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Brief Communication

Carnitine supplementation prevents carnitine deficiency caused by pivalate-conjugated antibiotics in patients with epilepsy prescribed valproate

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ABSTRACT

We measured carnitine levels before and after pivalate-conjugated antibiotic (PCA) use in six patients with epilepsy who were prescribed valproate (VPA). Three of the patients were on carnitine supplementation when PCA use started. Serum FC levels were within the normal range (37.2–49.0 μmol/L) in all six patients before PCA use. After PCA use, the serum free carnitine (FC) levels remained within the normal range (48.0–68.2 μmol/L) in all three patients on carnitine supplementation, but were below the normal range (18.7–30.8 μmol/L) in the three patients not on carnitine supplementation. No remarkable changes in serum VPA levels, platelet count, amylase or ammonia level was evident in any patients in relation to PCA use. Carnitine deficiency due to PCA use was prevented by carnitine supplementation in patients with epilepsy who were taking VPA. Carnitine supplementation can support patients at risk of carnitine deficiency.

1. Introduction

Carnitine plays an important role in the mitochondrial oxidation of fatty acids; its deficiency impairs fatty acid oxidation. Secondary carnitine deficiencies have been reported in patients taking valproate (VPA) and pivalate-conjugated antibiotics (PCAs). Valproate is widely prescribed as a broad-spectrum antiepileptic drug (AED). Several studies have reported low carnitine levels in patients with epilepsy taking VPA [1–7]. Some authors have recommended that carnitine levels be monitored in such patients. Pivalate-conjugated antibiotics are widely prescribed in Japan; PCA-related hypoglycemia and/or acute encephalopathy, which may reflect secondary carnitine deficiency, are not uncommon [8–10].

Carnitine supplementation is considered in patients at risk of carnitine deficiency. However, the effects of supplementation are not always easy to evaluate because carnitine deficiency is often asymptomatic. We monitored carnitine levels before and after PCA use in patients with epilepsy who were taking VPA. Some, but not all, had received carnitine supplementation. We compared the carnitine levels and other laboratory values by carnitine supplementation status.

2. Methods

We retrospectively reviewed the carnitine values of 87 patients with epilepsy treated with VPA, with or without other AEDs, and who were regularly followed up at the Department of Pediatrics, Aichi Medical University Hospital, in 2020. Carnitine supplementation had been prescribed for eight patients. We evaluated changes in carnitine levels associated with PCA use in six patients; three had been prescribed carnitine supplementation when PCA was started, but the other three had not. Patient characteristics are listed in Table 1. All PCAs were prescribed by local outpatient clinics for upper or lower respiratory infection.

The serum free carnitine (FC) and acylcarnitine levels were measured using an enzyme cycling method [11]. The 2018 Japanese guidelines for diagnosis and treatment of carnitine deficiency (http://www.jpeds.or.jp/uploads/files/20181207_shishin.pdf) define a normal FC serum level as >36 but ≤74 μmol/L. The standard deviation score (SDS) of the body mass index (BMI) was calculated using the Tools for Growth Evaluation of Children of the Japanese Society for Pediatric Endocrinology (http://jspe.umin.jp/medical/chart_dl.html). We collected data on serum VPA levels, platelet counts, and amylase and ammonia levels. The serum FC

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Table 1
Patients' characteristics.

Patient	Age	Sex	Etiology	Epilepsy syndrome	VPA dose	Serum VPA levels	BMI-SDS	Other AED	Feeding problems	Carnitine dose	PCA use
S1	8y	F	Structural (Bil. MCA infarct)	FE	300 mg (18.1 mg/kg)	57 μg/ml	−3.3	None	NG tube	500 mg	CDTR-PI 160 mg for 5 days
S2	6y	F	Genetic/Structural (Lissencephaly)	GE	450 mg (30.4 mg/kg)	131 μg/ml	−3.0	CLB	Unbalanced diet	1000 mg	CFPN-PI 150 mg for 5 days
S3	2y	M	Genetic (Undetermined)	GE	500 mg (37.8 mg/kg)	86 μg/ml	−0.35	TPM	Insufficient oral intake	500 mg	CDTR-PI 120 mg for 4 days
N1	8y	F	Genetic (Undetermined)	CAE	600 mg (21.7 mg/kg)	83 μg/ml	0.045	ESM	None	NA	CFPN-PI 250 mg for 3 days
N2	11y	M	Genetic (Undetermined)	FE	600 mg (13.3 mg/kg)	69 μg/ml	0.12	None	None	NA	CFPN-PI 300 mg for 5 days
N3	16y	M	Genetic (Undetermined)	FE	800 mg (11.5 mg/kg)	74 μg/ml	0.52	None	None	NA	CDTR-PI 300 mg for 4 days

MCA: middle cerebral artery, FE: focal epilepsy, GE: generalized epilepsy, CAE: childhood absence epilepsy, VPA; valproate, BMI-SDS: body mass index standard deviation score, CLB: clobazam, TPM; topiramate, ESM: ethosuximide, NG: nasogastric, NA: not applicable, PCA: pivalate-conjugated antibiotic, CDTR-PI: cefditoren pivoxil, CFPN-PI: cefcapene pivoxil

levels after PCA use were measured within 2 weeks after the last dose of PCA.

The study was approved by the ethics committee of Aichi Medical University Hospital. The need for informed consent was waived because we retrospectively analyzed anonymized data only, and patients were allowed to opt out.

3. Results

Patient characteristics are listed in Table 1. All three of the patients who had received carnitine supplementation had severe motor and intellectual disabilities, as well as feeding problems, and all but one had BMI-SDS values <−2. In these three patients, serum FC levels were below the normal range (22.9–29.7 μmol/L) before carnitine supplementation, but were normalized after carnitine supplementation (41.2–49.0 μmol/L) (Fig. 1). The three patients not on carnitine supplementation exhibited no motor or intellectual disabilities, nor any feeding problem. In those patients, the baseline serum FC levels were within the normal range (37.2–47.0 μmol/L) (Fig. 1). Thus, serum FC levels were within the normal range in all six patients before PCA use.

Serum FC levels after PCA use are shown in Fig. 1. The levels remained within the normal range (48.0–68.2 μmol/L) in the three patients on carnitine supplementation, but fell below the normal range (18.7–30.8 μmol/L) in those who were not taking carnitine. As no symptoms were observed in these patients, carnitine supplementation was not performed.

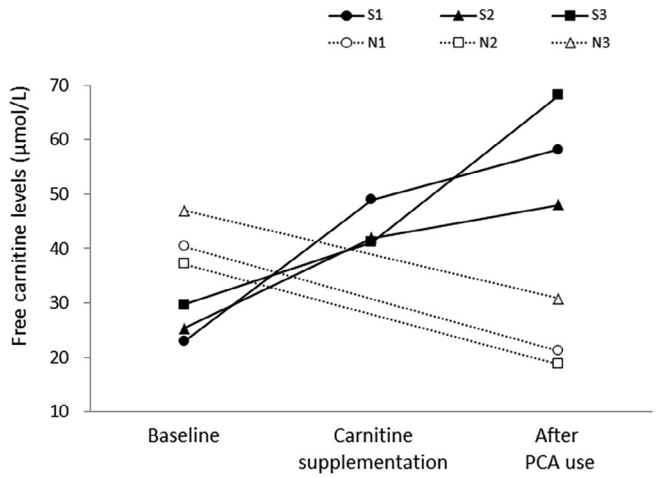

Fig. 1. Free carnitine levels in relation to pivalate-conjugated antibiotic use. Closed markers with thick line indicate patients with carnitine supplementation. Open markers with broken line indicate patients without carnitine supplementation. PCA: pivalate-conjugated antibiotic.

Fig. 2 shows the changes in serum VPA levels and laboratory parameters. The serum VPA level did not change after PCA use in any patient. The VPA dose was not changed in any patient. In Patient S3, the platelet count was low before carnitine supplementation but normalized after supplementation. In Patient S1, the ammonia level was above the normal range before carnitine supplementation but normalized after supplementation. There were no notable changes in any other laboratory values in any patient in relation to PCA use.

4. Discussion

This observational study found that carnitine deficiency caused by PCA use was prevented by carnitine supplementation in patients with epilepsy on VPA. Carnitine supplementation will be beneficial in patients at risk of carnitine deficiency.

All patients receiving carnitine supplementation had several risk factors for carnitine deficiency in addition to VPA use. All had feeding problems, which can lead to insufficient carnitine intake. The BMI-SDS was low in all but one patient, suggesting low-level carnitine storage in skeletal muscles. Indeed, the FC levels were below the normal range in all three patients prior to carnitine supplementation. PCA use is very likely to cause carnitine deficiency in such patients if carnitine supplemented is not provided. However, the FC level did not fall after PCA was prescribed for any patient on carnitine supplementation. Thus, we presume that carnitine supplementation was likely to have prevented carnitine deficiency caused by PCA use in patients at high risk of a deficiency.

None of the three patients lacking carnitine supplementation had any risk factors for carnitine deficiency apart from VPA use, but they all exhibited deficiency after 3–5 days of PCA use. Nakazaki et al. reported carnitine deficiency in an otherwise healthy infant after 3 days of PCA treatment [12]. In Japan, PCAs are commonly prescribed for patients with infections. Given such widespread use, adverse events attributable to PCA-induced carnitine deficiency have unsurprisingly been reported [8–10]. However, PCAs tend to be readily prescribed even for patients at risk of carnitine deficiency, such as those on VPA. The potential risks of PCA use should be more widely acknowledged to prevent serious adverse effects, such as hypoglycemia and acute encephalopathy.

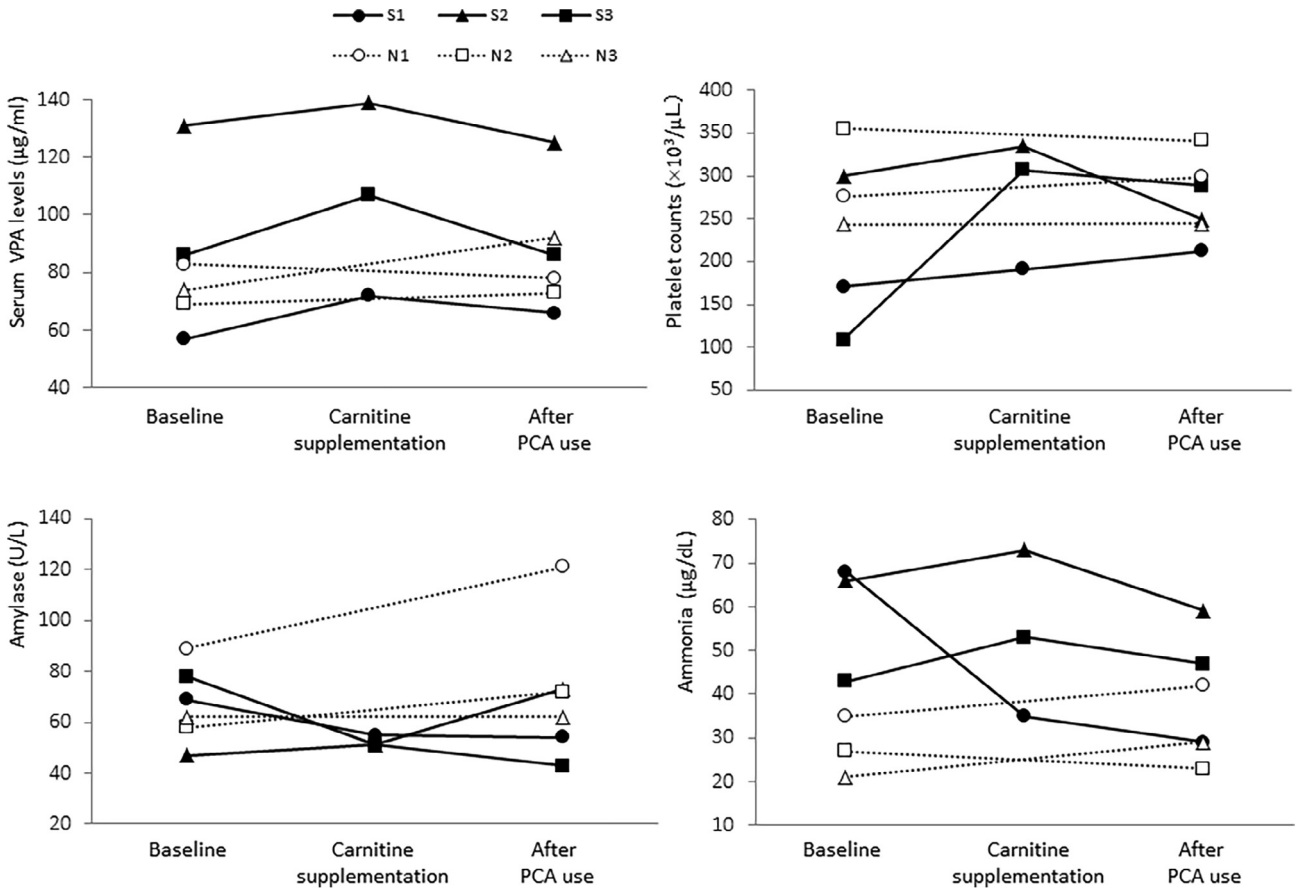

Fig. 2. Laboratory values in relation to pivalate-conjugated antibiotic use Closed markers with thick line indicate patients with carnitine supplementation. Open markers with broken line indicate patients without carnitine supplementation. PCA: pivalate-conjugated antibiotic, VPA: valproate.

This study had certain limitations, including its observational design and the small number of patients, who were all treated in a single hospital. The results should be validated in a larger cohort involving multiple hospitals. However, this may be ethically difficult because of the risks associated with PCA. Also, it is possible that we missed some patients treated with PCA. As we do not prescribe PCA for patients on VPA, PCA treatment status was difficult to determine in some cases.

In summary, carnitine deficiency was not seen in patients with epilepsy on VPA when carnitine supplementation was provided. Carnitine supplementation may benefit patients at high risk of carnitine deficiency.

Disclosure

None of the authors has any conflict of interest to disclose.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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