Received: 5 December 2022 | Accepted: 13 April 2023

DOI: 10.1002/epi4.12746

Epilepsia Open™ Open Access

ORIGINAL ARTICLE

Decreased serum concentrations of antiseizure medications in children with drug resistant epilepsy following treatment with ketogenic diet

Sigrid Pedersen[1,2] | **Magnhild Kverneland**[1] | **Knut Rudi**[3] | **Kristina Gervin**[4] | **Cecilie Johannessen Landmark**[1,5,6] | **Per Ole Iversen**[7,8] | **Kaja Kristine Selmer**[1,4]

[1]National Centre for Epilepsy, Member of the ERN EpiCare, Oslo University Hospital, Oslo, Norway

[2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3]Department of Chemistry, Norwegian University of Life Sciences, Ås, Norway

[4]Department of Research and Innovation, Oslo University Hospital, Oslo, Norway

[5]Department of Pharmacology, Oslo University Hospital, Oslo, Norway

[6]Department of Pharmacy, Oslo Metropolitan University, Oslo, Norway

[7]Department of Nutrition, University of Oslo, Oslo, Norway

[8]Department of Hematology, Oslo University Hospital, Oslo, Norway

Correspondence
Sigrid Pedersen, National Centre for Epilepsy, Oslo University Hospital, P.O. Box 4950, Nydalen, Oslo 0424, Norway.
Email: sigrpe@ous-hf.no

Funding information
EkstraStiftelsen Helse og Rehabilitering (Stiftelsen Dam); Novo Nordisk Fonden; the National Advisory Unit on Rare Disorders, Norway; the Norwegian Epilepsy Association's Research Fund

Abstract

Objective: To examine the potential influence of a ketogenic diet on serum concentrations of antiseizure medications (ASMs) in children with drug resistant epilepsy.

Methods: We investigated the serum concentrations of ASMs in 25 children with drug resistant epilepsy, 2–13 years of age, treated with a classical ketogenic diet for 12 weeks. The patients were recruited from the National Centre for Epilepsy from August 15th, 2017, to January 24th, 2022. Changes in ASM serum concentrations were analyzed using a mixed effect model analysis. Significance level was set at $P < 0.05$ for all comparisons.

Results: The participants used 12 different ASMs during the study. The mean number of ASMs was 2.4 (±SD 0.7). None of the participants changed the type or dose of the ASMs during the intervention period. The serum concentrations of clobazam ($n = 9$, $P = 0.002$), desmethylclobazam ($n = 9$, $P = 0.010$), and lamotrigine ($n = 6$, $P = 0.016$) decreased significantly during the dietary treatment. The analytes with the largest reduction in serum concentration after 12 weeks of dietary treatment were clobazam (mean change −38%) and desmethylclobazam (mean change −37%). We found no significant change in the serum concentrations of levetiracetam, topiramate, and valproic acid.

Significance: We identified a significant decrease in the serum concentrations of clobazam, desmethylclobazam, and lamotrigine following a 12-week ketogenic diet intervention in children with drug resistant epilepsy. An unintended decrease in the serum concentrations of ASMs may render the patient prone to seizures. Measurements of ASM serum concentrations might be useful in patients on a ketogenic diet, especially in patients with lack of efficacy of the dietary treatment.

KEYWORDS

antiseizure medications, dietary treatment, food-drug interactions, high-fat, low-carbohydrate diet, therapeutic drug monitoring

1 | INTRODUCTION

Epilepsy is a common brain disorder that causes recurrent, unprovoked seizures. Worldwide, more than 65 million people are affected.[1] The mainstay of epilepsy treatment is antiseizure medications (ASMs). However, despite an increasing number of available ASMs, about 30% of the epilepsy patients do not achieve seizure control.[2,3] Other treatment options include brain surgery and vagus nerve stimulator (VNS) therapy. Unfortunately, a large share of the patients are not eligible for epilepsy surgery or VNS therapy. Another treatment option is a dietary therapy known as the ketogenic diet.

The ketogenic diet is a collective term for various diets high in fat and low in carbohydrate, originally designed to mimic the metabolic state of fasting.[4] The term "ketogenic" comes from the diets' ability to induce "ketosis" (elevated level of ketone bodies in the blood). However, as the ketogenic diet is a comprehensive treatment mainly used by patients with severe epilepsy, the majority use the dietary treatment in combination with ASMs.

In recent years, clinical observations have raised questions about potential pharmacokinetic interactions between the ketogenic diet and ASMs. We have previously reported a substantial decrease in the serum concentration of several commonly used ASMs in adults treated with a modified ketogenic diet.[5] Other studies show mixed result, but are hampered by a retrospective design, few ASMs investigated, or changes in ASM dose during the study duration.[6–8]

Potential consequences of interactions between the ketogenic diet and ASMs includes reduced efficacy of the ASMs, risk of adverse effects, as well as misinterpretation of the efficacy of the ketogenic diet in clinical trials. In order to optimize epilepsy treatment, it is, therefore, important to know if the dietary treatment interact with the ASMs. At the National Centre for Epilepsy, Norway, we measure the serum concentrations of ASM in all patients regularly (therapeutic drug monitoring).[9] In the present study, we aimed to examine the potential influence of a ketogenic diet on serum concentrations of ASMs in children with drug resistant epilepsy. Based on the results from our previous study in adults, we hypothesized a decline in ASM serum concentration following the diet intervention.

Key Points

- In this prospective study, we examined the influence of a ketogenic diet on serum concentrations of ASMs in children with drug resistant epilepsy.
- We identified a significant decrease in the serum concentrations of clobazam, desmethylclobazam, and lamotrigine following 12 weeks of dietary treatment.
- Unintended alterations in ASM serum concentrations may reduce the seizure protection and increase the risk of adverse effects.
- Measurements of ASM serum concentrations might be useful in patients on a ketogenic diet, especially in patients with lack of efficacy of the dietary treatment.

2 | METHODS

2.1 | Participants

The study participants were recruited from the National Center for Epilepsy, Norway, between August 15, 2017, and January 24, 2022. Patients between 2 and 18 years of age, with a diagnosis of drug resistant epilepsy according to the classification by the International League Against Epilepsy's (ILAE),[10] with two or more seizures per week on average, and willingness to try the classical ketogenic diet for at least 12 weeks were eligible to participate in this study. If one or more of the following exclusion criteria were present, the patient was excluded from the study: glucose transporter protein 1 deficiency syndrome, pyruvate dehydrogenase deficiency, pyruvate carboxylate deficiency, diseases which contraindicated the dietary treatment, epilepsy surgery, including VNS implantation the past 6 months before diet initiation, steroid medication the past 2 months before diet initiation, prophylactic antibiotic treatment, breastfeeding, psychogenic nonepileptic seizures, eating disorders, feeding disabilities expected to unable the dietary treatment, inability to follow the study protocol, lack of motivation by patient or caregivers, previous treatment with a ketogenic diet, medical need to start dietary treatment immediately, and pregnancy or planned pregnancy.

2.2 | Study design and diet intervention

The participants ate their habitual diet during a 4-week baseline period and subsequently a classical ketogenic diet in a 12-week diet intervention period. No changes in epilepsy treatments were allowed during the 16-week study.

The classical ketogenic diet was initiated during a 16-day hospital admission without prior fasting. A registered dietitian tailored all diets individually. The diet was started at a ketogenic ratio (ratio of gram fat: gram carbohydrate

plus gram protein) of 1:1–2:1 with a gradual increase up to a maximum of 4:1 according to efficacy and tolerability. All diets were supplemented with vitamins and minerals according to the child's need. A daily fluid intake based on standard pediatric guidelines was recommended. The meals consisted of regular food items and/or special medical foods for epilepsy. The macro nutrient composition of the meals was estimated using the electronic meal planner Dietist Net (Kost och Näringsdata, Bromma, Sverige) with associated databases, including the Norwegian Food Composition Database.[11] All food items were weighed on a scale with an accuracy of 0.1 g.

2.3 | Seizure recording

All parents/caregivers received training in how to record seizures systematically in a seizure diary. The seizure frequency during the 4-week baseline period was compared with the seizure frequency during the last 4 weeks before the 12-week study visit. We defined patients as a responder when the seizure frequency was reduced with ≥50% compared to the seizure frequency at baseline.

2.4 | Participant adherence

Adherence to the study protocol was assessed at each study visit by structured questions regarding compliance with the diet intervention and the prescribed ASMs. The importance of not doing any changes in the pharmacological treatment during the study was underlined to all participants and caregivers. In addition, fasting blood glucose, hemoglobin A_{1c} (HbA_{1c}), and blood ketones (β-hydroxybutyrate) was measured at baseline (pre-diet), and after 6 and 12 weeks of dietary treatment.

2.5 | ASM serum concentration measurements

Analyses of serum concentrations of all ASMs were performed as part of the follow-up to all patients. The standard blood-sampling time for serum concentration measurements of ASMs was food- and drug fasting in the morning at assumed steady state of the ASMs. Blood samples were collected at baseline (pre-diet), and after 6 and 12 weeks of dietary treatment. The analyses of all ASMs were based on routine measurements by validated methods at the Section for Clinical Pharmacology, Oslo University Hospital (Oslo, Norway).

Clonazepam, clobazam, and its active metabolite desmethylclobazam, were measured by high pressure liquid chromatography with ultraviolet detection (HPLC-UV) on a Dionex Ulitimate 3000 instrument with a 4.6 × 30 mm 3.5 μm ZORBAX Eclipse Plus C18 column.

The other ASMs were analyzed by ultra-high performance liquid chromatography with mass spectrometric detection (UHPLC-MS/MS) on a Prelude MD HPLC/Endura MD mass spectrometer, using the Antiepileptic Drugs ClinMass TDM Platform Kit System (MS9000, MS9200) from Recipe (Munich, Germany) (https://www.recipe.de/en/products_ms_tdm_ms09000-ms09200_ord.html#MS9200).

2.6 | Statistics

Data are presented as means with standard deviations (SD) or medians with quartiles and minimum – maximum (min – max) scores for continuous variables. Categorical variables are presented as frequencies and percentages (%). We ran a linear mixed effect model analysis of the relationship between serum concentrations of ASMs and time on ketogenic diet. As fixed effect, we entered time on ketogenic diet into the model and as random effects intercepts for patients. Visual inspection of residual plots did not reveal obvious deviations from normality. Three cases with large residuals were identified; however, reruns of the model without these cases did not change the results. Of the 12 ASMs, seven were used by fewer than six patients, which was considered too few to allow for meaningful comparisons over time. One-sample *t*-tests were used to compare percentage changes in the serum concentration of all ASMs combined after 6 and 12 weeks of dietary treatment. Levels of blood glucose, HbA_{1c}, β-hydroxybutyrate, albumin, and body weight after 6 and 12 weeks of dietary treatment were compared with baseline values by either paired *t*-test (normally distributed data) or Wilcoxon signed rank test (non-normally distributed data). All tests were two-sided. For all comparisons, significance was set at P value < 0.05. Statistical analyses were performed with SPSS (v.28, IBM).

3 | RESULTS

3.1 | Patient characteristics

The study material consisted of 25 children (age 2–13 years) with drug resistant epilepsy (Figure 1). An overview of the baseline characteristics and demographics is given in Table 1. Seventeen children had generalized epilepsy, three children had focal epilepsy, and five children had combined generalized and focal epilepsy. Fifteen children had a known epilepsy etiology, while the etiology

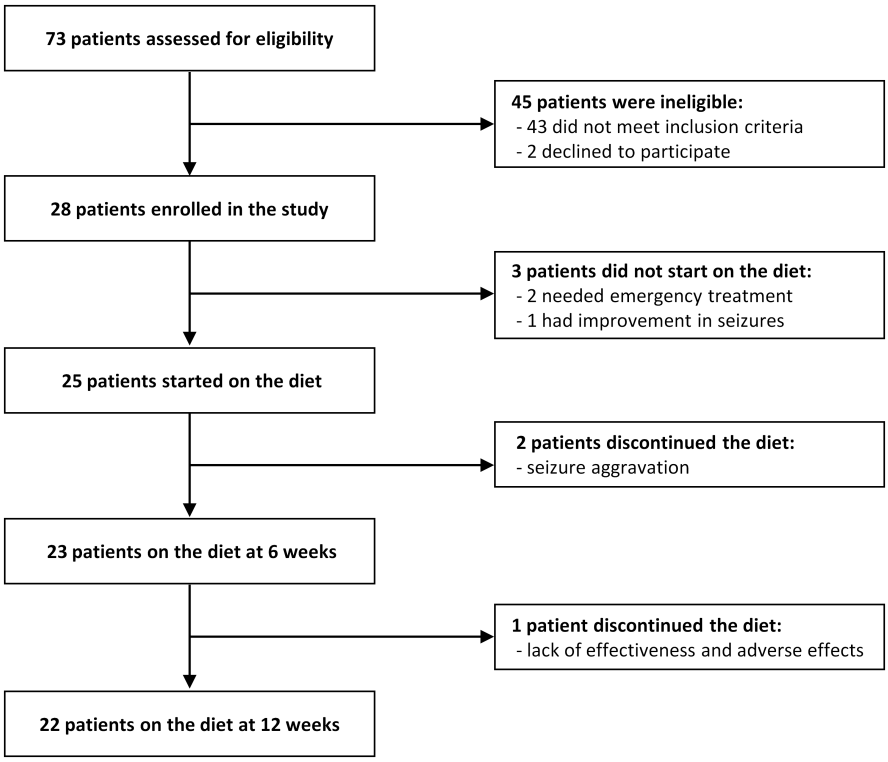

FIGURE 1 Flow chart illustrating the recruitment process of participants into the study

was unknown in ten children. Median years with epilepsy before starting the ketogenic diet was 4.0 (quartiles 2.6–5.9). Ten children had a gastrostomy tube used either for total enteral feeding or for supplemental feeding, fluids, and medications.

3.2 | Diet intervention

The ketogenic ratio after 6 and 12 weeks of dietary treatment is presented in Table 2. Twenty-two children completed the 12-week diet intervention. Median ketogenic ratio was 3:1 at both 6 and 12 weeks of diet intervention. The ketogenic ratios ranged from 2:1 to 3.5:1.

3.3 | Blood biochemistry

Blood biochemistry results are presented in Table 3. Fasting β-hydroxybutyrate was, as expected, almost negligible (median 0.1 mmol/L [quartiles: 0.1–0.2]) at baseline, but increased during the dietary treatment, median 3.5 mmol/L (quartiles: 2.8–4.5) at 6 weeks ($P < 0.001$), and 3.0 mmol/L (quartiles: 2.3–4.5) at 12 weeks ($P < 0.001$). Fasting blood glucose decreased significantly from mean score of 4.7 mmol/L (±SD 0.5) at baseline to a mean of 4.1 mmol/L (±SD 0.5) at 12 weeks ($P < 0.001$). In accordance, HbA_{1c}, which reflects the blood glucose concentration over the past six to eight weeks, declined significantly during the dietary treatment (mean 29.7 mmol/mol (±SD 4.0) at baseline vs mean 23.8 mmol/mol (±SD 3.3) at 12 weeks; $P < 0.001$). Together, these results indicate a good adherence with the diet intervention.

3.4 | Body weight

No significant difference in body weight was observed during the study period, median 23.2 kg (quartiles: 18.1–39.4) at baseline vs median 23.2 kg (quartiles: 18.4–39.2) at 6 weeks ($P = 0.77$), and median 24.0 kg (quartiles: 19.0–40.4) at 12 weeks ($P = 0.17$).

3.5 | Seizure outcomes

Nine (36%) patients had 50% or more seizure reduction, including one (4%) that became seizure free. Sixteen patients (64%) had less than 50% seizure reduction, including three patients that did not complete the 12-week diet intervention due to seizure exacerbation ($n = 2$) or lack of effectiveness and adverse effects ($n = 1$).

3.6 | ASM serum concentrations

An overview of the ASMs used in the study, the number of samples, and the mean serum concentrations are given in Table 4. A visual presentation of the serum concentration at baseline, and after 6 and 12 weeks of dietary

TABLE 1 Clinical and demographic characteristics of the study participants at baseline

		Min – Max
Number of patients	25	
Gender, male/female *n* (%)	13/12 (48/52%)	
Age at diet start, years, median (quartiles)	6.0 (4.3–11.2)	2.4–13.3
Epilepsy classification, *n* (%)		
Focal	3 (12%)	
Generalized	17 (68%)	
Combined focal and generalized	5 (20%)	
Epilepsy etiology, *n* (%)		
Structural	5 (21%)	
Genetic	6 (25%)	
Genetic/structural	2 (8%)	
Structural/infectious	1 (4%)	
Unknown	10 (40%)	
Epilepsy syndromes		
Dravet syndrome	1 (4%)	
Doose syndrome	1 (4%)	
Lennox–Gastaut syndrome	1 (4%)	
No specific syndrome diagnosis	22 (88%)	
Age at first seizure, years, median (quartiles)	2.8 (0.5–4.7)	0.25–8.0
Years with epilepsy, median (quartiles)	4.0 (2.6–5.9)	0.35–11.4
Gastrostomy tube, yes/no (%)	10/15 (40%/60%)	
Number of ASMs, mean (±SD)	2.4 (0.7)	1–4
Number of ASMs, *n* (%)		
1	2 (8%)	
2	12 (48%)	
3	10 (40%)	
4	1 (4%)	

Abbreviations: ASM, antiseizure medications; SD, standard deviation.

TABLE 2 Ketogenic ratio on the diet

	6 weeks (*n* = 23)	12 weeks (*n* = 22)
Ketogenic ratio[a], median (min – max)	3:1 (2:1–3.5:1)	3:1 (2:1–3.5:1)
Ketogenic ratio[a], *n* (%)		
2:1–2.25:1	6 (26%)	4 (18%)
2.5:1–2.75:1	5 (22%)	5 (23%)
3:1–3.25:1	11 (48%)	10 (45%)
3.5:1	1 (4%)	3 (14%)

[a]The ketogenic ratio is the ratio of grams fat to the sum of grams of protein and carbohydrate.

treatment for each ASM is provided in the Supporting Information (Figure S1). The participants used in total 12 different ASMs during the study, and none changed the type or dose of ASMs during the study period. All, except two participants, used two or more ASMs ($n = 23$, 92%), accounting for 22 different ASM combinations. The mean number of ASMs was 2.4 (±SD 0.7). The most frequently used ASMs were valproic acid ($n = 14$), clobazam (which also includes the active metabolite desmethylclobazam) ($n = 9$), topiramate ($n = 8$), and levetiracetam ($n = 8$).

Serum concentrations of clobazam and desmethylclobazam decreased significantly during the diet intervention (clobazam: $P = 0.002$, desmethylclobazam: $P = 0.010$). The mean serum concentration of clobazam declined from 0.54 μmol/L (±SD 0.12) at baseline to 0.34 μmol/L (±SD 0.09) at 6 weeks, and 0.31 μmol/L (±SD 0.16) at 12 weeks. The mean change of clobazam from baseline to 6 and 12 weeks of dietary treatment was −44% and − 38%, respectively. All participants experienced a reduction in clobazam serum concentration during the diet intervention. The changes ranged from −81% to −18% at 6 weeks and −54% to −18% at 12 weeks compared to baseline. Correspondingly, the mean serum concentration of desmethylclobazam decreased from 6.60 μmol/L (±SD 8.66) at baseline to 5.55 μmol/L (±SD 7.10) at 6 weeks, and 2.63 μmol/L (±SD 3.04) at 12 weeks. The mean change of desmethylclobazam from baseline was −33.4% at 6 weeks and −37.9% at 12 weeks of dietary treatment. Similar to clobazam, all participants had a decrease in the serum concentration of desmethylclobazam during the diet intervention. However, the degree of decline varied greatly across individuals, ranging from −56% to −10% at 6 weeks, and from −59% to −13% at 12 weeks of dietary treatment. One participant using clobazam/desmethylclobazam was identified as a cytochrome P450 2C19 (CYP2C19) poor metabolizer (i.e., the CYP2C19 enzyme has limited activity). Desmethylclobazam is mainly metabolized by CYP2C19, and consequently, the serum concentration was high (28 μmol/L, reference range 1–10 μmol/L) in this patient. However, the patient also experienced a reduction in the serum concentration and exclusion of this participants' data gave similar results (data not shown). Clobazam and its metabolite desmethylclobazam had the largest reduction after 12 weeks of dietary treatment.

Also, the serum concentration of lamotrigine decreased significantly after diet initiation ($P = 0.016$). Mean serum concentration of lamotrigine was reduced from 23.3 μmol/L (±SD 9.9) at baseline to 20.7 μmol/L (±SD 7.8) at 6 weeks of dietary treatment. After 12 weeks on the diet, the mean serum concentration decreased further to 19.5 μmol/L (±SD 8.4). Compared to baseline, the mean

TABLE 3 Blood biochemistry

Analysis	Baseline	*n*	6 weeks	*n*	*P* value	12 weeks	*n*	*P* value
Glucose, mmol/L, mean (±SD)	4.7 (0.5)	25	NA		NA	4.1 (0.5)	21	**<0.001**[a]
HbA_{1c}, mmol/mol, mean (±SD)	29.7 (4.0)	25	NA		NA	23.8 (3.3)	21	**<0.001**[a]
β-hydroxybutyrate, mmol/L, median (quartiles)	0.1 (0.1–0.2)	24	3.5 (2.8–4.5)	14	**0.001**[b]	3.0 (2.3–4.5)	22	**<0.001**[b]
Albumin, g/L, mean (±SD)	42.7 (3.5)	25	NA		NA	42.9 (3.6)	21	0.910[a]

Note: Blood biochemistry at baseline and after 6 and 12 weeks of dietary treatment. Paired *t*-test was used to compare values at baseline with values after 6 and 12 weeks of dietary treatment of all variables except β-hydroxybutyrate in which we used the nonparametric Wilcoxon signed rank test. Bold indicates $P < 0.05$.

Abbreviations: HbA_{1c}, Hemoglobin A_{1c}; NA, not applicable; SD, standard deviation.

[a]Paired *t*-test.

[b]Wilcoxon signed rank test.

TABLE 4 Serum concentration of ASMs at baseline and after 6 and 12 weeks of dietary treatment

		Baseline	6 weeks	12 weeks	
ASM (μmol/L)	*n*	Mean (±SD)	Mean (±SD)	Mean (±SD)	*P* value
Clobazam	9	0.54 (0.12)	0.34 (0.09)	0.31 (0.16)	**0.002**
Desmethylclobazam[a]	9	6.60 (8.66)	5.55 (7.10)	2.63 (3.04)	**0.010**
Lamotrigine	6	23.3 (9.9)	20.7 (7.8)	19.5 (8.4)	**0.016**
Levetiracetam	8	77.6 (32.5)	65.0 (33.6)	81.0 (25.4)	0.342
Topiramate	8	18.8 (9.5)	19.3 (3.1)	16.5 (7.6)	0.091
Valproic acid, total	14	470 (121)	415 (135)	397 (140)	0.104
Valproic acid, free	12	59.9 (36.0)	64.0 (32.2)	58.5 (24.1)	0.215
Valproic acid, free (%)	12	12.3 (5.1)	16.8 (6.6)	14.6 (3.4)	0.061

Note: Data are analyzed using a mixed effect model analysis. Bold indicates $P < 0.05$. Due to the low sample size, we did not perform statistical analyses of the serum concentrations of clonazepam ($n = 4$), lacosamide ($n = 3$), ethosuximide ($n = 1$), oxcarbazepine ($n = 1$), perampanel ($n = 1$), rufinamide ($n = 1$), and zonisamide ($n = 1$).

Abbreviations: ASM, antiseizure medication; SD, standard deviation.

[a]Desmethylclobazam is the pharmacologically active metabolite of clobazam.

change of lamotrigine serum concentration was −8% after 6 weeks and −15% after 12 weeks. The changes ranged from −27% to 13% at 6 weeks, and from −27% to 0% at 12 weeks of diet intervention.

We found no significant change in the serum concentrations of levetiracetam ($P = 0.36$), topiramate ($P = 0.09$), or valproic acid ($P = 0.13$) during the diet intervention. However, there was a trend towards a decreased serum concentration of valproic acid after 12 weeks of dietary treatment. Mean serum concentration of valproic acid was reduced from 470 μmol/L (±SD 121) at baseline to 397 μmol/L (±SD 140) at 12 weeks. In addition to the total valproic acid concentration, the free valproic acid concentration was measured and the free fraction was calculated. Free concentration of valproic acid did not change significantly during the diet intervention ($P = 0.22$). However, there was a trend towards an increase in the free fraction ($P = 0.06$), from mean 12% (±SD 5.1) at baseline to 17% (±SD 6.6) at 6 weeks, and 15% (±SD 3.4) at 12 weeks of dietary treatment.

Due to the low sample size, we did not perform statistical analyses of changes in serum concentrations of clonazepam ($n = 4$), lacosamide ($n = 3$), ethosuximide, ($n = 1$), oxcarbazepine ($n = 1$), perampanel ($n = 1$), rufinamide ($n = 1$), and zonisamide ($n = 1$).

Overall, the majority of ASM serum concentrations were reduced during the diet intervention. Compared to baseline, the mean change in serum concentration of all ASMs combined was −19% (±SD 23%) at 6 weeks ($P < 0.001$), and −18% (±SD 23%) at 12 weeks ($P < 0.001$) of dietary treatment. In nearly a third of the measurements ($n = 16$, 29%), the serum concentrations declined more than 30% after 12 weeks.

4 | DISCUSSION

In the present study, we examined the influence of a ketogenic diet on serum concentrations of ASMs in children with epilepsy. The main findings were statistically significant reductions in the serum concentrations of clobazam, desmethylclobazam, and lamotrigine during the diet intervention.

Our study is the first to demonstrate a decrease in the serum concentrations of clobazam and its active metabolite desmethylclobazam in children following treatment with a ketogenic diet. These results are in line with our previous prospective trial on adults treated with a modified ketogenic diet.[5] Clobazam was the ASM with the largest reduction in ASM serum concentration. Importantly, approximately half of the patients had around 50% decrease in serum concentration – a decline that may increase the risk of seizure aggravation. In all participants using clobazam, the serum concentration of both clobazam and desmethylclobazam decreased. Of note, consistent with our findings, clobazam was the ASM with the largest reduction in serum concentration also in our previous study in adults.[5] Another finding consistent with our previous study in adults[5] was the significant decrease in the serum concentration of lamotrigine. Although the decrease in lamotrigine serum concentration was smaller than the decline observed for clobazam and desmethylclobazam, this may still be clinically important for some patients, especially for those who initially had a low serum concentration.

Currently, the mechanisms that underpin the observed decrease in the serum concentration of ASMs are poorly understood. Studies investigating food-drug interactions have traditionally focused on changes in drug absorption and bioavailability. In general, the ASMs are lipophilic and has a high bioavailability.[12] Thus, we would not expect any pronounced alterations in the ASM serum concentrations when starting on a ketogenic diet.

Clobazam, desmethylclobazam, and lamotrigine are all metabolized by hepatic enzymes belonging to either the cytochrome P450s (CYPs) or the UDP-glucuronosyltransferase (UGT) superfamilies, which are major pathways for the metabolism of numerous commonly used drugs.[9,13,14] Importantly, in addition to their pivotal role in drug metabolism, they also have a central role in lipid metabolism.[15] High-fat diets have been shown to influence the gene expression and activity of hepatic drug-metabolizing enzymes in experimental animal studies.[16] Thus, upregulation of the drug-metabolizing enzymes may represent a mechanism for the observed decline in ASM serum concentrations.

Unlike most ASMs, levetiracetam is not metabolized in the liver, but is either metabolized in the blood by esterases (24%) or excreted unchanged in the urine (66%).[17] Therefore, perhaps levetiracetam is less prone to interactions than drugs dependent on hepatic metabolism. Indeed, our results and previous studies did not find any change in the serum concentration of levetiracetam during treatment with the ketogenic diet.[5,6]

Contrary to our previous findings in adults,[5] we were not able to demonstrate a significant change in the serum concentration of valproic acid. However, consistent with the results of Coppola,[8] we found a trend towards a decrease in total valproic acid. Moreover, there was a trend towards an increase in free fraction of valproic acid. Free valproic acid is responsible for the pharmacological effect. Since valproic acid is highly bound to protein (typically 90%–95%),[18] changes in the albumin level may increase the free concentration of valproic acid. However, albumin levels did not change during the dietary treatment in our study. Moreover, with regard to the trend towards a decrease in total valproic acid we would expect a decrease in the free fraction, as higher total concentrations (<415 μmol/L) lead to a higher unbound fraction.[19] Other factors that may influence the free fraction of valproic acid are the levels of free fatty acids,[18] which have been shown to increase in individuals on the ketogenic diet.[20] Thus, increased levels of free fatty acids may represent a possible mechanism for increased free fraction of valproic acid. However, more studies are needed to clarify the impact of the ketogenic diet on the serum concentration levels of both total and free valproic acid.

There are several possible explanations for the disparity of results between the studies investigating the influence of the ketogenic diet on ASM serum concentrations,[5–8] including differences in the type and duration of the diet intervention, pediatric vs adult study populations, variations in the type of ASMs used, as well as dissimilarities in the combinations of ASMs. In addition, changes in drug dosage during the diet intervention and trial follow-up may influence the results.[7]

For unknown reasons, a minority of epilepsy patients experience a paradoxical seizure aggravation when starting on a ketogenic diet.[21,22] Thus, one may speculate whether this, at least partly, might be related to a decrease in ASM serum concentration levels. In the present study, two patients experienced a substantial seizure aggravation. However, none of them used the ASMs that had a statistically significant decrease in serum concentration. Hence, based on our data, there is no indication that changes in ASM serum concentration contributed to a poorer seizure outcome. Indeed, in our adult study, we did not find any correlation between change in seizure frequency and change in serum concentrations of ASMs.[5]

Strengths of our study include the prospective study design, complete patient follow-up, and that all ASMs were kept unchanged throughout the entire study period. Control group data from our previous adult trial showed negligible changes in ASM serum concentration during a 12-week period on their habitual diet when epilepsy treatments were kept unchanged.[5] Thus, it seems unlikely that the changes observed in our study are a result of random

variation. Our systematic and objective measures of diet adherence confirmed good compliance with the diet intervention.

Limitations of the study include lack of a control group and few patients with several different ASMs, many of them in combinations. ASMs are known for their susceptibility for drug interactions, thus a diet-induced change of one ASM may influence the serum concentration of other ASMs. However, none of the participants used carbamazepine, phenytoin, or phenobarbital known to be strong inducers of several hepatic enzymes.[23] Also, we cannot exclude that the decrease in ASM serum concentrations is not due to participants not taking the medication as prescribed. However, all parents/caregivers confirmed adherence with the prescribed ASMs at each study visit. Also, since the children in this study had a long history of severe epilepsy, we believe the parents and caregivers were highly motivated to follow the ASM treatment recommendations.

5 | SIGNIFICANCE

We identified a significant decrease in the ASM serum concentrations following a 12-week ketogenic diet intervention. An unintended decrease in the serum concentrations of ASMs may render the patient prone to seizures. Measurements of ASM serum concentrations might be useful in patients on a ketogenic diet, especially in patients with lack of efficacy of the dietary treatment. Future studies should investigate the clinical significance of pharmacokinetic interactions between ketogenic diets and ASMs.

AUTHOR CONTRIBUTIONS

POI, KR, KKS, and SP contributed to the study conception and design. Data collection were performed by SP and CJL. Statistical analyses were performed by SP. The first draft of the manuscript was written by SP and all authors provided critical feedback and commented on the manuscript.

ACKNOWLEDGMENTS

This work was supported by the Dam Foundation, the Norwegian Epilepsy Association's Research Fund, the Novo Nordisk Foundation, and the National Advisory Unit on Rare Disorders, Norway. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the paper. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. We are grateful to the patients and their caregivers who participated in the study. We would like to thank Magne Thoresen and Dag Hofoss for valuable advice regarding the statistical analysis. The Section for Clinical Pharmacology, Oslo University Hospital, Norway, is acknowledged for the analyses of all ASMs. We also acknowledge the National Centre for Rare Epilepsy-Related Disorders for their support throughout the study. Finally, we would like to thank our colleagues at the National Centre for Epilepsy, Norway, for their contributions. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CONFLICT OF INTEREST STATEMENT

MK has received two honoraria from Nutricia. CJL has received speakers' or expert group honoraria from Angelini, Eisai, Jazz and UCB Pharma. KKS has been reimbursed for travel and accommodation as a speaker at a sponsored workshop by Kolfarma and has received speaker's honoraria from Roche and Eisai. The remaining authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

The raw data from this project is not available due to privacy and ethical restrictions of the project approval. Metadata generated in the study and code used in the analysis are available from the corresponding author upon reasonable request within the privacy policy of the informed consent by the participants.

ETHICAL APPROVAL

The study was approved by the Regional Committee for Medical and Health Research in South East of Norway (2016/2016). All participants or parents/caregivers provided written informed consent before enrollment. All procedures in this study were in accordance with the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (ID: NCT04063007) and HelseNorge.no (https://oslo-universitetssykehus.no/kliniske-studier/diett-hos-barn-ved-epilepsi).

ORCID

Sigrid Pedersen https://orcid.org/0000-0003-4035-3073
Magnhild Kverneland https://orcid.org/0000-0003-1778-0835
Cecilie Johannessen Landmark https://orcid.org/0000-0002-0877-8912

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pedersen S, Kverneland M, Rudi K, Gervin K, Landmark CJ, Iversen PO, et al. Decreased serum concentrations of antiseizure medications in children with drug resistant epilepsy following treatment with ketogenic diet. Epilepsia Open. 2023;00:1–9. https://doi.org/10.1002/epi4.12746