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Pharmacist impact on adherence of valproic acid therapy in pediatric patients with epilepsy using active education techniques

Mubai Ma [a], Qilin Peng [a], Xurui Gu [a], Yani Hu [a], Shusen Sun [b], Yanghao Sheng [a], Ping Wang [a], Hongying Ma [a], Boting Zhou [a,*]

[a] Department of Pharmacy, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China
[b] College of Pharmacy and Health Sciences, Western New England University, Springfield, MA, USA

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ABSTRACT

There is limited information on the impact of active education by a pharmacist in the population of pediatric patients with epilepsy (PWE) in China. The objective of this study was to assess the effect of education by pharmacists on medication adherence and percentage of valproic acid (VPA) samples reaching therapeutic reference range in these patients. This study was conducted at two teaching hospitals in Changsha, China. Patients were retrospectively identified from January 2016 to December 2017. Active education by a pharmacist in both oral and written formats was provided at the intervention hospital whereas standard passive pharmacist service (dispensing and answering questions) was provided at the control hospital. Medication adherence was assessed by the simplified medication adherence questionnaire (SMAQ), and serum concentrations of VPA were collected. The correlation between pharmacist education and medication adherence and percentage of VPA samples reaching therapeutic reference range were analyzed. A total of 2165 patients and 4343 serum VPA concentrations were included in the analysis. For the first therapeutic drug monitoring (TDM) measurement, there was no statistical difference between the two hospitals: 41.3% of VPA samples reached therapeutic range at the intervention hospital compared with 45.4% at the control hospital ($\chi^2 = 3.686$, $P > 0.05$). After pharmacist intervention at the intervention hospital, however, there were significant differences in the percentage of therapeutic VPA samples reaching therapeutic range between the first and the second, third, fourth, and fifth TDM measurements ($\chi^2 = 9.756$, $P < 0.01$; $\chi^2 = 22.840$, $P < 0.01$; $\chi^2 = 15.816$, $P < 0.01$; $\chi^2 = 27.613$, $P < 0.01$).
Based on the SMAQ adherence assessment, adherence increased from a minimum of 56.0% to a maximum of 73.9% with stabilization during the last six months of follow-up at the intervention hospital. Both the medication adherence rate and the percentage of VPA samples reaching therapeutic range increased as the result of active education by a pharmacist, suggesting that continuous pharmacist intervention had a positive impact in outpatient pediatric PWE.

1. Introduction

Epilepsy is one of the most common neurological disorders in China, with an overall prevalence of 2.89% that disproportionately affects patients 10–19 years old [1]. Antiepileptic drugs (AEDs) are the mainstay treatment for patients with epilepsy (PWE), and patients often require lifelong AED therapy [2]. Currently, there are more than 20 AEDs available, including both older and newer ones [3]. Older AEDs, such as valproic acid (VPA), phenytoin, and carbamazepine continue to be widely used in clinical practice. However, these drugs tend to cause significant adverse effects and drug–drug interactions because of their variable and nonlinear pharmacokinetics and narrow therapeutic index. Adverse effects of AEDs are significant predictors of quality of life in PWE [4]. Therefore, these drugs usually require therapeutic drug monitoring (TDM) for efficacy and toxicity [5]. Therapeutic drug monitoring is helpful for dosing adjustments, and to gauge patient adherence and search for intervention opportunity [6,7].

Medication adherence is essential to epilepsy management, and pharmacists are in a unique position to positively affect outcomes. Nonadherence in PWE increases the risk of serious clinical events including increased mortality [8] and places a significant financial burden on the healthcare system resulting to recurrent seizure management [9,10]. Studies have shown that pharmacists have a positive influence on the treatment of epilepsy by increasing patients' medication adherence [11–13]. A cross-sectional study found that many PWE want their pharmacists to be more involved in disease management, especially by discussing drug interactions

* Corresponding author.
E-mail addresses: qilinpeng@csu.edu.cn (Q. Peng), ssun@wne.edu (S. Sun), mhy808@csu.edu.cn (H. Ma), 381465810@qq.com (B. Zhou).

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(76%) and adverse drug effects (74%) with them [14]. Pharmacists also have an important role in TDM and its interpretation [11].

Most studies on adherence and TDM are for adult PWE. However, pediatric PWE is a special population that deserves attention considering pharmacokinetic differences may play a part in age-related differences in the incidence of adverse effects. We therefore established a medication education and consultation service for pediatric PWE in an outpatient pediatric clinic. The roles of the pharmacists were to (1) monitor drug therapy for efficacy and adverse reactions; (2) provide education to pediatric PWE and patients' caregivers on epilepsy and AEDs to increase patients' medication adherence; and (3) ensure that TDM is performed appropriately based on adherence and dosing history. The aim of this study was to assess the impact of education by a pharmacist on medication adherence in pediatric PWE.

2. Methods

2.1. Patients and study setting

The study population included outpatient pediatric PWE (age: <14 years) who were treated between January 2016 and December 2017 at two study hospitals: the control hospital (Hunan Children's Hospital) and the intervention hospital (Xiangya Hospital, Central South University). Both hospitals are academic tertiary hospitals located in Changsha, Hunan Province, China. Inclusion criteria were (1) a diagnosis of epilepsy and treated with VPA for more than one month and (2) patients with at least one plasma VPA level measurement. Patients were invited by pharmacists to participate in the study at their first clinic visit. The study was approved by the Medical Ethics Committee of Xiangya Hospital, Central South University (approval number 2019020078). As study participants were younger than 14 years old, they provided assents if they were able to, and their guardians/parents signed the written consents on their behalf.

The following patient's demographic and clinical information were collected from medical records and during pharmacist–patient encounters: (1) gender, age, and weight; (2) epilepsy history: age at seizure onset and duration of epilepsy; and (3) medication use: AED characteristics (dosage, dosage form, and manufacturer) and plasma drug concentration.

2.2. Pharmacy service provided to patients/families

At the control hospital, only standard passive pharmacy service was provided, mainly consisting of dispensing and answering patients' questions as they arise. In contrast, the intervention hospital provided active patient education and consultation service. The content of the verbal education at the intervention hospital included the following: 1) epilepsy disease state education; 2) AED therapy (treatment rationale, benefits, importance of medication adherence, and treatment length); 3) medication administration (dosing, when to take a dose, how to store the medication, and what to do in case of a missed dose); 4) drug–drug or drug–food interactions; 5) side effects of medications and what to do when experiencing side effects; 6) how to correctly stop or switching medications; 7) laboratory monitoring of drug concentrations; and 8) when to contact clinicians. This patient/family verbal education was provided at multiple patient encounters: initial and follow-up clinic visits and at each TDM blood draw (the content of the education might be tailored based on pharmacists' perceptions of patient's needs). Written materials were provided to complement verbal education. Pharmacists were required to provide this education to patients/families at the intervention hospital per study protocol in order to assess the impact of patients' education by pharmacists.

2.3. Assessment of medication adherence

Medication adherence was assessed using the simplified medication adherence questionnaire (SMAQ) [15]. Although this questionnaire is not specific for epilepsy, it is proven to be a valid indicator of medication nonadherence to treatment of chronic diseases [15–17]. The English questionnaire was translated into a Chinese version according to the standard translation procedures [18]. The SMAQ includes both qualitative and quantitative questions. Qualitative questions include the following: (1) "Do you ever forget to take your medicine?"; (2) "Are you careless at times about taking your medicine?"; (3) "When you feel better, do you sometimes stop taking your medicine?"; (4) "If at times you feel worse, do you stop taking your medicine?"; and (6) "Did you not take any of your medicine over the last weekend?". Quantitative questions include the following: (5) "Thinking about the last week, how often have you not taken your medicine?"; and (7) "Over the past 3 months, how many days have you not taken any medicine at all?". A nonadherent patient was detected when there was a positive response (yes) to any of the qualitative questions (1, 2, 3, 4, and 6); or more than two doses missed over the past week; or over 2 days of total nonmedication during the past 3 months. The SMAQ was administered every time a VPA blood concentration was sampled.

2.4. Bioassays

Fasting venous VPA samples (2–5 mL) were collected using Ethylenediaminetetraacetic acid (EDTA) anticoagulant test tubes and subsequently stored at −4 °C until same-day sample analysis. Blood samples were separated by centrifugation at 3500 rpm/min. Supernatants of plasma were then suctioned and analyzed. Previously reported high performance liquid chromatography (HPLC) and gas chromatography (GC, Agilent7820A, United States) methods were used to determine VPA concentrations at the control hospital and at the intervention hospital, respectively [19,20]. The HPLC method was validated over a linear range of 10–200 μg/mL with a correlation coefficient of 0.9998 and an assay quantitation limit of 2 μg/mL. The reproducibility of this method was represented by the percentage of the relative standard deviation (RSD) with the precision within 5.1%, and the intra- and interday reproducibility ranging from 1.54 to 5.14% and from 1.59 to 4.97%, respectively. The GC method was validated over a linear range of 3.23–172.08 μg/mL with a correlation coefficient of 0.9998 and an assay quantitation limit of 3.23 μg/mL. The reproducibility of this method was represented by the %RSD with the precision within 5.5% and the intra- and interday reproducibility ranging from 0.59 to 2.04% and from 2.67 to 5.2%, respectively. Both hospitals set the VPA treatment reference range as 50 to 100 mg/L [21,22]. Although two testing methods were used, testing indicated that results were comparable.

2.5. Statistical analysis

Descriptive analyses were calculated for all quantitative values and compared using the Analysis of Variance (ANOVA) test. Differences between groups were compared using the Pearson's chi-square test or Fisher's exact test for qualitative values. Statistical analyses were performed using Statistical Product and Service Solutions (SPSS) (version 24.0). Cronbach's α was adopted for the measurement of the reliability of the SMAQ. Statistical significance was defined as $P < 0.05$.

Table 1
Patients' demographic and clinical characteristics.

Characteristics	Intervention hospital	Control hospital
Number of patients (n)	1031	1134
Number of VPA samplings (n)	1902	2441
Male, n (%)	645 (62.6)	680 (60.0)
Age, years	5.0 (0.2–13.9)	4.0 (0.0–13.8)
VPA concentration, mg/L	50.2 (0.0–175.0)	52.2 (0.0–143.1)
Body weight, kg	18.8 (5.0–91.6)	15.6 (4.5–72.3)
Age at seizure onset, years	1.8 (0.0–13.4)	2.4 (0.0–13.8)
Duration of epilepsy, months	25.6 (0.5–163.9)	22.8 (1.0–161.4)

VPA, valproic acid.

Table 2
Analysis of valproic acid (VPA) therapeutic drug monitoring.

Number of TDM	Intervention hospital			Control hospital		
	VPA concentration (mg/L)	VPA sample numbers (n)	Number of samples (%) reaching therapeutic range	VPA concentration (mg/L)	VPA sample numbers (n)	Number of samples (%) reaching therapeutic range
1	47.6 ± 22.5	1031	426 (41.3%)	51.7 ± 24.1	1134	515 (45.4%)[a*]
2	53.1 ± 24.6	445	223 (50.1%)[b**]	55.7 ± 26.2	593	284 (47.9%)[c, n.s]
3	56.9 ± 21.4	209	124 (59.3%)[d**]	57.1 ± 24.5	367	193 (52.6%)[f*]
4	61.5 ± 26.3	102	63 (61.8%)[g**]	56.8 ± 24.1	210	115 (54.8%)[h*]
≥5	63.1 ± 22.8	115	77(67.0%)[m**]	70.3 ± 28.3	137	89 (65.0%)[n**]

n.s = not significant; * = significant at $P < 0.05$; ** = significant at $P < 0.01$.
[a*] Comparing number/percentage samples reaching therapeutic range between the intervention hospital and the control hospital.
[b**] Comparing number/percentage samples reaching therapeutic range between the first visit and the second visit in the intervention hospital.
[c] Comparing number/percentage samples reaching therapeutic range between the first visit and the second visit in the control hospital.
[d**] Comparing number/percentage samples reaching therapeutic range between the first visit and the third visit in the intervention hospital.
[f*] Comparing number/percentage samples reaching therapeutic range between the first visit and the third visit in the control hospital.
[g**] Comparing number/percentage samples reaching therapeutic range between the first visit and the fourth visit in the intervention hospital.
[h*] Comparing number/percentage samples reaching therapeutic range between the first visit and the fourth visit in the control hospital.
[m**] Comparing number/percentage samples reaching therapeutic range between the first visit and the fifth visit in the intervention hospital.
[n**] Comparing number/percentage samples reaching therapeutic range between the first visit and the fifth visit in the control hospital.

3. Results

3.1. Patient characteristics

A total of 2165 patients and 4343 serum VPA concentrations were included in the analysis. From the intervention hospital, there were 1031 patients with 1902 VPA samplings. The average age was 5.0 years, with 62.6% being males. From the control hospital, there were 1134 patients with 2441 VPA samplings. The average age was 4.0 years, with 60.0% being male (Table 1).

3.2. Analysis of VPA blood concentration changes with the number of clinic visits

Patients were divided into five groups according to VPA TDM frequencies: 1, 2, 3, 4, and ≥5 TDMs. We analyzed differences with regard to the number (percent) of VAP concentrations reaching therapeutic range at the two hospitals (Table 2). For the first TDM measurement, there was no statistical difference between the two hospitals: 41.3% VPA samples reached therapeutic range in the intervention hospital compared with 45.4% at the control hospital ($\chi^2 = 3.686$, $P > 0.05$).

At the intervention hospital, after each session of active clinical pharmacist intervention, there were significant differences in the percentage of VPA samples reaching therapeutic range between the first and the second, third, fourth, and fifth TDM measurements ($\chi^2 = 9.756$, $P < 0.01$; $\chi^2 = 22.840$, $P < 0.01$; $\chi^2 = 15.816$, $P < 0.01$; $\chi^2 = 27.613$, $P < 0.01$). At the control hospital, where only standard passive pharmacy service was provided, the differences in the percentage of VPA samples reaching therapeutic range between the first and the second TDM were not statistically significant ($\chi^2 = 0.961$, $P > 0.05$). However, there were statistically significant differences between the first and third, fourth and fifth TDMs ($\chi^2 = 5.726$, $P < 0.05$; $\chi^2 = 6.217$, $P < 0.05$; $\chi^2 = 18.731$, $P < 0.01$). Changes in the proportion of VPA samples reaching therapeutic range with TDM frequencies are shown in Fig. 1.

3.3. Analysis of medication adherence and percentage of VPA samples reaching therapeutic range in medication-adherent patients at the intervention hospital

We assessed medication adherence based on SMAQ at the intervention hospital before each TDM. Patients were divided into five groups according to VPA TDM frequencies: 1, 2, 3, 4, and ≥5 TDMs. The medication adherence rate and the percentage of VPA samples reaching therapeutic range were calculated for each group. The medication adherence rate was the number of patients with medication adherence divided by the total number of patients in each group. Among 1031 patients who had the first TDM, 647 patients were adherent with an adherence rate of 62.8%. In these patients, 398 (61.5%) samples reached therapeutic. A total of 115 patients had the fifth or subsequent TDM. Of these patients, 81 patients were adherent with an adherence rate of 70.1%. Of those

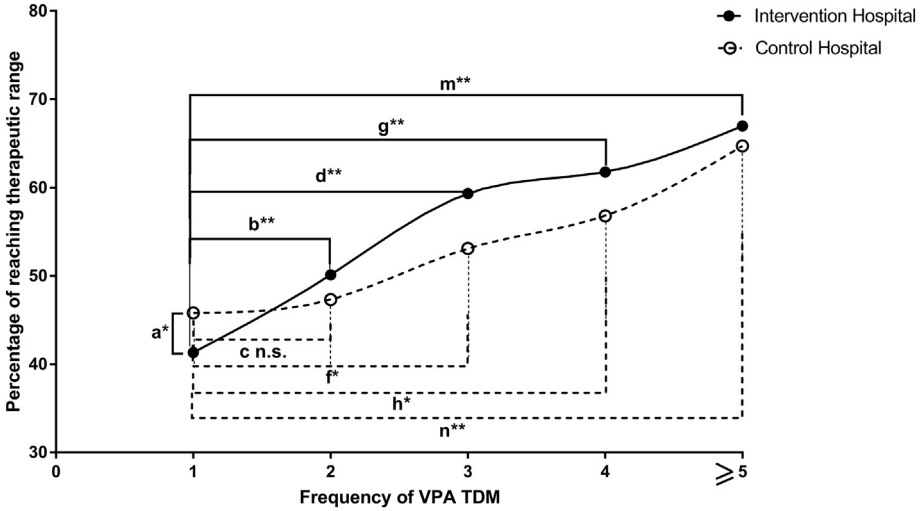

Fig. 1. Changes of valproic acid (VPA) samples reaching therapeutic range. n.s. = not significant; * = $P < 0.05$; ** = $P < 0.01$.

Table 3
Analysis of percentage of VPA samples reaching therapeutic range and percentage of medication-adherent patients at the intervention hospital.

	Number of TDM					
		1	2	3	4	≥5
All samplings	VPA concentration (mg/L)	47.6 ± 22.5	53.1 ± 24.6	56.9 ± 21.4	61.5 ± 26.3	63.1 ± 22.8
	Sample numbers	1031	445	209	102	115
Characteristics of samplings	Number (%) of medication adherent patients	647(62.8%)	302(67.8%)	144(68.7%)	71(69.6%)	81(70.1%)
	Number (%) of samples reaching therapeutic range in adherent patients	398(61.5%)	215(71.2%)	115(79.9%)	57(80.3%)	67(82.7%)

TDM, therapeutic drug monitoring; VPA, valproic acid.

patients, 67 (82.7%) samples reached therapeutic range. Details are shown in Table 3.

Nonadherence with AEDs decreases the proportion of patients who have therapeutic VPA levels, this leading to poor epilepsy control. Therefore, we calculated monthly adherence rates during the follow-up period based on SMAQ assessment. The monthly adherence rate was the number of adherent patients divided by the total number of patients assessed. Fig. 2 is the visual presentation of the change of adherence rates with each study month at the intervention hospital. As shown in Fig. 2, the adherence rate increased from a minimum of 56.0% to a maximum of 73.9%, with the rate stabilizing during the last 6 months of follow-up.

4. Discussion

To the best of our knowledge, this is the first study in China evaluating pharmacist impact on medication adherence in pediatric PWE on valproate acid therapy using both TDM and SMAQ assessments. The study demonstrates that active patient education by pharmacists not only increases the proportion of patients' medication adherence but also increases the percentage of VPA samples reaching therapeutic range.

Nonadherence rates in the population of pediatric PWE range from 3.5% to 68% depending on populations studied and methods used to assess adherence [23–25]. There is currently no standard method to measure medication adherence in PWE [26]. Both subjective methods such as the Medication Adherence Report Scale (MARS) [24,27,28] and the Morisky scale [29] or objective methods such as electronic monitors [30,31], pill counts [32], and medication refills [33,34] were utilized in studies. In our study, the medication adherence rate at the intervention hospital increased from 56% at the start of active patient education by pharmacists (January 2016) to about 73% at the conclusion of the study (December 2017) based on the subjective SMAQ assessment. This indicates that repeated patient education sessions provided by pharmacists had a positive impact on medication adherence. The impact of active education by a pharmacist on medication adherence was also demonstrated through the objective TDM method in our study. Compared with the control hospital, more VPA samples reached therapeutic range during the study period, from 41.30% (the first TDM) to 67.0% (the fifth or subsequent TDM) at the intervention hospital. When VPA samples were analyzed only in medication-adherent patients, the percentage of VPA samples reaching therapeutic range increased from 61.5% (the first TDM) to 82.7% (the fifth or subsequent TDM). These objective TDM data correlate well with the increased medication adherence rate based on the subjective SMAQ assessment. Although our study was not aimed to assess treatment outcome from pharmacy interventions, it has been demonstrated in studies that an increased medication adherence leads to better pediatric epilepsy seizure control [35].

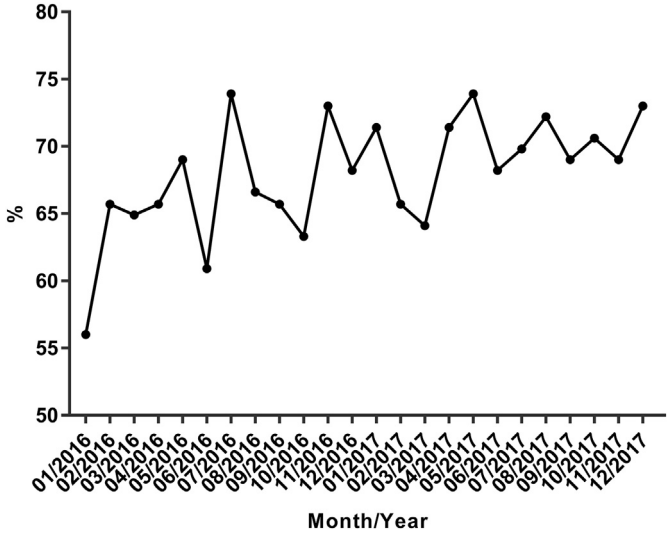

Fig. 2. Monthly adherence rate change at the intervention hospital (vertical axis % = percentage of samples reaching therapeutic range in adherent patients).

Our study focused on pediatric PWE under the age of 14 years old. The adherence of young children to AED therapy depends partly on their parents' or caregivers' decisions to administer AEDs appropriately. Barriers to medication adherence for children and their parents include parental lack of understanding of epilepsy, worries about the effectiveness and side effects of AEDs, and the length of treatment duration [36]. Antiepileptic drugs are associated with adverse effects in approximately 50% of pediatric patients on monotherapy. A recent study conducted in Serbia reveals that parental beliefs about AEDs were associated with the presence of adverse drug effects [36]. Education should be more focused towards understanding the adverse effects of AEDs, in order to potentially alleviate parental concerns and strengthen their beliefs about the necessity of medication use in their children. Another study conducted in Singapore demonstrates that a specialized counseling session given by pharmacists increased caregiver's knowledge about epilepsy and medication adherence [37]. In our study, pharmacists addressed barriers to medication adherence through active verbal education to patients/families during each encounter at the intervention hospital. These active measures may explain the increase in medication adherence to VPA therapy.

At the intervention hospital, the percentage of VPA samples reaching therapeutic range was still low at 67.0% even at the fifth TDM with active pharmacy education. However, this does not necessarily indicate poor seizure control. The dose of VPA in children is usually prescribed at the minimally tolerated dose, with some patients having their seizure control outside the reference range [38,39]. We only measured the total VPA serum concentration, but it is the free concentration (effective therapeutic concentration) that impacts epilepsy control.

Compared with other studies, our study has a large number of pediatric patient samples. We used both TDM and SMAQ to assess medication adherence. However, our study has the following limitations: (1) we only analyzed the impact of active pharmacy education on medication adherence and percentage of samples reaching therapeutic range but did not perform a follow-up on seizure control; (2) certain potential confounders might have affected the findings, such as comedications that affect VPA levels, genetic polymorphisms [40], and memory of patients/families may affect SMAQ assessment.

5. Conclusion

Our study demonstrates that active education by a pharmacist can improve adherence to VPA therapy in pediatric PWE. This improved

medication adherence leads to more TDM samples reaching a therapeutic reference range. Ultimately, pharmacist intervention in the pediatric subgroup with epilepsy can positively impact seizure control.

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Declaration of Competing Interest

Authors declare that they have no conflicts of interests with respect to the research, authorship, and/or publication of this manuscript.

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