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Retrospective Study of the Use of Levetiracetam in Epileptic Dogs with Chronic Kidney Disease

만성 신장 질환이 있는 개 발작 환자에서 Levetiracetam의 사용에 대한 후향적 연구

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지도교수 윤 화 영
이 논문을 김소연 석사 학위논문으로 제출함

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2020 년 8 월

위 원 장 _____ (인)
부 위 원 장 _____ (인)
위 원 _____ (인)

Abstract

Retrospective Study of the Use of Levetiracetam in Epileptic Dogs with Chronic Kidney Disease

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In human medicine, doses of levetiracetam (LEV) are individualized for patients with epilepsy, depending on the patient's renal-function status. However, there is no report on individualized dosing of LEV for small animals with seizures with pre-existing kidney disease in veterinary medicine. The object of this retrospective study is to investigate whether a dose adjustment of LEV is needed in dogs with pre-

existing chronic kidney disease (CKD). The patient databases of the Seoul National University Veterinary Medical Teaching Hospital were searched and 37 dogs with seizures or epilepsy were retrospectively included in this study. Based on pre-existing CKD, patients were divided into a CKD group (n = 20) and a non-CKD group (n = 17). We collected kidney panels before and after LEV treatment. All patients were given LEV of 10.0–45.0 mg/kg, orally, q8-12h. The duration of the LEV therapy was 2–2649 days. The LEV post-treatment blood test results were obtained between 2 and 64 days after LEV administration. Side-effects were monitored in 1 month after the start of LEV administration. In the CKD group, more dogs developed adverse effects (85%) than in the non-CKD group (52.94%). After LEV administration, an increase in serum BUN and/or creatinine was more often reported in the CKD group than in the non-CKD group. Our data indicate that, in dogs with seizures or epilepsy, with pre-existing CKD, a dose-adjustment of LEV is needed. During LEV treatment, CKD patients should be monitored for side-effects and may require laboratory evaluation of renal function.

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Key words: Adverse effect, Chronic kidney disease, Dogs, Levetiracetam

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1. INTRODUCTION

Epilepsy, which affects 50 million people around the world, is the most common neurological disorder (Reynold 2002). In veterinary medicine, epilepsy is also the most common neurological disorder (Podell, Fenner et al. 1995). The key treatment for this condition is antiepileptic drugs (AEDs), of which the most commonly used are phenobarbital and potassium bromide (Charalambous, Brodbelt et al. 2014). However, seizures are not well controlled in 20–30% of dogs with epilepsy (Lane and Bunch 1990). Additionally, the dogs experience severe adverse effects with conventional AED treatment (Lane and Bunch 1990). For these patients, assessment of new AEDs for management of epilepsy is essential (Muñana, Nettifee-Osborne et al. 2015).

Levetiracetam (LEV) is a structurally novel AED that was approved for use in humans as an adjuvant drug for partial-onset seizures in 1999 (Surges, Volynski et al. 2008). LEV is not metabolized via the hepatic cytochrome P450 system (Patsalos 2000). Because of its minimal hepatic metabolism, LEV is favored for use in geriatric or critical patients (Patsalos 2000, French 2001, Radtke 2001). Furthermore, in human medicine, LEV has a minimal effect on the distribution of other AEDs, because of its unique metabolic pathway (Patsalos 2000, French 2001, Radtke 2001). Therefore, LEV is particularly favored when initiating polytherapy (Munana, Thomas et al. 2012). Accordingly, LEV has particular use in special populations (Patsalos 2000, French 2001, Radtke 2001). Based on the results in humans, in

veterinary medicine, LEV is frequently used for management of epilepsy in dogs (Volk, Matiasek et al. 2008). Nevertheless, reports of LEV use, particularly in special populations, is limited in veterinary medicine.

In comparison with other AEDs, LEV has a broad margin of safety (Patsalos 2000, Radtke 2001). However, some patients experience undesirable side-effects and toxicity, particularly in special populations (Tozer 1974, Poggesi, Benedetti et al. 2009). The usual dosage of drugs is established for individuals with normal renal function and metabolism (Tozer 1974). In patients with impaired renal and/or hepatic function, elimination of drugs may be markedly reduced (Tozer 1974, French 2001). In such patients, the conventional dosage regimen causes accumulation of drugs (Tozer 1974, Lapmag, Lertsinudom et al. 2018). Therefore, in special populations, identifying the pharmacokinetic alterations is important to guide prescription strategies (Poggesi, Benedetti et al. 2009).

The half-life of LEV elimination is extended to 10–11 hours in elderly human patients, and is also extended in patients with renal disease (Tozer 1974, Poggesi, Benedetti et al. 2009). Therefore, LEV dosing is adjusted in patients with impaired renal function according to the patient's renal-function status (Poggesi, Benedetti et al. 2009). Numerous studies in human medicine report individualized LEV dosing according to the patient's renal-function status (Tozer 1974, French 2001, Radtke 2001, Poggesi, Benedetti et al. 2009). However, there is no report of individualized LEV dosing according to the patient's renal-function status in veterinary medicine.

Evaluating the use of LEV in preexisting CKD dogs was the goal of this retrospective study, resulting in the need for dose adjustment in patients with kidney disease.

2. MATERIALS AND METHODS

2.1. Study population

For this retrospective study, the patient databases of the Seoul National University Veterinary Medical Teaching Hospital (SNU VMTH) were searched for LEV prescription. The study period was between January 5, 2011 and December 28, 2019. In total, 138 dogs received LEV over a period of 9 years. Hospital records of all eligible patients were reviewed. Information and data necessary for the patient evaluation were obtained from the medical records in an electronic chart program (E-friends; pnV, Korea).

2.1.1. Inclusion criteria

The patient inclusion criteria of this study were as follows: 1) dogs with presence of seizure or epilepsy and treated with oral LEV; 2) who had been diagnosed with or without CKD before LEV administration; 3) and were being administered oral LEV for ≥ 7 days.

2.1.2. Exclusion criteria

The patient exclusion criteria of this study were as follows: 1) patients who

had not been screened for kidney impairments before LEV administration; 2) who were lost to follow up; 3) or who were missing serum blood urea nitrogen (BUN), creatinine, or phosphorus (P) data.

2.2. Blood test results analysis

At least 12 hours after fasting, blood samples were taken. The components of the blood tests were as follows: BUN, creatinine, P, and symmetric dimethylarginine (SDMA) levels. To determine the effects of LEV on patients' kidney condition, we compared the blood test results before and after LEV treatment. The LEV pretreatment blood test results were collected within 1 month prior to starting LEV administration. The LEV post-treatment results were obtained between 2 and 64 days after starting oral LEV administration.

Serum BUN was evaluated by using standard definitions for clinically significant differences from baseline (Berndt 1981, Hou, Bushinsky et al. 1983). In patients with normal or low baseline BUN values, a relevant increase in serum BUN was defined as a 25% increase over the upper normal limit, and for patients with initially greater than normal BUN values, a 25% increase higher than baseline (Berndt 1981, Hou, Bushinsky et al. 1983). Serum creatinine and P values were evaluated following the same method as for serum BUN evaluation.

2.3. CKD evaluation using the IRIS CKD diagnosis guidelines

We investigated whether CKD, defined by the International Renal Interest Society (IRIS) CKD diagnostic guidelines, had been diagnosed before starting LEV administration. CKD staging (CKD stages 1–4) was determined according to the IRIS guidelines for staging CKD (J Elliott 2019). All available information, including serial serum creatinine concentrations, urinalysis, and diagnostic imaging findings, were used for diagnosis of CKD and determination of CKD stage, before starting LEV administration (J Elliott 2019).

2.4. Epilepsy frequency and days prior to and during LEV treatment

The data collected from the patient records included age and weight at the start of LEV treatment, total number and days of epilepsy prior to starting LEV administration, and total number and days of epilepsy occurring during LEV treatment. The total number of epilepsy incidents during LEV treatment that occurred within 1 month after starting LEV administration was counted (Packer, Nye et al. 2015). Additionally, the total number of days on which epilepsy occurred during the 1 month after starting LEV treatment was counted (Packer, Nye et al. 2015).

2.5. Levetiracetam administration

All patients in this study were given a maintenance daily dose of LEV (Keppra; UCB Pharma SA, Belgium; Levetiracetam; Rhino Bio, Korea) per os (PO),

depending on the patient's status, and side-effects and therapeutic responses were monitored. LEV was administered at an initial dose of 10.0–45.0 mg/kg PO, q8-12h. The LEV dose was adjusted based on the clinical responses. LEV was used as primary or as add-on therapy, depending on the patient's conditions. In add-on therapy, LEV was used in combination with phenobarbital, potassium bromide (KBr), zonisamide, or diazepam.

Side-effects of oral LEV were recorded; in particular, it was monitored whether the following variable symptoms were more frequently provoked during LEV treatment: ataxia, sedation, decreased appetite, polydipsia, vomiting, diarrhea, hypersalivation and behavior changes (showing aggression) (Volk, Matiasek et al. 2008, Munana, Thomas et al. 2012, Packer, Nye et al. 2015). The Side-effects during LEV treatment were monitored in 1 month after the start of LEV.

2.6. Statistical analysis

Statistical analysis was performed using commercial software (R package, ver. 3.1.1; The R Foundation for Statistical Computing, Austria). Analytical data are presented as mean ± standard deviation (SD). Data are presented as median, with range and SD. Differences between variables of the CKD group and the non-CKD group were tested using Fisher's exact test or the chi-square test. *P*-values < 0.05 were regarded significant.

3. RESULTS

3.1. Study animals

In total, 138 dogs with seizure or epilepsy were given oral LEV over a period of 9 years, of which 62 patients met the inclusion criteria. A further 25 patients were excluded based on the exclusion criteria. Finally, 37 dogs were included in this study. We divided these patients into a CKD group (n = 20) and a non-CKD group (n = 17).

The CKD group included 20 dogs with a mean age of 12.53 ± 3.78 years (range, 2.58–17.5 years) and a median weight of 5.03 ± 2.78 kg (range, 1.8–13.1 kg) at starting LEV (Table 1). Several breeds were included, with Maltese being the most common (20%) (Table 1). Dogs included both intact and neutered females and males (Table 1). The CKD group's etiological diagnoses are presented in Table 2.

The non-CKD group consisted of 17 dogs with a mean age of 10.26 ± 3.73 years (range, 2.08–17.25 years) and a median weight of 5.44 ± 5.56 kg (range, 1.25–25.5 kg) at starting LEV (Table 1). Several breeds were recorded, again with Maltese being most frequent (Table 1), and both intact and neutered males and females were included (Table 1). The non-CKD group's etiological diagnoses are also presented in Table 2.

3.2. Pre-existing CKD evaluation based on IRIS CKD diagnostic guidelines

In the CKD group, most patients (60%) were CKD stage 1, while the remainder were CKD stage 2; there was no CKD stage 3 or 4 patient (Table 1).

3.3. LEV-based therapy in both groups

All patients in this study were given LEV of 10.0–45.0 mg/kg, orally, q8-12h. Most patients (n = 33, 89.19%) did not receive a loading dose. The mean duration of the oral LEV therapy in this study was 263.62 ± 547.81 days (range, 2–2649 days days).

In the CKD group, the initial LEV dose was 21.94 ± 8.36 mg/kg (range, 10.0–45.0 mg/kg) PO, q8-12h. In the non-CKD group, this dose was 20.58 ± 8.72 mg/kg (range 10.0–30.0 mg/kg) PO, q8-12h (Table 2). The mean duration of the oral LEV therapy in the CKD group was 147.85 ± 183.54 days (range, 8–613 days) and in the non-CKD group it was 399.82 ± 761.05 days (range, 2–2649 days) (Table 2).

Of the 20 CKD patients, 10 patients (50%) received LVE monotherapy while the others received LEV in combination with phenobarbital, KBr, zonisamide, and diazepam. Four patients (20%) received LEV in combination with phenobarbital, 2 patients (10%) received LEV in combination with zonisamide, 1 patient (5%) received LEV in combination with diazepam, 1 patient (5%) received LEV in combination with phenobarbital and zonisamide, 1 patient (5%) received LEV in combination with phenobarbital and potassium bromide, and 1 patient (5%) used all 5 drugs simultaneously.

Of the 17 non-CKD patients, 9 patients (52.94%) received LEV monotherapy. Two patients (11.76%) received LEV in combination with phenobarbital, 1 patients (5.88%) received LEV in combination with zonisamide, 1 patient (5.88%) received LEV in combination with phenobarbital and zonisamide, 1 patient (5.88%) received LEV in combination with phenobarbital and diazepam, 2 patients (11.76%) received LEV in combination with zonisamide and gabapentin, 1 patient (5.88%) received LEV in combination with phenobarbital, KBr, and zonisamide simultaneously. No drug interactions with LEV were identified among the study patients.

3.4. Outcomes of patients on LEV therapy

In the CKD group, the mean number of seizures prior to starting LEV was 59.7 ± 161.7 (range, 0–735) and the mean number of seizure days before LEV was 17.55 ± 30.96 (range, 0–122) (Table 3). In the non-CKD group, the mean number of seizures prior to starting LEV was 42.59 ± 71.313 (range, 1–275) and the mean number of seizure days was prior LEV 16.65 ± 25.72 (range, 1–89) (Table 3). The total number of seizures and the total days of seizures during LEV treatment in 1 month after the start of LEV was 13.55 ± 38.89 (range, 0–162) and 2.8 ± 7.05 (range, 0–30), respectively, in the CKD group (Table 3). In the non-CKD group, during LEV treatment, the total mean number of seizures on LEV was 7.18 ± 12.60 (range, 0–48) and the total mean number of seizure days on LEV was 1.59 ± 1.94 (range, 0–6) (Table 3).

In general, the side-effects of LEV include ataxia, sedation, anorexia, polydipsia, vomiting, diarrhea, hypersalivation and behavior changes (showing aggression). Of the 37 patients, 26 patients (70.27%) showed adverse effects during LEV administration. Most patients showed more than 1 side-effect at the same time (Table 4). More dogs in the CKD group were reported to have adverse effects than in the non-CKD group, and there was statistically difference between 2 groups (85% vs. 52.94%, p = 0.033). In the CKD group, a significant increase in sedation was identified during LEV treatment as compared to baseline, but it was not statistically significant as compared to the non-CKD group (55 versus 41.18%, p = 0.40). No dogs showed life-threatening adverse effects.

3.5. Clinically relevant increases in serum BUN, creatinine, and phosphorus after LEV administration

When all eligible patients were considered, the occurrence of “clinically relevant increases” in serum BUN, which consider the magnitude of the increase in relation to the baseline value, was statistically significantly different between the CKD group and non-CKD group (P = 0.028; Table 5). The incidence of clinically relevant increases in serum creatinine (P = 0.003; Table 5) and in both serum BUN and creatinine concurrently (P = 0.014, Table 5) was statistically significantly different between the groups. However, there was no significant difference in the occurrence of clinically relevant increases in serum phosphorus between the groups (P = 0.50; Table 5).

4. DISCUSSION

In human patients with impaired renal function, levetiracetam (LEV) dosing is individualized depending on the patient's renal-function status (Tozer 1974, Patsalos 2000, French 2001, Poggesi, Benedetti et al. 2009), but in veterinary medicine, there has been no report on individualized LEV dosing according to the patient's renal-function status, to date, and there have been few studies on the use of LEV in particular dog populations (Fryer, Levine et al. 2011, Mullins, Sanchez Villamil et al. 2019). Thus, the impact of oral LEV on dogs with pre-existing CKD has not been previously reported; the present study provides insights into this matter.

The initial LEV dose was 21.94 ± 8.36 mg/kg (range, 10.0–45.0 mg/kg) PO, q8-12h in the CKD group, and 20.58 ± 8.72 mg/kg (range 10.0–30.0 mg/kg) PO, q8-12h, in the non-CKD group in this study. In humans, the elimination half-life of LEV is extended in patients with renal impairment (Tozer 1974, Patsalos 2000, French 2001, Radtke 2001, Poggesi, Benedetti et al. 2009), and LEV dosing is therefore adjusted according to the patient's renal-function status (French 2001, Radtke 2001, Poggesi, Benedetti et al. 2009). Pharmacokinetic studies suggest a dose of LEV 20 mg/kg, q8h to obtain plasma concentrations in normal dogs, which is similar to clinically significant plasma concentrations in humans (Isoherranen, Yagen et al. 2001, Moore, Muñana et al. 2010). Consequently, these studies suggest that dogs with renal impairments should be given a LEV dose < 20 mg/kg, q8h (Isoherranen, Yagen et al. 2001, Moore, Muñana et al. 2010). It is estimated that some of our CKD

patients had higher LEV concentrations than the therapeutic range, as they were administered LEV more than 20 mg/kg, q8h (Isoherranen, Yagen et al. 2001, Moore, Muñana et al. 2010). We did not obtain serum concentrations of LEV. However, based on previous studies, we assumed that LEV serum concentrations might be higher in the CKD group than in the non-CKD group, which was also concordant with our other study results. Statistically significantly more dogs in the CKD group were reported to have any side-effects than those in the non-CKD group (85% vs. 52.94%, P = 0.033). Further study is necessary to determine individualized LEV dosing according to dogs' renal-function status.

In comparison with other AEDs, LEV has a broad margin of safety (Patsalos 2000, Radtke 2001). In this study, LEV was used as add-on therapy or primary therapy. Many patients in the current study had concurrent diseases, because they were middle-aged or older. Because of the minimal hepatic metabolism, LEV is favored for geriatric or critical human patients (Patsalos 2000, French 2001, Radtke 2001). Furthermore, in human medicine, LEV was shown to have minimal effects on the distribution of other AEDs, due to its unique metabolic pathway (Patsalos 2000, French 2001, Radtke 2001). Therefore, use of LEV in specific complex medical situations, particularly polytherapy, has been encouraged (Munana, Thomas et al. 2012). In this study, we found that LEV was mostly well tolerated in dogs, but it was not free from side-effects.

In general, the side-effects of LEV include ataxia, sedation, anorexia, polydipsia, vomiting, diarrhea, hypersalivation, and behavior changes (aggression) (Volk, Matiasek et al. 2008, Munana, Thomas et al. 2012, Packer, Nye et al. 2015).

In this study, most patients showed more than 1 side-effect simultaneously. In the CKD group, there was a significant increase in sedation during LEV administration as compared to baseline, but this increase was not remarkably different from that in the non-CKD group (P = 0.40) (Berndt 1981, Hou, Bushinsky et al. 1983). Because of sedation, chronic recurrent dehydration, associated with periodic water intake, may occur (Hilliard, Colafella et al. 2016), which can be problematic, particularly in CKD patients. A key management factor in CKD patients is access to fresh water anytime, because the ability to concentrate urine and excrete water is impaired in CKD patients (Nelson and Couto 2019). If a patient with CKD is sedated, water intake may be irregular, which may accelerate dehydration (Hilliard, Colafella et al. 2016), decreasing blood flow to the kidneys (Nelson and Couto 2019). Consequently, uremic toxins are retained (Nelson and Couto 2019). This was supported by the results of the present study. In the CKD group, 9 patients (45%) demonstrated clinically significant increases (Berndt 1981, Hou, Bushinsky et al. 1983) in serum BUN (Table 5) and 8 demonstrated clinically relevant increases in serum creatinine (Table 5). Moreover, in that group, 6 patients (30%) had concurrent clinically significant increases (Berndt 1981, Hou, Bushinsky et al. 1983) in serum BUN and creatinine (Table 5). On the other hand, in the non-CKD group, there were no clinically significant increases in BUN and/or creatinine (Table 5). Therefore, canine CKD patients administered LEV should be monitored, and they may require physical and/or laboratory evaluation for dehydration (Hurwitz, Ingulli et al. 2009, Mahta, Kim et al. 2012).

The statically significant difference in the incidence of clinically relevant

increases in serum BUN and/or creatinine between the CKD and non-CKD groups (Table 5) may be due to the acute kidney injury (AKI) that is superimposed on pre-existing CKD. In human medicine, although it has been shown that kidney function can fully recover after overcoming an AKI, cumulative observational data have revealed that AKI can worsen underlying CKD (Lee 2015). There have been 4 case reports in humans where LEV was identified as a possible contributor to AKI (Hurwitz, Ingulli et al. 2009, Chau, Yong et al. 2012, Mahta, Kim et al. 2012, Spengler, Montouris et al. 2014). Based on those reports, patients taking LEV who present with abdominal pain, oliguria, nausea/vomiting, and a high creatinine concentration may require laboratory assessment for hidden renal adverse effects (Hurwitz, Ingulli et al. 2009, Mahta, Kim et al. 2012), and renal function during treatment with LEV should be monitored (Hurwitz, Ingulli et al. 2009, Chau, Yong et al. 2012, Mahta, Kim et al. 2012, Spengler, Montouris et al. 2014). In the differential diagnosis for any unexplained acute renal failure, AKI due to LEV should be considered (Chau, Yong et al. 2012). However, in veterinary medicine, there has been no report of renal toxicity attributed to LEV, and further studies are necessary to assess renal toxicity secondary to LEV in dogs.

As in other retrospective studies, this study had some limitations. First, we had some missing values, such as serum SDMA values, because data were collected retrospectively and SDMA was included in the diagnostic criteria for the diagnosis of CKD only since 2015 (Relford, Robertson et al. 2016). We rarely measured SDMA values before this time-point. Therefore, future studies including SDMA results are needed. Second, in this study, patients were chronically ill, because they

were middle-aged or older. Consequently, it is possible that the CKD stage might have been falsely high or falsely low (J Elliott 2019, Nelson and Couto 2019); the CKD stage of patients with prerenal azotemia could have been falsely high (J Elliott 2019, Nelson and Couto 2019), and that of patients who had lost muscle mass could have been falsely low (J Elliott 2019, Nelson and Couto 2019). In retrospective studies, it is difficult to solve this issue. Third, we did not measure plasma LEV concentration values, as there is no therapeutically effective LEV concentration known in dogs (Munana, Thomas et al. 2012). Therefore, in practice, LEV concentration monitoring is rarely performed (Munana, Thomas et al. 2012). However, based on previous studies, it could be assumed that the CKD group had higher LEV concentrations than the non-CKD group (Patsalos 2000, French 2001, Isoherranen, Yagen et al. 2001, Radtke 2001, Moore, Muñana et al. 2010). Nevertheless, a prospective study that measures LEV concentrations could support the relationship between LEV concentration and side-effects.

In conclusion, no previous study has evaluated the use of oral LEV in canine patients with pre-existing CKD. We showed that dogs in the CKD group had more side-effects than those in the non-CKD group. In the CKD group, the incidence of clinically significant increases in serum BUN and/or creatinine was more frequent than in the non-CKD group. The findings of this study may assist in the treatment of many epileptic dogs with CKD, resulting in proper dosing of LEV in animals with pre-existing renal impairment.

Table 1. Characteristics of patients with the CKD group/non-CKD group in the present study.

		CKD group (n = 20)	non-CKD group (n = 17)
Characteristics	Variables	No. of Dogs (%)	No. of Dogs (%)
CKD stage before LEV administration	non-CKD	0 (0%)	17 (100%)
	CKD stage 1	12 (60%)	0 (0%)
	CKD stage 2	8 (40%)	0 (0%)
	CKD stage 3 or 4	0 (0%)	0 (0%)
Breeds	Maltese	4 (20%)	7 (41.18%)
	Yorkshire Terrier	2 (10%)	2 (11.76%)
	Pekingese	2 (10%)	0 (0%)
	Cocker Spaniel	2 (10%)	2 (11.76%)
	Poodle	2 (10%)	0 (0%)
	Mixed breed	2 (10%)	3 (17.65%)
	Chihuahua	0 (0%)	2 (11.76%)

	Afghan Hound	0 (0%)	1 (5.88%)
Sex	Male	3 (15%)	4 (23.53%)
	Male castrated	3 (15%)	4 (23.53%)
	Female	4 (20%)	1 (5.88%)
	Female spayed	10 (50%)	8 (47.06%)
Variables		Value	Value
Body weight at start of LEV, kg Mean ± SD (range)		5.03 ± 2.78 kg (range, 1.8–13.1 kg)	5.44 ± 5.56 kg (range, 1.25–25.5 kg)
Age at start of LEV, years (min–max years) Mean ± SD (range)		12.53 ± 3.78 years (range, 2.58–17.5 years)	10.26 ± 3.73 years (range, 2.08–17.25 years)

CKD, chronic kidney disease; LEV, levetiracetam; SD, standard deviation

Table 2. LEV-based therapy in dogs of the CKD group/non-CKD group.

	Variables	CKD group (n = 20) No. of Dogs (%)	non–CKD group (n = 17) No. of Dogs (%)
Indications of LEV	Undiagnosed seizure	0 (0%)	3 (17.65%)
	Undiagnosed epilepsy	11 (55%)	3 (17.65%)
	Idiopathic epilepsy	3 (15%)	3 (17.65%)
	Hydrocephalus	1 (5%)	3 (17.65%)
	Hydrocephalus with Syringohydromyelia	2 (10%)	1 (5.88%)
	Chiari-like malformation	0 (0%)	2 (11.76%)
	Meningoencephalitis of unknown etiology	1 (5%)	0 (0%)
	Hydrocephalus with meningoencephalitis of unknown etiology	0 (0%)	1 (5.88%)

	Geriatric vestibular disease suspected	1 (5%)	0 (0%)
	Reactive epilepsy	1 (5%)	0 (0%)
	Brain tumor	0 (0%)	1 (5.88%)
Variables		Value	Value
Initial dose of LEV administered Mean ± SD (range)		21.94 ± 8.36 mg/kg (range, 10.0–45.0 mg/kg)	20.58 ± 8.72 mg/kg (range 10.0–30.0 mg/kg)
Duration of oral LEV therapy (days) Mean ± SD (range)		147.85 ± 183.54 days (range 8–613 days)	399.82 ± 761.05 days (range 2–2649 days)

CKD, chronic kidney disease; LEV, levetiracetam; SD, standard deviation

Table 3. Seizure frequency of the CKD group/non–CKD group.

Variables	CKD group (n = 20) Value	non–CKD group (n = 17) Value
Epilepsy frequency prior to LEV treatment	59.7 ± 161.70	42.59 ± 71.31
Mean ± SD (range)	(range, 1–735)	(range, 1–275)
Days of epilepsy prior to LEV treatment	17.55 ± 30.96	16.65 ± 25.72
Mean ± SD (range)	(range, 1–122)	(range, 1–89)
Epilepsy frequency during LEV treatment[a]	13.55 ± 38.88	7.18 ± 12.60
Mean ± SD (range)	(range, 0–162)	(range, 0–48)
Days of epilepsy during LEV treatment.[b]	2.8 ± 7.05	1.59 ± 1.94
Mean ± SD (range)	(range, 0–28)	(range, 0–6)

CKD, chronic kidney disease; LEV, levetiracetam; SD, standard deviation

[a]The total number of epilepsy during LEV treatment was counted within 1 month after starting LEV.

[b]The total days in which epilepsy occurred during LEV treatment was counted within 1 month after starting LEV.

Table 4. Side-effects of the oral LEV were observed in the CKD group/non–CKD group.

Variables	CKD group (n = 20) No. of Dogs (%)	non–CKD group (n = 17) No. of Dogs (%)	P–value
Any adverse event*	17 (85%)	9 (52.94%)	0.033
Sedation	11 (55%)	7 (41.18%)	0.40
Ataxia	5 (25%)	3 (17.65%)	NA
Anorexia	9 (45%)	2 (11.76%)	NA
Polydipsia	2 (10%)	0 (0%)	NA
Vomiting	7 (35%)	1 (5.88%)	NA
Diarrhea	3 (15%)	2 (11.76%)	NA
Hypersalivation	3 (15%)	0 (0%)	NA
Behavior changes (showing aggression)	1 (5%)	0 (0%)	NA

CKD, chronic kidney disease; LEV, levetiracetam

* Most patients showed more than 1 side-effect concurrently

NA, not assessed. Statistically significantly different: $p < 0.05$

Table 5 Clinically relevant serum BUN, creatinine, and P increase in the CKD group/non–CKD group.

Variables	CKD group (n = 20) No. of Dogs (%)	non–CKD group (n = 17) No. of Dogs (%)	P–value
BUN elevation	9 (45%)	2 (11.76%)	0.028
P elevation	2 (10%)	0 (0%)	0.50
Creatinine elevation	8 (40%)	0 (0%)	0.003
BUN and creatinine elevation	6 (30%)	0 (0%)	0.014

CKD, chronic kidney disease; LEV, levetiracetam; BUN, blood urea nitrogen, P, phosphorus

Statistically significant difference: $p < 0.05$

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국 문 초 록

만성 신장 질환이 있는 개 발작 환자에서 Levetiracetam의 사용에 대한 후향적 연구

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김 소 연

인의학에서, 간질환자에 투여하는 레베티라세탐 (LEV)의 용량은 각 환자의 신장 기능 상태에 따라 조정됩니다. 하지만 아직까지 수의학에서는, 신장 질환을 가지고 있는 발작환자에게 LEV을 투여할 때, 용량 조절을 시도한 보고가 없습니다. 이 후향적 연구의 목적은 기존에 만성신장질환(CKD)이 있는 개에서, LEV의 용량 조정이 필요한지

여부를 조사하는 것입니다. 서울대학교 수의과대학 동물병원의 환자 데이터베이스를 조사하여 발작이나 간질이 있는 37 마리의 개가 후향적으로 연구에 포함되었습니다. 환자가 기존에 CKD가 있었는지 여부로 환자군을 분류하여, CKD 그룹 (n = 20)과 비 CKD 그룹 (n = 17)으로 나누었습니다. LEV 치료 전후에 혈액검사결과(신장지표)를 수집했습니다. 환자들은 10.0-45.0 mg/kg의 LEV을 8시간에서 12시간 간격으로 경구로 투여 받았습니다. LEV 치료 기간은 2-2649일이었고, LEV 치료 후 얻은 혈액 검사 결과는, LEV 투여 시작 후 2 일과 64 일 사이에 얻은 결과입니다. LEV 투여에 대한 부작용은, LEV 투여를 시작하고 1 개월 이내에 확인된 부작용을 모니터링한 결과입니다. 부작용은 발현은 비 CKD 그룹 (52.94%)보다 CKD 그룹 (85%)에서 더 많이 발생했습니다. LEV 투여 후, 혈중요소질소(BUN) 또는 혈청 크레아티닌의 증가가 비 CKD 그룹보다 CKD 그룹에서 더 높게 보고되었습니다. 이번 연구의 결과는 발작이나 간질이 있는 개에서 LEV을 투약할 때, CKD가 있는 환자는 LEV의 용량 조정이 필요하다는 것을 나타냅니다. LEV 치료 동안, CKD가 있는 환자는, LEV의 부작용에 대해 모니터링 해야 하며 신장 기능의 실험실적 평가가 필요할 수 있습니다.

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주요어 : 부작용, 만성 신장 질환, 개, 레베티라세탐

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