Signal

Levetiracetam and Hypokalaemia

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Summary

Levetiracetam is considered a remarkable antiepileptic drug due to its mechanism of action, which is unrelated to the Na+ channels or to GABAergic transmission. Few interactions are described for this drug due to its minimal hepatic metabolism; however, sixty-six percent of its elimination depends on the renal function. Drug-induced hypokalaemia is a hazardous reaction that could lead, in the worst cases, to death. A screening of VigiBase, the WHO global database of individual case safety reports, identified disproportionate reporting of the MedDRA Preferred Term (PT) "Hypokalaemia" with levetiracetam. A selection of the cases with a completeness score above 0.60 was made to analyse drug–reaction association patterns. A consistent time to onset and a biological plausibility support this signal. Through this analysis, it seems reasonable to consider the association between hypokalaemia and levetiracetam use. Currently, only the product information from Canada warns of hypokalaemia as an adverse reaction to levetiracetam, but all clinicians should be aware of this adverse event.

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Introduction

In December 1999, levetiracetam was approved in the United States (US) as an antiepileptic drug for the treatment of adults with partial seizures, and approval by the European Union (EU) followed in September 2000. Around 2005, oral tablets and solutions were approved for children, and in 2006, it began to be used for the treatment of status epilepticus. At the time of writing, levetiracetam is indicated for the treatment of epilepsy in adults, adolescents, children, and infants. It is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances. Regarding its mechanism of action, it is well known that the interaction is between levetiracetam and the synaptic vesicle protein 2A. In this way, it does not exhibit the classical action of other antiepileptic drugs because there is no effect on voltage-dependent Na+ channels or GABAergic transmission.[1]

Hypokalaemia is a common and sometimes serious electrolyte imbalance. Its presence can aggravate the baseline clinical conditions of patients. The hypokalaemia categories are well known: mild with plasma levels of >3.0–3.5 mmol/L generally asymptomatic; moderate 2.5–3.0 mmol/L its symptoms are cramping, malaise, myalgia, weakness; and severe < 2.5 mmol/L associated with electrocardiogram changes (including ST-segment depression, U-wave elevation, T-wave inversion), arrhythmias and paralysis. Drug-induced hypokalaemia could be associated with a decrease in potassium intake, or with increased potassium shifting (transcellular shifts). This electrolyte disbalance is commonly associated with diuretics, β2-receptor agonists drugs, corticosteroids, some antimicrobials, or high doses of insulin.[2]

Reports in VigiBase

During 2017, the MedDRA Preferred Term "hypokalaemia" was highlighted for the drug levetiracetam in VigiBase, the WHO global database of individual case safety reports. This combination was kept under review in order to gather more cases. As of 15 September 2019, in an updated and extended search in the database, there were 74 reports of this drug–adverse drug reaction (ADR). Seventeen cases were suspected as duplicates; therefore, 57 were considered. Due to the high number of cases, an analysis of the reports with a completeness score over 0.6 was undertaken. In the present case series, 23 cases were evaluated.

The reports came from eight countries. Eleven patients were female, the other eleven were male, and gender was not specified in one report. The age was recorded in twenty-one patients. Ten out of twenty-one were adults, nine were elderly, one was aged 5, and one a new-born. More than half of the cases were submitted by physicians (sixteen reports). In fourteen cases the ADR was considered as serious, mainly because of prolonged hospitalization (eight cases), or concomitant medically important conditions (five cases). One case was reported as serious because the patient died. The summary of case characteristics is set out in Table 1.

Levetiracetam was the unique suspected drug in 14 reports, the therapeutic indication being epilepsy (focal seizures, convulsions, partial seizures with secondary generalization). The time to onset was mentioned in eighteen reports, in seventeen cases a range from the same day up to two months was given. In one case the patient experienced the ADR after two years of treatment. Half of the patients had a time to onset around ten days after starting levetiracetam. The route of administration was mentioned in twenty reports, the more frequent being oral route (ten reports), followed by intravenous (nine) and transplacental (one). In the case of the transplacental route, it seems according to the narrative text that exposure of the new-born was during the pregnancy span. Regarding the concomitant medicines, hydrocortisone was reported as a co-suspected drug in two cases, however, in one report, the starting date was given in the same timeframe as levetiracetam. Lacosamide was also mentioned as co-suspected in two other cases, within the same timeframe as levetiracetam. In four reports the use of proton pump inhibitors such as esomeprazole (one as co-suspected and another one as concomitant) and pantoprazole (two cases as concomitant) was mentioned.

Hypokalaemia was described as the single ADR in eleven cases. Hypomagnesemia was reported in four cases as a co-reported reaction, and in two of these cases, the starting dates mentioned were the same as hypokalaemia. Likewise, three reports mentioned diarrhoea, two during the same time period as hypokalaemia. The plasmatic level of potassium

concentrations was registered in fourteen cases, with a range of 2.2 – 3.3 mmol/L, in all cases the levels being reported after the levetiracetam was started.

Levetiracetam was withdrawn from three patients and the dose reduced in another one, all these being reported as recovered. In ten patients the dose was not changed, and of these, four were described as recovered, another four as recovering, one as not recovered, and for the last one the outcome was unknown. Sixteen cases had a narrative; in seven of these a supplement of potassium was mentioned. One patient died; this was an elderly person (aged 83), with co-reported ADRs pneumonia, atrial fibrillation, tachycardia, hypoproteinaemia, hypoalbuminemia, and blood lactate dehydrogenase increased, but there was no narrative. It is difficult to attribute the fatal outcome to the hypokalaemia.

Literature and labelling

The literature suggests that levetiracetam is widely used due to high tolerability comparing favourably with other antiepileptic drugs used in epilepsy, and because it can be used when other drugs are contraindicated or patients have a refractory condition to other antiepileptics.[1]

Sixty-six percent (66%) of levetiracetam is excreted unchanged by glomerular filtration in the kidney, with subsequent tubular reabsorption, as well as its primary metabolite (ucb L057). The plasma half-life of levetiracetam across studies is 6 to 8 hours, however the labelling mentions it could be greater in subjects with renal impairment and in the elderly, primarily due to impaired renal clearance. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore

Table 1. Summary characteristics of 57 case reports in VigiBase of hypokalaemia in association with Levetiracetam in VigiBase.

Characteristic	23 cases with high completeness score (above 0.6)	34 cases with low completeness score (less than 0.59)
Age (median / range)	57 years / 0* - 90 years	45 years / 5 – 87 years
Patient sex distribution	11 female / 11 male / 1 unknown	21 female / 13 male
Geographical spread	India (n=7), Germany (n= 4), Italy (n=3), Japan (n=3), Greece (n=2), France (n=2), US and Ireland (n=1 each)	US (n=17), Germany (n=6), United Kingdom n=2 and Italy, Korea, Japan, Turkey, Denmark, France, Hungary, Belgium , Ireland (n= 1 each)
Reporter types	16 physicians; 4 pharmacists; 3 other health professionals	17 physicians; 3 pharmacists; 9 other health professionals; 2 consumers; 3 unknown
Single suspect drug	14 reports	9 reports
Single reported drug	7 reports	4 reports
Category of hypokalaemia	3 reported as mild, 7 reported as moderate, 4 reported as severe, 9 reports unknown	5 reported as mild, 1 reported as severe, 28 reports unknown
Time-to-onset	Mentioned in 18 reports with a median of 10 days 12 reports after 1 to 10 days, 3 reports after 11 to 20 days, 2 report after 60 days, 1 report after 2 years	Mentioned in 2 reports 30 and 60 days
Withdrawn/recovered	1 report with dose reduced, 3 reports with drug withdrawn and all with reaction abated 8 reports with dose not changed and reaction abated or in recovering	1 report with drug withdrawn and the reaction abated

a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is <60 mL/min/1.73m^2. [3, 4]

The Summary of Product Characteristics (SPC) of levetiracetam in the US and Europe does not list hypokalaemia as an ADR. However, the SPC in Canada mentions hypokalaemia as an ADR observed in the post-marketing surveillance.[5–8]

In the literature, a case report published in 2014 from Turkey described a 23-year-old man where hypokalaemia was found during routine blood tests six weeks after taking 500 mg levetiracetam twice daily. After the nephrology consultation, his hypokalaemia (3.1 mmol/L; normal: 3.5–5.5 mmol/L) and hypomagnesaemia (0.56 mmol/L; normal: 0.75–1.30 mmol/L)) were considered to be associated with levetiracetam; it was withdrawn and the electrolytes returned to normal after two weeks.[9] In 2015 a publication from Greece described hypokalaemia and hypomagnesemia associated with levetiracetam in two patients. A 90 year-old female patient had received levetiracetam 500 mg twice daily intravenously; two days later a low plasma level of potassium and magnesium were identified (2.4 mmol/L, and 0.58 mmol/L, respectively). The other patient was a 79 year-old female who had been administrated levetiracetam at 1 gr twice daily intravenously, and three days later the level of potassium was 2.4 mmol/L and magnesium 1.35 mg/dL. Despite the potassium supplement at the hospital, the patients did not fully recover, and consequently levetiracetam was withdrawn.[10] In 2018, another case from Turkey described a 34 year-old woman who was admitted to hospital after attempting to commit suicide. In the laboratory test hypokalaemia (3.1 mEq/lt) and hypomagnesemia (1.2 mg/dl) were observed; the patient was taking 2500 mg/day levetiracetam for epilepsy although the duration of treatment was not described.[11] These publications suggest that the hypokalaemia observed could be due to a transcellular shift mechanism, an unknown side effect of the levetiracetam, given that they ruled-out other potential causes such as metabolic alkalosis or gastrointestinal losses.[9–11]

Discussion and Conclusion

In this case series, it is difficult to rule out other potential causes as there is a lack of information regarding the baseline condition of the patients. However, the association should be considered, given the high suspicion of the reporters and the fourteen reports where levetiracetam was the only drug mentioned. On the other hand, diarrhoea – another potential cause – was only mentioned in two cases. It is worth noting that the time to onset in most cases (twelve patients out of twenty-three) was within ten days after starting levetiracetam.

Regarding other drugs that can be associated with hypokalaemia, corticosteroids, and methylxanthines are strongly associated with drug-induced hypokalaemia and other electrolyte imbalances.[2] In one patient, hydrocortisone and theophylline were reported as co-suspected drugs. However, levetiracetam was used in the same temporal sequence of these drugs, and for that reason it is not possible to rule out their potential association with hypokalaemia.

Magnesium deficiency exacerbates potassium wasting by increasing distal potassium secretion. However, hypomagnesemia alone does not necessarily cause hypokalaemia.[12] In this case series, four patients had hypomagnesemia, but in two cases the starting dates were unknown and in the other two cases, they had the same starting date as hypokalaemia, making the analysis of the potential causal relationship between hypomagnesaemia and hypokalaemia difficult. Then again, there are several reports regarding the association of proton pump inhibitors and hypomagnesemia.[13, 14] Esomeprazole was mentioned as a co-suspected drug for hypokalaemia and hypomagnesemia in one patient. This potential interaction needs further analysis in large studies.

In a prospective study of 32 children in Greece (18 females, 14 males, mean age 5.94 ± 4.1 years, range 1- 15 years) being treated with levetiracetam for the onset of epilepsy, no statistical differences were observed in the alteration of serum sodium, potassium, and magnesium from two to six months with the use of levetiracetam.[15] However, the authors point to the small number of patients studied as a major limitation of their study, and suggest that the young age of patients may have played a protective role in the prevention of electrolyte imbalance. Following clinical trials made in this age group, levetiracetam has been authorized for use in children, and is therefore considered a *safe* therapeutic option for this group of patients.[16] However, our sample has

two patients under 18 years old, even one case of a new-born patient with hypokalaemia.

In the twenty-three patients, only four had their dose of levetiracetam reduced or withdrawn, and these patients were reported as recovered. However, some patients started with the potassium supplement, such as in three cases reported as recovered, despite no change in the dose of levetiracetam, nor withdrawal. In the same way, in two other patients in whom the action with levetiracetam was reported as unknown, the outcome was reported as recovered. It is important to consider the treatment received for this ADR, and whether patients would have an asymptomatic hypokalaemia; the dechallenge as an outpatient could be difficult to identify and report, because the levels of potassium could return to normal two to four weeks after withdrawal, and the reporter might not have had this information at the time that they sent the report.

The biological plausibility comes through a transcellular shift imbalance of potassium, as discussed in the case reports.(9–11) This hypothesis goes in tandem with the alterations of the potassium homeostasis described as a cause of drug-induced hypokalaemia.[17, 18] A previous signal regarding acute renal failure associated with levetiracetam was published in 2016 by Uppsala Monitoring Centre; this ADR is already mentioned in the US SPC as an ADR identified in post-marketing surveillance, and in the EU SPC as having a rare frequency.[19] The occurrence of renal adverse effects seems reasonable, based on to levetiracetam pharmacokinetics.

In conclusion, patients being treated with levetiracetam should be closely monitored for changes in their potassium levels. Our analysis, and the available evidence based on the pharmacokinetics of the drug, suggest a potential causal relationship between levetiracetam and hypokalaemia. Current product information for levetiracetam does not sufficiently inform physicians about electrolyte imbalance, and the product labelling may need to be revised worldwide since the Canadian SPC already includes hypokalaemia as an ADR identified in post-marketing.[6]

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SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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