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Valproic acid and phenobarbital blood levels during the first month of treatment with the ketogenic diet

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Objective – The aim of this study was to assess how the ketogenic diet influences the blood levels of antiepileptic drugs in the first month of treatment in a pediatric population with drug-resistant epilepsy. *Methods* – The plasma concentrations of antiepileptic drugs were investigated in an open study on 36 consecutive children and adolescents (20 males), aged between 6 months and 16 years (mean age 4.7 years), who were put on the ketogenic diet because of medically refractory epilepsy. The plasma levels of antiepileptic drugs were determined 30 days and immediately before the diet and on days 8, 15, 22 and 29 after the start of the diet. The daily dose of each drug was not changed during the first month of treatment, while the daily dose of benzodiazepines was reduced by up to 30% if excessive sedation or drowsiness occurred. *Results* – While plasma concentrations of phenobarbital did not change in the first month on the ketogenic diet (mean increase of 2.3 mg/l ± 1.0), valproic acid showed a slight but not significant decrease (mean decresase of 6.7 mg/l ± 3.2), 2 weeks after the start of the diet. *Conclusions* – Adjustments in the daily dose of either drug before the start of the diet do not however appear to be justified.

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Key words: blood levels; antiepileptic drugs; ketogenic diet; first month

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Introduction

The ketogenic diet has been used for the treatment of drug-resistant seizures, particularly in pediatric age, for almost a century (1–6). It is usually added to the drug therapy, which may subsequently be reduced or withdrawn clinical conditions permitting. The patient's previous drug therapy thus remains unchanged in the first weeks after the diet starts, unless adverse side effects warrant a partial reduction in the daily dose of the drugs being taken, according to the clinical criteria used by each epilepsy center.

Although the ketogenic diet has been in use for a long time, few data concerning its early effects on the serum levels of antiepileptic drugs are available.

Recently, Dahlin et al. (7) reported that the serum levels of valproic acid (VPA), lamotrigine (LTG), topiramate (TPM), clonazepam (CNZ) and phenobarbital (PB) were not significantly different 3 months after the start of the ketogenic diet. To our knowledge, no data are yet available regarding the first month of diet, which is a critical phase as regards the potential adverse side effects linked to the interactions between the ketogenic diet and the anticonvulsant drugs. Indeed, a blood level's increase of up to 100% has been reported for PB in clinical practice (8–10). Some authors recommend that the daily dose of PB be reduced by 30% before the start of the diet to lower the risk of excessive sedation (11).

The aim of this study was to assess to what extent the ketogenic diet influences the blood levels of antiepileptic drugs in the first month of treatment in a pediatric population with drug-resistant epilepsy.

Materials and methods

This study was performed in consecutive pediatric patients followed by the child and adolescent epilepsy service in our clinic. We enrolled patients between 2006 and 2008 to put them on the ketogenic diet because of drug-resistant seizures.

Patients were enrolled in the study according to the following inclusion criteria: (i) age 6 months or over; (ii) treated with one, or more, antiepileptic drug during the last 3 months prior to the start of the diet; (iii) informed consent to participation in the study from patients, when possible, or parents/caregivers. The study was approved by the ethical committee of the Second University of Naples.

The exclusion criteria were: (i) diseases primarily involving the metabolism or progressive heredodegenerative disorders; (ii) kidney or hepatic chronic failure; (iii) chronic treatment with drugs other than anticonvulsants; (iv) poor compliance with the study protocol.

Upon entry, 1 month and the day before the diet was scheduled to start, a blood sample was obtained to evaluate total red and white blood cells, platelet count, iron, transaminases, gamma-glutamyl-transferase, total cholesterol and triglycerides, urea, creatinine, total proteins and albumin, urinalysis, and serum levels of the anticonvulsant drugs. All the blood samples were drawn before the morning dose of antiepileptic drugs, and all samples were obtained at the steady state level of the drugs. Blood samples were then obtained again on days 8, 15, 22 and 29 after the start of the diet, following the same routine as that described above. The daily dose of each drug was not changed during the first month of treatment; the daily dose of benzodiazepines (BDZ) was reduced by up to 30%, if excessive sedation or drowsiness occurred. Liver and kidney echoes were performed in all patients prior to the start of the diet.

Children were started on a 4:1 ketogenic diet (ratio = 4 g of lipids/1 g of proteins plus carbohydrates), either as a ketocal® formula on its own or providing approximately 80% of the daily caloric intake. Children and adolescents who complied poorly with the ketocal® milk were shifted to a classic 4:1 ketogenic diet. The children were fasted in the hospital for 24 h until 4+ ketonuria was achieved. Fasting could be avoided or shortened in the youngest children or in those who did not tolerate it. Urine ketones and glucose blood levels were checked and recorded daily by parents using ketostix and dextrostix strips in the first week after the start of the diet and three times a week in the following study period, to check on a stable ketosis throughout the trial. Wake and sleep video-electroencephalograph (EEG) recordings and clinical examinations were performed prior to the start of the diet and at 1-month follow-up.

The total plasma concentrations of VPA and PB were always assessed by the same clinical pharmacology laboratory in our university by means of approved routine immunochemical assays. A blood sample was obtained at the same time to assess the albumin level.

Body weight was also monitored before the start of the diet and at 1-week intervals to assess potential changes in the body mass index (BMI) that might result in changes in the blood levels of the antiepileptic drugs and require changes in the daily dose. Medications were changed to carbohydrate-free formulations at least 1 month before starting the diet.

Data are expressed as mean ± standard deviation (SD). All results were analyzed by means of the Wilcoxon Rank Sum test (two-tailed) for non-parametric data and Student's *t*-test. Significance was set at $P \leq 0.05$.

Results

Thirty-six consecutive patients were enrolled in the study. The group was composed of 20 males and 16 females, aged between 6 months and 16 years (mean age 4.7 years). The epilepsy type was symptomatic partial epilepsy with/without secondary generalization in 10, crypto/symptomatic generalized encephalopathies in 23, Dravet syndrome in 2 and Angelman syndrome in 1. The mean duration of the epilepsy was 47.2 months (range 3–141). The mean seizure frequency during the 3 months before the start of the diet was 18.1/24 h (range 3.5–29). Table 1 shows the demographic data of the children in the study.

The etiology of epilepsy was cryptogenic in 18 patients and symptomatic in the other 18 (brain malformations in 6, hypoxic-ischemia in 10, Angelman syndrome in 1 and SCN1A microdeletion in 1).

Sixteen patients were on monotherapy: (8 on VPA, 8 on PB), and the other 20 on polytherapy (4 on VPA + PB + TPM; 4 on VPA + PB + LEV; 10 on VPA + PB + Clobazam; 2 on VPA + PB + CBZ).

Neither the type nor daily dose per kg of body weight of the anticonvulsant drugs was changed during the first 4 weeks after the start of the diet, with the exception of a reduction in the BDZ dose in three patients owing to excessive sedation. The total plasma level of each drug was related to the

Table 1 Demographic data of the children in the study

No. of patients	36
Sex: male/female	20/16
Mean age at start of diet (months; range)	52.9 (6–198)
Mean duration of epilepsy (months; range)	47.2 (3–141)
PMD/IQ	
Normal	0
Mild delay	2
Moderate	8
Severe	8
Profound	18
Neurological examination	
Normal	6
Tetraparesis	20
Ataxia	4
Hypotonia	6
Etiology of epilepsy	
Crypto/symptomatic	18/18

PMD, psychomotor development; IQ, intelligence quotient.

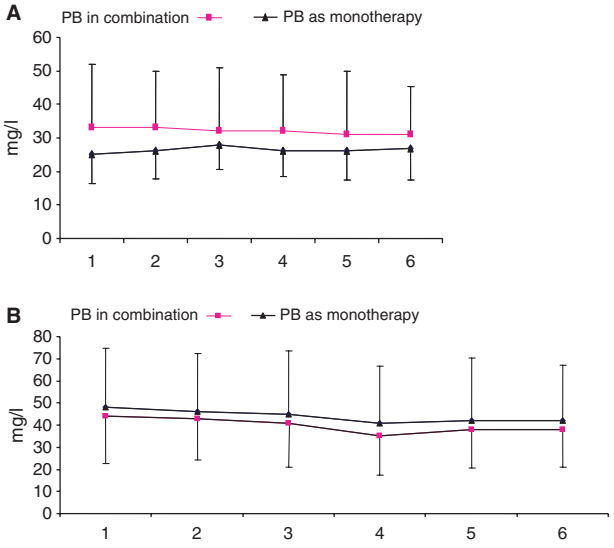

Figure 1. (A) Phenobarbital (PB) as monotherapy or in combination with valproic acid (VPA), (B) VPA as monotherapy or in combination with PB.

daily dose/kg of body weight because of the potential changes in the BMI. The mean BMI was 15.1 ± 3.0 upon entry and 15.6 ± 3.9 at day 29 (P = NS). We did not need to recalculate the total daily amount of calorie intake on the basis of the ideal weight in any of our patients.

Table 2 and Fig. 1 show the mean (mg/l ± SD) serum levels of PB and VPA, as alone and in combination, before the start of the diet and after 1, 2, 3 and 4 weeks.

Overall, there was a mean increase of PB blood level of 2.3 mg/l ± 1.0 at day 8, while the mean levels returned to being almost the same as upon entry in the subsequent 3 weeks (P = NS). As to VPA, there was a mean decrease of 4 mg/l ± 0.2 and of further 2.7 mg/l ± 3.2 at weeks 1 and 2, respectively. In the following 2 weeks, the gap decreased to nearly 4 mg, compared to baseline value (P = NS).

In the subgroup on monotherapy with PB (n = 8), there was a mean increase of 2 mg/l ± 2.2 at day 8, while the mean levels of this drug returned to being almost the same as upon entry in the subsequent 3 weeks. In the group taking PB and VPA (n = 20), there was a mean decrease of 1 mg/l ± 0.8 at day 15 on ketogenic diet, which persisted at day 29 (2 mg/l ± 1.3). In the group on monotherapy with VPA (n = 8), there was a mean decrease of 5 mg/l ± 0.9 at day 15, which persisted for the next 2 weeks (4 mg/l ± 1.5).

In the group taking VPA and PB (n = 20), there was a mean decrease of VPA of 2 mg/l ± 0.1 at day 8 and of 8 mg/l ± 1.1 at day 15, which then dropped to 5 mg/l ± 1.7 in the subsequent 2 weeks (Fig. 1).

Fig. 2A, B shows the mean plasma levels of each drug, either as monotherapy or combination therapy, at 1-week intervals in the first month on the diet. In the whole, the total plasma concentration of PB was increased in 5, decreased in 2 and unchanged in 19 of 26 patients, while that of VPA was increased in 2, decreased in 19 and unchanged in 7 of 28 patients.

Discussion

The results of this study show that the plasma levels of VPA and PB did not change significantly in the first month on the ketogenic diet in children and adolescents with drug-resistant epilepsy.

Table 2 Mean plasma levels (mg/l ± SD) of phenobarbital and valproic acid, as monotherapy or in combination, before and during the first month on ketogenic diet in epileptic children

Type of AED	No.	1 month before diet onset (mean ± SD)	1 day before diet onset (mean ± SD)	Week 1 (mean ± SD)	Week 2 (mean ± SD)	Week 3 (mean ± SD)	Week 4 (mean ± SD)	P-value
Phenobarbital	26	28.5 ± 9.1	28.9 ± 8.9	31.2 ± 7.9	30.2 ± 7.8	30.9 ± 8.0	31.1 ± 9.8	NS
Valproic acid	28	45.6 ± 27.1	44.1 ± 26.9	40.1 ± 29.1	37.7 ± 25.9	39.9 ± 28.9	40.0 ± 29.5	NS

AEDs: antiepileptic drugs; SD: standard deviation; NS: not significant.

Figure 2. Xxxxxxxxxx. 4

To our knowledge, this is the first study that focuses on the potential early changes in the blood levels of antiepileptic drugs. An added advantage of this study is that neither the daily dose per kilogram nor the number of antiepileptic drugs was modified during the study. Moreover, a reduction in the daily dose of the main drugs owing to drowsiness or excessive sedation was not required in any of the patients in our series. Lastly, none of our patients displayed adverse events, such as intense vomiting, diarrhea or infectious diseases, that required additional therapies (e.g. antibiotics) that might interfere with the anticonvulsant plasma levels.

In our series, PB increased only slightly 1 week after the start of the diet (mean increase of 2.3 mg/l $\pm$ 1.0), while VPA decreased by mean of 6.7 mg/l $\pm$ 3.2, 2 weeks after the start of the diet. Probably, the great variance of the plasma levels of PB and VPA can be the reason of the lack of significance, as well as such changes, though not significant, may be clinically important in some cases.

Freeman et al. (12) suggest that the daily dose of drugs most likely to cause drowsiness and sedation, such as PB and BDZ, be decreased. Though there is evidence that anticonvulsants can be reduced successfully even during the first month of the ketogenic diet (13), caution has been recommended especially when PB and BDZ are tapered (14).

Recently, Dahlin et al. (7) assessed the effect of the ketogenic diet on plasma levels of antiepileptic drugs in an open study on 51 children with refractory seizures. No significant changes were observed in the plasma concentrations of VPA, LTG, TPM, carbamazepine (CBZ) or PB between values at the baseline and those 3 months after the start of the diet. Dahlin et al. concluded that the daily drug doses do not need to be adjusted because of possible pharmacokinetic interactions when starting the diet.

The ketogenic diet is hypothesized to influence the plasma levels of antiepileptic drugs in different ways, including partial dehydration, a modified binding of serum proteins due to a varied daily intake of proteins, and high brain levels of anticonvulsant drugs (15–17). Measures taken to avoid predisposing factors such as dehydration and abnormal albumin serum levels may help explain the slight changes in the drug blood levels observed in our patients.

As regards the potential role played by the increased free fatty acid levels in the blood that may induce competition in protein binding, Dahlin et al. (7) ruled out any increase in the free concentration of antiepileptic drugs, at least for VPA.

In conclusion, the present study shows that the plasma levels of VPA and PB, either as monotherapy or in combination, do not change significantly during the first month on the ketogenic diet. Clinicians should however be aware that VPA may decrease more significantly, at least in some cases. This finding warrants confirmation in further studies on larger numbers of patients. Adjustments in the daily dose of these drugs before the start of the diet do not therefore appear to be justified, though changes in the pharmacokinetic and/or pharmacodynamic properties linked to the metabolic and energetic changes caused by the diet cannot be ruled out. Furthermore, such a decrease in valproate level might be considered, especially in patients with a favorable clinical response, as a first step in the antiepileptic drug (AED) reduction. Consequently, a monitoring of the AED blood levels should be considered, at the start of the diet, only if there is an increase in the seizure frequency. The daily dose of medications that cause sedation, such as BDZ, should instead be reduced if sleepiness occurs.

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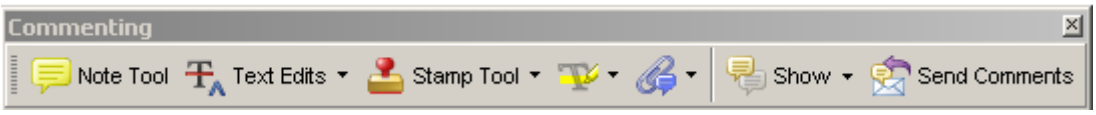

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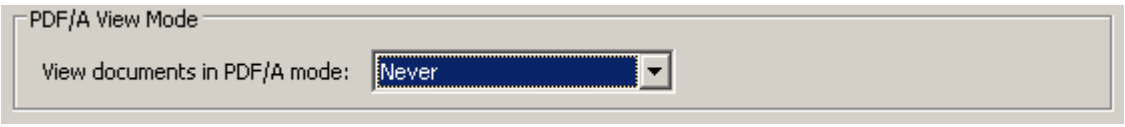

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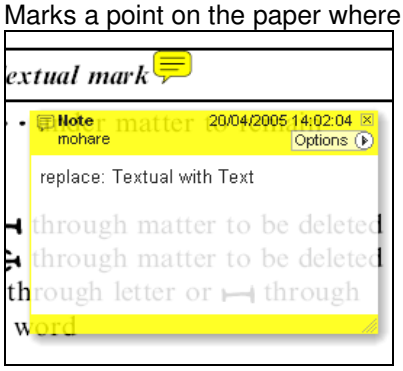

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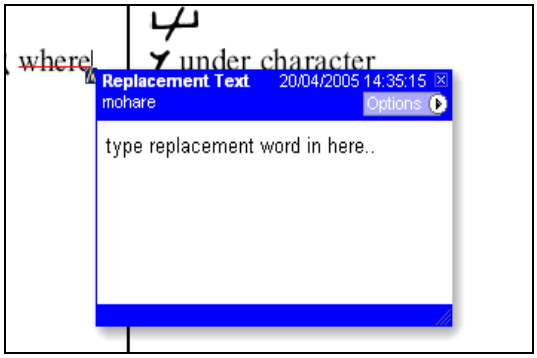

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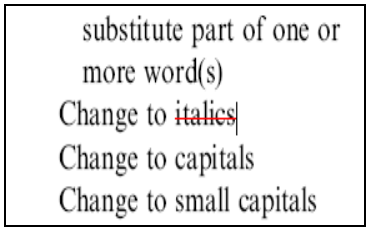

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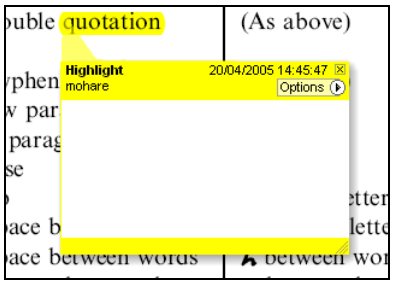

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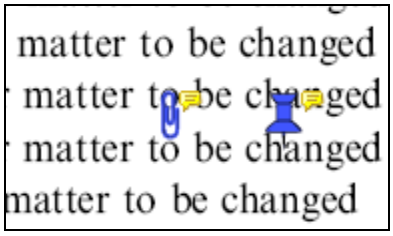

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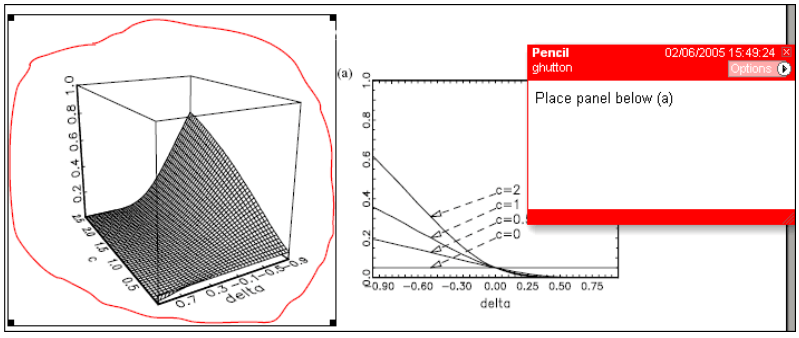

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