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Experience of Subcutaneous Levetiracetam in Palliative Care

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Highlights of the Study

- Seizures are common in palliative care. Patients near the end of life might lose the oral or intravenous route; thus, an alternative route for antiseizure medications is mandatory.
- In our experience, subcutaneous levetiracetam is well tolerated and effective in controlling seizures in palliative care patients with epilepsy.
- This study contributes to knowledge on subcutaneous levetiracetam as an effective and tolerable option in patients with epilepsy at the end of life.

Keywords
Levetiracetam · Palliative care · Epilepsy · Subcutaneous levetiracetam

Abstract
Background: Seizures are common in palliative care patients and its control is essential in the management of these patients as it helps to reduce suffering at the end of life. Subcutaneous levetiracetam has been used off-license for seizure control in palliative care. ***Objective:*** The objective of the study was to describe our experience with subcutaneous levetiracetam in two hospitals in Bogota, Colombia. ***Methods:*** We conducted a retrospective review of patients treated with subcutaneous levetiracetam in two hospitals in Colombia during 2019–2021. Data were extracted from medical records, and participants were followed up as outpatients. ***Results:*** Twenty-one patients were included into the study. No severe adverse effects or rise in ictal frequency were documented. Twelve patients died during hospitalization and nine continued treatments as outpatients. The principal diagnosis was structural focal epilepsy. The daily dose of levetiracetam ranged from 1,000 mg to 3,000 mg, and the duration of treatment varied among subjects between 1 and 360 days. ***Conclusion:*** Subcutaneous levetiracetam was well tolerated and effective in controlling seizures in palliative care when oral administration or intravenous access was not an option. Randomized controlled trials are needed to elucidate the efficacy and tolerability of subcutaneous levetiracetam in clinical practice.

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Introduction

Seizures are common in patients near the end of life. Seizure control is considered a palliative care emergency and a way of improving quality of life [1]. Among the underlying causes of seizures in palliative care, brain tumors are present in 56% of cases and high-grade glioma is seen in one-third of cases, with seizures presenting during the last month or last week before death [2]. Stroke also contributes to cases of seizures in palliative care, with an incidence of 5–12% after arterial ischemic stroke and 10–35% in hemorrhagic stroke or subarachnoid hemorrhage. There is a higher risk in the period known as late post-stroke (i.e., later than 2 weeks after the stroke), and it is related to increased mortality and disability in these patients [3–5]. Some patients stop oral antiseizure medications (ASMs) once the enteral route is lost or the intravenous route is not possible or desirable. In fact, dysphagia among subjects with brain tumors have been reported from 40% to 70% [1]. In such cases, the subcutaneous (SC) route may be an alternative; however, among ASMs, formulations for SC administration are not available. Treatment with midazolam and phenobarbital can be administered through the SC route [6, 7]. However, these medications induce sedation, and this side effect is not desirable in all patients with palliative care. Hence, exploring others ASMs, that can be administered via the SC route, with fewer side effects is key to improving the quality of life in subjects with epilepsy. SC levetiracetam has been used off-license for seizure control in palliative care [1, 7, 8]. Because of the pharmacokinetic safety profile, low sedation rate, and good tolerability of levetiracetam, its use could be an option for seizure control at the end of life in patients with epilepsy in whom oral administration is no longer possible (8). The aim of our study was to describe our experience using SC levetiracetam in two hospitals in Bogota, Colombia, during 2019–2021.

Methods

We conducted a retrospective review of patients treated with SC levetiracetam in Hospital Universitario Mayor Méderi and Hospital Militar Central, in Bogota, between June 2019 and November 2021. We included hospitalized adults who received SC levetiracetam during this period. We reviewed their medical records. Patients who continued treatment as outpatients were followed up by telephone. The primary outcome was the efficacy and tolerability of SC levetiracetam assessed based on ictal frequency and adverse effects. Secondary results included the principal diagnosis, daily dose, duration of treatment, and patient outcomes.

Results

We identified 21 patients who received SC levetiracetam during the study period. Their demographics and medical characteristics are shown in Table 1. Patients were between 26 and 96 years old, and 14 were female. We did not identify a rise in the frequency of seizures. Only one patient had local adverse effects (edema and erythema); levetiracetam treatment was stopped in this patient because of their prognosis, and she died the next day. All subjects were inpatients when they started SC levetiracetam treatment. Twelve subjects died during their hospitalization because of the natural course of their disease; none of these deaths were a direct result of epilepsy, and 9 continued the treatment as outpatients. The principal diagnosis was structural focal epilepsy in the context of ischemic stroke. Other diagnoses included hemorrhagic stroke, probable Creutzfeldt-Jakob disease, traumatic subdural hematoma, glioblastoma, meningitis, and major cognitive disorder.

The main reason for switching to SC administration route was severe dysphagia or severe encephalopathy. All patients had received ASMs before switching to SC administration (Table 1).

Levetiracetam was diluted in 50 mL of 0.9% sodium chloride and infused over 1–2 h through a pump using a pectoral or deltoid catheter. The oral and intravenous-to-SC conversion ratio was 1:1 in almost all patients. The duration of treatment among subjects varied between 1 and 360 days. All patients tolerated SC levetiracetam. Five patients were followed up after discharge with a mean of duration at home of 136.2 days. We did not document adverse effects or rise in ictal frequency in those subjects.

Discussion

SC levetiracetam constitutes an important alternative therapeutic option in palliative care when the enteral route is nonviable, mainly because of dysphagia or a reduced level of consciousness or when the use of the intravenous route is not allowed or desired [9]. According to current evidence, SC levetiracetam is well tolerated and achieves seizure control.

The efficacy of ASMs is defined by seizure control. In our study, all patients were seizure free after SC levetiracetam treatment. In fact, we used SC levetiracetam in 4 patients with possible or confirmed nonconvulsive status epilepticus (Table 1). Our results are similar to others studies. Papa et al. [8] reported seizure control in 6 out of

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Table 1. Patient characteristics

Case	Sex	Age, years	Principal diagnosis	Secondary diagnosis	ASM before SC levetiracetam	Co-medication SC	Dose of SC levetiracetam	Dose changes	Seizure frequency prior to levetiracetam SC	Seizure frequency during SC	Reactions at injection site	Duration of levetiracetam SC (days) during hospitalization	Inpatient death
1	F	94	Structural focal epilepsy	Ischemic stroke	Levetiracetam 500 mg intravenous twice a day	Hydromorphone 0.2 mg once a day, haloperidol 1 mg twice a day	500 mg twice a day	None	Unknown	None	None	6	Yes
2	F	83	Structural focal epilepsy	Ischemic stroke	Valproic acid 500 mg intravenous twice a day	Hydromorphone 0.1 mg three times a day	500 mg twice a day	None	1 seizure (semiology not described)	None	None	7	Yes
3	F	67	Possible nonconvulsive status epilepticus	Rapidly progressive dementia (probably Creutzfeldt Jakob)	Valproic acid 250 mg intravenous twice a day	No	500 mg twice a day	None	Unknown	None	None	4	No
4	F	26	Structural focal epilepsy	Subdural hematoma, meningitis	Levetiracetam 500 mg intravenous twice a day	Hydromorphone 0.2 mg once a day	500 mg twice a day	None	2 episodes of unknown onset and tonic clonic seizures	None	None	14	No
5	F	71	Nonconvulsive status epilepticus	Hypothyroidism	Levetiracetam 1,000 mg oral three times a day, valproic acid 500 mg oral three times a day	No	1,000 mg three times a day	None	1 episode of status epilepticus	None	None	3	Yes
6	F	78	Structural focal epilepsy	Left thalamic astrocytoma	Lacosamide 100 mg intravenous twice a day	Hydromorphone 0.2 mg once a day, dexamethasone 8 mg once a day, hyoscine 20 mg four times a day	1,000 mg twice a day	None	1 episode of status epilepticus	None	None	5	Yes
7	F	96	Structural focal epilepsy	Alzheimer – ischemic stroke	Valproic acid 500 mg intravenous twice a day	Morphine 1 mg once a day, hyoscine 20 mg twice a day -	500 twice a day	None	3 seizures (semiology not described)	None	None	1	No
8	M	70	Symptomatic seizure (hypoglycemia)	SARS-CoV2	Valproic acid 500 mg intravenous twice a day, levetiracetam 500 mg intravenous twice a day	Haloperidol 2 mg three times a day	500 twice a day	Increase: 500 mg	2 episodes of unknown onset and tonic clonic seizures	None	None	3	No
9	M	50	Structural focal epilepsy	Glioblastoma, small-cell PNET-like variant	Phenytoin 250 mg intravenous three times a day suspended due to rash, valproic acid 250 mg oral twice a day	Omeprazole 20 mg once a day	500 mg twice a day	None	Unwitnessed seizure	None	None	2	No
10	M	88	Structural focal epilepsy	Ischemic stroke	Valproic acid 250 mg oral twice a day, levetiracetam 500 mg intravenous twice a day	No	500 mg twice a day	None	None	None	None	12	Yes

Table 1 (continued)

Case	Sex	Age, years	Principal diagnosis	Secondary diagnosis	ASM before SC levetiracetam	Co-medication SC	Dose of SC levetiracetam	Dose changes	Seizure frequency prior to levetiracetam SC	Seizure frequency during SC	Reactions at injection site	Duration of levetiracetam SC (days) during hospitalization	Inpatient death
11	M	58	Structural focal epilepsy	Hemorrhagic, major neurocognitive disorder	Levetiracetam 1,000 mg oral twice a day	No	1,000 mg twice a day	None	3 seizures per month (semiology not described)	None	None	15	Yes
12	F	92	Structural focal epilepsy	Traumatic frontal subdural hematoma, major neurocognitive disorder	Levetiracetam 500 mg intravenous twice a day	No	1,000 mg twice a day	None	1 seizure per month (semiology not described)	None	None	90	No
13	M	69	Structural focal epilepsy	Glioblastoma	Valproic acid 250 mg three times a day	Morphine 1 mg twice a day	500 twice a day	None	1 episode of unknown onset and tonic clonic seizure	None	None	30	Yes
14	F	85	Structural focal epilepsy	Aneurysmatic subarachnoid hemorrhage	Phenytoin 125 mg intravenous three times a day	Hydromorphone 0.4 mg four times a day, hyoscine 20 mg four times a day	500 twice a day	None	None	None	None	2	Yes
15	F	94	Structural focal epilepsy	Ischemic stroke and subarachnoid hemorrhage	Phenytoin 125 mg three times a day	Piperacillin tazobactam and clarithromycin	500 mg twice a day	None	None	None	None	90	Yes
16	F	68	Structural focal epilepsy	Frontotemporal dementia	Phenytoin 200 mg intravenous three times a day	No	500 mg twice a day	None	1 seizure per month (semiology not described)	None	None	60	No
17	M	85	Nonconvulsive status epilepticus	Prostate cancer	Levetiracetam 500 mg intravenous twice a day	Morphine 3 mg three times a day	500 mg twice a day	None	Nonconvulsive status epilepticus	None	None	6	Yes
18	M	78	Structural focal epilepsy	Ischemic stroke Parkinson disease	Levetiracetam 500 mg intravenous twice a day	No	500 mg twice a day	None	1 episode of unknown onset and tonic clonic seizure	None	None	30	yes
19	F	92	Structural focal epilepsy	Ischemic stroke	Levetiracetam 500 mg intravenous twice a day	No	500 mg twice a day	None	3 episodes of motor focal onset and impaired awareness seizure	None	None	45	No
20	F	84	Nonconvulsive status epilepticus	Traumatic acute subdural hematoma, delirium	Valproic acid 500 mg intravenous twice a day	Morphine 2 mg three times a day	1,000 mg twice a day	Due to local reactions and prognosis, levetiracetam was stopped	Unknown	Unknown	Local edema and erythema	16	Yes
21	F	52	Structural focal epilepsy	Glioblastoma multiforme	Valproic acid 250 mg three times a day	Morphine 2 mg four times a day	500 mg twice a day	None	1 seizure (semiology not described)	None	None	3	No

F, female; M, male; SC, subcutaneous; PNET, primitive neuroectodermal tumor.

7 patients with SC levetiracetam. If seizure control was not achieved, an adjustment of the levetiracetam dose was made or midazolam was added [8]. Moreover, Remi et al. [7] conducted a retrospective study evaluating the safety and tolerability of SC levetiracetam in the palliative care setting and found it to be effective in 80% of patients who did not present with further epileptic seizures or in whom status epilepticus ceased. Sutherland et al. [1] performed a combined analysis of 73 reported cases; they concluded that SC levetiracetam is well tolerated, but data had very low quality data and randomized controlled trails are need to elucidate the efficacy and tolerability.

The duration of treatment described in the literature ranges from 21 h to 55 days [1, 7]. The reasons to stop SC levetiracetam described in the literature include improvement in the clinical status and adverse effects [1, 7, 8]. Some adverse effects reported in previous studies were somnolence (1/7) associated with higher plasma level (74.8 mg/L) and local reactions related to the injection site, which resolved by rotating the SC site of administration [8] or by changing the needle [7]. Moreover, injection site reaction necessitated discontinuation; one patient developed a sterile abscess after 25 days of treatment, and in 1 patient a rash was reported with the concomitant use of methimazole [7]. These injection site reactions occurred in 75% of patients when other medications were added to the syringe [1, 10]. No systemic adverse effects were reported in our study, and only 1 patient had a local reaction. Nevertheless, it was a retrospective study, and the data may not have been registered in all medical records. Most patients continued to receive SC levetiracetam until they died.

Pharmacokinetics studies related to SC levetiracetam are scarce; thus, there is a lack of information regarding SC bioavailability and plasma levels. The dose used in the oral or intravenous route is maintained when the SC route is started and adjustments are directed by ictal frequency or adverse effect [8]. The therapeutic range for intravenous levetiracetam reported in the literature is 12–46 mg/L [11]. The mean standard plasma levetiracetam concentration for a SC dose of 1,000 mg/day was reported to be 14.4 mg/L and for a dose of 2,000 mg/day the mean concentration was 27.7 mg/L; only one plasma level for a dose of 3,000 mg/day was determined (74.8 mg/L) [8].

For a dose of 4,000 mg/day in one patient, the plasma level was found to be 29.3 μg/mL [7]. In our study, we used a range of doses between 1,000 and 3,000 mg/day; plasma levels of levetiracetam were not performed as it constitutes an invasive procedure in a palliative care patient; however, our patients were seizure free.

One of the limitations of this study is the retrospective design, which leads to missing data in medical records. We did not measure plasma levels; however, in the context of patients receiving palliative care, measurement of plasma levels is an invasive procedure. There is still a lack of evidence regarding long-term tolerance; in our study, the longest duration on SC levetiracetam was 360 days.

Conclusions

This cases series enhances the current experience of SC levetiracetam in palliative care. Our data suggest that SC levetiracetam is well tolerated and effective in controlling seizures when oral administration or intravenous access was not an option. We suggest assessing its efficacy using the ictal frequency. Randomized controlled trials are needed to elucidate the efficacy and tolerability of SC levetiracetam in clinical practice. Moreover, protocols must be designed and followed to evaluate the efficacy, tolerability, and safety of other antiseizure medications administered via the SC route.

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Statement of Ethics

This study follows national and international ethical standards as detailed in the last modification of Helsinki Declaration by the World Medical Association and resolution 8,430 of 1,993 of the Ministry of Health of Colombia. This project was approved by the Ethics Committee of Universidad del Rosario (No. 448). Informed consent was obtained for all patients, either from the patient directly or authorized surrogates in the case of patients who lacked capacity.

Conflict of Interest Statement

The authors declare that there is no conflict of interest associated with this manuscript.

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Author Contributions

All authors contributed to this article.

Data Availability Statement

All data collected in this study are presented in Table 1. Further inquiries can be directed to the corresponding author.

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