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ORIGINAL ARTICLE

Cross-sectional evaluation of prescription of valproate and other antiepileptic drugs to pregnant women

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Abstract
Drug counseling is important in women with epilepsy since data about the effects of maternal antiepileptics on the developing fetus are limited. Although pregnant patients on the most teratogenic drugs are treated in accordance to the European Medicines Agency guidelines, a large amount of them may be exposed to the teratogenic medications unintentionally. We performed a tertiary center observational study about medications of pregnant women who were consulted to Teratology Information Service (TIS) unit for evidence-based teratogenic risk analysis. The registration records of 134 pregnant women between 2014 and 2018 were examined. We evaluated the diagnoses, prescriptions, usage of antiepileptic drugs, and distribution of drug subtypes and investigated the drug-related congenital anomalies after delivery. Women were recontacted after delivery to obtain information about health status of infants. We found that 33 women were diagnosed with neurological disorders. A total number of 60 neurologic drugs was prescribed, including 13 antiepileptics. Antiepileptic drugs covered 38.4% valproate ($n=5$), 15.4% pregabalin/gabapentin ($n=2$), 15.4% levetiracetam ($n=2$), 15.4% lamotrigine ($n=2$), 7.7% phenytoin ($n=1$), and 7.7% carbamazepine ($n=1$). Delivery outcomes revealed that valproate exposure resulted in one baby with congenital cataracts, one postnatal exitus with cardiac dysfunction, and one therapeutic abortion. Various antiepileptic drugs were prescribed to pregnant women prenatally or at different times of pregnancy and valproate was the most common antiepileptic drug consulted to TIS for teratogenic risk analysis. Disseminating TIS units and reporting the outcomes to the teratogenesis literature provide proper evaluation of teratogenic risks of drugs accordingly.

Keywords Valproate · Antiepileptic drugs · Pregnant women · Clinical pharmacology

Introduction

Antiepileptic agents are frequently prescribed to women due to the neurological diseases that manifest before or during pregnancy. Drug counseling is important in such women with, particularly, unplanned pregnancies since data about the effects of maternal antiepileptics on the developing fetus are limited. Many women with epilepsy have limited data about the fetal effects of the drugs that they use. In addition, pregnant women under antiepileptic drug therapy are worried about the continuation of pregnancy, because of the potential harmful effects of medications on the developing fetus [1].

The rates of major congenital malformations in the general population range from 1.6 to 3.2%, and similarly, pregnant women who do not use antiepileptic drugs but have epilepsy history, show similar major congenital malformation rates [2]. Some antiepileptic drugs may lead to major congenital malformations such as spina bifida and cardiac anomalies. Valproate was reported to have the highest risk of congenital malformations (10.93% in 2565 pregnancies) among antiepileptic drugs compared to the offspring of women without epilepsy (2.51% in 2154 pregnancies). On the other hand, maternal exposure to the lamotrigine (2.31% in 4195 pregnancies) and levetiracetam (1.77% in 817 pregnancies) were associated with the lowest risk of congenital malformation in previous studies [3].

Teratogenicity Information Service (TIS) provides evidence-based information to the pregnant women and clinicians about possible fetal teratogenic risks of the drugs.

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Drug counseling is a risk communication between the clinical pharmacologist and the patient about possible risks of drugs on the fetus. The counseling starts with informing the pregnant patient about baseline risk of major congenital malformations in the general population, and continues with quantifying the possible teratogenic risk of particular drug exposure, and comparing it with the baseline teratogenic risk. The European Network of Teratology Information Services (ENTIS) and MotherToBaby (Organization of Teratology Information Specialists, OTIS) are well-established networks of TIS, which counsel thousands of patients in the developed countries every year [4]. Unfortunately numerous pregnant women have limited access to this kind of specialized information sources, because of the scarcity of these services. Additionally, the scarcity of these services limits wider data acquisition [5–8].

In this study, we performed a tertiary center observational study about medications of pregnant women who were referred to our TIS unit for evidence-based teratogenic risk analysis. We evaluated the diagnoses, prescription and usage of antiepileptic drugs and distribution of drug subtypes in pregnant women, and investigated the drug-related congenital anomalies after delivery.

Methods

Design of the study

The study was planned as a single center and observational study and approved by the Ethics Committee of Clinical Trials of the Faculty of Medicine (Approval Date: 24.10.2018; Approval No.: 2018/19/15).

The registration records of 134 pregnant women between January 2014 and December 2018 were examined. The demographic data for maternal drug exposure were obtained from our registration form of our Clinical Pharmacology TIS unit of University Hospital, which were filled by face to face interview. Disease diagnostic codes, prescribed drugs, and distribution of the drug subtypes were evaluated accordingly. Among them, 33 pregnant women were diagnosed with neurological disorders. Pregnant women who had not used antiepileptic drugs were excluded from the study.

The prescribed antiepileptic drugs were divided systematically according to the subgroups, doses, intervals, combined amounts, and the exposure period. In addition to the active substance of the antiepileptics, concomitant drug usage was also documented.

Subsequently, risk assessment for teratogenicity was performed for each case based on the literature. At the end of this procedure, we represented a risk analysis score for each case on a written structured form and gave it to the patient to inform both the patient and her obstetrician. After the expected date of birth, women were contacted to obtain information about the neonatal health status and delivery outcomes. The current valid way to assess the teratogenicity risk is by phone calls with the families to obtain information about the health status of their newborns. Although having all infants examined by a pediatrician in the same center would be a more valid approach, all TIS worldwide still implement phone calls such as ENTIS and OTIS [4].

Statistical analysis

The data was analyzed using the SPSS 17.0 program. Categorical variables were expressed as absolute number (%). Kolmogorov–Smirnov test was performed if continuous variables were homogenous and normally distributed. Non-normally distributed variables were expressed as median (range).

Results

Data about pregnant women and patterns of antiepileptic drug exposure

The prescribed medication data of 134 pregnant women who were directed to TIS unit between January 2014 and December 2018 were evaluated. We determined that 49 different diagnoses were encoded. Among 134 pregnant women, 24.6% ($n=33$) were diagnosed with neurological disorders. A total number of 60 neurologic drugs were prescribed, including 13 patients with antiepileptics. As shown in Table 1, antiepileptic drugs covered 38.4% valproate ($n=5$), 15.4% pregabalin/gabapentin ($n=2$), 15.4% levetiracetam ($n=2$), 15.4% lamotrigine ($n=2$), 7.7% phenytoin ($n=1$), and 7.7% carbamazepine ($n=1$). The remaining neurological drugs included antimigraine, analgesic, muscle relaxant, antivertigo, and stimulant drugs.

Neurological diseases were as: 36.4% were neuropathic pain ($n=12$), 24.2% were migraine ($n=8$), 15.2% were epilepsy ($n=5$), 12.1% were stroke ($n=4$), 6.1% were bipolarity ($n=2$), 3.0% were movement disorders ($n=1$), and 3.0% were narcolepsy ($n=1$). Although bipolarity is examined under the title of psychiatric diseases, bipolar patients included in this study had used valproate as antiepileptic and antimanic agent [9], so they were included in this study.

We examined the prescribed drugs and found that the groups other than antiepileptic agents were determined as anticoagulants, anesthetics, proton pump inhibitors, antipsychotics, antibiotics, antispasmotics, nonsteroidal anti-inflammatory drugs, and muscle relaxants. We evaluated the number of drugs prescribed to pregnant women under antiepileptic therapy and determined that 22.2% of the patients were prescribed a single drug, 33.3% had two drugs, 11.2% had three drugs, and 33.3% of the patients were prescribed five or more drugs. All

Table 1 The distribution of the prescribed antiepileptic drugs (AED)

AED drugs	% Per AED, number of patients	Indications	Administration doses (mg/day)	Administration routes
HD inhibitors				
Valproate	38.4%, 5[a]	Epilepsy Bipolarity	500–1000 mg	p.o, i.v
GABA analogs				
Pregabalin Gabapentine	15.4%, 2	Neuropathic pain	75 mg 100 mg	p.o p.o
Levetiracetam	15.4%, 2	Epilepsy	1000 mg	p.o
Lamotrigine	15.4%, 2	Epilepsy	25 mg	p.o
Phenytoin	7.7%, 1[b]	Epilepsy	750 mg	i.v
Carbamazepine	7.7%, 1[c]	Epilepsy	800 mg	p.o

AED Antiepileptic drugs, *HD* histone deacetylase, *GABA* gamma-amino butyric acid, *p.o* per oral, *i.v* intravenous

[a]1 combination of valproate + phenytoin + levetiracetam; 1 combination of valproate + lamotrigine

[b]1 combination of phenytoin + valproate

[c]1 combination of carbamazepine + levetiracetam

pregnant patients were treated at standard doses. The administration routes were intravenous (i.v) (phenytoin, valproate) in two patients and oral in the remaining patients. The median start time of exposures was before conception and median last exposure time was week 10.

Data about delivery and major congenital anomalies

We found that one infant, whose mother used valproate with a daily dose of 1000 mg/day between the weeks 3–7, was born on the week 38 via cesarean, with a birth weight of 3000 g. The infant was diagnosed with congenital cataracts. The maternal exposure included lamotrigine as well. The mother had discontinued the valproate therapy after drug counseling via TIS and switched the treatment to lamotrigine which had a safer profile on the fetus.

Another infant, whose mother had been treated with valproate with a daily dose of 1000 mg/day on the first 10 weeks of gestation, had exitus on the 44th day postnatally. The family claimed that the infant was born on the week 38 via cesarean, with a birth weight of 2500 g. The baby had abdominal organ anomalies, including cardiac dysfunction. The maternal exposure included risperidone and quetiapine as additional drugs.

The other report of valproate exposure with a daily dose of 500 mg/day was a therapeutic abortion after exposure to the drug on the first 5 weeks of gestation. The concomitant drug was diclofenac and the mother underwent termination following spontaneous vaginal hemorrhage on the week 6. The adverse delivery results were summarized in Table 2.

Discussion

In this study, the prescription and usage of antiepileptic drugs in pregnant women, who consulted the TIS unit, were examined cross-sectionally. We evaluated the types

Table 2 The adverse delivery results after antiepileptic drug exposure

Maternal age	Drugs (daily dose)	Start time (week)	Drug exposure (week)	Co-medication (daily dose)	Co-medication exposure (week)	Results
19	Valproate (2 × 500 mg) Lamotrigine (1 × 25 mg)	3 7	3–7 7-till term	–	–	Congenital cataracts
36	Valproate (2 × 500 mg)	Before conception	0–10	Risperidone (1 × 4 mg) Quetiapine (1 × 200 mg)	0–10 0–10	Postnatal exitus on 44 day
31	Valproate (1 × 500 mg)	Before conception	0–5	Diclofenac (1 × 50 mg)	0–5	Therapeutic abortion on 6 week

and prescriptions of antiepileptic drugs and investigated the drug-related congenital anomalies after delivery.

The results showed that 24.6% of pregnant women had neurological disorders, and among them 15.2% were diagnosed with epilepsy. Besides, 6.72% of women, who consulted our TIS, were prescribed at least one antiepileptic drug during pregnancy. It has higher frequency than previous studies that evaluated perinatal antiepileptic drug use. A study reported that approximately 2% of deliveries included at least one prescription for an antiepileptic drug during pregnancy (from 60 days prior to the last menstrual period through the date of delivery) [10]. Another study that compared the prevalence of antiepileptic drugs prescriptions reported that it varied across countries. For all deliveries, the prevalence of antiepileptic drugs prescribed during pregnancy was 51 per 10,000 pregnancies and was lowest in the Netherlands (43/10 000) and highest in Wales (60/10 000) [11]. The study designs and observation periods may differ, and thus the results of studies cannot be fairly compared. We showed that certain psychiatric conditions such as bipolarity or pain disorders were reported to be indications, other than epilepsy, for antiepileptic drug prescriptions, which may have resulted in the higher frequency of antiepileptic drug exposure in our study.

In the present study, the antiepileptic drug usage was discontinued in the first trimester or switched to the levetiracetam or lamotrigine which have safer profile. A study that identified pregnant women with epilepsy has reported that lamotrigine was the drug of choice in Denmark, Norway, and the UK, while carbamazepine, valproate, and phenobarbital were more popular in Italy and the Netherlands [11]. In our study, valproate was the most common prescribed antiepileptic drug. The risk of major congenital malformations is known to be relatively low for levetiracetam, lamotrigine, and carbamazepine and relatively high for phenytoin, phenobarbital, and topiramate [12, 13]. Valproate has been associated with a higher risk of major congenital malformations than other antiepileptic drugs [12, 13].

A correlation has been shown between the valproate dosage and the risk of congenital anomalies. The EURAP International Registry of Antiepileptic Drugs and Pregnancy data showed that malformation rates following first trimester exposure to valproate were 5.6% for < 700 mg/day exposure, 10.4% for 700–1499 mg/day exposure, and 24.2% for 1500 mg/day or higher doses exposure [14]. Valproate has been associated with a variety of major and minor malformations, including a 20-fold increase in neural tube defects, cleft lip and palate, cardiovascular abnormalities, genitourinary defects, developmental delay, endocrinological disorders, and limb defects [15]. In the present study, valproate exposures of the pregnant women were in the first trimester and valproate doses varied between 500 and 1000 mg/day. We found that an infant, whose mother had been treated with valproate with a daily dose of 1000 mg/day on the first 10 weeks of gestation, had exitus on the 44th day postnatally. The baby had abdominal organ anomalies, including cardiac dysfunction. Another valproate exposure with a daily dose of 500 mg/day during the first five gestational weeks underwent termination following spontaneous vaginal hemorrhage on the 6th week. Bleeding/abortion in 6th week of pregnancy might be a naturally occurring phenomenon. It is, actually, not possible to confirm whether the actual cause was valproate. Exposure to 500 mg/day of VA, defined as low dose, may eliminate the actual cause of fetal loss from valproate.

Dose dependency of the major congenital malformations risk for other antiepileptic drugs such as carbamazepine and lamotrigine has also been reported. In the present study, carbamazepine and lamotrigine doses were 800 mg/day and 25 mg/day, respectively, and these low doses did not increase the major congenital malformations risk in the previous studies [16, 17]. We found that one infant was diagnosed with congenital cataracts under maternal exposure to lamotrigine, starting from the 7th week till to the term. The mother, had been also exposed to valproate with a daily dose of 1000 mg/day between the weeks 3–7, had discontinued her valproate therapy after drug counseling via TIS, and switched the treatment to lamotrigine throughout the pregnancy.

Combination therapy with antiepileptic drugs has been considered a risk factor and has been associated with an increased risk of major congenital malformations [18, 19]. In our study, 22.2% of the patients under antiepileptic therapy were prescribed a single drug, 33.3% had two drugs, and 11.2% had three drugs. 33.3% of the patients were prescribed five or more drugs. In principle, women of reproductive age who require antiepileptic therapy should be treated with the appropriate antiepileptic drug at the lowest effective dose and as a monotherapy before becoming pregnant [20]. Discontinuation of antiepileptic drugs after becoming aware of pregnancy should be carefully considered to prevent an increase in the rate of spontaneous seizure. In Table 2, we demonstrated the delivery results of three pregnant patients on valproate treatment and we revealed that two of them were on other concomitant drugs: risperidone, quetiapine, and diclofenac. These concomitant drugs were not classified as major teratogenic drugs. A substantial and reassuring amount of data overall do not suggest a clinically meaningful increased risk of congenital malformations about risperidone and quetiapine [21]. Intrauterine NSAID exposure, such as diclofenac, is related to prenatal constriction of the ductus arteriosus, persistent pulmonary hypertension of the newborn, oligohydramnios, necrotizing enterocolitis, renal dysfunction or failure, and intracranial hemorrhage [22].

Previous studies supported active monitoring of antiepileptic drug levels in the maternal serum during pregnancy. This is particularly true for lamotrigine, where changes in blood levels are associated with increases in seizure frequency [23]. To maintain a level close to the pre-pregnancy level, it seems reasonable to personalize the blood level of drugs for each patient. Pregnancy probably leads to an increase in clearance. Thus, lamotrigine, phenytoin, and carbamazepine concentrations are decreased accordingly. Pregnancy also reduces the level of levetiracetam and active oxcarbazepine metabolite [23].

We had two drugs with i.v administrations, valproate and phenytoin. These medications were administered due to the status epilepticus in one woman. She was treated with valproate and phenytoin i.v. on the 10th week for the management of status epilepticus in the intensive care unit, when she was first consulted to TIS. Before TIS counseling, she gave no history of antiepileptic drug use. Status epilepticus is a neurological emergency associated with a high mortality rate and cognitive squeal. Thus, status epilepticus during pregnancy is a major threat to both mother and fetus. The correct diagnosis and treatment of this neurological emergency during pregnancy is a challenging task [24]. The mother with status epilepticus gave birth to a baby on the week 38, with 3000 g weight and healthy.

The teratogenicity of maternal drug exposure is also influenced by both the maternal and fetal genotypes in the fetal response to medications. Genetic variations in the expression of transport proteins were reported to be an important cause of individual variability in pharmacokinetics and pharmacodynamics of many drugs. The polymorphisms on placental expression of these transporters may contribute to fetal susceptibility [25].

It is important to note the limitations of our study. First, we could not evaluate the severity or symptoms of epilepsy, the actual indications of antiepileptic drug prescriptions, why each antiepileptic drug and its doses were selected or why multiple antiepileptic drugs were prescribed. Drug dosage decisions depend on the clinical severity of the patient's disease and were decided by the neurologists. Moreover, we could not be involved in the decision of treatment protocols unless the neurology physicians requested a reliable dose regimen. Second, the prescribed antiepileptic drugs may not be used properly. Third, our sample size was relatively small and lacks a control group. However, this study is a small contribution to the available data of neurologic drugs and antiepileptics until epidemiological studies during pregnancy are completed. In fact, the problem arising from the lack of data on the use of many drugs during pregnancy can only be solved by reporting these findings (small or huge number) to the teratogenesis literature. All TIS around the world should report teratogenic risk assessments of drugs during pregnancy and contribute their data to the literature. Appropriate assessment of drug-related teratogenic risks can be achieved through the development of drug databases and global reporting records. In addition, by this way, we may develop information about many drugs with unknown safety. Finally, we could not perform genetic analysis for possible chromosomal abnormalities in living babies, nor autopsy for the possible congenital malformation patterns of the case in postnatal exitus. Thus, the real teratogenic effect rate might be higher than our data.

In conclusion, the results of the present study showed that various antiepileptic drugs were prescribed to the pregnant women prenatally or at different times during pregnancy and valproate was the most common antiepileptic drug consulted to TIS for teratogenic risk analysis. Since teratogenicity is relatively new area of the last decade in clinical pharmacology, pregnant women are not aware of such sources of drug information. Disseminating the TIS units and reporting the outcomes to the teratogenesis literature should contribute to the drug databases, and thus helps providing proper evaluation of the drug-related teratogenic risks to improve our knowledge of many drugs with unknown safety.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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