Salivary Antiepileptic Drug Levels in Thai Children

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Abstract

A total of 123 patients were enrolled in this study. 88 patients were enrolled in the first stage of the study, which was to evaluate the commercial salivary collecting devices: Orasure® and Omnisol®. 35 patients were enrolled in the second stage of the study and were asked to spit whole saliva samples for further analysis of AED levels. Serum AED levels and corresponding saliva AED levels were paired and analyzed for the correlation coefficients with the linear regression model. None of the commercial salivary collecting devices can provide the linear regression correlation between the serum AED level and saliva AED level in all three AEDs studied. The correlation coefficients of serum and whole saliva AED levels of phenobarbital, phenytoin, and carbamazepine were highly correlated (r-squared were 0.981, 0.976, and 0.888, respectively).

Saliva samples can be used clinically to monitor the AEDs level in phenobarbital, phenytoin and carbamazepine. This would be another alternative method of therapeutic drug monitoring that can be done painlessly and is easier in children than the blood sampling method.

Key word : Antiepileptic Drug - Salivary Level - Thai Children

Antiepileptic drug (AED) therapy is the major form of therapy in the vast majority of children with seizure disorder. One important part of the standard medical treatment of epilepsy is to optimize the serum antiepileptic drug level in the therapeutic range. It has been estimated that appropriate monitoring of serum antiepileptic drug levels can improve treatment of epilepsy with an almost 20 per cent reduction in seizures(1). However, regular blood sampling for monitoring of the serum antiepileptic drug level is quite traumatic, especially in children with whom it may be more technically difficult. This also may jeopardize the patient-doctor relationship and poor compliance. Besides, regular monitoring is often hampered by the long distances which some patients may have to travel. Moreover, seizures and acute alterations in the child's condition often occur at home where blood sampling is not feasible.

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Numerous investigators have suggested that saliva, which may be collected with minimal patient discomfort, can serve as a viable body fluid for therapeutic drug monitoring[2,3]. However, this method has never been implemented in Thailand. The purpose of this study was to determine, whether or not, salivary concentrations of carbamazepine, phenobarbital and phenytoin can be substituted for serum concentrations and can be used immediately in the clinic environment to assess patient dosage requirements when analyzed using the fluorescence polarization immunoassay (FPIA) (TDX, Abbot Laboratories, North Chicago, IL, U.S.A.)

Objectives

1. To define the statistical correlation of serum and salivary concentrations of antiepileptic drugs; carbamazepine, phenobarbital, phenytoin in order to use the saliva antiepileptic drug concentrations in clinical antiepileptic drug monitoring in Thai children.

2. To evaluate the suitable salivary collecting system for antiepileptic drug monitoring.

3. To develop and evaluate a laboratory-supported, service model using the TDX in pediatric epilepsy clinics at Siriraj Hospital.

MATERIAL AND METHOD

Patients with epilepsy scheduled for routine appointments in the Child neurology clinic at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital who were taking antiepileptic drugs, were asked to participate in this study. Written informed consent was obtained from the parents of the children who participated. This study was approved by the Faculty Committee on the Protection of the Human Rights.

Sample collections

Blood samples were collected by venipuncture under aseptic technique. Three to five milliliters of blood were collected for analysis of the antiepileptic drug levels. The saliva samples were collected simultaneously with the blood samples. In order to evaluate the salivary collecting system that was suitable for use in collecting the saliva samples for antiepileptic drug monitoring, the study was done in two stages.

The first stage was to evaluate two different salivary collecting devices, Orasure® (Epitope, Inc., Beaverton, Oregon, U.S.A.) and Omnisol® (Salivary Diagnostic System, Inc., Singapore). Both Orasure® and Omnisol® salivary collecting devices using a the paper pad (approximately 2.5 cm by 1.5 cm by 2.0 mm; liquid holding capacity, approximately 1 ml) to collect the patient's saliva by putting the paper pad into the patient's oral cavity. Both collecting devices had different time intervals that the paper pad needed to be in the patient's mouth. For the Orasure®, the paper pad needed to be placed there for at least 2 minutes, and for the Omnisol® the paper pad needed to be in place until its indicator turned blue. Immediately after collection, the pad was placed in a tube with buffer solutions that were provided by the manufacturers. The buffer solutions that contained the paper pad soaked with saliva and the blood samples were then sent for analysis of the antiepileptic drug levels by using the fluorescence polarization immunoassay (FPIA) method.

For the second stage of study, patients were asked to spit whole saliva into a small plastic cup. Saliva was collected by direct aspiration from under the tongue of infants and others who were unable to cooperate. Saliva collection was delayed for at least 30 minutes for patients who had recently ingested food. Because of the risk of residual drug contamination[4], saliva collection was delayed for at least 2 hours following the last doses if the patient was taking a liquid or chewable AED. Saliva and blood samples were analyzed by fluorescence polarization immunoassay (FPIA) method.

Data analysis :

Paired serum and salivary samples were tabulated and analyzed for their correlation by using the statistical program SPSS® for Windows version 7.5. Serum and saliva AED concentrations were compared by calculating the Pearson's correlation coefficient(r), r-squared, slope (ß), y-intercept (B-constant), and standard error of estimate.

Table 1. First stage of the study: Patient characteristics.

Antiepileptic drug (AED)	n	Mean age	Sex (male/female)
Phenobarbital	42	5y6mo	25:17
Phenytoin	31	8y7mo	17:14
Carbamazepine	15	6y3mo	8:7

Table 2. First stage of the study: Serum phenobarbital level compared with phenobarbital level by Orasure® and Omnisol® salivary collecting devices.

Case No.	SERUM (mcg/dl)	ORASURE® (mcg/dl)	OMNISAL® (mcg/dl)
1.	25.54	1.75	2.12
2.	21.87	4.76	13.51
3.	15.97	0.86	0.34
4.	20.55	3.73	2.09
5.	9.51	0.93	1.11
6.	15.72	1.20	1.80
7.	14.11	1.34	2.01
8.	24.78	2.39	2.72
9.	23.71	0.83	2.10
10.	23.34	4.41	*
11.	24.65	2.10	1.71
12.	26.24	2.03	3.03
13.	15.59	1.75	*
14.	6.28	1.74	1.38
15.	16.11	2.47	*
16.	46.80	6.35	*
17.	24.69	3.60	*
18.	24.70	2.68	*
19.	17.18	0.92	*
20.	8.69	0.43	*
21.	15.00	3.37	*
22.	9.26	1.70	*
23.	5.53	1.35	*
24.	9.00	1.06	*
25.	1.60	0.81	*
26.	13.90	1.42	*
27.	15.39	2.23	*
28.	11.76	2.09	*
29.	30.40	3.32	*
30.	28.86	7.34	5.47
31.	13.49	2.13	2.09
32.	2.86	1.38	1.25
33.	11.57	1.21	1.18
34.	19.47	3.57	3.12
35.	22.07	3.43	3.87
36.	23.60	1.10	3.73
37.	19.35	2.33	1.97
38.	34.53	5.23	4.35
39.	15.98	1.86.	0.72
40.	7.14	0.46	0.04
41.	18.40	3.07	2.90
42.	20.67	7.19	5.61
43.	26.86	0.25	1.79
44.	56.57	8.34	9.76
45.	15.09	1.60	1.19
46.	14.84	2.80	1.88
47.	32.52	4.03	3.12
48	16.93	1.63	1.33
49.	33.57	3.26	2.05

* During these period of the first stage of the study, the Omnisol® collectors were out of supply.

Table 3. First stage of the study: Serum phenytoin level compared with phenytoin level by Orasure® and Omnisol® salivary collecting devices.

Case No.	SERUM (mcg/dl)	ORASURE® (mcg/dl)	OMNISAL® (mcg/dl)
1.	.25	.26	.22
2.	10.33	.42	.41
3.	23.73	.32	.68
4.	6.73	.24	.18
5.	4.97	.23	.27
6.	24.62	1.54	1.18
7.	13.69	.35	.34
8.	9.08	.32	.33
9.	12.67	.53	.52
10.	13.34	.57	.55
11.	26.52	.76	.75
12.	20.39	.64	.62
13.	11.01	.70	.48
14.	11.51	.59	.56
15.	3.86	.24	.29
16.	17.27	1.3	.80
17.	6.85	.28	.20
18.	8.05	.08	.05
19.	19.47	.30	.30
20.	31.61	1.46	.94
21.	13.59	.31	.18
22.	4.31	.11	.04
23.	2.19	.36	.21
24.	33.50	1.69	.92
25.	28.53	2.29	1.97
26.	1.57	.33	.38
27.	3.55	.42	.36
28.	18.96	.46	.29
29.	15.74	.98	.70
30.	10.08	.27	.29
31	29.67	1.62	1.48

RESULTS

Stage I: Evaluation of salivary collecting devices

In the first stage of this study (between January 1995 and January 1996), the blood and saliva samples were collected from 88 patients. Table 1 summarizes the characteristics of the patients in each AED group. Table 2 summarizes the results of serum phenobarbital compared to phenobarbital level measured by using the Orasure® and Omnisol® salivary collecting devices. Table 3 summarizes the results of serum phenytoin compared to phenytoin level measured by using the Orasure® and Omnisol® salivary collecting devices. Table 4 summarizes the results of serum carbamazepine compared to carbamazepine level measured by using the Orasure® and Omnisol® salivary collecting devices.

Table 4. First stage of the study: Serum carbamazepine level compared with carbamazepine level by Orasure® and Omnisol® salivary collecting devices.

Case No.	SERUM (mcg/dl)	ORASURE® (mcg/dl)	OMNISAL® (mcg/dl)
1.	6.66	0.50	0.43
2.	5.70	0.97	7.67
3.	1.47	3.58	6.48
4.	7.64	.57	.53
5.	9.92	1.17	1.07
6.	2.87	0.10	0.14
7.	4.96	0.05	0.01
8.	4.84	0.18	0.16
9.	4.80	0.27	0.15
10.	5.25	0.39	0.18
11.	5.72	0.28	0.17
12.	5.36	0.09	0.26
13.	5.12	0.35	0.22
14.	4.96	0.19	2.36
15.	8.60	0.70	0.44

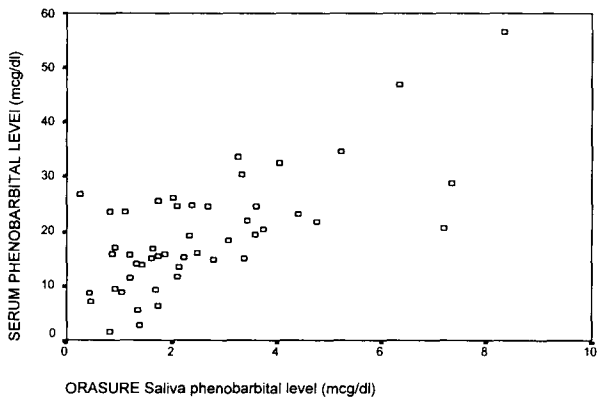

Fig. 1. Scattergram between serum phenobarbital and saliva phenobarbital levels using Orasure salivary collecting device.

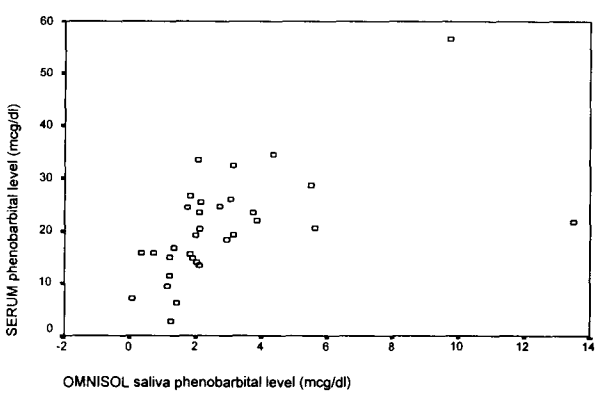

Fig. 2. Scattergram beween serum phenobarbital and saliva phenobarbital levels using Omnisol salivary collecting device.

Data analysis :

Phenobarbital :

The correlation coefficients(r) of the relationship between the serum phenobarbital level and saliva level using the Orasure® and Omnisol® salivary collecting devices were low. By using linear regression analysis, the coefficient using the Orasure® was 0.703 (r-squared 0.494). The scattergram between serum phenobarbital and saliva phenobarbital using Orasure® was as shown in Fig. 1.

With the Omnisol® it was 0.553 (r-squared 0.306) and the scattergram was as shown as in Fig. 2.

Phenytoin :

The correlation coefficients(r) of the relationship between the serum phenytoin level and saliva level using the Orasure® and Omnisol® salivary collecting devices were also low. By using linear regression analysis, with Orasure® it was 0.780 (r-squared 0.609) and the scattergram between serum phenytoin and saliva phenytoin using Orasure® was as shown in Fig. 3.

In the case of Omnisol® the correlation coefficients was 0.770 (r-squared 0.593) and the scattergram was as shown in Fig. 4.

Carbamazepine

The correlation coefficients(r) of the relationship between the serum and saliva levels using the Orasure® and Omnisol® salivary collecting

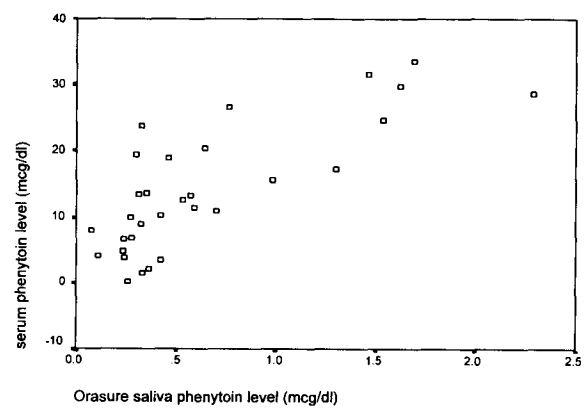

Fig. 3. Scattergram between serum phenytoin and saliva phenytoin levels using Orasure salivary collecting device.

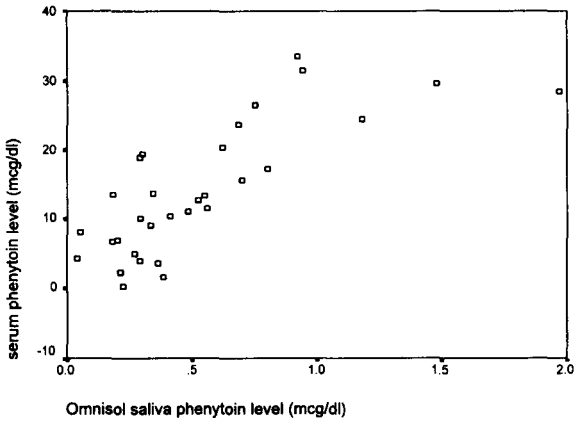

Fig. 4. Scattergram between serum phenytoin and saliva phenytoin levels using the Omnisol salivary collecting device.

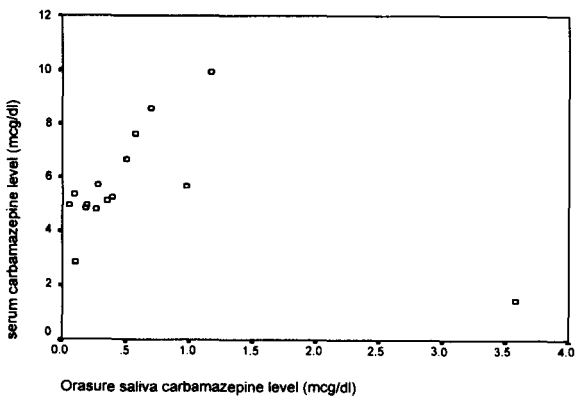

Fig. 5. Scattergram between serum carbamazepine and saliva carbamazepine levels using the Orasure salivary collecting device.

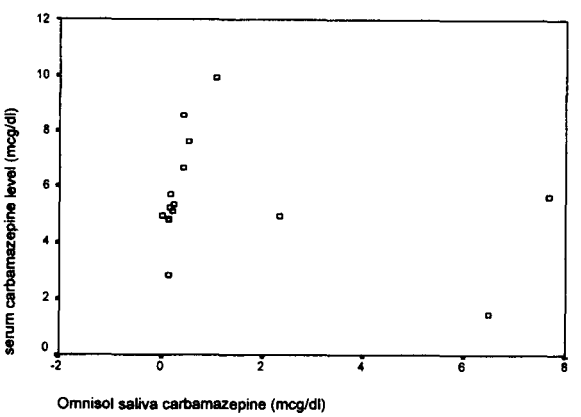

Fig. 6. Scattergram between serum carbamazepine and saliva carbamazepine levels using the Omnisol salivary collecting device.

devices were also very low, being 0.268 (r-squared 0.072) and 0.297 (r-squared 0.088) respectively. Their scattergrams were as shown in Fig. 5 and 6.

Stage II: Serum AED level and whole saliva AED correlation

In the second stage of the study (between January 1996 and January 1997), the blood and saliva samples were collected from 35 patients. Table 5 summarizes the characteristics of the patients in each AED group. Table 6 summarizes the results of serum phenobarbital levels compared to whole saliva phenobarbital levels. Table 7 summarizes the results of serum phenytoin levels compared to whole saliva phenytoin levels and Table 8 summarizes the results of serum carbamazepine levels compared to whole saliva carbamazepine levels.

Data analysis:
Phenobarbital

The correlation coefficient(r) of the relationship between the serum phenobarbital level and whole saliva phenobarbital level was highly corre-

Table 5. Second stage of the study: Patient characteristics.

Antiepileptic drug (AED)	n	Mean age	Sex (male/female)
Phenobarbital	13	9y9mo	8:5
Phenytoin	10	10y5mo	7:6
Carbamazepine	12	10y2mo	5:7

Table 6. Second stage study: Serum phenobarbital levels compared with whole saliva phenobarbital levels.

Case no.	age(year)	Serum phenobarbital (mcg/dl)	Whole saliva phenobarbital (mcg/dl)
1	11	33.49	9.50
2	4	17.05	6.51
3	11	13.51	4.04
4	7	1.08	0.37
5	11	30.4	10.87
6	8	11.04	4.07
7	8	23.53	7.80
8	8	33.76	11.09
9	10	19.2	7.12
10	14	2.97	1.40
11	4	5.48	1.19
12	12	6.04	0.92
13	10	20.15	8.65

Table 7. Second stage of study: Serum phenytoin levels compared with whole saliva phenytoin levels.

Case no.	age(year)	serum phenytoin (mcg/dl)	Whole saliva phenytoin (mcg/dl)
1	7	1.74	0.63
2	10	3.96	0.35
3	12	20.67	2.34
4	13	7.23	0.35
5	14	2.99	0.21
6	15	8.51	0.75
7	10	9.39	0.68
8	7	4.27	0.38
9	11	29.55	2.84
10	9	5.89	3.74

Table 8. Second stage of study: Serum carbamazepine levels compared with whole saliva carbamazepine levels.

Case No.	age(year)	serum carbamazepine (mcg/dl)	Whole saliva carbamazepine (mcg/dl)
1	11	3.73	0.28
2	10	5.85	1.69
3	12	6.36	1.38
4	8	6.3	1.25
5	7	6.88	1.83
6	8	6.16	1.19
7	9	6.05	1.44
8	17	12.13	3.85
10	10	10.21	2.26
11	8	3.32	0.65
12	11	8.55	2.54

Table 9. Analysis of linear regression for serum AED level and whole saliva AED level.

AED	Coefficients	B-constant (y-intercept)	Slope (y/x)	Standard error of estimate
Phenobarbital	0.981[a]	Through the origin	2.921	2.7378
Phenytoin	0.976[a]	Through the origin	10.011	1.9469
Carbamazepine	0.888	2.644 ± 0.538	2.530	0.8652

a. Analysis with the linear regression through the origin (the no-intercept model) because when calculated with B-constant the p-value were not statistically significant.

lated. By using linear regression through the origin, it was 0.991 (r-squared 0.983, adjusted r-squared 0.981) and the standard error of estimate was 2.7378. The slope (y/x) between the serum phenobarbital level (y) and the whole saliva phenobarbital level (x) was 2.921 ± 0.112 (p 0.000, see Table 9).

The scattergram between serum phenobarbital and whole saliva phenobarbital levels was as shown in Fig. 7.

Phenytoin

The correlation coefficient(r) of the relationship between the serum phenytoin level and whole saliva phenytoin level was also highly correlated. By using linear regression through the origin, it was 0.989 (r-squared 0.979, and adjusted r-squared 0.976) and the standard error of estimate was 1.9469. The slope (y/x) between the serum phenytoin level (y) and the whole saliva phenytoin level (x) was 10.011 ± 0.493 (p 0.000, see Table 9).

The scattergram between the serum phenytoin and whole saliva phenytoin levels was as shown in Fig. 8.

Carbamazepine

The correlation coefficient(r) of the relationship between the serum carbamazepine level and whole saliva carbamazepine level was also highly correlated, being 0.948 (r-squared 0.889, adjusted r-squared 0.888) and the standard error of estimate was 0.8652. From this analysis, the y-intercept (constant) was at 2.644 ± 0.538 (p-value 0.001). The

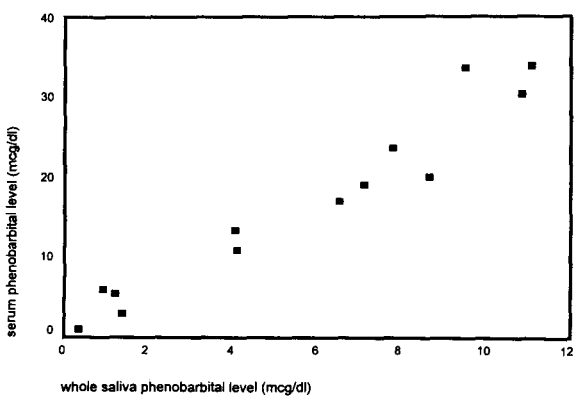

Fig. 7. Scattergram between serum phennobarbital and whole saliva phenobarbital levels.

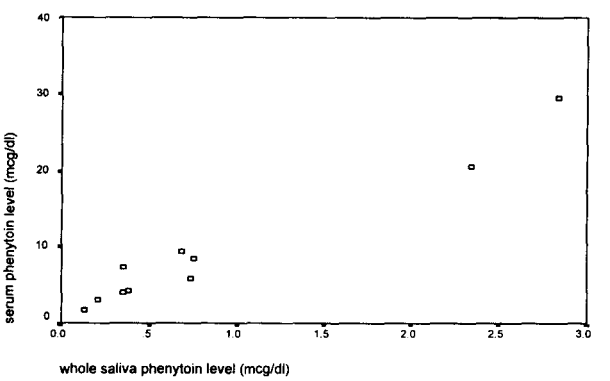

Fig. 8. Scattergram between serum phenytoin and whole saliva phenytoin levels.

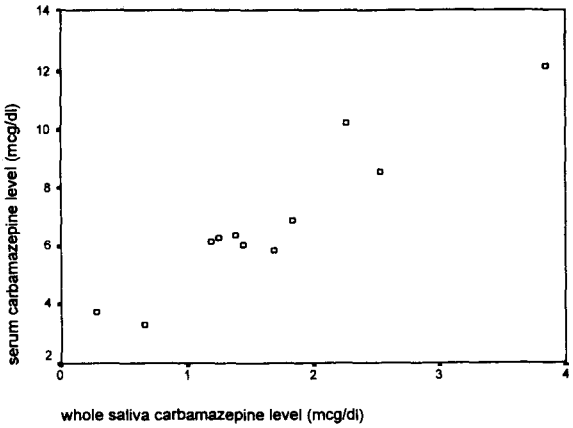

Fig. 9. Scattergram between serum carbamazepine and whole saliva carbamazepine levels.

slope (y/x) between the serum carbamazepine level (y) and the whole saliva carbamazepine level (x) was 2.530 $\pm$ 0.282 (p 0.000, see Table 9).

The scattergram between the serum carbamazepine and whole saliva carbamazepine levels was as shown in Fig. 9.

DISCUSSION

Many investigators have demonstrated that saliva is a suitable body fluid for therapeutic monitoring of certain antiepileptic drugs (AEDs), including phenobarbital, phenytoin, and carbamazepine[5-8]. All previous studies have demonstrated that the relationships between saliva AED level and serum AED level followed the linear regression model with a very high coefficient correlation value (above 0.9). From the linear regression model[9], when serum AED level is the dependent variable (y) and saliva level is independent variable (x), the formula to predict serum AED would be

Y (predicted serum AED level) = B-constant + slope (y/x) x (measured saliva AED level)

However, each method of analysis gives the difference in its formula to predict the serum AED level from the saliva level, especially in terms of the value of the slope (y/x) and the y-intercept (B-constant). Each laboratory may have a different standard in terms of measuring the AED level in saliva specimens as well as a different technique in their calibration of the result of the AED level. In order to use saliva specimens as a practical method to monitor the AED level in children at Siriraj Hospital, the present study was carried out.

The first stage of the study was designed to evaluate the feasibility to develop the technique and standardized method of how to implement the antiepileptic drug monitoring by using commercial salivary collecting devices for saliva instead of blood samples. Stage I of the study was to evaluate the salivary collecting devices; the correlation coefficients between the saliva AED levels from the salivary collecting devices and the formula to predict the serum AED level from the saliva AED levels. Only two commercial salivary collecting devices, Orasure® and Omnisol® are available in Thailand. From our analysis, it was found that the correlation between the serum levels of all three AEDs: phenobarbital, phenytoin, carbamazepine and the corresponding saliva AED levels were not consistent with the linear regression model. The correlation coefficients of serum AED level and corresponding saliva AED level using either commercial salivary collecting devices in all three medications were below the acceptable level to commit that the correlation between serum AED level and saliva AED were linear. Saliva AED levels from both salivary collecting devices cannot predict the serum AED level by using the linear regression model. This could be due to the buffer solutions that were mixed with the saliva specimens. The dilution effects of the buffer solutions make the FPIA method not sensitive to detect the AED level in the buffer solutions. Most of the previous studies that used the salivary collecting devices used the more sensitive methodology to analyze the saliva AED level other than the FPIA method, such as high-performance liquid chromatography with photodiode-array detection (HPLC) which is very expensive and not available in our hospital. The other pitfall in the first stage of the study was the technicality of collection of the saliva samples. Because both commercial salivary collecting devices used in this study required a certain amount of time for the patient to hold the stick of the collector in the oral cavity before the saliva could be collected, we found that most of the small children could not follow the instruction. They could hold the collector stick in their oral cavity as the manufactures recommended. Some of these collector sticks had even been severely bitten and need to be changed many times before the saliva sample collection could be accomplished.

After the result of the data analysis in stage I of the study, it prompted us to reevaluate the methodology and the reliability of the salivary collecting devices used in this study. So we did stage II of the study. In this second phase of the study, we carefully looked at the feasibility to use the whole saliva AED levels instead of commercial salivary collecting devices. The results of this study were satisfactory and were compatible with most previous studies. All three saliva AED levels: phenobarbital, phenytoin, carbamazepine, were correlated with corresponding serum AED levels in the linear fashion with the correlation coefficients in the acceptable range for the linear regression model (see Table 9). All except carbamazepine the linear regression through the origin model could be used to plot the graph to predict the serum AED level from the measured saliva AED level.

For phenobarbital, the predicted serum level was 2.921 times the phenobarbital level measured in the saliva sample. For phenytoin, the predicted serum level was 10.011 times the phenytoin level measured in the saliva sample, and for carbamazepine, the predicted serum level was equal to 2.644 (B-constant of *y*-intercept) + 2.530 times the carbamazepine level measured in the saliva sample.

Finally, we concluded that the saliva fluid can be used as a simple and convenient access to monitoring antiepileptic drug levels. Each laboratory that wants to implement the use of saliva AED level should collect the pair serum and saliva specimens. The standardized values such as the B-constant (*y*-intercept) and the slope (*y/x*) of the linear regression model of serum versus saliva AED levels from each laboratory as well as previous studies may be different.

SUMMARY

This is the first study in Thailand to evaluate and implement the use of saliva specimens as an alternative method of antiepileptic drug monitoring. Saliva specimens can be simply collected directly from the patient's oral cavity without using a commercial salivary collecting device. The salivary AED levels of phenobarbital, phenytoin and carbamazepine can be used to predict the serum levels of corresponding AED with good correlation and is less painful for the patients.

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การศึกษาระดับยากันชักในน้ำลายในเด็กไทย

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ได้ทำการศึกษาวัดระดับยากันชักในน้ำลายเปรียบเทียบกับระดับยากันชักในเลือดของยากันชัก 3 ชนิด คือ phenobarbital, phenytoin, และ carbamazepine ในผู้ป่วย จำนวนทั้งสิ้น 123 ราย โดยแบ่งเป็น 2 กลุ่มศึกษา คือ กลุ่มแรก มีจำนวน 88 ราย ใช้อุปกรณ์เก็บตัวอย่างน้ำลาย Orasure® และ Ominsol® เป็นตัวเก็บน้ำลายเพื่อส่งห้องปฏิบัติการตรวจวัดระดับยากันชักในน้ำลาย ส่วนกลุ่มที่ 2 มีจำนวน 35 ราย ทำการเก็บตัวอย่างน้ำลายจากกระพุ้งแก้มผู้ป่วยโดยตรง

จากการศึกษาพบว่าระดับยากันชักในน้ำลายที่วัดจากตัวอย่างน้ำลายซึ่งเก็บจากกระพุ้งแก้มผู้ป่วยโดยตรง เปรียบเทียบกับระดับยากันชักในเลือดของยากันชักที่ทำการศึกษาทั้ง 3 ชนิด ในกลุ่มศึกษาที่ 2 มีความสัมพันธ์กันทางสถิติความถดถอยเชิงเส้นตรง (linear regression correlation) อย่างมีนัยสำคัญ โดยมีค่าสหสัมพันธ์ (R-squared) สำหรับยา phenobarbital เท่ากับ 0.981 สำหรับยา phenytoin เท่ากับ 0.976 และสำหรับยา carbarmazepine เท่ากับ 0.888 ส่วนผลการวิเคราะห์ทางสถิติในกลุ่มศึกษาแรก ไม่พบว่าระดับยากันชักในน้ำลายโดยใช้อุปกรณ์การเก็บน้ำลายทั้ง 2 ชนิด (Orasure® และ Omnisol®) มีความสัมพันธ์กับระดับยากันชักที่วัดได้ในเลือดของยากันชักที่ทำการศึกษาทั้ง 3 ชนิดในเชิงเส้นตรง

สรุประดับยากันชักที่วัดจากน้ำลายของผู้ป่วยเป็นอีกทางเลือกหนึ่งที่สามารถนำมาใช้ในการปรับขนาดยากันชักในผู้ป่วยเด็กที่เป็นโรคลมชักให้อยู่ในระดับยาที่ต้องการ โดยที่ไม่ต้องเจาะเลือดผู้ป่วย ซึ่งนอกจากจะไม่ทรมานต่อผู้ป่วยแล้ว ยังสะดวกกว่าการเจาะเลือดในเด็ก

คำสำคัญ : ยากันชัก – ระดับในน้ำลาย – เด็กไทย

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