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APPENDIX I

Comparison between the predicted steady state theophylline serum concentrations calculated from the equation of the short infusion model and the predicted steady state theophylline serum concentrations calculated form the equation of the bolus model

Pt.no.	C1	C2
1	4.14	4.13
2	4.10	4.28
3	5.32	5.32
4	1.99	1.99
5	3.71	3.71
6	4.87	4.87
7 (1)	4.39	4.39
7 (2)	6.92	6.92
8	8.66	8.65
9	4.73	4.74
10 (1)	7.55	7.54
10 (2)	4.79	4.79
11	7.43	7.43
12	4.18	4.18
13	3.14	3.14
14	8.81	8.81
15	7.73	6.18
16	3.32	3.32
17	6.97	6.97
18	3.51	3.51

Pt.no.	C1	C2
19	10.26	10.27
20	8.40	8.40
21	2.57	2.57
22	10.54	10.53
23	5.38	5.37
24	13.25	13.32
25 (1)	4.25	4.25
25 (2)	3.04	3.04
26	3.66	3.66
27	1.81	1.81
28	5.71	5.71
29	5.04	5.04
30	6.27	6.27
31	2.84	2.84
32 (1)	8.99	8.99
32 (2)	15.94	15.94
32 (3)	14.46	14.46
33	6.88	6.88
mean	6.20	6.16
SD	3.36	3.35

C1 : The steady state theophylline serum concentrations were calculated from equation 5.1 (short infusion model) by using individual Ke calculated from equation 1 and individual Vd calculated from equation 3.1.

C2 : The steady state theophylline serum concentrations were calculated from equation 5.2 (bolus model) by using individual Ke calculated from equation 1 and individual Vd calculated from equation 2 and 3.2.

The precision of the predicted steady state theophylline serum concentrations calculated from equation of the bolus model compared with the predicted steady state theophylline serum concentration calculated from the equation of the short infusion model

Pair of comparison	Root mean square prediction error (rmse)	95% confidence interval
C1 VS C2	0.25	(-0.26 , 0.44)

APPENDIX II

Algorithm used for evaluation of theophylline adverse reaction

Naranjo 's algorithm

Total score	≥ 9	Definite ADR
Total score	5 - 8	Possible ADR
Total score	1 – 4	Probable
Total score	0	Unlikely

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on the reaction ?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered ?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered ?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered ?	+2	-1	0	
5. Are there alternative cause (other than the drug) that could on their own have caused the reaction ?	-1	+2	0	
6. Did the reaction reappear when the placebo was given ?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic ?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased ?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure ?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence ?	+1	0	0	

APPENDIX III

Equations used in this study

1. Equation used for calculation of theophylline pharmacokinetic parameters and the serum concentrations during steady state

Equation 1 : $Ke = \ln (C_1/C_2) / T$

Equation 2 : $Cp_0 = Cp_t / e^{-Ket}$

Equation 3.1 : $$Vd = \frac{SF(Dose/tin)(1-e^{-Ketin})(e^{-Ket})}{Cp_t Ke}$$

Equation 3.2 : $Vd = SFDose / Cp_0$

Equation 4 : $Cl = KeVd$

Equation 5.1 : $$Cpss = \frac{SF(Dose_1 / tin) (1 - e^{-Ketin}) (e^{-Ket1})}{KeVd (1 - e^{-Kel})}$$

Equation 5.2 : $$Cpss = \frac{SFDose(e^{-Ket})}{Vd(1-e^{-Kel})}$$

Equation 6 : $C_{md} = SFDose / Cl$)

Ke = Elimination rate constant (hr^{-1})

C_1 = Theophylline serum concentration at the time t_1 (mcg/ml)

C_2 = Theophylline serum concentration at the time t_2 (mcg/ml)

T = The time interval between t_1 and t_2 (hrs)

Cp_0 = Theophylline serum concentration at time = 0 (mcg/ml)

Cp_t = Theophylline serum concentration at time = t (mcg/ml)

T = The time interval between t = 0 to t (hrs)

Vd = Theophylline volume of distribution (L)

S = Salt form factor (Aminophylline = 0.8)

F = Bioavailability

Dose = Aminophylline loading dose (mg)

Cl = Theophylline clearance (L/hr)

Cpss = Theophylline serum concentration during steady state (mcg/ml)

$Dose_1$ = Aminophylline maintenance dose (mg)

tin = Infusion time (hrs)

t_1 = The time interval between the end of the infusion to the time that the serum concentration was drawn (hrs)

τ = Dosing interval (hrs)

C_{md} = Average theophylline serum concentration during steady state (mcg/ml)

2. Equation used for calculation of statistical values

2.1 rmse (root mean square predicttion error)

: rmse was calculated from equations as follow :

Equation 7 :

$$\text{prediction error (pei)} = \text{predicted value i - measured value i}$$

Equation 8 :

$$\text{mean square error (mse)} = \frac{1}{N}\sum_{i=1}^{N} pei^2$$

Equation 9 :

$$\text{rmse} = (\text{mse})^{1/2} = \left[\frac{1}{N}\sum_{i=1}^{N} pei^2\right]^{1/2}$$

2.2 95% confidence interval (95% CI)

95% confidence interval of the rmse calculated by extraction the square root of mse

Equation 10 :

$$95\%\ CI\ (mse) = X - t_{0.975}\,(N-1)\,se_x < x_t < X + t_{0.975}\,(N-1)\,se_x$$

$$se_x\,(mse) = \left(\frac{1}{N(N-1)}\sum_{i=1}^{N} (Xi - X)^2\right)^{1/2}$$

$Xi = pei^2$

X = mean of all value Xi

t = t-factor for N-1 degrees of freedom

X_t = true value of X

VITAE

Miss Aree Nalampang was born on February 17, 1970, in Chiangrai, Thailand. She graduated with Bachelor Degree of Science in Pharm in 1993 from the Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand. Her current position is a staff in Department of Pharmacy, Phayao Hospital, Phayao, Thailand.