measured. The transient form of HH is known to occur among infants of diabetic mothers and infants with perinatal asphyxia, [16] as observed in the index child.

It is not routine practice to analyse critical sample during hypoglycaemic episodes in resource-poor settings. This is owing to low awareness, high cost and non-availability of diagnostic tools. The cost of the investigation is more than double the current national minimum monthly wage of about \$80 (USD). This will

indeed be distressing and unaffordable for many families in the country who belong to the middle and lower socioeconomic cadres. In this report, the importance of the critical sample is clearly emphasized in suggesting the aetiology of hypoglycaemia. Due to a combination of persistent hypoglycaemia, the abnormal growth hormone level in the critical sample, as well as the subsequent occurrence of growth retardation, congenital hypopituitarism was suspected in the index child. However, this is yet to be confirmed due to financial constraint to further evaluation as the care of the patient was based solely on out-of-pocket spending.

Diazoxide is known as an important medication in managing HH and was included in the 2019 World Health Organisation (WHO) Essential Medicines List for children (EMLc).^[17] Ideally, any drug on the EMLc must be readily available and affordable.^[18] Unfortunately, the prohibitive cost of \$1.6 (USD) per tablet of diazoxide and its poor accessibility make its use difficult in low-income settings as it was challenging getting it to manage the index patient. Nevertheless, a remarkable effect was observed with diazoxide use as the blood glucose level normalised during routine glucose check an hour after administration and remained normal thereafter. This observation is particularly important as the early commencement of diazoxide may prevent the various complications of NH in children.

A known side effect of diazoxide is fluid retention which occurs via increased salt retention and reduced free water clearance.^[19] Therefore, concomitant thiazide diuretic e.g. hydrochlorothiazide (2-10 mg/kg/day, in two divided doses) is recommended to prevent this complication.^[20] Due to pre-existing fluid retention and hypoalbuminaemia, it was difficult eliciting fluid retention complicating diazoxide use in the index case. In a Japanese national survey among preterm infants with HH treated with diazoxide mostly without diuretics,

a high prevalence of circulatory overload was reported.^[13] This outcome emphasizes the importance of co-administration of a diuretic with diazoxide. The low-dose and short duration of diazoxide therapy for our patient did not allow for monitoring of other side effects which are largely dose-dependent.

Conclusion

This report emphasizes the importance of diazoxide in the management of neonatal hyperinsulinaemic hypoglycaemia. The availability and cost of diazoxide, as well as access to endocrine and metabolic investigations, are of major concern in resource-poor settings and need to be addressed. The importance of critical sample in relation to the aetiology of neonatal hypoglycaemia was also highlighted. It is hoped that more documentations from Nigeria and the African continent on the use of diazoxide for neonatal HH will be available in the nearest future to relate with other regional experiences.

Authors' Contributions: AAO, ATE and AOO contributed to the conception and design of the study. AOO, AFG and AED acquired the data. All authors contributed to the drafting and critical review of the manuscript and approved the final version of the manuscript.

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