Comparative Studies of Quality and Bioavailability of Methotrexate in Thai Patients with Rheumatoid Arthritis

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Abstract

The bioavailability of the two generic methotrexate oral preparations (Emtrexate®, Pharmachemie Company, Hollland and Methotrexate Remedica®, Remedica, Cyprus as the test preparations), were compared to the innovator (Methotrexate Lederle®, Lederle, U.S.A. as the reference) in 10 patients with rheumatoid arthritis. A single 7.5 mg oral dose of each preparation was given to the subjects in a randomized, double-blind, three-period crossover design with a 1 week washout period. Serum methotrexate concentrations were determined by using Fluorescence Polarization Immunoassay (Abbott TDx®). No significant differences in pharmacokinetic parameters (AUC, C_{max}, and T_{max}) were observed between the test and reference preparations. The mean and 90 per cent CI of the ratio Emtrexate/Methotrexate Lederle® and Methotrexate Remedica®/ Methotrexate Lederle® of the C_{max} , AUC_{0-8}, and $AUC_{0-\alpha}$ were 0.93 (0.87-1.00), 0.9 (0.82-0.98), 0.88 (0.79-0.99) and 0.97 (0.93-1.02), 0.95 (0.90-0.99), 0.94 (0.86-1.02), respectively. These values were well within the acceptable bioequivalence range of 0.8-1.25. The mean and 90 per cent CI of T_{max} difference between Emtrexate®-Methotrexate Lederle® and Methotrexate Remedica®- Methotrexate Lederle® also overlapped the stipulated bioequivalence range of the T_{max} differences of $\pm$ 0.25 hour. Thus, Emtrexate® and Methotrexate Remedica® were considered bioequivalent to the reference Methotrexate Lederle® regarding the rate of absorption and the extent of absorption.

Methotrexate (MTX) is a folic acid antagonist used in the treatment of certain neoplastic diseases, dermatologic diseases and rheumatic diseases, including rheumatoid arthritis[1-3]. For the treatment of rheumatoid arthritis, methotrexate is classified as a disease-modifying agent and has

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been approved for use in severe arthritic cases who were refractory to conventional therapy[4]. Therapeutic effects of methotrexate usually occur at 1-3 months after drug initiation and in most cases, remain effective for several years with continued therapy[2-5]. The recommended dose is a low-dose pulse regimen ranging from 7.5 to 15 mg per week[2-5]. Although the drug can be given orally, intramuscularly or intravenously, methotrexate administered orally is more convenient and less expensive. However, methotrexate oral absorption is variable[6-8] and relatively little is known about the pharmacokinetic profiles of low dose oral methotrexate in Thai patients with rheumatoid arthritis. Oral preparations of methotrexate available in Thailand comprise the innovator (Methotrexate Lederle®) and various generic commercial preparations. Since the price of the generic preparations are less expensive than the innovator, generic substitution is strongly recommended by health authorities[9,10]. Nevertheless, generic substitution of methotrexate is problematic due to its narrow therapeutic window and its serious toxicity[1,2]. In addition, generic substitution of methotrexate in rheumatoid arthritis patients may lead to the risk of treatment failure and/or increase in its toxicity. The purpose of this study was to determine the pharmacokinetic parameters of methotrexate and to conduct the bioequivalence testing of the two generic oral preparations of methotrexate (Emtrexate® and Methotrexate Remedica®, as the test preparations) in comparison with the innovator (Methotrexate Lederle®, as the reference) after a single oral administration in Thai patients with rheumatoid arthritis.

MATERIAL AND METHOD

Subjects

Ten patients with definite rheumatoid arthritis (3 men and 7 women) were recruited from the outpatient department of the Division of Rheumatology of the Faculty of Medicine, Chiang Mai University Hospital. All patients had a history of severe arthritis for 1-3 years and had been receiving oral methotrexate therapy at a dose of 7.5 mg weekly for less than 1 year. Their mean age, weight, and height were 39.3 ± 8.6 years (range 28-53), 50.9 ± 6.74 kg (range 42-61), and 156 ± 8.5 cm (range 147-172), respectively. None had a history of alcoholism, hepatic disease, active peptic ulcer disease, or renal insufficiency. All clinical and routine laboratory evaluation tests including complete blood count with differential count, blood urea nitrogen, and liver function test were within medically acceptable limits. At least one week before and during the study day, each subject was instructed abstain from taking any drug as well as alcohol, xanthine and caffeine containing foods and beverages. Female subjects were not pregnant at the time of study (confirmed by a urine pregnancy test). The study protocol was approved by The Research Ethical Committee of the Faculty of Medicine, Chaing Mai University and written consent was obtained from each patient before study entry.

Study design

This study was a randomized, double-blind, three-period crossover design. Each subject received 3 treatments, 1 week apart, given in a randomly assigned order. All subjects, the physician administering the assigned treatment and the technician who performed the drug analysis were blinded. Each treatment consisted of a 7.5 mg (3 tablets of 2.5 mg methotrexate) oral administration of either Methotrexate Lederle® [lot no. 426-77, purchased from the Maharaj Nakorn Chiang Mai Hospital's Pharmacy Service] or Emtrexate® [lot no. 94H12N, purchased from Pacific Healthcare (Thailand)] or Methotrexate Remedica® [lot no. 8338, purchased from Pharmadica (Thailand)], with 200 ml water after an over night fast. The patients fasted for 2 hours after drug administration. Blood samples were collected immediately before and at 15, 30 min, 1, 1.5, 2, 4, 6, and 8 hours after the drug administration. The blood samples were allowed to clot at room temperature, then centrifuged for 7 minutes at 3,000 rpm to separate the serum. The serum was immediately kept at -20°C until analysis.

Drug Assay

Blood samples were analyzed for methotrexate concentrations by fluorescence polarization immunoassay (FPIA) technique using the Abbott TDx clinical analyzer (Abbott Laboratory, North Chicago IL, U.S.A.)[11]. The FPIA procedure is automated and rapid. The assay was performed in Model1, since the methotrexate concentrations in patients samples were expected to be less than 1.0 μmol/L. The sensitivity of the method was 0.01 μmol/L, therefore, the dynamic range of the assay was from 0.01 to 1.0 μmol/L. The calibration curve

could be stored for at least 2 weeks and cross-reactivity with 7-hydroxy methotrexate and prednisolone was less than 1 per cent. The coefficient of variation (CV) for the within-run and between-run precision was less than 10.0 per cent and the average recovery was 97.6 ± 2.8 per cent.

Statistical Methods and Data Analysis

The serum methotrexate concentration-time curves were analyzed by non-compartmental model. Maximal serum concentration (C_{max}) and time to reach the peak concentration (T_{max}) were obtained directly by visual inspection of each subject's serum concentration-time profile. Other pharmacokinetic parameters including elimination half-life ($t_{1/2}$), area under the serum concentration-time curve (AUC), mean resident time (MRT), plasma clearance (Cl), and volume of distribution (Vd) were derived with the use of TopFit 2.0, a pharmacokinetic and pharmacodynamic data analysis program for PC.

A three-way analysis of varience (ANOVA) was used to determine the statistical differences of these pharmacokinetic parameters (C_{max}, T_{max}, and AUC). The ANOVA evaluated variability in subjects, treatment groups, study period, and formulations. To reduce the possibility of failing to detect small differences between the test product, the two one-sided tests procedure was performed. This procedure is referred to as the confidence interval approach. In this test, presently required by the FDA, a 90 per cent confidence interval (CI) about the ratio of means of the two drug products must be within ± 20 per cent for measurement of the rate and extent of drug bioavailability. Statistic analysis was performed on the natural log (ln) transformed data and the three-way ANOVA. Thereafter, using the variance estimate (VAR, or S^2) obtained from the ANOVA, calculated the 90 per cent CI from the formulation :

$$(\mu_A - \mu_B) = (\bar{X}_A - \bar{X}_B) \pm t^{v}_{0.1}\sqrt{\frac{2VAR}{n}}$$

Where $\bar{X}_A$ and $\bar{X}_B$ were the observed means of the (ln) transformed parameters (either C_{max} or AUC) for the test product (A) and the reference (B), VAR was the error variance obtained from the three-ways ANOVA (the residual mean square of a three-way crossover study), n was the number of subjects and $t^{v}_{0.1}$ was the tabulated two-tail t value for 90 per cent CI and v was the number of degree of freedom of the error mean square from the ANOVA. The antilogarithm of the confidence interval would express the bioequivalence as a ratio for the test and the reference products. The bioequivalence intervals of 0.8-1.25 for the ratio [test/reference] of the average AUC and C_{max} are accepted by the FDA, the Canadian and European authorities[10,12]. Regarding analysis of T_{max}, the limits for the bioequivalence range were expressed as untransformed data (absolute differences) and the stipulated bioequivalence range of difference T_{max} [test-reference] was ± 20 per cent of the T_{max} of the reference formulation[10,12].

The other pharmacokinetic parameters were expressed as mean ± SD. The relative bioavailability of the generic preparation was obtained from the equation :

$$\text{Relative bioavailability } (F_{rel}, \%) = \frac{AUC(test) * Dose(reference)}{AUC(reference) * Dose(test)} \times 100\%$$

RESULTS

Ten patients with rheumatoid arthritis tolerated and completed this study without any serious adverse effect. The mean serum concentration-times of each preparation were compared and presented in Fig. 1. The serum concentration-time profiles of each preparation were relatively consistent with little variation in serum methotrxate levels at each point of time. The calculated pharmacokinetic parameters following a single oral dose of 7.5 mg Methotrexate Lederle®, Emtrexate®, and Methotrexate Remedica®, respectively were then summarized and presented as mean ± SD to compare between the three preparations (Table 1).

Table 2 illustrates the mean and 90 per cent CI of the ratio [test/reference] of the C_{max}, AUC_{0-8}, and $AUC_{0-\alpha}$ as well as the differences of T_{max} between the test and reference preparations. The mean and 90 per cent CI of the ratio of the C_{max}, AUC_{0-8}, and $AUC_{0-\alpha}$ were 0.93 (0.87-1.00), 0.90 (0.82-0.98), 0.88 (0.79-0.99) and 0.97 (0.93-1.02), 0.95 (0.90-0.99), 0.94 (0.86-1.02) for [Emtrexate®/Methotrexate Lederle® and Methotrexate Remedica®/ Methotrexate Lederle®], respectively. These values were well within the acceptable bioequivalence ranges of 0.8-1.25, proposed by the US FDA. The means and 90 per cent

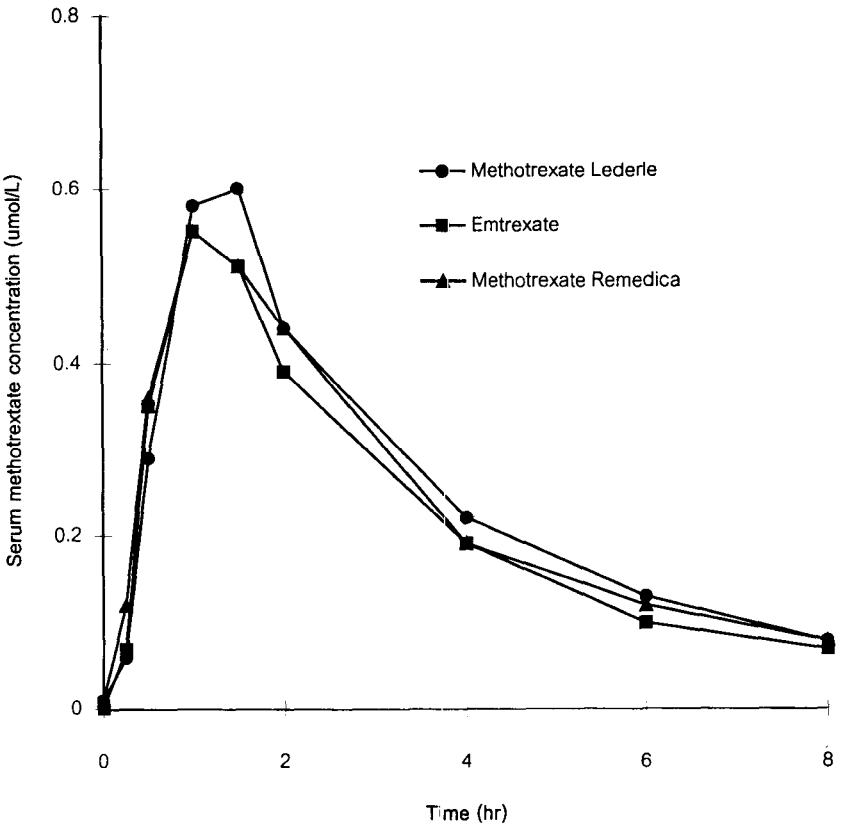

Fig. 1. **Mean serum concentration time curve following oral administration of 7.5 mg Methotrexate Lederle, Emtrexate, and Methotrexate Remedica.**

Table 1. **Pharmacokinetic parameters following single oral administrations of 7.5 mg methotrexate (Methotrexate Lederle®, Emtrexate® and Methotrexate Remedica®) in 10 Thai patients with rheumatoid arthritis.**

Parameters	Methotrexate Lederle®	Emtrexate®	Methotrexate Remedica®
C_{max} (μmol/L)	0.67 ± 0.15	0.65 ± 0.21	0.66 ± 0.17
T_{max} (h)	1.20 ± 0.35	1.15 ± 0.47	1.10 ± 0.39
MRT (h)	4.25 ± 1.43	4.10 ± 1.08	4.13 ± 0.87
CL (ml/min)	133.40 ± 58.58	147.92 ± 52.02	139.19 ± 50.97
Vd (L)	33.25 ± 14.36	37.08 ± 16.74	34.70 ± 10.41
$t_{1/2}$ (h)	3.03 ± 1.09	2.91 ± 0.71	2.99 ± 0.48
AUC_{0-8} (μmol.h/L)	2.04 ± 0.81	1.84 ± 0.81	1.90 ± 0.68
$AUC_{0-\alpha}$ (μmol.h/L)	2.44 ± 1.04	2.14 ± 0.96	2.25 ± 0.90
Frel (%)[a]		91.31 ± 15.28	95.18 ± 10.44

Data expressed as mean ± SD.
[a] : Determined at the time 0-8 h.

Table 2. Parametric 90 per cent CI for the mean pharmacokinetic parameters of methotrexate 7.5 mg.

Parameters	[Emtrexate®/Methotrexate Lederle®] ratio		[Methotrexate Remedica®/ Methotrexate Lederle®] ratio	
	Mean	90% CI	Mean	90% CI
C_{max} (μmol/L)	0.93	0.87 - 1.00	0.97	0.93 - 1.02
AUC_{0-8} (μmol.h/L)	0.90	0.82 - 0.98	0.95	0.90 - 0.99
$AUC_{0-\alpha}$ (μmol.h/L)	0.88	0.79 - 0.99	0.94	0.86 - 1.02
Parameter	Difference between [Emtrexate®- Methotrexate Lederle®]		Difference between [Methotrexate Remedica®- Methotrexate Lederle®]	
	Mean	90% CI	Mean	90% CI
T_{max} (h)	-0.05	-0.25 - 0.15	-0.10	-0.31 - 0.11

Table 3. Mean (± SD) of pharmacokinetic parameters following a single 7.5 mg oral administration of methotrexate from this study and previous studies.

Parameters	This study	Other studies *
C_{max} (μmol/L)	0.66 ± 0.17	0.51 ± 0.19[14]
T_{max} (h)	1.15 ± 0.40	1.47 ± 0.49[14]
		1.3 ± 0.4[15]
AUC_{0-8} (μmol.h/L)	1.93 ± 0.75	-
$AUC_{0-\alpha}$ (μmol.h/L)	2.28 ± 0.94	2.76 ± 1.2[14]
MRT (h)	4.16 ± 1.11	4.2 ± 0.5[15]
CL (ml/min)	140.17 ± 52.42	95.8 ± 37.9[14]
Vd (L)	35.01 ± 13.68	20.9 ± 2.49[16]
$t_{1/2}$ (h)	2.98 ± 0.78	3.3 ± 1.1[13]
		1.23 ± 0.05[16]

* The values from various studies[13-16]
Data expressed as mean ± SD.

CI of T_{max} differences [Emtrexate®-Methotrexate Lederle® and Methotrexate Remedica®-Methotrexate Lederle®] were -0.05 (-0.25-0.15) and -0.10 (-0.31-0.11) hour, respectively. The values also overlapped the stipulated bioequivalence range of T_{max} differences (± 20% of the T_{max} of the reference formulation) of ± 0.25 hour.

Methotrexate was rapidly absorbed after oral administration. Average times to attain the peak concentration (T_{max}, hour) were 1.20 ± 0.35, 1.15 ± 0.47 and 1.10 ± 0.39 for Methotrexate Lederle®, Emtrexate® and Methotrexate Remedica®, respectively. The mean differences of T_{max} between the test and reference products were less than 20 per cent, an US-FDA acceptable value for bioequivalence. The T_{max} value were also similar to the ones reported in the literature (1-2 hours) (Table 3).

The average C_{max} value (μmol/L) observed after 7.5 mg Methotrexate Lederle®, Emtrexate®, and Methotrexate Remedica® were 0.67 ± 0.15, 0.65 ± 0.21 and 0.66 ± 0.17, respectively. The average areas under the plasma concentration (AUC_{0-8} and $AUC_{0-\alpha}$, μmol.h./L) were 2.04 ± 0.81 and 2.44 ± 1.04, 1.84 ± 0.81 and 2.14 ± 0.96, 1.90 ± 0.68 and 2.25 ± 0.90 for Methotrexate Lederle®, Emtrexate®, and Methotrexate Remedica®, respectively. The means (parametric 90% confidence intervals) of the ratios of AUC and C_{max} [μ Emtrexate®, (test)/ μ Methotrexate Lederle® (reference)] were 0.88 (0.79-0.99) and 0.93 (0.87-1.00), respectively. The means (parameric 90% confidence intervals) of the ratios of AUC and C_{max} [μ Methotrexate Remedica® (test)/ μ Methotrexate Lederle® (reference)] were 0.94 (0.86-1.02) and 0.97 (0.93-1.02), respectively. These

values were well within the bioequivalence range of 0.8-1.25 for the mean ratio (test/reference) of AUC and C_{max} as established by the US-FDA (Table 1). The average AUC and C_{max} of methotrexate in this study were also comparable to those values reported in the literature (Table 3).

The mean resident times (MRT, hour) of the three products were nearly identical (4.25 ± 1.43, 4.10 ± 1.08, and 4.13 ± 0.87 for Methotrexate Lederle®, Emtrexate®, and Methotrexate Remedica®, respectively). The average half-life ($t_{1/2}$), clearance (CL) and volume of distribution (Vd) were comparable between the three preparations (Table 1). The average $t_{1/2}$, CL and Vd of the three preparations were 2.98 ± 0.78 hours, 140.17 ± 52.42 ml/min, and 35.01 ± 13.68 L, respectively, which were consistent with those values reported in previous studies (Table 3).

DISCUSSION

Low dose mehtotrexate given weekly for rheumatoid arthritis refractory to conventional therapy was well tolerated in our study. Serious adverse effects, including elevated liver enzymes, myelosuppression (leukopenia), and mucositis were not observed.

The pharmacokinetics and bioequivalence of the three preparations of mehtotrexate tablets (Methotrxate Lederle® *vs* Emtrexate® and Methotrexate Remedica®) were evaluated in this study. No significant differences in AUC, C_{max} or T_{max} between the three preparations were observed individually or collectively in our rheumatoid arthritis patients. The FDA criterion for relative bioequivalence of the ratio test/reference [Emtrexate®/Methotrexate Lederle® and Methotrexate Remedica®/Methotrexate Lederle®] within 90 per cent CI of 0.8-1.25 were demonstrated for the above parameters, representing the similar rate and extent of methotrexate absorption. The 90 per cent CI of Emtrexate®/Methotrexate Lederle® were 0.87-1.00, 0.82-0.98 and 0.79-0.99 for the C_{max}, AUC_{0-8} and $AUC_{0-\alpha}$, respectively. Similarly, the 90 per cent CI of Methotrexate Remedica®/Methotrexate Lederle® were 0.93-1.02, 0.90-0.99 and 0.86-1.02 for the C_{max}, AUC_{0-8} and $AUC_{0-\alpha}$, respectively. A small range of 90 per cent CI of the C_{max}, AUC_{0-8} and $AUC_{0-\alpha}$ observed in this study, verified that an adequate number of subjects were enrolled and the three methotrexate preparations possessed a high probability of demonstrating practical equivalence. Although this study was considered preliminary because of a small sample size, our data supported that the generic Emtrexate® and Methotrexate Remedica® could be used interchangeably with Methotrexate Lederle®.

The pharmacokinetic variables for methotrexate in this study were quite similar to those values observed previously in patients with rheumatoid arthritis (Table 3). Absorption of oral methotrexate was rapid (T_{max} 1.15 ± 0.40 hour) and a wide inter-patient variability in the C_{max} ranged from 0.36-0.96 μmol/L was found. The mean volume of distribution (Vd) was 35.01 ± 13.68 L or approximately 0.5-1 L/kg. The mean methotrexate clearance (CL) was 140.17 ± 52.42 ml/min. A wide inter-patient variation in methotrexate clearance was due to individual renal function, since the drug was mainly eliminated by glomerular filtration and tubular secretion. In our study, patients with normal BUN levels were included and this selection procedure did not exclude the possibility that some of the patients had mild impaired renal function. Generally, methotrexate clearance ranges from one to as much as two times the creatinine clearance (CrCL), therefore, patients with low methotrexate clearance should receive close monitoring for renal functions and risk of drug toxicity. The average half-life of methotrexate in this study was 2.98 ± 0.78 hours. This value represented primary renal elimination ($t_{1/2\beta}$), ranges from 3-5 hours. Triphasic elimination has been reported in the literature. The terminal phase half-life ranged from 8-26 hours which represented redistribution of methotrexate from deep tissue sites and has been correlated with methotrexate toxicity[17]. The sampling interval of 8 hours seemed appropriate because it exceeded the two drug half-lives and the drug concentrations during the 8-hour sample period approximated the limits of detection of the assay.

The use of nonsteroid anti-imflammatory drugs (NSAIDs) except aspirin were allowed during the study period since there was no observable interaction between low dose methotrexate and various NSAIDs, with respect to the AUC, C_{max} C_{max}/dose T_{max} and serum half-life[14, 15,18,19].

The metabolite 7-hydroxymethotrexate has displayed significant blood concentration during metabolism and may contribute to the cli-

nical effect of methotrexate. However, the concentration of this metabolite was not determined in this study, because its formation did not influence the extent of drug absorption.

SUMMARY

We conducted a bioequivalence testing of three different preparations of 7.5 mg formulations of Methotrexate Lederle® (the innovator) *vs* the generic Emtrexate® and Methotrexate Remedica® in 10 Thai patients with rheumatoid arthritis. The result showed no significant difference between the three brands concerning the rate of absorption (C_{max}, T_{max}, MRT) and the extent of bioavailability (AUC). The parametric 90 per cent CI and point estimates of the mean difference of these parameters were within the acceptable range based on standard bioequivalence guidelines. Methotrexate plasma clearance (CL), volume of distribution (Vd) and elimination half-life ($t_{1/2}$) obtained from this study were also comparable to those values reported in the literature. Therefore, the generic Methotrexate Lederle®, Emtrexate® and Methotrexate Remedica® can be used interchangeably when cost-effectiveness is concerned.

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การศึกษาเปรียบเทียบคุณภาพและไบโออะไวลาบิลิตีของยาเตรียมเมโธเทรกเซทในผู้ป่วยคนไทยที่เป็นโรคข้ออักเสบรูมาตอยด์

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การศึกษาคุณภาพและไบโออะไวลาบิลิตีของยาเมโธเทรกเซทชนิดเม็ด (เอมเทรกเซท®, บริษัทฟาร์มาเคมี จำกัด, เมโธเทรกเซท เรเมดิกา®, บริษัทเรเมดิกา จำกัด) เปรียบเทียบกับยาต้นตำรับ (เมโธเทรกเซท เลเดอเร®, บริษัทเลเดอเร จำกัด) ในผู้ป่วยโรคข้ออักเสบรูมาตอยด์ชาวไทยจำนวน 10 คน การศึกษาเป็นแบบ randomized, double blind, three-period cross over trial โดยผู้ป่วยแต่ละคนจะรับประทานยาเมโธเทรกเซทครั้งละ 7.5 มิลลิกรัม จำนวน 3 ครั้ง ตรวจวัดความเข้มข้นของยาเมโธเทรกเซทในซีรัมด้วยวิธีฟลูออเรสเซนต์ อิมมูโนเอสเสส การศึกษาพบว่าค่าทางเภสัชจลนศาสตร์ของยาเมโธเทรกเซททั้ง 3 ตำรับไม่มีความแตกต่างกัน มีค่าเฉลี่ยและช่วงระยะความเชื่อมั่นร้อยละ 90 ของอัตราส่วนระหว่าง เอมเทรกเซท®/เมโธเทรกเซท เลเดอเร® และเมโธเทรกเซท เรเมดิกา®/เมโธเทรกเซท เลเดอเร® ของความเข้มข้นสูงสุดของยาในเลือด, ไบโออะไวลาบิลิตีของยาหรือพื้นที่ใต้กราฟที่เวลา 0-8 ชั่วโมง, และพื้นที่ใต้กราฟที่เวลา 0-อสงไขย มีค่าเท่ากับ 0.93 (0.87-1.0) และ 0.97 (0.93 -1.02), 0.90 (0.82-0.98) และ 0.88 (0.79-0.99), 0.95 (0.9-0.99) และ 0.94 (0.86-1.02) ตามลำดับ ค่าต่างๆเหล่านี้อยู่ในช่วงของชีวสมมูลที่ยอมรับได้คือ 0.8-1.25 ค่าเฉลี่ยและช่วงระยะความเชื่อมั่นร้อยละ 90 ของความแตกต่างของเวลาที่ระดับยาสูงสุดในเลือด [เอมเทรกเซท®-เมโธเทรกเซท เลเดอเร® และเมโธเทรกเซท เรเมดิกา® -เมโธเทรกเซท เลเดอเร®] มีค่าเท่ากับ -0.05 (-0.25-0.15) และ -0.1 (-0.31-0.11) ตามลำดับ ซึ่งอยู่ในช่วงของชีวสมมูลที่ยอมรับได้คือ ± 0.25 ชั่วโมง จากการศึกษาครั้งนี้ สรุปได้ว่ายาเตรียมเมโธเทรกเซทจากทั้งสามบริษัทนี้มีชีวสมมูลกันในด้านปริมาณการดูดซึมยาและในด้านอัตราการดูดซึมของยา

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