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Original Article

THE ESTIMATION OF PHARMACOKINETIC PARAMETERS AND ACCURACY OF THE PREDICTED EQUATION FOR LITHIUM DOSE IN CHILDREN: A PILOT STUDY AT THE YUWAPRASART WAITHAYOPATHUM CHILD PSYCHIATRIC HOSPITAL

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ABSTRACT

Objective: The purpose of the study was to estimate the pharmacokinetic parameters and calculate the precision (%RMSE) of the predicted lithium concentration equation.

Methods: This research was studied from blood Lithium levels of Children who had visited Yuwaprasart Waithayopathum Child Psychiatric Hospital from 31 December 2009-1 January 2011 The accuracy and precision of the equation were evaluated by the mathematical principle. The assist package software (WIN-NONLIN) was used to create pharmacokinetic parameters.

Results: Twenty-nine patients were recruited. The characteristics (mean+SD) presented as the following; age = 15.79+2.64 y, weight = 69.75+22.28 kg and the daily dose = 858.62+274.53 mg. The trough Lithium concentrations (mean+SD) = 0.56+19 mg/l. The kinetic parameter (Mean+SD) presented as the following; $t_{1/2}$ =7.23+3.38 hr., ke =0.12+0.07 hr-1, Vd = 48.83+15.60 L, AUC0-12 =11.01+5.61 mg x hr/l. The population pharmacokinetic parameters; ke, and AUC (0-∞) = 0.151 hr-1 and 169.81, mg x hr./l respectively. The modified equation from Yukawa for lithium clearance calculation and prediction lithium concentrations were CL (mL/min) = [36.5+(0.242x BW (kg)-7.79]/Scr (mg/dL) and lithium concentration (mg/l) = 4 x Dose (mg)/CL (mL/min)x73.89, respectively with 6.39 %RMSE (test for 20 patients data).

Conclusion: In conclusion, the modified Yukawa equation may be used for the prediction of lithium concentration with 6.39% RMSE.

Keywords: Pharmacokinetics parameters, Lithium, Children, Accuracy

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INTRODUCTION

Lithium is the drug of choice in treating patients with mood disorders, especially in children [1-3]. However, the difficulty for drug use is adverse drug reactions [4-7] that needed to monitor serum drug concentrations [8-13]. Yuwaprasart Waithayopathum Child Psychiatric Hospital which one of the hospital that responsible for caring child psychiatric disorders patient, for example; autistic child also use lithium. While lithium prescribing is most common in this group, it has a problem of initiative lithium dosing design and monitoring. The application of the individual pharmacokinetic model for dosing adjustment by estimation pharmacokinetic parameters in individualized patients will be useful for lithium therapy monitoring.

Therefore, the aim of the study is to estimate the pharmacokinetic parameters and calculate the precision (% RMSE) of the predicted lithium concentration equation in child psychiatric patients.

MATERIALS AND METHODS

Population

The information of serum lithium concentration in children less than 18 y who used lithium treatment in Yuwaprasart Waithayopathum Child Psychiatric Hospital was collected since 1 January 2009 to 31 December 2011.

Inclusion criteria

The information of the following patients was used.

1. Patients who aged less than 18 y old.
2. Patients who used lithium continuously more than 1 w.
3. Patients who had information of renal and hepatic laboratory examination values.
4. Patients who had good compliance of drug therapy.

Exclusion criteria

Patients who had in-completed information such as laboratory values, drugs co-administration therapy.

Research design

The research design in this study was retrospective. The information was collected from children who received Lithium treatment from Yuwaprasart Waithayopathum Child Psychiatric Hospital during1 January 2009 to 31 December 2011. The accuracy and precision of the equation were evaluated was evaluated based on the mathematical principle, and WIN-NONLIN program (with authorized code PHXWNL092) was used for calculation of the pharmacokinetic parameters of the population. This research was approved by the ethical committee of the hospital. (Reg. no. 0 07).

Data analysis

The information was analyzed by Excel program version 2013. The data presented in percentage, mean and standard deviation. The percent of Root mean square errors (% RMSE) was used for evaluating the precision of the equation, and Student-paired t-test statistic was used for comparison of predicted and observed serum lithium concentrations with the level of significance equal to 0.05.

RESULTS

Patient characteristic

Twenty-nine patients information were collected as present in table 1. From the results, the mean age of participants was 16 y with the average

weight of 70 kg. The mean lithium dose was 900 mg/day. The serum lithium concentration (mean+SD) was 0.56+0.19 mg/l. All patients had normal serum creatinine (mean+SD) was 0.60+0.19 mg/dl.

The number of patients who had serum lithium within therapeutic range (0.6-1.2 mg/l) was 13 (44.82%). While there were 16 patients (55.18%) had serum lithium outside therapeutic range.

According to use the win-nonlin program to estimate population pharmacokinetics parameters and individual pharmacokinetics parameters via mathematical formulations, the individual patients' values were presented in table 2 with population value was shown below the table. In addition, lithium clearance and predicted serum lithium concentrations of patients were presented in table 3. With the modified Yugawa equation with adjusted by measurement unit for calculation of lithium clearance as seen below.

$$CL\ (\frac{ml}{min}) = [36.5 + \frac{(0.242xBW\ (kg) - 7.79]}{Scr(\frac{mg}{dL})}$$

Then, it can calculate serum lithium concentration by the following equation

$$Conc\ (\frac{mg}{L}) = 4\ x\ \frac{Dose(mg)}{CL\ (ml/min)}\ x\ 73.89$$

*73.89 is the molecular weight of lithium carbonate

The lithium clearance and predicted serum lithium concentration from 20 patients who had completed data calculated from the above equation illustrated in table 4. Then the determination precision of estimation steady-state serum lithium concentration by comparison of observed value is available in table 5. The graph between observed serum lithium concentration and predicted serum lithium concentration demonstrated in fig. 1.

The distribution of serum lithium concentration by lithium dose was presented in fig. 2 and 3, respectively.

The distribution of calculated pharmacokinetic parameters compared with mean were explained by the graph in fig. 4-8.

Table 1: Patients' characteristics

No	Age (y)	Weight (kg)	lithium dose (mg)	Serum lithium concentration (mg/l)	Serum creatinine (mg/dl)
1	15	74.0	900	0.49	NA
2	15	51.0	1200	0.76	0.5
3	14	68.0	900	0.7	0.7
4	18	44.0	600	0.59	0.4
5	17	118.0	1200	0.49	0.7
6	17	65.0	900	0.32	NA
7	16	70.0	900	0.54	0.5
8	24	92.4	900	0.55	0.5
9	15	51.0	1200	0.76	0.5
10	14	49.0	900	0.6	NA
11	15	56.0	900	0.8	0.5
12	14	71.0	1200	0.73	NA
13	14	54.0	300	0.5	NA
14	13	57.5	300	0.58	0.6
15	14	65.0	600	0.1	0.49
16	17	93.4	600	0.64	0.8
17	15	58.0	300	0.16	0.6
18	8	38.0	600	0.39	0.3
19	15	50.0	900	0.8	NA
20	18	78.0	1200	0.78	0.8
21	19	125.0	600	0.29	NA
22	16	65.0	900	0.65	0.5
23	19	62.0	900	0.63	0.2
24	15	62.5	900	0.42	NA
25	16	118.0	1200	0.49	0.7
26	15	75.0	900	0.77	NA
27	17	88.0	900	0.75	0.8
28	17	77.0	1200	0.47	1
29	16	47.0	900	0.49	0.4
Mean	15.7	69.8	859	0.56	0.6
SD	2.6	22.28	274	0.19	0.19

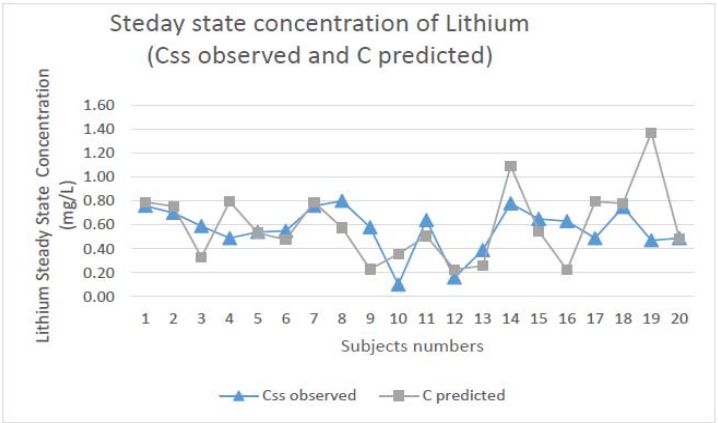

Fig. 1: Graph of observed steady-state serum lithium concentration (Css observed, mg/l) and predicted serum lithium from the modified Yukawa equation. (C predicted)

Table 2: **The estimation of pharmacokinetic parameters**

No.	t1/2 (h)	ke (h)	Vd (L)	AUC (0-12) (mg h/l)
1	NA	NA	51.80	NA
2	5.02	0.14	35.70	14.62
3	8.52	0.08	47.60	13.95
4	3.62	0.19	30.80	6.10
5	11.66	0.06	82.60	14.67
6	NA	NA	45.50	NA
7	6.20	0.11	49.00	9.86
8	7.31	0.09	64.68	8.81
9	5.02	0.14	35.70	14.62
10	NA	NA	34.30	NA
11	5.36	0.13	39.20	10.65
12	NA	NA	49.70	NA
13	NA	NA	37.80	NA
14	6.54	0.11	40.25	4.22
15	5.79	0.12	45.50	6.62
16	11.77	0.06	65.38	9.35
17	6.58	0.11	40.60	4.21
18	2.43	0.29	26.60	4.75
19	NA	NA	35.00	NA
20	10.60	0.07	54.60	20.17
21	NA	NA	87.50	NA
22	5.91	0.12	45.50	10.13
23	2.29	0.30	43.40	4.12
24	NA	NA	43.75	NA
25	11.66	0.06	82.60	14.67
26	NA	NA	52.50	NA
27	11.38	0.06	61.60	14.40
28	13.15	0.05	53.90	25.35
29	3.79	0.18	32.90	8.98
Mean	7.23	0.12	48.83	11.01
SD	3.38	0.07	15.60	5.61

NA= not available, the population pharmacokinetic parameters, the population pharmacokinetic parameters as shown below, ke (h-1) = 0.151429 AUC (0-∞) (mghr/l) = 169.8113

Table 3: Lithium clearance and predicted serum lithium concentration

No.	lithium clearance (ml/min)	Predicted lithium concentration (mg/l)
2	82.10	0.79
3	64.52	0.76
4	98.40	0.33
5	81.81	0.79
7	91.30	0.53
8	102.14	0.48
9	82.10	0.79
11	84.52	0.58
14	71.04	0.23
15	90.69	0.36
16	64.14	0.51
17	71.24	0.23
18	126.35	0.26
20	59.48	1.09
22	88.88	0.55
23	218.57	0.22
25	81.81	0.79
27	62.51	0.78
28	47.34	1.37
29	100.21	0.49
Mean	88.46	0.60
SD	35.51	0.30

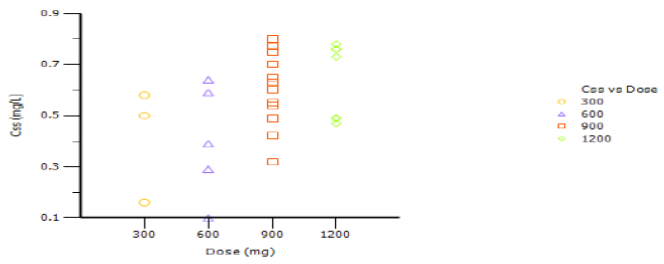

Fig. 2: **The distribution of serum lithium concentration (mg/l) versus dose**

Table 4: Observed serum lithium concentration and predicted serum lithium concentration

No.	Observed serum lithium concentration (ml/min)	Predicted lithium concentration (mg/l)	Difference
2	0.76	0.79	0.03
3	0.70	0.76	0.06
4	0.59	0.33	-0.26
5	0.49	0.79	0.30
7	0.54	0.53	-0.01
8	0.55	0.48	-0.07
9	0.76	0.79	0.03
11	0.80	0.58	-0.22
14	0.58	0.23	-0.35
15	0.10	0.36	0.26
16	0.64	0.51	-0.13
17	0.16	0.23	0.07
18	0.39	0.26	-0.13
20	0.78	1.09	0.31
22	0.65	0.55	-0.10
23	0.63	0.22	-0.41
25	0.49	0.79	0.30
27	0.75	0.78	0.03
28	0.47	1.37	0.90
29	0.49	0.49	0.00
%RMSE	0.0639 (6.39)		
t-test (p-value)	0.72		

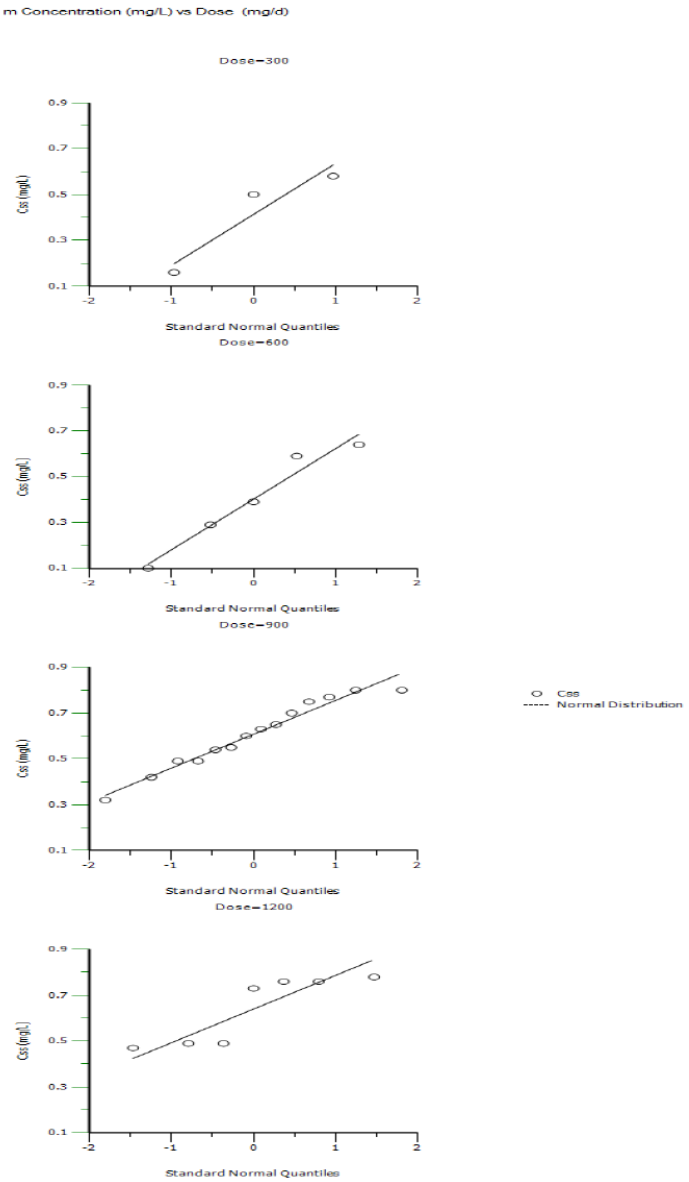

Fig. 3: The graph of serum lithium concentrations (mg/l) versus dose (mg)

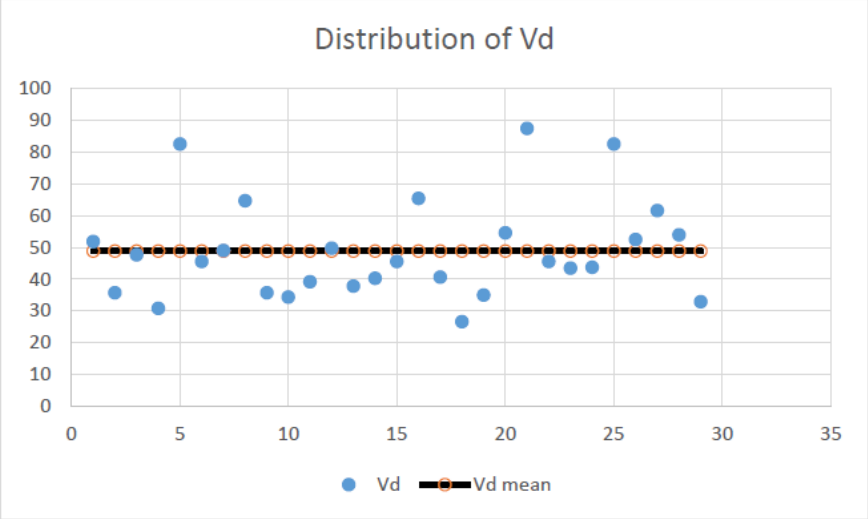

Fig. 4: The distribution of the volume distribution of lithium (L)

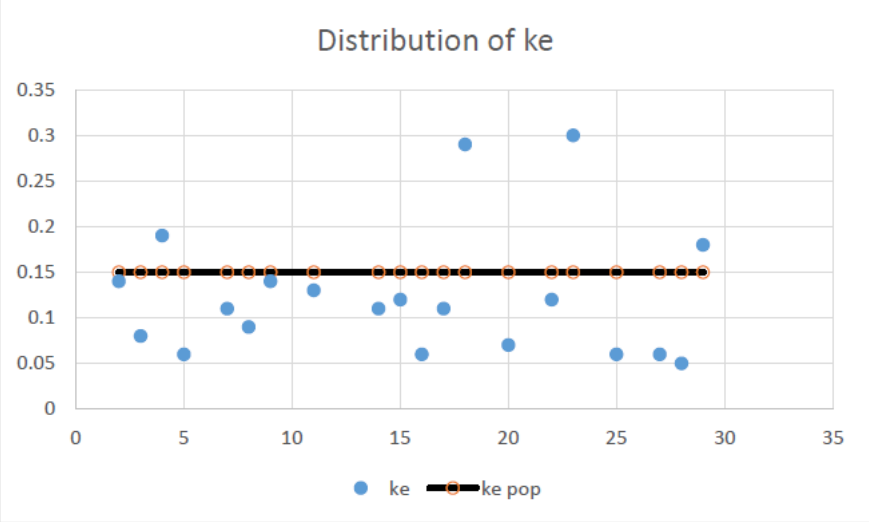

Fig. 5: The distribution of the elimination rate constant (ke) of lithium (h^{-1})

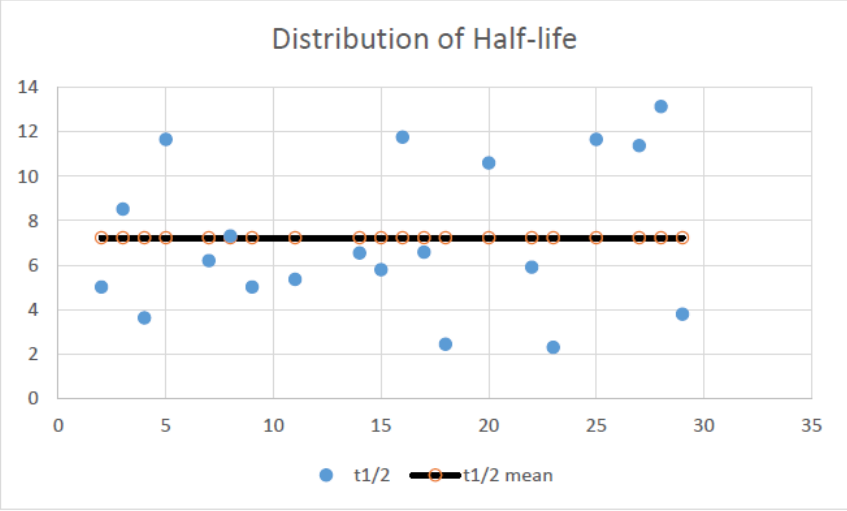

Fig. 6: The distribution half-life of lithium (h)

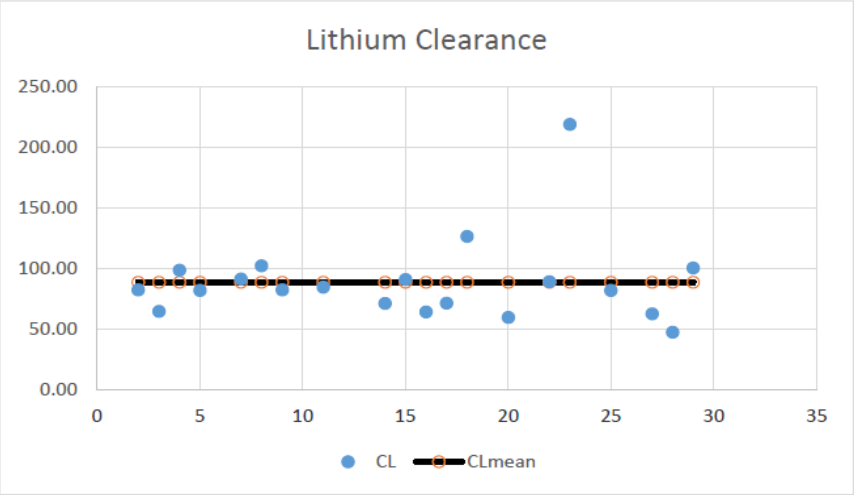

Fig. 7: The distribution of lithium clearance (ml/min)

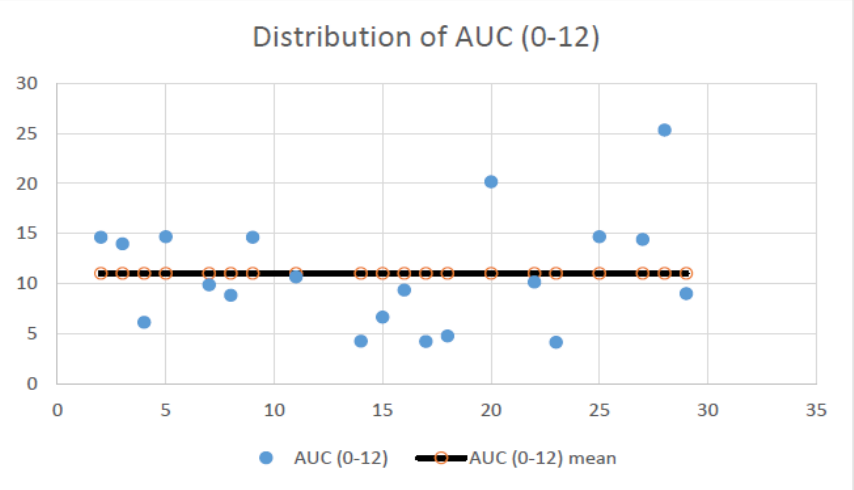

Fig. 8: The distribution of area under the concentration-time curve at 0-12 h (AUC) of lithium (mg h/l)

DISCUSSION

The results from this study demonstrated that the modified Yukawa equation can use to predict serum lithium concentration with 93.61% accuracy (error 6.39%). It is not statistically significant differences (p=0.72) between observed and predicted serum lithium concentration. However, the variations among this group also found. The reason is because the various factors of patients, especially weight. Comparison with the previous report of the population clearance value found that this study had more lithium clearance than the previous report (10-40 ml/min) [13]. Therefore, using lithium dose beyond population clearance may result in treatment failure. Motoki *et al.* [14] found that Yukawa equation produced 90.44% accuracy (error 9.56%) in prediction lithium clearance. However, when the modified Yukawa equation in Thai subject study was tested in Suwan P. study. The accuracy of this equation was 92.05% (error 7.95%). It is quite similar to this study which found 93.6% accuracy of modified Yukawa equation (error 6.39%). Therefore, the modified Yukawa equation in this study may appropriate for lithium dose calculation in children population.

Other mathematical models were reviewed [15-32]. The model that study in Thai population only established in Suwan P. study [26] and the results found that the modified Yukawa could be used for lithium clearance estimation in an Adult Thai population with good precision. Therefore, Yukawa equation was chosen to modify in this study for children population. Cornelia *et al.* [33] applied the pharmacokinetics and pharmacodynamics knowledge for find appropriate lithium dosage adjustment in children. However, the research design was retrospective data collection, and there was a limitation in the application of pharmacodynamics parameter to the present study because of incomplete data. Since the pharmacodynamics parameter of Cornelia *et al.* study was Yong Mania Rating Scale and the hospital setting in this study did not use for routine work. Another discussion point is in Cornelia *et al.* study, it was focus only in children with bipolar disorders which is a difference from this study. Therefore, the results from Cornelia *et al.* may not apply in the wider group of children with other psychological disorder as this study. The further study is needed.

According to there has been limited use of Lithium in psychiatric patients, especially in children in a healthcare setting. Therefore, leading this study had some limitation in term of "sample size". In addition, in-completed data through retrospective design were available. Moreover, it takes time and lots of expenditure if the prospective randomized design will be conducted.

CONCLUSION

The modified Yukawa equation with use to calculate Lithium clearance as the following CL (ml/min) = [36.5+(0.242x BW (kg)-7.79]/Scr (mg/dl).

This modified clearance equation can use to calculate serum lithium concentration as the following equation with % %RMSE = 6.39.

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AUTHORS CONTRIBUTIONS

Assistant Prof. Dr. Karunrat Tewthanom contributed to set the design activity, evaluation, interpretation and writing the manuscript for submission.

Dr. Rinsook Ongarjsakulman contributed to a screening of medical recorded, provide information on ordering serum lithium concentration monitoring.

Miss Theerarat Tankhum, RPh. contribute to coordinate with other healthcare professions to authorize using medical record, submit a proposal to the hospital ethical committee.

CONFLICTS OF INTERESTS

The author declares no conflict of interest

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