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RESEARCH ARTICLE
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The potential interaction between antiepileptic drugs and nutraceuticals used in pediatrics with epilepsy

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ABSTRACT

Background: The trend of using nutraceuticals in Indonesia increases every year. This study aims to describe nutraceuticals consumed in pediatrics with epilepsy as additional antiepileptic therapy and analyze their potential drug interactions.

Methods: This research was cross-sectional study with total sampling method which was carried out in the period of June to July 2020. Inclusion criteria were children with epilepsy aged 0-17 years who were members of the Indonesian Epilepsy Community, had a doctor's diagnosis of epilepsy, received oral antiepileptic medication, and took nutraceutical products/food supplements. Data were analyzed descriptively based on data obtained through electronic data filling sheets and interviews.

Results: There were 106 participants from the Indonesian Epilepsy Community in total, with 14 children (13.2 %) using nutraceutical supplements. They were male (n=8; 57.1%), 2-12 years old (n=10; 71.4%), and good nutritional status (n=10; 71.4%). Most nutraceuticals consumed were dietary supplements containing vitamins (n=10; 71.4%). Of the eight potential drug interactions identified, 25% (n=2) were significant interactions, and 75% (n=6) were minor interactions. The potential for major interactions occurred in administering nutraceutical products containing vitamin D with the antiepileptic drug phenytoin and phenobarbital.

Conclusion: In this study, nutraceuticals and antiepileptic drugs had little clinically meaningful interaction effect.

Keywords: antiepileptic, children, nutraceutical

Introduction

The use of nutraceutical products in Indonesia continues to increase every year. Nutraceutical products are gaining popularity in the food and pharmaceutical industries because people are becoming more concerned about their health [1]. Nutraceuticals are present as pharmaceutical dosage forms in powder, capsule, tablet, semi-solid, and liquid forms. Nutraceuticals are defined as foods or parts of foods that provide medical or health benefits in the form of pharmaceutical preparations for the prevention and or treatment of disease. According to Food and Drug Administration (FDA) regulation, most nutraceuticals are classified as "food supplements".

Nutraceutical contains functional foods and bioactive nutrients such as proteins, vitamins, minerals, and compounds derived from natural sources. Nutraceuticals can be found in various forms, including dietary supplements and herbal containing isolated compounds or extracts. Nutraceuticals are classified in various ways, including based on chemical properties and the mechanism of action of bioactive compounds [1].

People are more aware of nutraceutical functions, and mostly they take food supplements containing vitamin A, vitamin C, and vitamin E [2]. Herbal supplements as nutraceutical products can be helpful as antioxidants and reduce oxidative stress levels [3]. Nutraceutical is one of the adjunct therapies for the

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treatment of epilepsy as a complement to antiepileptic medication [4].

Adverse drug reactions and antiepileptic drug resistance are serious problems in treating epilepsy in children. For example, valproic acid have side effect of changing behavior that is often seen soon after initiation of therapy. Patients or family members are often unaware of the cognitive and mood changes associated with the therapeutic effects of these drugs [5]. Nutraceuticals can improve cognitive brain function, learning, and memory [6]. However, the product leaflet does not necessarily include information on product characteristics linked to drug interactions in nutraceutical preparations/food supplements; only 72.7 % of supplement product leaflets indicate drug interactions [7]. Therefore, this study aims to provide an overview of the use of nutraceuticals in pediatric epilepsy patients as adjuvant therapy and analyze the potential for drug interactions.

Methods

Research design

This study was an observational study with a cross-sectional design. Data was collected using electronic forms (Google forms). All information on research subjects were obtained from the parents or person in charge of the research subjects (guardians). The list of questions asked for the interview was standardized as a guide to get complete case report form (CRF). The information validity on antiepileptic drugs and nutraceuticals was obtained from photo documentation. The parents/guardians also showed the drug labels, prescriptions from doctors, and/or self-record of the patient's disease progress.

Ethic

This research has received approval from the Health Research Ethics Committee (KEPK) of the Faculty of Health Sciences, Jenderal Soedirman University, with registration number 100/EC/KEPK/V/2020 and the approval of the founder of the Indonesian Epilepsy Community.

Population and sample

The data were collected for two months (June-July 2022) using a total sampling technique on children with epilepsy who are members of the Indonesian Epilepsy Community. Subjects who did not participate in the study until the end and filled the form incompletely were excluded. Completeness of data involved the information on age, gender, weight, height, antiepileptic drugs used for at least six months, accompanying drugs/food supplements consumed, comorbidities, and parent's educational status. The inclusion criteria were children with epilepsy aged 0-17 years, had a doctor's diagnosis of epilepsy, received oral antiepileptic treatment for at least six months, consumed nutraceutical products/food supplements, agreed to participate in the study, as well as agreed to fill out a case report form that was recorded through telephone interviews.

Subject description

The data were analyzed descriptively to evaluate the characteristics of nutraceutical products used in children with epilepsy based on gender, age, type of epilepsy, comorbidities, antiepileptic drugs (monotherapy/ polytherapy), nutritional status, and parent educational status. Nutritional status was determined from weight and height information data and were calculated using Standard Guidelines for Child Anthropometry issued by the Ministry of Health of the Republic of Indonesia Number 2 of 2020. The nutritional status of children was categorized based on body mass index (BMI) to height (weight/height) including poor nutrition (<-3SD), mild malnutrition (-3SD to -2SD), good nutrition (-2SD to +2SD), overweight (+2SD to +3SD), and obesity (>+3SD).

Nutraceutical characteristic analysis

The MIMS Drug Information Reference and electronic search engines were employed to identify the data of the utilised nutraceutical products. The content of nutraceutical products was categorized based on nutrients, herbs and phytochemicals, and probiotics. The composition of a nutraceutical product was categorized as a combination if the product contains more than one composition group (nutrients, herbs and phytochemicals, or probiotics).

Drug interaction analysis

Identification of potential drug interactions was carried out using literature and electronic databases: Stockley's Drug Interaction Handbook (2010), Drugs Information Handbook Edition 24 (2011), and Medscape (https://reference.medscape.com/drug-

Table 1. Characteristic of subjects (n=14)

No	Characteristic of subjects	n	%
1	**Sex**		
	Male	8	57.1
	Female	6	42.8
2	**Age (years old)**		
	< 2	2	14.3
	2-12	10	71.4
	> 12	2	14.3
3	**Type of epilepsy**		
	General	5	35.7
	Focal	2	14.3
	Unknown	7	50.0
4	**Comorbidity**		
	Yes (cerebral palsy, brain atrophy, late in development)	7	50.0
	None	7	50.0
5	**Antiepileptic therapy**		
	Monotherapy (n=7)		
	- Valproic acid	6	42.8
	- Phenobarbital	1	7.1
	Polytherapy (n=7)		
	- Valproic acid + clobazam + carbamazepine	1	7.1
	- Valproic acid + gabapentin	1	7.1
	- Valproic acid + levetiracetam	1	7.1
	- Valproic acid + carbamazepine	1	7.1
	- Phenobarbital + phenytoin + topiramate	1	7.1
	- Valproic acid + phenobarbital	2	14.3
6	**Nutrition status**		
	Overweight	1	7.1
	Good	10	71.4
	Poor nutrition	2	14.3
	Unknown	1	7.1
7	**Parents education**		
	Junior high school	1	7.1
	Senior high school	2	14.3
	College	10	71.4
	Master	1	7.1

interactionchecker). The potential for drug interactions was then determined based on the mechanism and significance and then the percentage number was calculated.

Results

Subject characteristic

There were 106 participants from the Indonesian Epilepsy Community in total, with 14 children (13.2 %) using nutraceutical supplements. Ninety-two subjects were excluded because they refused to be interviewed, and no complete data (unknown height, not using food supplements, not using antiepileptic drugs used for less than six months). Based on the characteristics of the subjects (Table 1), most subjects were male (n=8; 57.1%), aged 2-12 years (n=10; 71.4%), and had good nutritional status (n=10; 71.4%). Five children (35.7%) had generalized seizures, and two (14.3%) had focal seizures. Meanwhile, the seizure type of seven children could not be categorized.

Most of the antiepileptic drugs used were valproic acid monotherapy (n=6; 42.8%). Valproic acid also was taken with other drugs (polytherapy) such as carbamazepine, gabapentin, phenobarbital, levetiracetam, phenytoin, clobazam, and topiramate. Only one patient (7.1%) was taking phenobarbital monotherapy, and one patient was using phenobarbital combined with phenytoin and topiramate.

Table 2. Nutraceutical used in research subjects (n=14)

Nutraceuticals	Dosage form	n	%
Nutrition (vitamin A, vitamin B_1, vitamin B_2, vitamin B_3, vitamin B_6, vitamin B_{12}, vitamin C, vitamin D, folic acid, iron, nicotinamide, choline, inositol, calcium, sodium, L-Lysine HCl, omega-3, DHA, magnesium sulfate, copper sulfate, fish oil)	Liquid, powder, soft capsule	10	71.4
Herbs (sea cucumber extract)	Liquid	1	7.1
Probiotic	Powder	1	7.1
Combination Multivitamin + curcuminoid (n=1) Multivitamin + probiotic (n=1)	Liquid Powder	2	14.3

Table 3. Potential interactions of antiepileptic drugs with nutraceutical products (n=13)

No	Antiepileptic drug	Ingredient	Drug interaction		n (%)
			Significance	Mechanism	
1	Phenytoin	Vitamin D	Major	Phenytoin reduces the effects of vitamin D through a metabolic pathway involving the CYP3A4	1 (7.7%)
2	Phenobarbital	Vitamin D	Major	Phenobarbital reduces the effects of vitamin D via metabolic pathways involving CYP3A4	1 (7.7%)
3	Phenobarbital	Vitamin C	Minor	Phenobarbital lowers vitamin C levels by increasing vitamin C elimination	1 (7.7%)
4	Phenobarbital	Vitamin B_{12}	Minor	Phenobarbital lowers vitamin B_{12} levels through inhibition of gastrointestinal absorption	1 (7.7%)
5	Phenobarbital	Folic acid	Minor	Phenobarbital lowers folic acid levels by inhibiting gastrointestinal absorption of folic acid. Folic acid lowers phenobarbital levels by increasing metabolism in the liver	2 (15.4%)
6	Valproic acid	Vitamin B_{12}	Minor	Valproic acid lowers vitamin B_{12} levels by inhibiting gastrointestinal absorption of vitamin B_{12}	5 (38.5%)
7	Carbamazepine	Vitamin B_{12}	Minor	Carbamazepine lowers vitamin B_{12} levels through inhibition of gastrointestinal absorption of vitamin B_{12}	1 (7.7%)
8	Carbamazepine	Folic acid	Minor	Carbamazepine lowers folic acid levels through a non-specific interaction mechanism	1 (7.7%)

Use of nutraceutical products

Nutraceutical products used in subjects contain multivitamins, minerals, electrolytes, amino acids, omega-3, fish oil, DHA (n=10; 71.4%) and the rest was a herbal supplement containing sea cucumber extract (n=1; 7.1%), probiotics (n=1; 7.1%), and a combination of nutraceutical products (n=2; 14.3%). Types of dosage forms of nutraceutical products were liquid, powder, and soft capsules (Table 2).

Potential interaction of antiepileptic drugs with nutraceutical

Most combinations have potential drug interactions, which were minor significance levels (Table 3). The interaction between valproic acid and vitamin B_{12} showed the largest percentage mediated by the pharmacokinetics mechanism. The major drug interactions were shown in phenytoin and phenobarbital, which both interacted with vitamin D. Moreover, no herbal supplements or probiotics interacted with antiepileptic drugs.

Discussion

Nutraceuticals, known as dietary supplements, are currently used to support treatment therapy and improve the quality of life in neurological diseases [6]. Dietary supplements can be obtained at pharmacies with or without a prescription. In the present study, nutraceuticals were classified based on the content of chemical compounds and the availability of food containing nutritious substances. All elements of chemical compounds in nutraceuticals can be available in one pharmaceutical dosage form.

Most nutritional content found in this study were vitamin (57.14%). Multivitamins contain more than one type of vitamin, such as vitamin A, vitamin B_1, vitamin B_6, vitamin B_{12}, vitamin C, and vitamin D. Vitamin A consists of fat-soluble retinoic acid that play a role in vision, growth, cellular differentiation, immunity, and gene expression. No evidence correlates between vitamin A supplementation and epilepsy, but vitamin A deficiency is associated with malnourished children in developing countries and Indonesia [8].

A previous report showed that administration of vitamin B complex (vitamin B1, vitamin B6, and vitamin B_{12}) for one week in rats decreased the seizure scores. Long treatment of vitamin B_1 (thiamine) plays a role in increasing the seizure threshold significantly. Thiamine is a water-soluble vitamin that cofactors several enzymes in brain function and neurotransmitter biosynthesis. Thiamine has a role in brain metabolism, and its antioxidant effects play a role in reducing oxidative stress levels. The previous report showed that thiamine deficiency correlates with epilepsy and that this deficiency causes a decrease in acetylcholine and a decrease in nerve terminal impulses. The combination of thiamine (100 mg/kg) and diazepam (0.1 mg/kg) has the potential to increase the seizure threshold [9].

Vitamin B_6 (pyridoxine) is a water-soluble vitamin that plays a role in developing and maintaining the central nervous system. The deficiency of vitamin B_6 can increase excitability in the brain, which can cause seizures. Vitamin B_6, as a cofactor enzyme (pyridoxal form), can cross the blood-brain barrier and play a role in the synthesis of neurotransmitters such as GABA, dopamine, glycine, serotonin, and histamine [4].

Both in children and adults, focal seizures are more common than generalized seizures [10]. Valproic acid monotherapy is an effective initial therapy for generalized and focal types of epilepsy [11,12]. However, valproic acid treatment has side effects on folate and vitamin B_{12} deficiency [13]. This side effect also occurs in carbamazepine and phenytoin therapy. The mechanism of these deficiencies is competition between the two drugs, which causes a decrease in folate binding to folate receptors on intestinal mucosal cells and decreases folate absorption. Vitamin B_{12} plays a role in folate transport and storage and is involved in nucleic acid synthesis [14].

Potential drug interaction studies were conducted to identify possible interactions when nutraceuticals are used with antiepileptic drug orally. Many studies have reported the interaction of antiepileptic drugs in epilepsy treatment [15,16]. In the present study, most interactions were of minor significance, suggesting the administration of nutraceutical may not clinically affect antiepileptic drugs. These interactions were mediated by pharmacokinetic mechanisms in the phase of absorption, metabolism, and excretion.

Major and minor drug interactions need to be monitored and considered for intervals of drug administration if the interaction involves drug pharmacokinetics, especially interactions that affect drug absorption. In this study, major drug interactions involve the metabolic enzymes that phenobarbital and phenytoin interacted with vitamin D, leading to vitamin D deficiency. Vitamin D acts as a neuromodulator by binding with GABA-A receptors in the brain and plays a role in calcium metabolism to reduce neuronal hyperexcitability and seizures [17]. Tantri et al reported that children over five years old who received antiepileptic therapy for more than two years experienced significant vitamin D deficiency with an average vitamin D level of 22.80 ± 7.58 ng/ml [18]. Besides, antiepileptic polytherapy has a greater potential for lowering vitamin D levels than antiepileptic monotherapy [19]. Therefore, the support of vitamin D intake is essential in treating epilepsy in children. Therefore, an evaluation of the vitamin D level and/or supplementation of vitamin D are essential in treating epilepsy in children.

Although interactions between antiepileptic drugs and nutraceuticals are primarily minor, managing drug interactions can increase optimal drug therapy for patient recovery. Labeling drug interactions on packaging insert of nutraceutical and antiepileptic drugs will increase awareness of public to comply with the recommendations for taking medication appropriately.

Conclusion

In this report, nutraceutical and antiepileptic drug may have no clinically relevant effect because 75% of the cases were minor categories. The potential for significant interactions occurred by pharmacokinetic mechanism. This study is limited since the data was based solely on information supplied by the responder and did not include the patient's laboratory findings.

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Declaration of interest

The authors declare no competing interests.

Author contributions

DLI, MWS, and TAP conceptualized the study design and investigated the data; NEE DLI, MWS, and TAP wrote original draft; NEE, TAP reviewed and edited final version. All authors have read the final manuscript.

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