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Absorption and Disposition Kinetics of Trimethoprim following Intramuscular Injection in Rabbits

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ABSTRACT

The absorption and disposition kinetics of an antimicrobial agent, trimethoprim (TMP) were investigated using New Zealand white male rabbits. The blood and plasma concentration-time curves obtained subsequent to the intravenous administration of trimethoprim lactate solution (TMP 15.3 mg/kg body weight) were fitted to a two-compartment body model ($C=Ae^{-\lambda_1 t} + Be^{-\lambda_2 t}$). The rate constants of TMP based on the blood data were λ_1: 6.72 ± 2.37 h^{-1} (mean ± SD); λ_2: 0.898 ± 0.149 h^{-1}; k_{10}: 1.81 ± 0.24 h^{-1}; k_{12}: 2.48 ± 1.25 h^{-1}; k_{21}: 3.34 ± 1.31 h^{-1} and the volumes of distribution were V_1: 1.87 ± 0.21 l and V_2: 1.39 ± 0.9 l (2.67 ± 0.16 kg body weight). The body clearance of TMP was 1.25 ± 0.12 l/h/kg. The availability of TMP in lactate (TMPL) and in glycofurol (TMPG) solutions administered to the vastus lateralis muscle was equivalent to that of the intravenous administration at the same dosage. However, the mean absorption time (MAT) of TMP from muscle was significantly shorter with TMPL solution (0.4 ± 0.1 h) than with TMPG solution (1.0 ± 0.1 h). The mean C_{max} obtained with TMPL (8.91 ± 1.48 mg/l) was higher than that obtained with TMPG (5.97 ± 0.88 mg/l). The fraction of TMP in the rabbit blood cells averaged 0.388 ± 0.015 (i.v.) and 0.279 ± 0.019 (i.m.).

Key words : **trimethoprim, pharmacokinetics, i.m., i.v., bioavailability, rabbit.**

INTRODUCTION

Trimethoprim (TMP), an antagonist of dihydrofolate reductase, is active against a wide range of aerobic Gram-negative and Gram-positive organisms including strains of most Enterobacteriaceae. It has been extensively used clinically in combination with one of sulfa drugs for the treatment of various bacterial infection diseases since 1968[1]. Although the drug is usually administered orally, intravenous infusion of trimethoprim-sulfamethoxazole (weight ratio 1:5, known as Co-trimoxazole) has been reported[2]. Studies have also indicated kinetic advantages of intramuscular administration over the oral administration of Co-trimoxazole in beagles[3] and in man[4]. TMP is practically insoluble in water

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and commercial parenteral preparations of Co-trimoxazole containing 40% propylene glycol for intravenous infusion and 52% glycofurol for intramuscular injectables are available in the European countries[5]. The use of each 10% of ethanol and benzyl alcohol, and 5% of sorbitol as solvents for the preparation of Co-trimoxazole infusion is also patented in Germany[6]. However, recent studies indicate that the use of TMP alone may be even more advantageous than the combination with sulfa drugs[1,7]. Trimethoprim tablets (100 and 300 mg) and sterile trimethoprim lactate solution (20 mg/ml TMP) for intravenous infusion are available in the Great Britain[8]. Nevertheless, the intramuscular preparation of TMP alone is still not available. The incorporation of alcohols or polyols in the injection solution occasionally produce some adverse reactions. Studies have indicated the toxicity associated with propylene glycol[9,10] and dose-related hepatic toxicity of glycofurol[11]. Some local reactions due to the intramuscular administration of Co-trimoxazole containing glycofurol have been noted in man[12] and the tissue necrosis due to glycofurol has been demonstrated in pigs[10]. The development of an intramuscular formulation of TMP without the use of organic solvents would be useful. This report presents the results of a pharmacokinetic evaluation on trimethoprim lactate aqueous solution and trimethoprim glycofurol solution following intravenous and/or intramuscular administrations as a preliminary step in the development of an intramuscular formulation of trimethoprim.

MATERIALS AND METHODS

I. *Trimethoprim Lactate*

Trimethoprim (grade complies with B.P.1980, supplied by Danish Powder and Tabletting Factory, Denmark), 29 g was suspended in 350 ml of distilled water and 10 g of lactic acid (90% Extra Pure, E. Merck Co., Germany) was then added to the suspension with stirring. The resultant solution was filtered through 0.22μm filter (Millipore) and the filtrate concentrated under reduced pressure at 80℃ until total volume became about 100 ml. White trimethoprim lactate crystals were collected on cooling and washed with cold alcohol. The TMP content of the product was 76% upon drying and the product equivalent to one mole to one mole salt. The water solubility of trimethoprim lactate was 84.0 ± 0.7 mg/ml (mean ± SD, n = 3) as trimethoprim at 25 ± 0.2℃.

II. *Parenteral Solutions of TMP*

The injectable trimethoprim lactate solution was prepared by dissolving 5.1 g of trimethoprim lactate crystals in 100 ml of water for injection. After filtration through 0.22 μm filter, the filtrate was sealed in 10 ml sterile vials and autoclaved (121℃, 20 min). The TMP concentration was 38.3 mg/ml, pH 6.31 (TMPL solution). The injectable trimethoprim glycofurol solution was prepared by dissolving 4.4 g of trimethoprim in 100 ml of 60% glycofurol-water solution[13] with stirring and warming in a waterbath (80℃). The resultant solution was cooled to room temperature and filtered through 0.45μm filter (Durapore HBLP 14250) and then sealed into 10 ml sterile vials and autoclaved. The TMP concentration was 43.5 mg/ml, pH 8.16 (TMPG solution).

III. *Rabbits*

Nine New Zealand white male rabbits weighing 2.67 ± 0.16 kg were used. On the experiment day, rabbits were deprived of food and water.

IV. *Intravenous and Intramuscular Administration of TMP*

Intravenous administration was carried out with TMPL solution in the left marginal ear vein at a dose of 15.3 mg TMP/kg body weight within 4 seconds. One ml of blood was collect-

ed from the marginal ear vein at 3, 6, 9, 12, 20, 30, 35, 45 min, 1.0, 2.0, 3.0 and 4.0 h subsequent to the intravenous bolus administration. After a two-week washout time, an intramuscular injection with TMPL solution was administered in the left vastus lateralis muscle (15.3 mg/kg). After another two-week washout time, intramuscular injection of TMPG solution to the right vastus lateralis muscle was carried out at a dose of 20 mg TMP/kg body weight. The blood collection schedules in the intramuscular administrations were same as that in the intravenous bolus study.

V. *Determination of TMP*

TMP concentration in the whole blood and in the plasma samples were determined by the high performance liquid chromatographic method (HPLC) after Vree et al[14]. Namely, 80μl of whole blood or plasma was vortexed with 320μl of distilled water for 30 seconds and then vortexed with 1.6 ml of 0.33 M $HClO_4$ solution (Perchloric acid, 70% GR grade, E. Merck Co.). After centrifugation (8000 rpm, 10 min), the supernatant 1 ml was neutralized with 0.2 ml of 0.3 M NaOH solution and filtered. The filtrate 100μl was injected into HPLC. An HPLC apparatus (Hitachi model 638-50, LC detector 635M, Japan) was used, equipped with μ-Bondapak C_{18} column (Waters, 4 mm id x 30 cm). TMP was detected at 230 nm and the attenuation of 0.005 aufs. The mobile phase was a mixture of 390 ml of 0.067 M KH_2PO_4, 10 ml of 0.067 M K_2HPO_4 (pH 6.5) and 80 ml of ethanol, and run at rate of 1.0 ml/min. Duplicate determinations were performed using the external standard method. The maximum range in the duplicate determinations was 8% (for concentrations 1.0 to 26 mg/l) and the recovery of TMP from the blood and plasma were 84.5 ± 1.1% (n = 4, 5 mg/l) and 84.8 ± 0.5% respectively.

VI. *Concentration of TMP in Blood Cell*

Concentration of TMP in the blood cell was calculated using the hematocrit value (H) and is defined by the equation (2)[15].

$$C_b = C_{BC}(H) + C_p(1 - H) \quad \ldots\ldots\ldots (1)$$

$$C_{BC} = [C_b - C_p(1 - H)]/H \quad \ldots\ldots\ldots (2)$$

where C_b is the TMP concentration in the whole blood, C_p is the TMP concentration in the plasma, C_{BC} is the TMP concentration in blood cells and H is the hematocrit value.

VII. *Fraction of TMP Uptake by the Blood Cell*

The fraction of TMP uptake by the blood cell was calculated with the ratio of the amount of TMP in the blood cells (A_{BC}) and in the whole blood (A_b) using equation (3).

$$\frac{A_{BC}}{A_b} = \frac{C_{BC}(H)}{C_b} \quad \ldots\ldots\ldots (3)$$

VIII. *Estimation of Area Under the Concentration Curve and Fraction of TMP Absorbed (F) and Body Clearance (Cl)*

The total AUC (AUC) was calculated by the linear trapezoidal and extrapolation methods. The fraction of TMP absorbed (F) was calculated by the ratio of AUC on intramuscular administration to the AUC on intravenous administration in the same rabbit with the correction of dose. Body clearance was calculated by dividing the intravenous dose with the AUC based on the blood concentration data.

IX. *Estimation of Mean Residence Time (MRT), Mean Absorption Time (MAT), Variance of Residence Time (VRT) and Variance of Absorption Time (VAT)*

Statistical moment analysis in terms of MRT and VRT was performed for the blood concentration-time curves[16]. The MRT and VRT were calculated by the linear trapezoidal and extrapolation methods. The MAT and VAT were calculated from the difference of the MRT and the VRT between the intramuscular and intravenous administrations[17] respectively.

X. *Statistical Analysis*

Analysis of variance and the classical 90%

confidence interval were employed to determine the mean differences of AUC, C_{max} and MAT among the different administration routes and formulations. The minimum detectable difference (Δ) in percent of the mean (intravenous or the corresponding reference mean) was estimated at $\alpha = 0.05$ (two-sided) and $1 - \beta = 0.80$. Fraction of overlapping for the two 90% confidence ellipses constructed with C_{max} and AUC which reflected the overall similarity in bioavailabilty between the two formulations (TMPL and TMPG) was also estimated by the method of Hsu et al.[18].

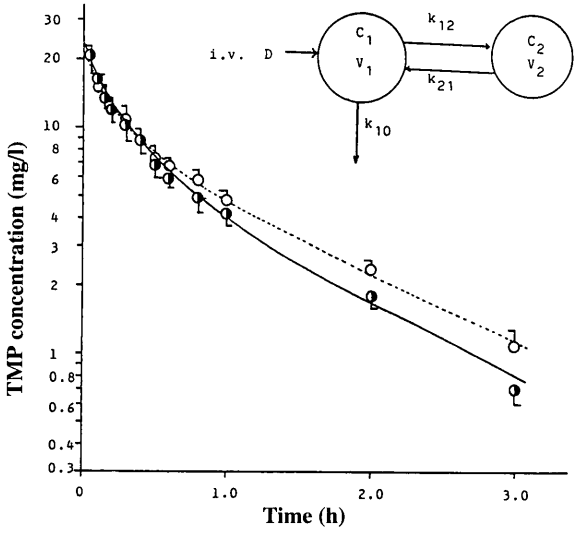

Figure 1. Disposition profiles of trimethoprim in the blood (◑) and plasma (○). mean ± SD.

RESULTS AND DISCUSSION

I. *Disposition Profiles of TMP following Intravenous Administration*

Fig. 1 shows the disposition profiles of TMP in the whole blood and in the plasma following intravenous administration of TMPL solution. The profiles show a biphasic pattern

Table 1. Pharmacokinetic parameters of trimethoprim in rabbits following intravenous administration (15.3 mg/kg body weight, n = 9)

Parameters	Whole blood	Plasma
A, mg/l	13.0 ± 2.3	9.16 ± 2.51
B, mg/l	9.38 ± 1.69	11.3 ± 1.40
λ_1, h^{-1}	6.72 ± 2.37	8.11 ± 3.97
λ_2, h^{-1}	0.898 ± 0.149	0.893 ± 0.114
k_{10}, h^{-1}	1.81 ± 0.24	1.49 ± 0.22
k_{12}, h^{-1}	2.48 ± 1.25	2.64 ± 1.86
k_{21}, h^{-1}	3.34 ± 1.31	4.87 ± 2.34
V_1, l	1.87 ± 0.21	2.05 ± 0.27
V_2, l	1.39 ± 0.90	1.11 ± 0.96

Value represents mean ± SD, V_1 and V_2: 2.67 ± 0.16 kg body weight.
Blood and plasma concentration equation: $C=Ae^{-\lambda_1 t}+Be^{-\lambda_2 t}$.

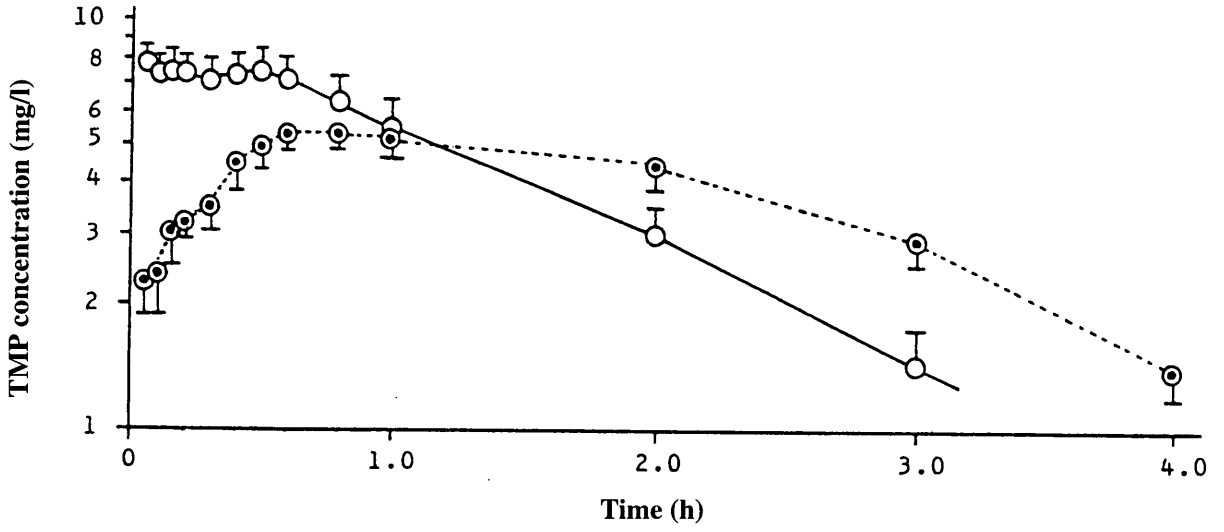

Figure 2. Blood concentration profiles of trimethoprim after intramuscular administration with TMPL (○) and TMPG (⊙) solutions. mean ± SD.

and were fitted to a two-compartment body model and the estimated pharmacokinetic parameters by the weighted ($1/C^{(2)}$, C: drug concentration) least-squares method (Software written by Professor Jun Watanabe, Nagoya City University, Japan) are presented in Table 1. The estimated mean parameter values of blood and plasma were not statistically different. The values are also consistent with that reported by Ladefoged[19] for the plasma TMP in rabbits by fluorometry.

II. *Blood Concentration Profiles of TMP following Intramuscular Administration*

Fig. 2 depicts the blood concentration profiles resulted from the intramuscular administration with TMPL and TMPG solutions. The statistical moment analysis was carried out to

Table 2. Statistical moments and other parameters of trimethoprim in rabbits based on the blood data

Formula	TMPL	TMPL	TMPG
Administrat.	Intravenous	Intramuscular	Intramuscular
No. of Rabbit	9	9	9
AUC, (mg/l)h	12.9 ± 1.4	14.6 ± 1.9	16.0 ± 1.0
Dose	15.3 mg/kg	15.3 mg/kg	20.0 mg/kg
MRT, h	1.0 ± 0.1	1.4 ± 0.1	2.0 ± 0.1
VRT, h^2	2.1 ± 0.2	3.4 ± 0.3	5.8 ± 0.3
MAT, h	—	0.4 ± 0.1	1.0 ± 0.1
VAT, h^2	—	1.0 ± 0.2	3.8 ± 0.4
F	1.0	1.15 ± 0.14	1.06 ± 0.14
Cl, l/h/kg	1.25 ± 0.12	—	—
C_{max}, mg/l	—	8.91 ± 0.49	5.97 ± 0.29
T_{max}, h	—	0.289 ± 0.082	0.733 ± 0.162

Values represent the mean ± SD.

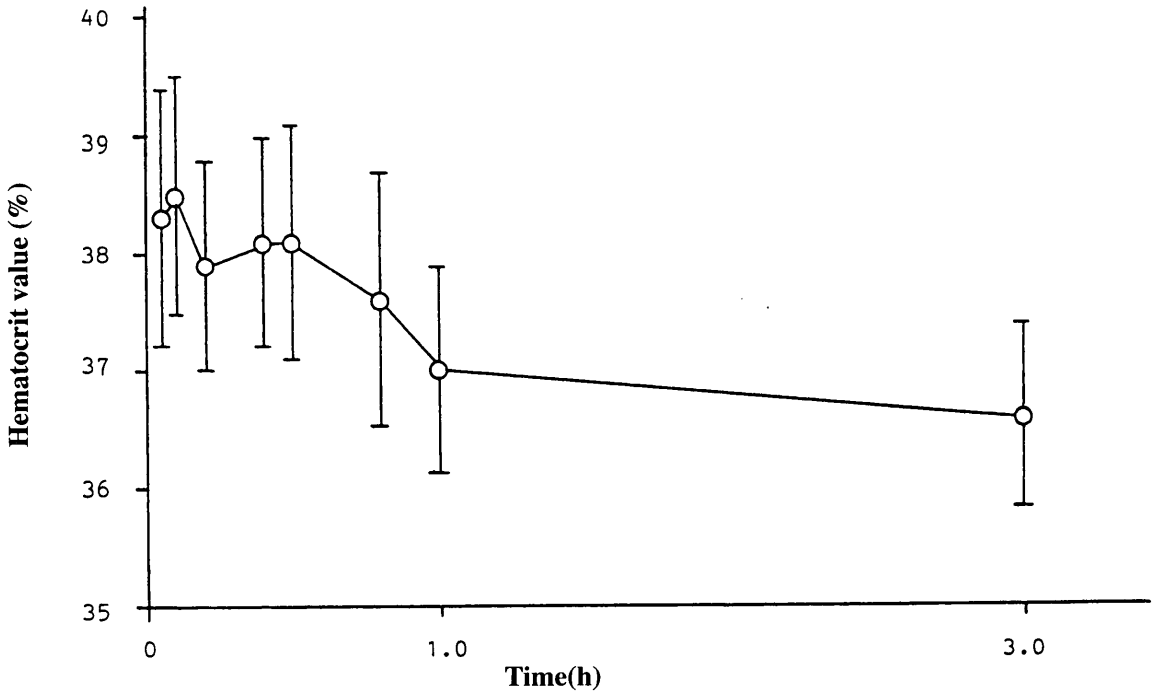

Figure 3. Change of hematocrit values in intravenous administration experiment. mean ± SD.

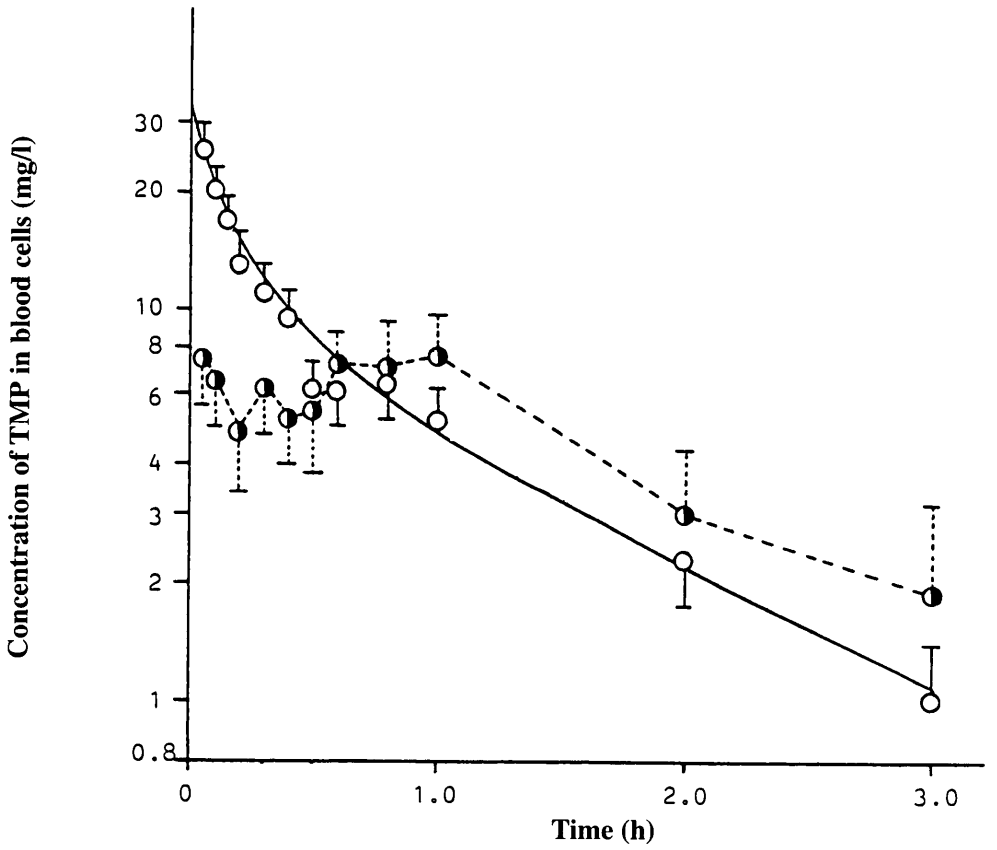

Figure 4. Concentration profiles of trimethoprim in blood cells after intravenous (○) and intramuscular (◑) administrations of TMPL. mean ± SD.

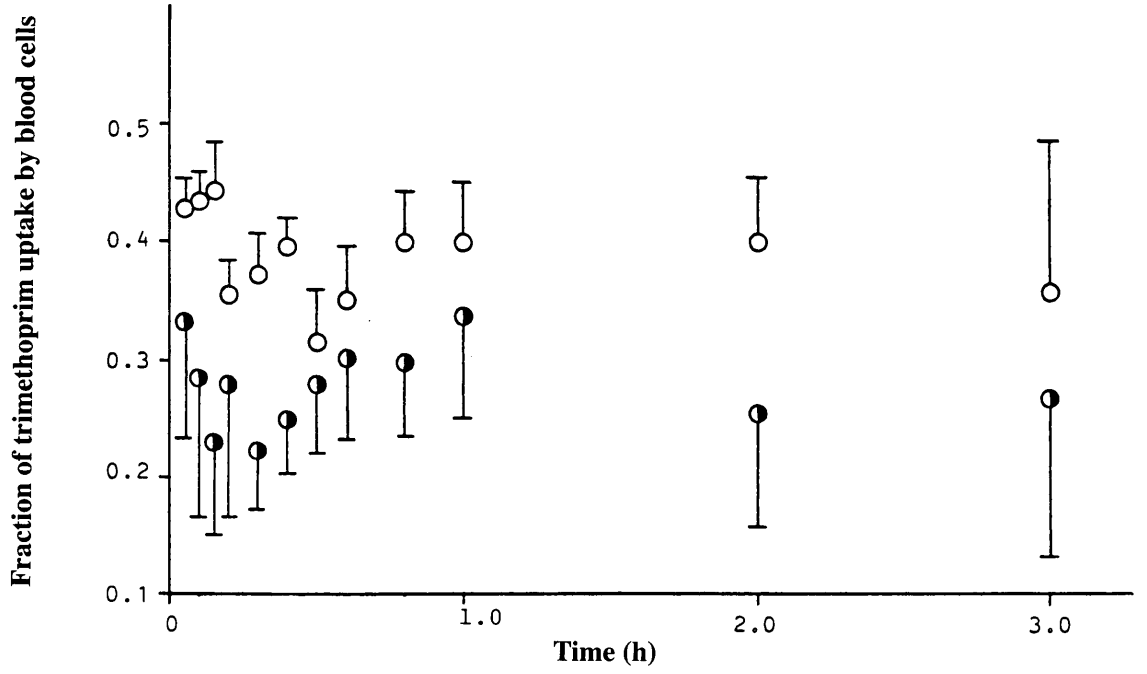

Figure 5. Fraction of trimethoprim uptake by blood cells after intravenous (○) and intramuscular (◑) administrations of TMPL. mean ± SD.

estimate the moments and the results were described along with other parameters in Table 2. The blood TMP concentration profile showed that TMP was rapidly absorbed after intramuscular injection of TMPL solution; whereas the absorption of TMP with TMPG solution was by comparison slow but steady. The difference in the absorption pattern may be due to the different solubility of TMP in TMPL (soluble salt) and in TMPG (practically insoluble trimethoprim base) solutions.

The difference of AUC among the intravenous and intramuscular administrations (TMPL and TMPG) was not significant at equal dose basis ($p > 0.05$, $\Delta < 20\%$). Under the same dose, the 90% confidence interval of the population mean ratio of AUC (using log-transformed data) for TMPL im/iv and TMPG im/iv are respectively (0.96, 1.05) and (1.10, 1.16). Hence, the availability of TMP may be equivalent between intramuscular administrations of TMPL and TMPG. However, the differences of MRT, MAT and C_{max} obtained after the intramuscular administrations of TMPL and TMPG solutions were very highly significant ($p < 0.005$). The 90% confidence interval of the population mean ratio of C_{max} (log-transformed data) for TMPG/TMPL was (0.59, 0.76). The overall degree of similarity in bioavailability between intramuscular administrations of TMPL and TMPG estimated by the bivariate approach[18] (C_{max} and AUC are evaluated simultaneously) was only approximately 54% for the untransformed C_{max} and AUC; whereas 43% for the log-transformed C_{max} and AUC. The results indicate the rate of TMP absorption is much faster with TMPL than with TMPG solutions. Lesko et al.[20] reported that TMP in Co-trimoxazole injectable solution (containing 40% propylene glycol) was precipitated rapidly in dilutions of 1:5 (v/v) in either 5% dextrose or normal saline solutions. It was also observed in this study that a turbid solution rapidly formed when 0.5 ml of TMPG solution was mixed with 0.1 ml of plasma (pH 7.4) but there was no precipitation formed when 0.5 ml of TMPL solution was mixed with 0.1 ml of plasma. Since TMP is practically insoluble, semi-polar solvents such as propylene glycol or glycofurol are utilized to increase its solubility. TMP would precipitate when the concentration of semi-polar solvent is decreased by dilution. Therefore, TMP in TMPG solution may be precipitated in the muscle during the interstitial fluid dilution and the rapid diffusion of the semi-polar solvent after intramuscular injection. On the other hand, TMP is in soluble salt form in the TMPL solution and is soluble on dilution. The significantly large VAT values for TMPG also indicate the sustained characteristics of TMPG formulation due to the slow dissolution of precipitated TMP in muscle.

III. *Changes of Hematocrit Value as a Function of Time*

Fig. 3 shows the changes in the intravenous experiment of hematocrit value as a function of time. Student t-test for the values at time 0.05 h (0.383 ± 0.03, $n = 9$) and 3.0 h (0.366 ± 0.024) showed the hematocrit value was not significantly decreased after successive blood collections ($\Delta = 10.6\%$ of the initial hematocrit value).

IV. *Concentration-Time Profiles of TMP in Blood Cells following Intravenous and Intramuscular Administrations*

The concentration-time profiles of TMP in blood cells following intravenous and intramuscular administrations of the TMPL solution are illustrated in Fig. 4. The TMP concentration in blood cells was high immediately following the intravenous administration and the concentration declined biexponentially with time; whereas the time-course of TMP concentration in blood cells following the intramuscular administration was considerably erratic. Shah et al.[21] also described an erratic profile for chlorthiazide in blood cells following oral administration. The erratic pattern observed in the time-course of TMP concentra-

tion in blood cells may be related to the dynamics of TMP absorption and elimination in the extravascular administration.

V. *Fraction of TMP Uptake by the Blood Cells*

Fig. 5 shows the time-course of the fraction of TMP in blood cells following intravenous and intramuscular administrations of TMPL solution. The fraction of TMP in blood cells averaged 0.388 ± 0.015 (i.v.) and 0.279 ± 0.019 (i.m.). The higher drug concentration in the blood showed the larger fraction of TMP uptake in blood cells. It was reported that blood cells showed a TMP content equal to that of plasma in man[22]. The difference on the partition of TMP in blood between man and rabbit may be due to the different hematocrit values (rabbit: 38.3 ± 1.2%; man: 47 ± 7%[23]).

The results obtained from this preliminary study may provide some basic pharmacokinetic information for developing an intramuscular formulation of trimethoprim.

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Trimethoprim在家兔體內的動態

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摘 要

本文報告以九隻紐西蘭雄性白兔（2.67 ± 0.16 kg）探討抗菌藥Trimethoprim（TMP）經靜脈及肌肉注射後之體內動態，作爲開發TMP肌肉注射劑型之基礎資訊。以TMP乳酸鹽溶液（TMPL） 15.3 mg / kg劑量靜脈注射後，其血中TMP之經時變化可用二室體模式加以歸納（$C=Ae^{-\lambda_1 t}+Be^{-\lambda_2 t}$）。其藥物動力學速率常數及動力學參數分別爲$\lambda_1$：6.72 ± 2.37 h^{-1}, λ_2：0.898 ± 0.149 h^{-1}, k_{10}：1.81 ± 0.24 h^{-1}, k_{12}：2.48 ± 1.25 h^{-1}, k_{21}：3.34 ± 1.31 h^{-1}, V_1：1.87 ± 0.21 l, V_2:1.39 ± 0.9 l, Cl：1.25 ± 0.12 l/h/kg。肌肉注射TMPL及TMP glycofurol溶液（TMPG）後，TMP皆完全吸收（F=1.0）。然而TMPL注射後TMP之吸收遠比注射TMPG快速。其平均吸收時間各爲TMPL：0.4 ± 0.1h，而TMPG：1.0 ± 0.1h。注射TMPL於肌肉後之C_{max}爲8.91 ± 1.48 mg / l也比注射TMPG後之C_{max} 5.97 ± 0.88 mg / l爲高。TMP在家兔血球內之分佈分率各爲0.388 ± 0.015（靜注）和0.279 ± 0.019（肌注）。

關鍵詞：Trimethoprim，藥物動力學，肌肉注射，靜脈注射，生體可用率，家兔。