SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pediatrics

The Drug-Induced Hypoglycemia in Children: Is Levetiracetam Incriminated?

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DOI: 10.36347/sasjm.2023.v09i05.021 | **Received:** 04.04.2023 | **Accepted:** 10.05.2023 | **Published:** 18.05.2023

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Abstract **Case Report**

Levetiracetam is a well-tolerated anticonvulsant drug, but associated with some adverse effects. To date, there is no report of hypoglycemia associated with levetiracetam. We report the case of a 6-year-old female patient who developed symptomatic hypoglycemia after initiation of treatment with levetiracetam for her refractory status epilepticus and we review the literature to identify other reports of hypoglycemia. Associated with levetiracetam in children in order to highlight this rare adverse effect and a possible dose effect. Hypoglycemia is a rare and underestimated adverse effect of Levetiracetam and which must be taken into account and treated appropriately, in particular when high doses are given; allowing a saving of a multiple of unnecessary additional examinations.

Keywords: Hypoglycemia, children, levetiracetam, drug, toxicity.

INTRODUCTION

Levetiracetam is a well-tolerated anticonvulsant drug, which was first approved by the United States Food and Drug Administration (FDA) in 1999 as an add-on therapy for the treatment of partial-onset seizures refractory and has since gained additional indications in the pediatric population [1]; but still associated with some adverse effects. Indeed, hypoglycemia is not a side effect mentioned in the drug information or in any drug trial.

Here, we described a non-diabetic patient who developed hypoglycemia with levetiracetam following refractory epilepsy. We also discussed the possible mechanisms of hypoglycemia and all the rare cases reported in the literature.

OBSERVATION

Patient NY, 6 years old, known to have epilepsy since the age of 4, under antiepileptic treatment with: sodium valproate at a rate of 38mg/kg/day. She was currently presenting for persistent generalized seizures resistant to treatment which required the initiation of Levetiracetam at a dose of: 10 mg/kg/j then 40 mg/kg/j progressively. Its evolution was marked a few days later by the accentuation of the convulsive seizures associated with episodes of cold sweats, headaches, agitation or even a feeling of fainting expressed by the patient. Her clinical examination showed no abnormalities; her capillary blood sugar was 0.45 g/L. An hour glycemic control had objectified recurrent episodes of hypoglycemia during the day. Despite being put under systemic correction, she kept having blood sugar levels not exceeding 0.7g/L. An etiological assessment was carried out to explore this hypoglycemia revealing: Hb - 10.1 g/dl, WBC: 9800 cells/mm3, PLQ: 226000, Calcium 88 mEq/L, sodium: 138 mEq/L, Potassium: 3.8 mEq/ L, Mg2+ - 2.0 mg/dl, Creatinine: 2.4 mg/dl, Urea: 0.6 mg/dl, ALAT: 19, ASAT: 14 with a TP at 97%. An endocrinological assessment in this context didn't show any abnormalities. Abdominal CT was also done normally showing no insulinoma. No etiology could be identified for his persistent hypoglycemia. The questioning was redone with the parents on the probability of taking an hypoglycemic or toxic drug. None were found; with the only recent introduction of Levetiracetam. Thus, the medication was gradually reduced to assess its effect on blood sugar until complete suppression. When the dose of levetiracetam was reduced to half, her blood sugar level stabilized around 0.7-0.9 g/dl on continuous infusion. Then, once the Levetiracetam was stopped, the glycemic values returned to normal, exceeding 1 g/L, thus allowing our patient to free herself from the continuous infusion. Levetiracetam has been replaced by her anterior treatment: sodium valproate again.

DISCUSSION

There is no real consensus definition of hypoglycemia. Currently, it can be defined biochemically or clinically by a plasma glucose level below an arbitrary value that varies according to the population; diabetic (70mg/dl) or non- diabetic (63mg/dl). However, a wide range of glucose levels can represent biochemical hypoglycemia, and the difficulty arises in determining at what glucose level it begins [1].

The definition proposed by Whipple remains the most useful and defines pathological hypoglycemia as a triad of hypoglycemia: biochemical, hypoglycemic symptoms and resolution of symptoms with correction of blood sugar [2]. Clinical symptoms can be variable; mild to moderate including signs such as palpitations, sweating, tingling, hunger, nausea, tremors and headache [3]. Later, and if hypoglycemia is not treated rapidly, neuroglycopenic symptoms are inevitable. They include blurred vision, psychopathic behavior, confusion, seizures, focal neurological deficits or in an extreme case coma. In addition, repeated episodes of hypoglycemia can over time lead to the syndrome of insensitivity to hypoglycemia with major cognitive dysfunction resulting in confusion and coma without preceding precursor symptoms [4]. Loss of hypoglycemia warning is associated with delayed and reduced neuroendocrine responses to falling blood sugar, frequently leading to severe hypoglycemia. It occurs following frequent and recurrent iatrogenic hypoglycemic events and is closely related to defects in hormonal counter regulation, particularly the adrenaline response [5].

Although the symptoms of drug-induced hypoglycemia are not specific, in some cases drug-induced hypoglycemia can be differentiated from other possible etiologies by assessing the temporal relationship between drug administration, onset of symptoms and changes in blood sugar. Drug withdrawal or sometimes even re-administration can be helpful in confirming the diagnosis. Thus, prompt detection of symptoms of drug-induced hypoglycemia and immediate treatment with frequent monitoring of the patient is mandatory.

Levetiracetam, a broad-spectrum antiepileptic drug with an unconventional mechanism of action, first discovered in 1974 and approved by the US FDA in 1999 for the adjunctive treatment of partial-onset seizures in adults [6]. It was in 2000 that the European Medicines Agency approved the marketing authorization for levetiracetam [7] then in 2003 by Health Canada.

Subsequently, prospective clinical trials have focused on its efficacy and tolerance as adjunctive therapy and as monotherapy in adult and pediatric patients for the treatment of partial-onset seizures, myoclonic seizures and generalized tonic-clonic seizures making Levetiracetam the antiepileptic of choice [8].

Levetiracetam is structurally unique and does not share the pharmacodynamic properties of other AED classes by acting on SV2A, a synaptic vesicle glycoprotein, and causing neuromodulator effects through regulation of neurotransmitter release as well as activity against inhibitory modulators of gamma-aminobutyric acid (GABA) signals [9].

Levetiracetam also exhibits linear pharmacokinetics and near-ideal characteristics for an AED. Young children and infants have a volume of distribution and total body clearance certainly higher than adults but still very correct compared to other antiepileptics [10].

The drug is administered orally and absorption has not been shown to be affected by food. The bioavailability is greater than 95% and less than 10% is bound to plasma proteins. The maximum recommended dose of levetiracetam in children under 6 months is 42 mg/kg divided twice daily. For children aged 6 months to 4 years, the maximum recommended daily dose is 50 mg/kg divided twice a day; for children aged 4 to 16 years, the maximum recommended daily dose is 60 mg/kg taken twice daily, up to a maximum total daily dose of 3000 mg. Levetiracetam is available in 250, 500, and 750 mg immediate-release tablets, 500 and 750 mg extended-release tablets, and 100 mg/mL oral solution [11].

Levetiracetam is generally considered a well-tolerated anticonvulsant but is associated with some adverse effects including drowsiness, irritability, asthenia and dizziness but at higher doses more serious but rare effects. Other cases of aggression, paranoia, psychosis and irritability have been noted in a pediatric population [12].

In contrast, the evidence for a relationship between serum levetiracetam concentrations and clinical response, whether for efficacy or safety, is conflicting and unclear. Only two studies assessed the relationship between levetiracetam concentrations and adverse drug effects, but no correlation was found [13, 14].

A list of non-hypoglycemic drugs responsible for hypoglycemia has been previously established but where levetiracetam does not find its place. However, an article from the French pharmacovigilance database reveals hypoglycemia with exposure to levetiracetam in 5 patients - 2 neonates, both female, who had developed neonatal hypoglycemia from mothers taking levetiracetam during pregnancy [13]. 2 other male patients were taking levetiracetam but in combination with valproate had an episode of hypoglycemia

resolved quickly after discontinuation of levetiracetam and another male patient with hypoglycemia following parenteral administration of levetiracetam who did not recur when changing to the per os administration [14].

In our patient, hypoglycemia occurred in the first days after administration of levetiracetam, decreased when the dose was reduced. However, the hypoglycemia was resolved only after total discontinuation of the drug, but an improvement in the glycemia was noticed from the initiation of the levetiracetam degression. This highlights the fact that the hypoglycemia was dose-dependent in our patient. Unfortunately, the dosage of blood levetiracetam could not be done in our case to be able to determine the toxic threshold limit. The mechanism by which Levetiracetam could be responsible for hypoglycemia is still unclear as literature is not available regarding any possible way.

CONCLUSION

In conclusion, Hypoglycemia is a rare and underestimated side effect of Levetiracetam and should be taken into account and treated appropriately, especially in case of high doses. Our article is an effort to report a dose-dependent association of hypoglycemia with levetiracetam but also an encouraging step in adverse event reporting for better drug review especially when it comes to the pediatric population.

REFERENCES

1. Frier BM. Defining hypoglycaemia: what level has clinical relevance? Diabetologia 2009 Jan; 52 (1): 31-4
2. Guettier JM, Gorden P. Hypoglycemia. Endocrinol Metab Clin North Am 2006 Dec; 35 (4): 753-66
3. Diabetes Canada Clinical Practice Guidelines Expert Committee et al. "Hypoglycemia." *Canadian journal of diabetes* vol. 42 Suppl 1 (2018): S104-S108. doi:10.1016/j.jcjd.2017.10.010
4. Bolli GB. Treatment and prevention of hypoglycemia and its unawareness in type 1 diabetes mellitus. Rev Endocr Metab Dis 2003 Dec; 4 (4): 335-41
5. Cryer PE. Hypoglycaemia: the limiting factor in the gly[1]caemic management of type I and type II diabetes. Dia[1]betologia 2002 Jul; 45 (7): 937-48
6. Tan, Jason et al. "Levetiracetam Clinical Pharmacokinetic Monitoring in Pediatric Patients with Epilepsy." *Clinical pharmacokinetics* vol. 56,11 (2017): 1267-1285. doi:10.1007/s40262-017-0537-1
7. European Medicines Agency. Keppra: EPAR – scientific dis[1]cussion. European Medicines Agency; 2005. pp. 17–19.
8. Abou-Khalil B. Levetiracetam in the treatment of epilepsy. Neuropsychiatric disease and treatment. 2008; 4(3):507–23. PMID: 18830435
9. Wright C, Downing J, Mungall D, et al. Clinical pharmacology and pharmacokinetics of levetiracetam. Front Neurol. 2013;4:192
10. Pellock JM, Glauser TA, Bebin EM, et al. Pharmacokinetic study of levetiracetam in children. Epilepsia. 2001;42:1574–9
11. Jarvie, Dael, and Sherif Hanafy Mahmoud. "Therapeutic Drug Monitoring of Levetiracetam in Select Populations." *Journal of pharmacy & pharmaceutical sciences* vol. 21,1s (2018): 149s-176s. doi:10.18433/jpps30081
12. Egunsola, Oluwaseun et al. "Safety of Levetiracetam in Paediatrics: A Systematic Review." PloS one vol. 11,3 e0149686. 1 Mar. 2016, doi:10.1371/journal.pone.0149686
13. Kilbridge, Peter M et al. "Automated surveillance for adverse drug events at a community hospital and an academic medical center." *Journal of the American Medical Informatics Association: JAMIA* vol. 13,4 (2006): 372-7. doi:10.1197/jamia.M2069
14. Azma Naaz Mohammed et al JMSCR Volume 07 Issue 11 November 2019. DOI: https://dx.doi.org/10.18535/jmscr/v7i11.118