



Effect of valproic acid on metabolic status and endocrine system in pediatric patients with epilepsy: systematic literature review

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ABSTRACT

Introduction: Valproic acid (VPA) is an acidic compound that is commonly used as an anticonvulsant and mood-stabilizing agent in the treatment of epilepsy, mania and bipolar disorders as well as the prevention of migraine headaches. But, it can affect metabolic and endocrine system resulting in hormonal disturbances and incidence of some metabolic disease, especially in pediatric patients. In this study, we aimed to systematically review the literature wherein metabolic and endocrine effect of valproic acid has been studied in pediatric patients with epilepsy.

Methods: To evaluate the relationship between VPA consumption and metabolic diseases, a systematic literature search was performed through searching for related documents in the PubMed and Scopus as two known databases using the following key terms "valproic acid", "metabolic disease" and "pediatrics" in the title, keywords, and abstract of literatures. Data were then extracted and described.

Result: Nearly 934 documents were collected and reviewed based on the main purpose of this study. Of the collected articles, 918 documents were excluded in several step by step processes of article selection, and only 16 relevant documents were included for further data assessment. The results showed that VPA can cause significant increase in plasma concentration of thyroid hormones and therefore increase the risk of metabolic disease in patients with epilepsy.

Conclusion: The results of included documents in this review showed that VPA may induce metabolic and hormonal disturbances in pediatric patients, who were on treatment with VPA.

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Introduction

Valproic acid (VPA) is an acidic compound that is commonly used as an anticonvulsant and mood-stabilizing agent in the treatment of epilepsy, mania and bipolar disorders as well as the prevention of migraine headaches. The VPA is prescribed based on the patient's clinical response and the serum level of drug. Although there is not enough data about the therapeutic range for unbound VPA, but it is generally accepted that the therapeutic range of VPA for the treatment of epileptic patients is 50 to 100 µg/mL (1). Due to

its acidic nature, VPA can strongly bind to protein, especially albumin. VPA is mainly metabolized and excreted by the liver through glucuronidation, β-oxidation, and α-hydroxylation (>95%). Due to its structural similarity to fatty acids, VPA can disrupt β-oxidation cycle; therefore, VPA toxicity is mainly due to the interference with beta-oxidation in the mitochondria (2). Also, it is shown that mitochondrial dysfunction is a major mechanism of drug-induced toxicity, especially in hepatocytes (3). Hepatotoxicity, teratogenicity and pancreatitis

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are the most important adverse effects caused by VPA (4-6). Findings suggested that VPA may cause serious damage to the liver, especially in children younger than 2 years (7,8). It is also shown that VPA can stimulate hyperandrogenemia by inducing androgen synthesis. In addition, chronic VPA therapy may induce steroid synthesis and follicle development in women (9). Since the therapeutic potency of VPA is mainly mediated through phosphatidylinositol (3,4,5)-trisphosphate (PIP3), blockade of voltage-gated sodium channels and gamma aminobutyric acid (GABA) receptors (10), and because there is no single mechanism of action for VPA; therefore, it may also cause side effects including dizziness, headache, diarrhea, constipation, weight changes, agitation, metabolic disease, etc. Overdose of VPA may also lead to sleepiness, irregular heartbeat and loss of consciousness. VPA therapy in patients with epilepsy may be associated with some metabolic disturbances such as weight gain, insulin resistance and hyperleptinemia (11). Findings also suggest that obese patients with epilepsy receiving VPA are at higher risk of metabolic syndrome (12).

Since VPA-induced neurological and gastrointestinal disorders are mainly mediated by metabolic processes; therefore, VPA can affect metabolic and endocrine systems resulting in hormonal disturbances and onset of some metabolic syndrome. The risk of developing side effects, especially liver toxicity is higher in pediatrics. Hence, in this systematic literature review, we have discussed metabolic diseases and endocrine effects of VPA in pediatric patients.

Methods

Search methods

To evaluate the relationship between VPA consumption and metabolic diseases, a methodical literature search was performed through searching for related documents in the PubMed and Scopus as two known databases using the following key terms "valproic acid" and "metabolic syndrome" in the title, keywords, and abstract of literatures in which the correlation between VPA consumption and the incidence of metabolic diseases had been investigated. For this purpose, following search method ((valproic acid OR valproate OR VPA)) AND (metabolic disease OR metabolic syndrome OR metabolic disorder OR endocrine system OR endocrine effect)) AND (pediatric OR children) was used to find potentially relevant documents in the PubMed and Scopus. Then using a customized search, the search results were limited to those articles published in English language. The database search was performed on November 2015. To minimize the possibility of missing data, and

any misinterpretation during data processing, reference lists of all included documents were also screened for potentially relevant articles. Afterwards, for comprehensive data collection, we also searched Google scholar for the previously defined key terms. The literature search was performed by two independent authors.

Study selection

We did not define time limitation, for the selection of relevant documents in the customized search method, and almost all eligible literatures to the purpose of this study that had been published up to November 2015 were included in this literature review. But, we limited the search to those articles published in English language. Articles with subject irrelevancy were excluded in the first step during article selection process. Moreover, to reduce possible misinterpretation, we included and used articles with almost all types of clinical design including prospective cohorts, case-controls, clinical trials, cross-sectionals and comparative studies. But, due to their inaccessible and incomplete data, we excluded conference proceedings, editorials, abstracts, review articles, and meta-analysis from further assessment. Likewise, we excluded literatures that reported similar data of the same population or other duplicated documents. Documents with unavailable full text were also excluded from additional data assessment. As well, we excluded those studies that had been conducted on animals.

Eligibility criteria

All articles reporting any possible relationship between VPA and the incidence of metabolic disease or any defects in the endocrine system that had been conducted on pediatric patients were eligible for additional assessment. For a comprehensive and reliable conclusion, we limited inclusion criteria to only the previously defined study types and those articles with English language. In addition, almost all eligible documents regardless of their publication date or the number of patients were included and used for data extraction.

Data extraction

All general data including the name of authors, date and country of publication, and the total number of studied population in each study, as well as the type of study design were extracted. Other accessible data including demographic information of studied population, methods of assessment in each article, and the main findings were collected based on the main purpose of this study. The data were extracted based on the results of articles reporting the possible relationship between

VPA administration and the incidence of metabolic disease. All data processing including literature search method, articles selection, and data extraction were performed by two independent authors according to the protocol commended in PRISMA checklist 2009 (13). To avoid any possible misinterpretation and errors during data processing, possible discrepancies between the authors were resolved prior to data description.

Measured variables

Various procedures had been used to evaluate the relationship between VPA administration and the incidence of metabolic disease in the included studies. These methods include thyroid function tests, laboratory and medical evaluation, assessment of metabolic hormone level, hormonal and transabdominal pelvic ultrasound assessment, examination for abdominal obesity, insulin resistance, dyslipidemia, hypertension and glucose intolerance, body weight and body mass index (BMI) evaluation, determination of leptin concentration, and evaluation of lipids and lipoprotein profile. Bone mineral density (BMD) and bone metabolism were also evaluated after several months of VPA therapy.

Results

Literature search results

Of total of 926 collected articles in database search, 316 were found in the PubMed and 610 in the Scopus. Two additional articles were also found by manual reference list screening of the included documents. Also, 6 articles were found through the search in Google scholar. By systematically reviewing the abstract and keywords of the collected articles, 477 irrelevant articles were crossed out in the first step. Other 167 articles were further excluded due to duplication. After limiting the results to articles with English language, 256 articles were remained for further evaluation. Moreover, 75 articles that had been performed on animal and additional 165 papers including 118 articles with data inadequacy and 47 review articles were excluded from additional assessment. Studies that had been conducted on adult patients were also excluded from further evaluation. Finally, full text of 63 articles in which the association of VPA administration and occurrence of metabolic and endocrine system disorder had been evaluated, were collected and used for further assessment. After reviewing the content of selected literatures, we selected only 16 relevant documents that fully met the inclusion/exclusion criteria and used for data synthesis and subsequent data analysis. In Figure 1, the step by step procedure of literature search and article selection is shown.

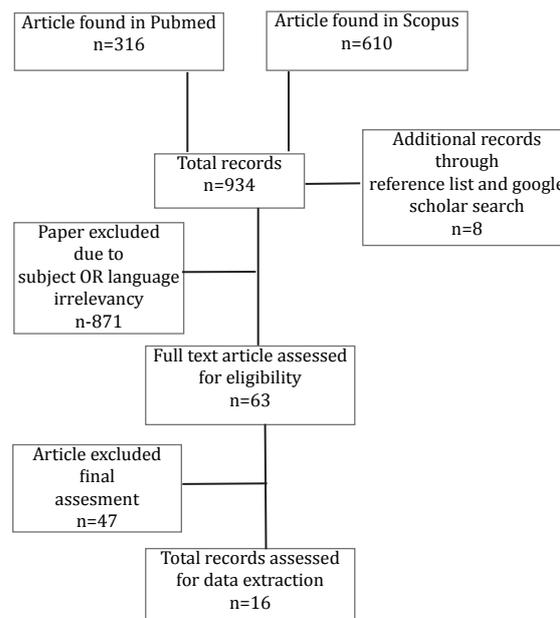


Figure 1. Flowchart of the literature search and strategy for the selection of relevant document.

General characteristics of the included articles

The number of studied population participated in the selected literatures in which the metabolic and endocrine effects of VPA had been investigated in pediatric patients with epilepsy was 822. In the included articles, the number of studied patients varied from 14 to 129 in a prospective study. Patients of both genders had been participated in the selected literatures to evaluate possible metabolic and endocrine effects of VPA in pediatric patients. Amongst the selected literatures, 350 patients were male and 421 were female. In one study with 51 studied populations, the sex ratio had not been reported. The age of participated patients also varied from 2 to 18.5 years. The most old and recent articles evaluated in this literature review had been published in 1997 and 2014, respectively. Also, among the selected articles that were used for data synthesis, 9 was prospective cohort, 5 were cross-sectional and 2 were case-control study. In Table 1, the general characteristics of the included articles are demonstrated in chronological order of their published time.

Study results

The results of this review showed that the relationship between VPA therapy and metabolic disease was confirmed in all of 822 studied patients. In addition, it was shown that anti-epileptic agents, particularly VPA can lead to significant increase in the serum level of metabolic hormones including thyroid-stimulating hormone (TSH), leptin, and insulin, and decrease in the level of thyroxine (T4), free thyroxine (fT4) and triiodothyronine (T3).

Table 1. General information of the included literatures.

| No | Author Reference | Year | Country | Study design * | Sex ratio | Patients number |
|----|-----------------------|------|---------|----------------|------------------------|-----------------|
| 1 | Goldberg-Stern H (14) | 2014 | Israel | PS | Male: 0 Female: 42 | 42 |
| 2 | Turan MI (15) | 2014 | Turkey | CCS | Male: - Female: - | 51 |
| 3 | Yilmaz U (16) | 2014 | Turkey | PS | Male: 76 Female: 53 | 129 |
| 4 | Sonmez FM (17) | 2013 | Turkey | CSS | Male: 11 Female: 10 | 21 |
| 5 | Kim SH (18) | 2012 | Korea | CCS | Male: 34 Female: 27 | 61 |
| 6 | Kanemura H (19) | 2012 | Japan | PS | Male: 5 Female: 10 | 15 |
| 7 | Verrotti A (20) | 2012 | Italy | PS | Male: 54 Female: 60 | 114 |
| 8 | Abaci A (21) | 2009 | Turkey | PS | Male: 18 Female: 12 | 30 |
| 9 | Attilakos A (22) | 2009 | Greece | PS | Male: 15 Female: 15 | 30 |
| 10 | Verrotti A (23) | 2009 | Italy | PS | Male: 7 Female: 7 | 14 |
| 11 | Rauchenzauner M (24) | 2008 | Austria | CSS | Male: 38 Female: 49 | 87 |
| 12 | Rauchenzauner M (25) | 2008 | Austria | CSS | Male: 36 Female: 48 | 84 |
| 13 | Cansu A (26) | 2006 | Turkey | PS | Male: 18 Female: 12 | 30 |
| 14 | Vainionpää LK (27) | 2004 | Finland | CSS | Male: 0 Female: 41 | 41 |
| 15 | Guo CY (28) | 2001 | Canada | PS | Male: 16 Female: 12 | 28 |
| 16 | Verrotti A (29) | 1997 | Italy | CSS | Male: 22 Female: 23 | 45 |

PS: Prospective study, CCS: Case-control study, CSS: Cross-sectional study.

Also it was shown that VPA therapy is associated with higher total serum cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), and uric acid concentration, and lower 25-hydroxyvitamin D or 25 (OH) D, and high-density lipoprotein (HDL) level. Findings also showed that VPA therapy may lead to subclinical hypothyroidism as well as reduced bone formation. According to the reviewed literatures, increased level of TSH and weight gain due to VPA administration and therefore correlation of VPA and metabolic disease or endocrine system abnormality are reported in almost all included documents. Hence, the results of this review suggest that VPA therapy can lead to hormonal imbalance in pediatric patients with epilepsy, which can be considered as the main leading cause of metabolic disorders. Table 2 shows the main clinical features of included documents.

Discussion

Effects of drugs on hormone level and metabolism have long been discussed. Findings show that epileptic drugs, particularly VPA as one of the widely prescribed antiepileptic drugs can cause hormonal disturbances and metabolic disorders. VPA is shown to cause hepatotoxicity by inhibiting mitochondrial respiration leading to oxidative damage and cell death (30). It is also shown that VPA therapy can lead to vanishing bile duct syndrome (31). On the other hand, VPA therapy is associated with increased risk of VPA-induced hyperammonemia (VHA) and hyperammonemic encephalopathy (VHE), especially in patients with juvenile ceroid lipofuscinosis (JNCL) (32). There is growing evidence that VPA in addition to hepatotoxicity can cause renal tubular injury and osteoporosis in pediatric patients, resulting in VPA-induced Fanconi's syndrome in which the

Table 2. Specific characteristics of the selected studies.

| No | Author Reference | Assessment methods | Variables * | Follow-up duration | Main findings |
|----|-----------------------|---|---|--------------------|---|
| 1 | Goldberg-Stern H (14) | Clinical, hormonal and transabdominal pelvic ultrasound | BMI, Body fat mass, TSH | 12 months | VPA had no effect on body weight, metabolic status and endocrine function |
| 2 | Turan MI (15) | Thyroid function tests | FT3, FT4, TSH, and 25(OH) D | 6 months | VPA causes subclinical hypothyroidism |
| 3 | Yilmaz U (16) | Thyroid function tests | FT3, FT4, TSH | 12-month | VPA has deleterious effects on thyroid function |
| 4 | Sonmez FM (17) | Evaluation of diabetic factors | BMI, insulin, c-peptide, neuropeptide Y, leptin | 12 months | VPA increase weight and BMI |
| 5 | Kim SH (18) | Hormonal evaluation | FT3, FT4, TSH | 6 months | VPA causes subclinical hypothyroidism |
| 6 | Kanemura H (19) | Assessment of serum glucose, insulin and carnitine | BMI, serum glucose, insulin | 24 months | VPA cause weight gain and increases in the serum insulin level |
| 7 | Verrotti A (20) | Laboratory assessment | BMI, lipid profile | 24 months | VPA causes considerable increase in body weight and lipid profile |
| 8 | Abaci A (21) | Laboratory and clinical evaluation | BMI, insulin, LDL | 12 months | VPA increases BMI and LDL-C |
| 9 | Attilakos A (22) | Thyroid hormonal evaluation | FT3, FT4, TSH | 24 months | VPA cause significant alteration in thyroid profile |
| 10 | Verrotti A (23) | Evaluation of thyroid hormones, TPO-Ab, TG-Ab | FT3, FT4, T4, TSH | 12 months | VPA therapy does not change thyroid hormones |
| 11 | Rauchenzauner M (24) | Leptin level and glucose homeostasis | Leptin, BMI, body fat and serum insulin concentration | 6 months | VPA therapy was associated with higher body weight, body fat, serum leptin concentrations, metabolic syndrome, and impaired glucose homeostasis |
| 12 | Rauchenzauner M (25) | Serum leptin, adiponectin and visfatin | Serum leptin, Adiponectin and visfatin | 6 months | There is relationship between VPA-therapy, overweight and the adipocytokineaxis. |
| 13 | Cansu A (26) | Evaluation of thyroid hormones, TPO-Ab, TG-Ab, urine iodine | FT3, FT4, T4, TSH, TPO-Ab, TG-Ab, urine iodine | 6 months | VPA increases TSH |
| 14 | Vainionpää LK (27) | Thyroid hormone and antibody assays | FT3, FT4, T4, TSH | 5.8 year | VPA increases TSH |
| 15 | Guo CY (28) | Growth and bone mass | growth, physical activity, BMD, BI | Not mentioned | Long-term VPA therapy is associated with short stature, low BMD, and reduced bone formation |
| 16 | Verrotti A (29) | Evaluation of lipids and lipoprotein profile | Lipids and lipoprotein profile | 2.5 years | VPA significantly modifies serum lipids and lipoproteins |

* BMI: Body mass index, TSH: Thyroid-stimulating hormone, FT3: Free triiodothyronine, FT4: Free thyroxine, 25(OH)D: -25hydroxyvitamin D, TPO-Ab: Thyroid peroxidase antibodies, TG-Ab: Thyroglobulin antibodies, BMD: Bone mineral density, BI: Biochemical indices.

ability of renal tubules to reabsorb electrolytes, protein, urea and glucose is impaired (33,34). Moreover, it is shown that VPA can increase renal losses of carnitine esters leading to decrease the plasma concentration of free carnitine (35). VPA therapy is also suggested to cause reproductive endocrine dysfunction in both men and women with epilepsy (36,37).

Several studies have suggested that VPA administration may be associated with alteration of adipocytokine homeostasis, insulin resistance, weight gain and incidence of non-alcoholic fatty liver disease (NAFLD) (38,39). Findings have shown that genetic variations such as superoxide dismutase 2 (SOD2) Val16Ala polymorphism can influence the relationship between VPA exposure and γ -glutamyltransferase (γ -GT) elevation, a diagnostic marker of hepatotoxicity (40). Also, results of studies show that utero exposure to VPA may increase the risk of episodic hypoglycemia in those newborns of mothers with epilepsy who use VPA during pregnancy (41).

The results of this study showed that VPA may influence endocrine function through the changes in metabolic hormone level leading to incidence or exacerbation of metabolic disease. Based on the results of documents included in this literature review, VPA may cause an increase in serum TSH level, weight, body fat, and serum leptin concentrations, leading to metabolic syndrome, and impaired glucose homeostasis. There were some limitations in this study that may influence the significance of the results. Some major limitations in this study included the lack of enough documents in which the association between VPA administration and incidence of metabolic disease had been evaluated prospectively in a well-designed cohort study. Another major limitation was little number of patients enrolled in the selected literatures.

Conclusion

According to the results of articles included in this study, VPA may change normal endocrine function and some metabolic hormone concentration of the serum resulting in the incidence or even exacerbation of metabolic disorders, particularly hormonal disturbances.

Conflict of Interest

The authors declare no conflict of interest.

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