Chrono Impact versus Enteric Coated Valproate in Thai Epileptic Patients

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Background: *Since its first clinical use more than 30 years ago, Valproic acid is still being widely prescribed. It has been available in Thailand for more than 20 years. Sodium valproate slow-released (SVSR) form has been used in clinical practice in Thailand since 1990. The objectives of this open study were to access the compliance and satisfaction consequences in the epileptic patients.*
Material and Method: *In this prospective, multi-center study, the authors compared the compliance and satisfaction consequences in epileptic patients switched from more than two times daily sodium valproate enteric-coated tablet (SVEC) regimen to the same total daily dose of SVSR form given once or twice daily.*
Results: *Eighty-nine of the 100 patients completed the study. 43.8% were male (39 of 89 patients). Mean age was 34.74 $\pm$ 12.67 years. Most common etiology of epilepsy was idiopathic 40.4%. Patients were very/fairly happy with the SVSR form 94.4% compared to the SVEC form 56.2% (p = 0.000). Patients had been experiencing no problem with the SVSR form 67.4% compared to SVEC form 38.2% (p = 0.000) and also never missing taking SVSR. form 77.5% compared to SVEC form 40.4% (p = 0.000). According to convenience, patients preferred to administer SVSR form once a day 92.1% and never over taking dosed the antiepileptic drug 96.6%. SVSR form had fewer side effects than the enteric-coated form interms of memory problem (40.4% vs 48.3%) (p = 0.000), sleepiness (30.3% vs 42.7%) (p = 0.041) and difficulty in thinking clearly (38.2% vs 44.9%) (p = 0.001). The patients were seizure free during the study period comparing SVSR form 76.4% to SVEC form 65.2% (p = 0.011).*
Conclusion: *Patients preferred once daily regime. Switching from SVEC to SVSR form increased seizure free, reduced side effects, improved patient's compliance and satisfaction.*

Keywords: *Epilepsy, Sodium valproate, Compliance, Anti-epileptic therapy*

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Epilepsy is one of the most frequent neurological diseases. In 1990 approximately 5.3 million people had chronic, recurrent epilepsy and this number is expected to rise to roughly 5.8 million by 2005.

The sole treatment available for the majority of patients with epilepsy is antiepileptic drug (AED) therapy[1]. Research has shown that missing or altering antiepileptic drug dosages can have adverse reactions, that is, increasing the chance of seizure recurrence. Mattson et al reported that over one quarter of seizures occurred at or before reports of inadequate medication levels[2]. Stanaway et al found that over one-third (38%) was due to either missed medication or inadequate drug levels[3]. Seizures can not only lead to embarrassment, injury and loss of a driver's license or job, but these preventable seizures may prompt expensive and unnecessary additional interventions.

Despite these consequences of non-compliance, and that need for anti-epileptic drug therapy are discussed as part of the diagnosis, 25-75% of patients fail to take their medication[4-7]. Among the contributing factors are forgetfulness, uncertainty about the necessity for drugs, the complexity of the drug regimen[7], and a wish to be rid of the stigma of epilepsy[8,9].

The factor that effect compliance is the number of times of taking - medication per day. In one trial, 87% of prescribed once a day dose successed and only 39% successed for four times daily instruction[10,11]. The compliance was found to decrease reverse to the number of doses increased per day. Probable contributing factors to this effect include forgetfulness and also the complexity of the drug regimen. To improve this,controlled-release anti-epileptic drug formulation was introduced.

Since its first clinical use more that 30 years ago, valproate has rapidly established itself worldwide as a major antiepileptic drug with a broad spectrum of antiepileptic activity, and it is still the subject of numerous studies and publications. It is recognized as a first-line drug in the treatment of epilepsy: it is highly effective for patients with idiopathic or primary generalized epilepsy and it has also been shown to be effective in the treatment of partial seizures and has a favorable side effect profile[12-14].

Slow-release formulation has been developed to improve the kinetic profile of the drug, which has been proved to be effective and well tolerated[15,16]. Such formulations can be given one or twice daily which is expected to result in an improved compliance[11]. They have demonstrated less variation in peak-to-trough plasma drug concentration, and thus may allow more reliable monitoring of plasma levels where this is clinically necessary, and minimize the potential for concentration-dependent adverse events [11,17].

Objective

The primary objective of the present study was to assess under daily practice, the compliance and patient satisfaction consequences induced by the prescription of SVSR form as mono-therapy with any type of epileptic patients. The secondary objective was to assess side effects, adverse events and serious adverse events in patients who switched from more than two times daily SVEC. tablet regimen to the same total daily dose of SVSR form given once daily or twice daily.

Design of study

The patients with any kind of epilepsy treated by valproic acid tablets in monotherapy from 3 months at least at the inclusion moment, were enrolled in a three-month cohort study.Two visits were scheduled: the first visit Day 0 (Inclusion day) and 3 months after the inclusion day +/- one week, During the first visit, the investigator collected: socio-demographic profile, characteristics of epilepsy, Clinical Global Impression scale (CGI), relevant events such as professional, familial change, concomitant disease, surgical event or any modification on the patient's health etc. compliance and satisfaction. During the day 90 visit, the investigator collected: Clinical Global Impression scale, relevant events, compliance and satisfaction..

Study Population: 100 subjects

Inclusion

Patients treated by SVEC tablet on monotherapy form at least 3 months, male or female patients aged between 18- 65 years, Patients currently cared for in an ambulatory setting,patients must be able to read and write, patients must be relied upon to perform the full study and sign the informed consent form after the study has been fully explained.

Exclusion criteria

According to the SVSR patients with a history of hypersensitivity of SVSR or one of the excipients. Patient who did not completed follow up.

Material and Method

In cases of a patient who switched from SVEC to slow-release 500 mg form, a switch dose by dose is recommended. Indeed the switch day, SVEC morning intake must be taken in addition to the administered

dosage with SVSR.This addition intake was repeated later. A three-intake sodium valproate treatment could be administered in 2 intakes, even in a single intake in well-controlled epilepsies with a 20 to 30 mg/kg once daily.

Statistic analysis

Outcome measurement: the compliance and patient satisfaction questionnaire was completed alone without help. Secondary outcome: the clinical global impression scale was completed by the physician at day-90 visit. Adverse events and serious adverse events (according to the ICH definition). The patients dropped out of the study at any time and irrespective of the reason, or under the investigator decision. All dropouts were documented and the investigator gave the reason in the "End of Study" form. In case of dropout for safety reasons, the physician was asked to provide additional information on the relevant form located in the case report form.

The demographic characteristics data the compliance and satisfaction questionnaire were analyzed using the SPSS program with descriptive statistics (mean $\pm$ SD), number and percentage. Nonparametric statistics were used to compare between SVEC and SVSR forms. Multivariate analysis was used to ascertain which factors might be important in predicting compliance and satisfaction. A p-value of less than 0.05 was considered statistically significant.

Results

Of the 100 patients who enrolled in the trial, 89 completed the trial. The demographic characteristics of the patients are shown in Table 1, 39 patients (43.8%) were male. Average age was 34.74 $\pm$ 12.67 years. Mean weight was 59.35 kg. Mean age onset of epilepsy was 26.14 (range 1-64 years) years. Mean duration of epilepsy was 7 years (0.3-38.4). Types of seizure were tonic-clonic seizure 46%, tonic-clonic and other type seizure 27%. Of these patients, 8 withdrawals from the study were due to protocol violation, 3 due to adverse events (vertigo 1, vomiting 1, rash1 patient.).

Treatment and evaluation (Table 2)

The ratio of drug administration: SVSR versus SVEC form once daily was 85.4% vs 12.4%. Patients very /fairly happy satisfaction statistic significant comparing SVSR to SVEC form ($p = 0.000$). Frequency of seizure was decreased after switching from SVEC to SVSR form (Fig. 1) and also significant seizure controlled fairly/very well controlled (Fig. 3).

The number of patients who missed taking the drug in visit 1, SVEC form were 53 patients and visit 2, SVSR form were 20 patients. The most frequent reasons were rush hour, too busy, working time; forgot to bring the drug respectively (Table 3). The most preferable regimen was once daily dosage 92.1% due to easy or convenient (93.2%) (Table 4).

The significant side effect or complication comparing SVEC (visit 1) to SVSR form (visit 2) were sleepiness, memory problem, difficulty thinking clearly. (Table 5, 6 and Fig. 2)

Evaluation of clinical global impression, which assessed therapeutic effect based on patients' global, found a marked improvement 50.6%, moderate improvement 20.2%, unchanged 19.1% and worsened 2.2% (Table 7).

Table 1. Demographic data of the patients

Variables	Patient (number)	Percentage
Male	39	43.8
Female	50	56.2
Age (mean $\pm$ SD) (years)	34.74 $\pm$ 12.67	
Weight (mean, kg)	59.35 (32-76)	
Marital status		
Single	40	44.9
Married	45	50.6
Divorced	1	1.1
Widowed	3	3.4
Employment status		
Working full time	48	54.0
Working part time	4	5.0
Business owner	1	1.0
House wife	14	16.0
Student	13	14.0
Retired	1	1.0
Unemployment	8	9.0
Educational level		
< Elementary	2	2.2
Elementary	21	23.6
Secondary	16	18.0
College	17	19.1
$\geq$ University	33	37.1
Etiology		
Idiopathic	36	40.4
Cryptogenic	19	21.3
Symptomatic	29	32.6
Undetermined	5	5.6

Table 2. Main outcome according to treatment groups

Anti-epileptic therapy	SVSR (%)	SVEC (%)	p value
Administration			0.000
Once daily	85.4	12.4	
Twice daily	14.6	34.8	
> 2 times/day	0.0	52.8	
Satisfaction			0.000
Very/fairly happy	94.4	56.2	
Neither happy/unhappy	3.4	21.3	
Fairly/very unhappy	2.2	22.5	
Experiencing problem			0.000
Never	67.4	38.2	
Sometimes/often	23.6	41.6	
Occasional	9.0	20.2	
Missing medication			0.000
Never	77.5	40.4	
Less1/month	19.1	31.5	
≥ 1 month but < 1/week	2.2	18.0	
≥ 1 week	1.1	10.1	
Over taking of drug dose			0.206
Never	96.6	91.0	
Sometimes/occasional	2.2	9.0	
Often	1.1	0.0	

SVSR: Sodium Valproate slow-release , SVEC: Sodium Valproate Enteric coated form

Table 3. Reasons for noncompliance

Reasons*	SVEC (N53)	SVSR
1. Rush hour/busy/working time	(26)	10
2. Outcome, forget to bring it	(12)	10
3. Several time to take daily	6	0
4. Have not eat anything, miss to take it	3	2
5. Forget	8	3
6. Awareness of drug interaction	1	0
7. Other: Sleep before taking medicine	2	1

* 1 patient may give more than 1 reasons

Table 4. Reasons of prefer to take the regime

Questions	Percent
Which regimen the patients prefer to take?	
Once a day only	92.1
Twice a day	7.9
Why do the patients prefer to take the regime?	
Easy/convenience/not forget	93.3
Decrease frequency of seizure attack	1.1
Physician's suggestion	2.2
Don't bring it out when out of home	2.2
Would like to know the efficacy of new regime	1.1

Discussion

Patient's opinion about AED mono-therapy was significantly different ($p < 0.05$) on all items between SVEC and SVSR form. More patients agreed with the statement about taking AED medication once a day. There was a significant decreasing frequency of seizure reported when comparing SVEC and SVSR form ($p < 0.05$). Fewer side effects with SVSR form compared to enteric-coated ($p = 0.000$). The most significant improvement of side effects was sleepiness, memory problems and difficulty thinking clearly. Only 3 serious adverse events reported which were all episodes of convulsion led to hospitalization. During the study period, only 6 adverse events were reported: nausea, dyspepsia and palpitation 1, vomiting 1, tremor, alopecia and drowsy 1, vertigo 1, amenorrhea 1, and rash 1.

Table 5. Comparing side effects of SVEC to SVSR

Side Effect	SVEC (X ± SD)	SVSR (X ± SD)	p-value
1. Unsteadiness	1.81 ± 0.93	1.69 ± 0.87	0.202
2. Tiredness	2.06 ± 1.09	1.92 ± 1.01	0.132
3. Restlessness	1.58 ± 0.93	1.49 ± 0.84	0.212
4. Feeling of aggression	1.46 ± 0.83	1.47 ± 0.74	0.706
5. Nervousness and/or agitation	2.02 ± 1.07	1.92 ± 1.00	0.307
6. Headache	1.93 ± 0.95	1.79 ± 0.94	0.186
7. Hair loss	1.56 ± 1.02	1.42 ± 0.88	0.087
8. Problems with skin e.g. acne, rash	1.26 ± 0.63	1.18 ± 0.56	0.265
9. Double or blurred vision	1.40 ± 0.88	1.33 ± 0.72	0.331
10. Upset stomach	1.60 ± 0.82	1.52 ± 0.77	0.164
11. Difficulty in concentrating	1.82 ± 1.09	1.70 ± 1.00	0.177
12. Trouble with mouth or gums	1.21 ± 0.65	1.30 ± 0.71	0.311
13. Shaky hands	1.78 ± 1.15	1.74 ± 1.04	0.730
14. Weight gain	2.01 ± 1.20	1.99 ± 1.16	0.759
15. Dizziness	1.82 ± 0.98	1.71 ± 0.97	0.234
16. Sleepiness	2.37 ± 1.16	2.02 ± 1.10	0.000*
17. Depression	1.52 ± 0.93	1.40 ± 0.85	0.106
18. Memory problems	2.24 ± 1.20	2.06 ± 1.20	0.041*
19. Disturbed sleep	1.70 ± 0.96	1.54 ± 0.98	0.078
20. Difficulty thinking clearly	2.17 ± 1.12	1.89 ± 0.99	0.001*
21. Slurred speech	1.58 ± 1.01	1.45 ± 0.81	0.170

* Statistisfical Significant

Table 6. Side effects during the last three months (percent)

Side Effect	SVEC (%)				SVSR (%)			
	Never problem	Rarely problem	Sometimes problem	Always problem	Never problem	Rarely problem	Sometimes problem	Always problem
1. Unsteadiness	44.2	31.4	16.3	8.1	51.8	21.2	23.5	3.5
2. Tiredness	38.4	23.3	25.6	12.8	41.2	29.4	20.0	9.4
3. Restlessness	61.6	17.4	15.1	5.8	64.7	16.5	14.1	4.7
4. Feeling of aggression	69.8	14.0	14.0	2.3	63.5	21.2	12.9	2.4
5. Nervousness and/or agitation	36.0	30.2	22.1	11.6	43.5	24.7	22.4	9.4
6. Headache	38.4	33.7	19.8	8.1	45.9	30.6	17.6	5.9
7. Hair loss	69.8	10.5	9.3	10.5	72.9	16.5	2.4	8.2
8. Problems with skin e.g. acne, rash	79.1	14.0	4.7	2.3	88.2	5.9	4.7	1.2
9. Double or blurred vision	79.1	11.6	2.3	7.0	76.5	14.1	5.9	3.5
10. Upset stomach	55.8	31.4	8.1	4.7	58.8	31.8	5.9	3.5
11. Difficulty in concentrating	51.2	22.1	12.8	14.0	58.8	20.0	10.6	10.6
12. Trouble with mouth or gums	88.4	8.1	1.2	2.3	82.4	12.9	2.4	2.4
13. Shaky hands	64.0	10.5	11.6	14.0	55.3	18.8	15.3	10.6
14. Weight gain	50.0	11.6	16.3	22.1	45.9	23.5	11.8	18.8
15. Dizziness	44.2	31.4	15.1	9.3	51.8	27.1	10.6	10.6
16. Sleepiness	30.2	30.2	16.3	23.3	38.8	30.6	15.3	15.3
17. Depression	70.9	10.5	11.6	7.0	72.9	16.5	3.5	7.1
18. Memory problems	37.2	17.4	20.9	24.4	42.4	17.6	16.5	23.5
19. Disturbed sleep	62.8	16.3	14.0	7.0	68.2	17.6	3.5	10.6
20. Difficulty thinking clearly	36.0	24.4	20.9	18.6	41.2	31.8	15.3	11.8
21. Slurred speech	70.9	12.8	5.8	10.5	69.4	16.5	9.4	4.7

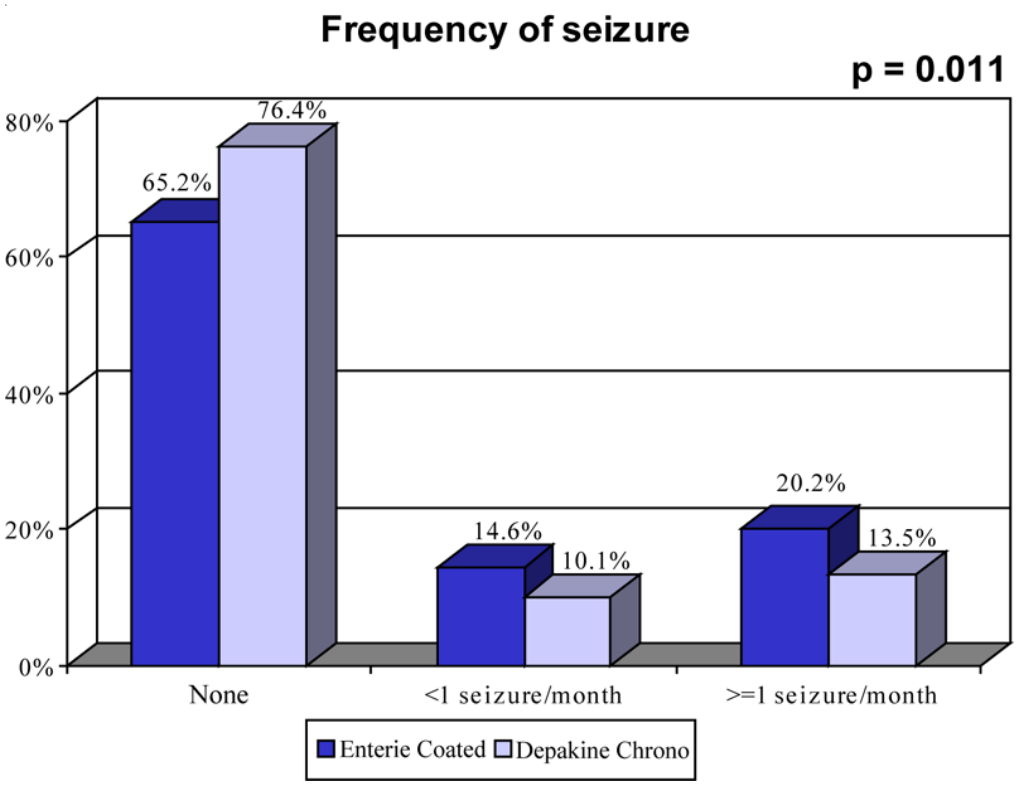
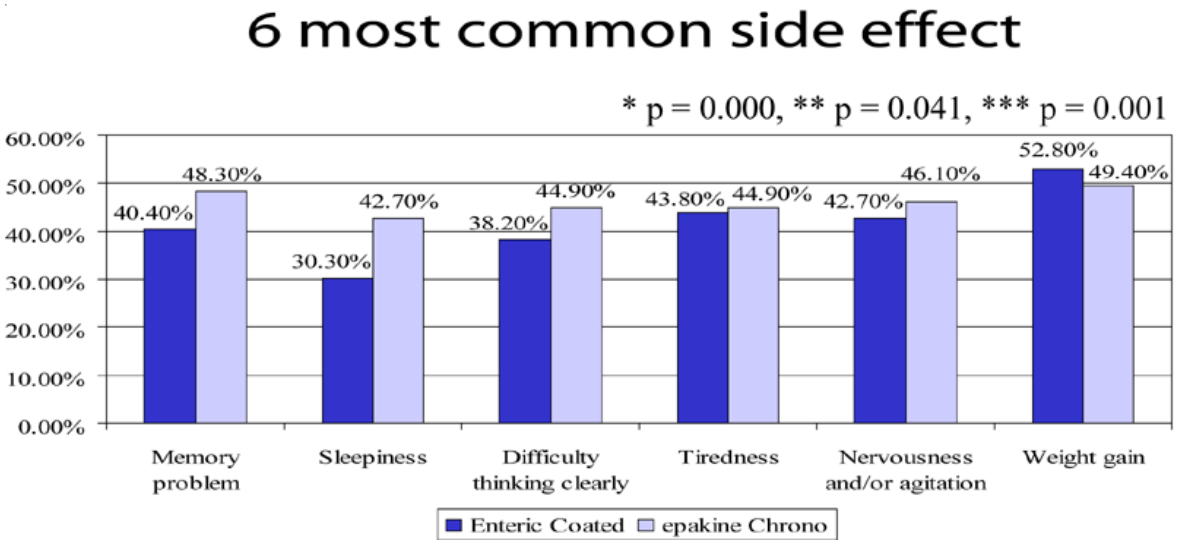
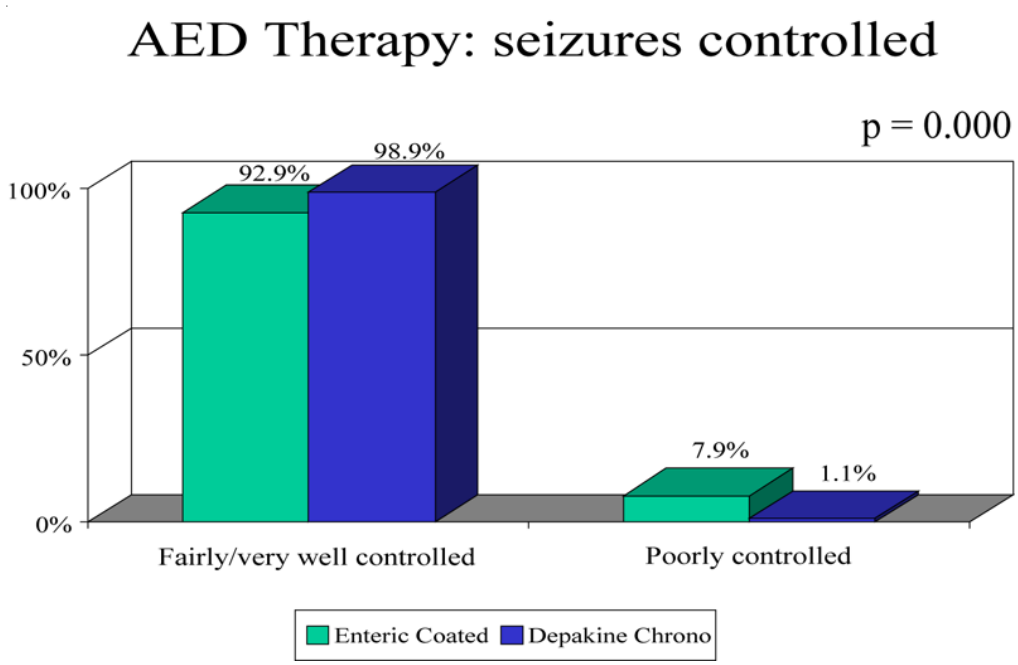


Fig. 1 Frequency of seizure comparing Depakine Enteric Coated to Depakine Chrono



Significant difference in Sleepiness, Memory problem and difficulty clearly thinking between Enteric Coated and Depakine Chrono, $p < 0.05$

Fig. 2 Six most common side effects of Depakine Enteric Coated versus Depakine Chrono



Significant difference in seizures control between Enteric Coated and Depakine Chrono, $p < 0.05$

Fig. 3 Antiepileptic Therapy comparing seizures controlled among Depakine Enteric Coated to Depakine Chrono

Table 7. Clinical Global Impression

EFFICACY INDEX		SIDE EFFECTS			
		None	Do not significantly interfere with patient's function	Significantly interferes with patient's functioning	Outweighs therapeutic effect
THERAPEUTIC EFFECT ASSESSMENT BASED ON PATIENTS GLOBAL	MARKED - vast improvement	45 (50.6%)	3 (3.4%)	2 (2.2%)	0
	MODERATE - partial improvement	18 (20.2%)	0	0	0
	UNCHANGED - neither improvement nor deterioration	17 (19.1%)	1 (1.1%)	0	0
	WORSENED - deterioration	2 (2.2%)	1 (1.1%)	0	0
	NOT ASSESSED =0				

There was a significant increase in compliance when comparing sodium valproate enteric-coated to slow-release form ($p = 0.000$) the same as previously reported [11,14,17]. Most patients preferred the once daily regime and were happy to take once daily more than the other regime ($p = 0.000$). Clinical Global Impression showed 50.6% of patients had marked improvement without side effects according to the investigator's opinion.

Conclusion

SVSR form has not only good compliance and satisfaction but also well controlled seizure and fewer

side effects. Switching from sodium valproate enteric-coated to slow-release form resulted in increased seizure-free; reduction of side effects, improvement in the level of compliance and patient satisfaction.

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ผลการใช้ยากันชักโซเดียมวาลโปรเอทชนิดออกฤทธิ์ช้าเทียบกับชนิดออกฤทธิ์ในลำไส้ในผู้ป่วยโรคลมชักไทย

สมชาย โตวณะบุตร, สมศักดิ์ เทียมเก่า, สุวรรณา ธรรมสุภาพงศ์, ราม กิจจารักษ์, อาคม อารยาวิชานนท์, นิพนธ์ พวงวรินทร์, ศศิธร ศิริมหาราช, รังสรรค์ ชัยเสวิกุล, ธนินทร์ อัศววิเชียรจินดา, สักรินทร์ มณีสุข, อรวรรณ ศิลปกิจ

***ที่มา**: ยาโซเดียมวาลโปรเอทเป็นยาต้านการชักที่รู้จักกันแพร่หลาย มากว่า 30 ปี และนำใช้ในประเทศไทยเป็นเวลานานกว่า 20 ปี และในปี พ.ศ. 2533 เริ่มมีการนำยาโซเดียม วาลโปรเอทชนิดออกฤทธิ์ช้ามาใช้*

***วัตถุประสงค์**: เพื่อประเมินความสม่ำเสมอของการบริหารยาว่าครบตามแพทย์สั่งหรือไม่และประเมินความพึงพอใจของผู้ใช้ยาด้วย*

***วัสดุและวิธีการ**: เป็นการศึกษาไปข้างหน้าจากหลายสถาบัน คณะผู้วิจัยทำการเปรียบเทียบความสม่ำเสมอในการรับประทานยาและความพึงพอใจของผู้ป่วยโรคลมชักที่เปลี่ยนการรับประทานยาโซเดียม วาลโปรเอทชนิดเม็ดเคลือบจากวันละ 2-3 ครั้งต่อวันมาเป็นยาโซเดียม วาลโปรเอทชนิดออกฤทธิ์ช้าวันละ 1-2 ครั้งต่อวัน*

***ผลการศึกษา**: ผู้ป่วย 89 รายจากผู้เข้าร่วมการศึกษาทั้งสิ้น 100 รายสามารถติดตามการรักษาจนสิ้นสุดการศึกษา เพศชายร้อยละ 43.8 อายุเฉลี่ย 34.74 $\pm$ 12.67 ปี สาเหตุของโรคลมชักที่พบบ่อยที่สุดคือ ไม่ทราบสาเหตุร้อยละ 40.4 ผู้ป่วยมีความสุขปานกลาง/มากจากการใช้ยาโซเดียม วาลโปรเอทชนิดออกฤทธิ์ช้าร้อยละ 94.4 เทียบกับยาชนิดออกฤทธิ์ในลำไส้ ร้อยละ 56.2 ($p = 0.000$) ผู้ป่วยไม่เกิดปัญหาจากการใช้ยาร้อยละ 67.4 เทียบกับยาชนิดออกฤทธิ์ในลำไส้ร้อยละ 38.2 ($p = 0.000$) และไม่เคยลืมรับประทานยาโซเดียม วาลโปรเอทชนิดออกฤทธิ์ช้าร้อยละ 77.5 เทียบกับยาชนิดออกฤทธิ์ในลำไส้ร้อยละ 40.4 ($p = 0.000$) เนื่องจากมีความสะดวก ผู้ป่วยนิยมใช้ยาโซเดียม วาลโปรเอท ชนิดออกฤทธิ์ช้ารับประทานวันละครั้งร้อยละ 92.1 และไม่เคยรับประทานยาเกินขนาดร้อยละ 96.6 ยาโซเดียม วาลโปรเอท ชนิดออกฤทธิ์ช้ามีผลข้างเคียงน้อยกว่ายาชนิดออกฤทธิ์ในลำไส้ เช่น ปัญหาเรื่องความจำ (ร้อยละ 40.4 ต่อร้อยละ 48.3) ($p = 0.000$), การนอนหลับ (ร้อยละ 30.3 ต่อร้อยละ 42.7) ($p = 0.041$) และความคิดไม่ปลอดโปร่ง (ร้อยละ 38.2 ต่อร้อยละ 44.9) ($p = 0.001$) ผู้ป่วยหยุดชักมากกว่าในกลุ่มที่รับประทานยาออกฤทธิ์ช้าร้อยละ 76.4 เปรียบเทียบกับกลุ่มยาออกฤทธิ์ในลำไส้ร้อยละ 65.2 ($p = 0.011$)*

***สรุป**: ผู้ป่วยนิยมรับประทานยาวันละครั้งมากที่สุด การปรับเปลี่ยนยาโซเดียม วาลโปรเอทชนิดออกฤทธิ์ในลำไส้เป็นชนิดออกฤทธิ์ช้า เพราะช่วยเพิ่มระยะเวลาหยุดชัก ลดผลข้างเคียง เพิ่มความสม่ำเสมอในการรับประทานยาและเพิ่มความพึงพอใจให้แก่ผู้ป่วย*