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ปฐมนิพนธ์

ORIGINAL ARTICLE

Analysis of Cimetidine Kinetics after Intravenous Administration Using Noncompartmental Methods

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ABSTRACT

The noncompartmental method was used to analyze the kinetics of cimetidine after a bolus intravenous injection. Results obtained were satisfactory. This is demonstrated by comparing the analytical ability of the method with that of the conventional two compartment open model. Both methods provide the same results. It can be employed as an alternative technique for analyzing the kinetics of a drug product. (Th. J. Pharm. Sci., Vol. 12, No. 2,121-126(1987)).

Key words : Analysis, cimetidine injection, kinetics, noncompartmental methods.

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INTRODUCTION

In the past, the kinetics of a drug or metabolite were analyzed according to compartmental model (Model dependent) (1-3). These methods require some specific assumptions and extensive use of equations that sometimes appear to be limited, especially for the kinetic analysis of the drug that was characterized by higher multicompartment model (4, 5).

Recently, a new technique, the noncompartmental methods (Model independent) based on statistical moment theory has been developed to estimate bioavailability and pharmacokinetic parameters of a drug product (6-8). However, there appear to be little information about its application and usefulness.

The present study was undertaken to use the noncompartmental methods to analyze the kinetics of cimetidine after a bolus intravenous injection. Data were compared to those of conventional two compartmental open model. Results obtained perhaps, provide some direction for future development of the method.

MATERIALS AND METHODS

Materials : Cimetidine injections (Tagamet 200 mg/2 ml) were obtained commercially. All chemicals were analytical grade and used without further purification.

Methods :

1. Drug administration and samples collection : A single dose of cimetidine 200 mg was given to 9 healthy subjects as a bolus intravenous injection. Blood samples (4-5 ml) were collected prior to dosing and at 0, 0.25, 0.5, 0.75, 1.0 1.5, 2.0, 3.0, 4.0, and 6.0 hours after drug administration. They were centrifuged at 2,000 rpm for 10 minutes. The plasma samples were then separated and stored at -20° C until subsequent assay.

2. Analytical method : Concentrations of cimetidine in plasma samples were determined using specifically high pressure liquid chromatographic method described by Mihaly et al (9). The cimetidine concentrations in plasma samples were quantified employing the standard curve.

3. Data analysis :

3.1 For noncompartmental methods : Individual plasma cimetidine profile from each subject was analyzed using the NCPT estimation program (10). The AUC, Vdss and MRT values were obtained directly from the computer outputs. The other parameters (Cl, K, $t_{1/2}$) were calculated using equations.

$$Cl = D/AUC \quad \text{Eq. 1}$$

$$K = 1/MRT \quad \text{Eq. 2}$$

$$t_{1/2} = 0.693\ MRT \quad \text{Eq. 3}$$

where ; Cl is the clearance, D is the i.v. dose, AUC is the area under the plasma vs. time profile from 0 to ∞, K is the first order elimination rate constant, MRT is the mean residence time after a bolus intravenous injection, and $t_{1/2}$ is the half-life.

3.2 For two compartment open model : The plasma cimetidine vs. time profile from each subject was analyzed using the PCNONLIN computer program (11). The AUC, β, and $t_{1/2}$ values were readily received from the outputs. The clearance (Cl) and volume of distribution at steady state (Vdss) were estimated using the following equations :

$$Cl = V_1 Kel \quad \text{Eq.4}$$

$$Vdss = \frac{(\alpha + \beta - Kel)\, V_1}{K_{21}} \quad \text{Eq.5}$$

where ; V_1 is the volume of distribution of the central compartment, Kel is the first order elimination rate constant from the central compartment, α and β are the first order rate constants for the distribution

and elimination, and K_{21} is the first order transfer rate constant from the peripheral compartment to the central compartment.

3.3 A test for the validity of the noncompartmental method : Individual parameter obtained was compared with that received from the conventional two compartment open model using regression techniques based on correlation analysis. This is performed employing the computer program ABSTAT (12).

RESULTS

Figure 1 shows the average time course of cimetidine concentration following a bolus intravenous injection of 200 mg of the drug into 9 subjects. After the injection, cimetidine concentration in plasma initially decreased rapidly and then more slowly. Kinetics of the noncompartmental and the two compartment open model calculation for cimetidine are presented in Table 1. Model-independent (Noncompartmental) and-dependent (Two compartment open model) values for the corresponding parameter were in good agreement and no statistically significant difference between these parameters were observed.

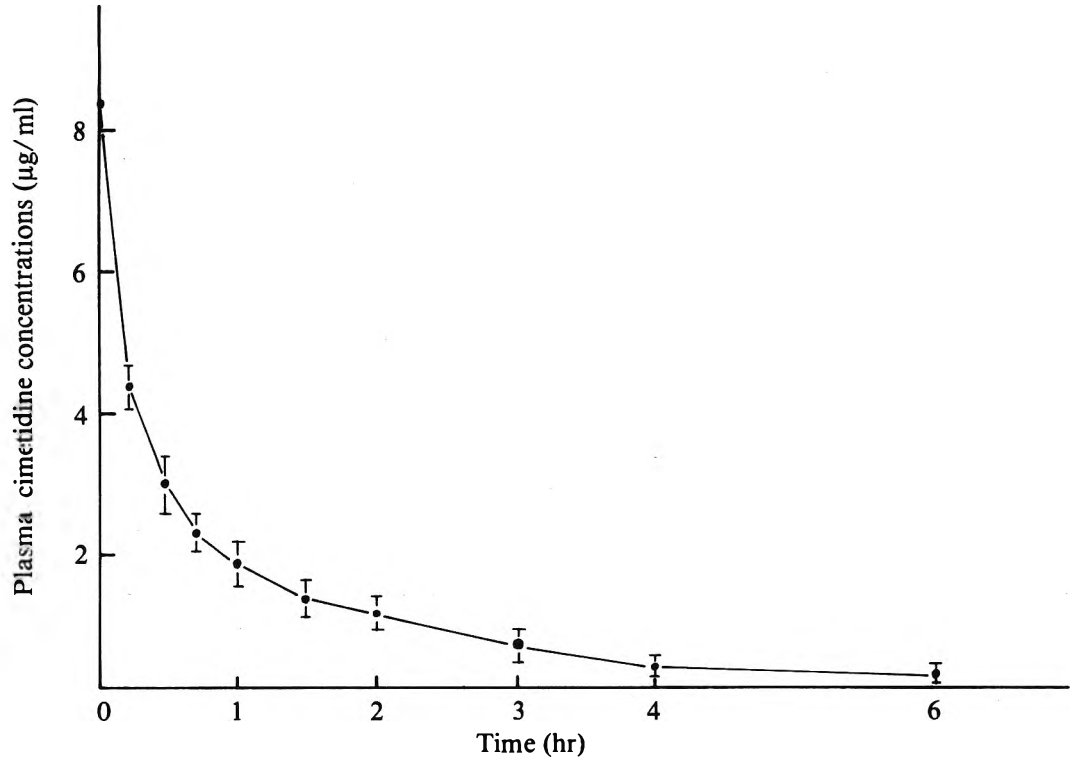

Figure 1. Average time course of cimetidine following intravenous administration.

DISCUSSION AND CONCLUSION

Results in Table 1 show that for cimetidine kinetics, the data are explained adequately by either method, with the noncompartmental method being slightly but insignificantly better.

This study also indicated, the noncompartmental method is valid. This is reasoned by the correlation coefficients between the corresponding parameters obtained from both methods were highly significant (13).

Thus, it can be concluded that the noncompartmental method may be used as an alternative approach for analyzing the kinetics of the drug products after intravenous administration.

The noncompartmental method has the advantage as a kinetic analyzer in that it does not require as many as assumptions, curves fitting and/or calculation of initial kinetic values for computer analysis

like a specific compartmental model for either drug or metabolite (14). It can be applied to any compartmental model, provided that we can assume linear pharmacokinetics. However, its use has been limited, especially in kinetic analysis following oral administration alone. In this case, the kinetic parameters of certain drug after intravenous administration must be readily obtained in order to employ for estimation of the absorption kinetics (14).

Because of reduced experimentation or calculation, it appears that the use of the noncompartmental method can be a valuable mean to aid the study of the kinetics of the drug products.

Table 1. Kinetics of Cimetidine after Intravenous Administration of 200 mg.

Subject	Noncompartmental method					Two compartment open model				
	AUC μg-hr/ml	Cl l/hr	Vdss l	K hr^{-1}	t½ hr	AUC μg-hr/ml	Cl l/hr	Vdss l	β hr^{-1}	t½ hr
1	9.17	21.81	52.80	0.41	1.68	9.19	21.67	58.87	0.33	2.12
2	7.49	26.70	41.29	0.65	1.07	7.50	26.80	47.27	0.44	1.58
3	9.83	20.35	31.34	0.65	1.07	9.45	21.25	30.89	0.64	1.07
4	6.52	30.67	41.69	0.74	0.94	6.21	32.19	42.28	0.66	1.05
5	7.70	25.97	60.18	0.43	1.61	7.30	27.18	58.42	0.40	1.71
6	9.50	21.05	49.56	0.43	1.63	9.73	20.61	57.79	0.30	2.30
7	7.05	28.37	45.10	0.63	1.10	6.93	28.80	52.72	0.43	1.63
8	8.82	22.68	41.91	0.54	1.28	8.56	23.47	43.44	0.47	1.48
9	7.65	26.14	51.71	0.51	1.37	7.57	26.49	58.42	0.40	1.75
Mean	8.19	24.86	46.18	0.55	1.31	8.05	25.38	50.01	0.45	1.63
SD.	1.17	3.56	8.41	0.12	0.28	1.23	3.90	9.77	0.12	0.41

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การวิเคราะห์ข้อมูลจลนศาสตร์ของยาฉีดเข้าหลอดเลือดดำไซเมททิดีนโดยใช้วิธี Noncompartmental

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บทคัดย่อ

ศึกษาการใช้วิธี Noncompartmental วิเคราะห์ข้อมูลจลนศาสตร์ของยาฉีดเข้าหลอดเลือดดำไซเมททิดีน การทดลองให้ผลเป็นที่น่าพอใจพิสูจน์ได้จากการเปรียบเทียบความสามารถในการวิเคราะห์ข้อมูลโดยใช้วิธีนี้กับวิธีเดิมซึ่งใช้แบบจำลองชนิด Two compartment open model วิธีทั้งสองให้ผลดีเท่าเทียมกัน วิธี noncompartmental สามารถใช้เป็นอีกวิธีหนึ่งสำหรับวิเคราะห์ข้อมูลจลนศาสตร์ของเภสัชภัณฑ์ (ไทยเภสัชสาร ปีที่ 12 (2) : หน้า 121-126 (2530)).

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