BIOEQUIVALENCE OF TWO METHOTREXATE FORMULATIONS IN PSORIATIC AND CANCER PATIENTS

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OBJECTIVE: To compare the bioequivalence of a generic methotrexate (MTX) tablet (Mylan) with that of a brand-name (Lederle) product.

DESIGN: A single-dose, randomized, crossover study.

SETTING: Clinical Research Center (CRC) at a university hospital.

PATIENTS: Men and women who had a diagnosis of malignancy or psoriasis who were at least 21 years old.

METHODOLOGY: Two overnight study periods were scheduled at the CRC at least one week, but not more than two weeks apart. Each period consisted of a 10-hour fast prior to and 4 hours following oral MTX 15 mg administered as six 2.5-mg tablets. Blood samples were collected over 48 hours. Plasma MTX concentrations were determined using an HPLC assay. Area under the curve from zero to infinity ($AUC_{0-\infty}$) was calculated by the log-trapezoidal method.

RESULTS: Twenty-two patients (21 psoriasis, 1 colon cancer) aged 23–61 years completed both study periods. Mean values for peak concentration, time to peak concentration, and $AUC_{0-\infty}$ were 0.80 µmol/L, 1.2 hours, and 3.0 µmol•h/L, respectively, for Mylan's MTX tablets and 0.81 µmol/L, 1.4 hours, 3.0 µmol•h/L, respectively, for Lederle's MTX. Normalization for weight or body surface area did not affect interpatient variability. Relative bioavailability of generic MTX was 99.2 percent. Rate and extent of absorption were not significantly different and the confidence intervals were within the range of 80–120 percent required by the Food and Drug Administration.

CONCLUSIONS: Mylan's MTX tablet is bioequivalent to Lederle's product.

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METHOTREXATE (MTX) is an antimetabolite that interferes with folate utilization. Oral, low-dose MTX is used during maintenance therapy of acute lymphocytic leukemia,[1] for treatment of psoriasis[2] and rheumatoid arthritis,[3,4] and investigationally for the management of steroid-dependent asthma.[5,6] These conditions may require long-term therapy with weekly MTX dosages of 4–40 mg/m². The availability of a generic MTX product may offer potential cost savings to patients receiving this therapy.

Of primary concern, however, is whether the generic product produces equivalent plasma concentration profiles as the brand-name product. Previous literature reports demonstrate variance in absorption parameters (peak concentration [C_{max}], time to peak concentration [T_{max}], area under the curve [AUC]) for formulations of tetracycline, digoxin, and other generic products.[7-10] An increase or decrease in rate or extent of MTX absorption could have clinical implications. Disease-free survival in children with cancer appeared to correlate with the rate and extent of MTX absorption.[11] Likewise, increased toxicity resulting from variable MTX absorption profiles has been reported.[12]

The purpose of this study was to determine if the generic MTX product was bioequivalent to the innovator's product.

Methods

STUDY POPULATION

The study was conducted at the Clinical Research Center (CRC) at the University of Iowa Hospitals and Clinics. The protocol was approved by the CRC and the institutional review boards of the University Hospital and the Veterans Affairs Medical Center. Patients were considered for participation in the study if they had a diagnosis of malignancy or psoriasis, were at least 21 years of age, had not received antineoplastic medication within the last 14 days, had recovered from toxic effects of prior chemotherapy or radiation therapy, had a life expectancy of at least eight weeks, and did not have any other serious, acute medical problems. Interested patients meeting the above criteria underwent physical examination and laboratory evaluation. Eligibility criteria consisted of: no evidence of gastrointestinal disease or dysfunction; serum creatinine <177 µmol/L, bilirubin <34 µmol/L, liver transaminases <3 times the upper limit of normal; absolute neutrophil count $>1000 \times 10^6$ cells/L, platelet count $>75 \times 10^9$ cells/L, hemoglobin >90 g/L, and a negative pregnancy test for women. Written informed consent was obtained from all eligible patients agreeing to participate in the study.

STUDY DESIGN

A randomized, crossover design was used in this study. Patients were stratified according to disease state and randomly assigned a dosing sequence using a random numbers table. Two overnight study periods were scheduled at the CRC, at least one but not more than two weeks apart. Each study period consisted of an overnight fast, a morning MTX

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dose, a 24-hour stay in the CRC, blood sampling, and a standardized diet for the first 24 hours. Patients were discharged from the CRC after 24 hours, but returned for blood sampling at 36 and 48 hours. Complete blood counts with differential, liver function tests, serum chemistries, and serum creatinine were obtained before the first dose of MTX and 48 hours after the last dose.

DRUG ADMINISTRATION

For each study period, patients arrived at the CRC at approximately 0800 h. Patients fasted at least 10 hours prior to dosing and had not consumed alcohol or aspirin within the previous 48 hours. After obtaining an initial blood sample and dietary information, all patients took MTX 15 mg (six 2.5-mg tablets) of the brand-name product[a] or the generic formulation[b] with 240 mL water. Patients were not informed which tablets were the generic or which were brand-name products. Patients continued to fast another 4 hours after the drug was administered, after which a standardized high-protein, low-fat lunch was served (20 percent protein, 25 percent fat, 55 percent carbohydrate; approximately 725 calories). The CRC dietary department provided all food and beverages within the first 24 hours, allowing documentation of type and amount of dietary intake for each patient during each study period. Patient activity was minimized during the first 6 hours after dosing. Except for urine collections, patients were instructed to remain in bed either sitting or lying down.

Twenty-four hours after MTX administration, patients were provided oral leucovorin[c] 10 mg to be taken every six hours for four doses. This was to minimize the risk of myelosuppression associated with MTX.

SAMPLE COLLECTION

A heparin lock was inserted for 24 hours in a forearm vein to facilitate serial blood sampling. The initial 1 mL of blood drawn was discarded; 10-mL samples were obtained immediately prior to MTX administration and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 10.0, 14.0, 18.0, and 24.0 hours after MTX administration. Patients returned to the CRC 36 and 48 hours after MTX administration for these blood samples. The samples were placed in glass blood tubes containing EDTA and immediately were centrifuged; the plasma then was extracted into labeled glass sample tubes and frozen between –15 and –25 °C. Each patient had a separate sample storage box, which contained all plasma samples from both study periods. Therefore, the patients' samples from each course were exposed to the same conditions. All samples were sent to Mylan Pharmaceutical on dry ice via Federal Express for MTX concentration determination. Samples were labeled as "Course I" or "Course II," and only the site investigator knew which product each patient had received. The product code was not revealed until after preliminary analysis indicated no difference between the two tablets.

ANALYTICAL METHODOLOGY

HPLC with ultraviolet detection was used to quantify MTX in the patient samples. The method had a lower limit of quantitation of 0.0044 µmol/L, intra- and interday precisions of less than 10 percent, and was linear between 0 and 1.1 µmol/L. Plasma extraction was accomplished by placing 0.5 mL of MTX-spiked plasma or patient sample in a 16 × 125 mm borosilicate glass test tube, adding 2 mL of HPLC-grade distilled water, and vortexing. Internal standard 100 µL (2.5 µg/mL triamterene in CH_3OH:H_20 [1:1]) then was added and vortexed. Then 130 µL of 0.5N HCl was added and vortexed. The plasma sample then was loaded onto a solid-phase extraction column (Supelclean LC-SCX) preconditioned with 2 mL CH_30H followed by 2 mL H_20. The plasma sample was allowed to pass through the packing completely while a slow dropwise flow rate was maintained. The column then was washed with 2 × 1.0 mL aliquots of H_20 followed by 2 × 1.0 mL aliquots of CH_3OH, allowing packing to dry completely between washings. Samples were eluted with 4 × 500 µL aliquots of CH_3OH:NH_4OH (98:2). The eluate was dried at 30–35 °C on an N-EVAP. Samples were diluted to 150 µL with mobile phase, vortexed, and transferred to WISP vials for analysis.

The HPLC system was made up of a Waters Associates 6000 A pumps with a Waters Associates Intelligent Sample Processor Model 710B,[d] Spectroflow Model 773 UV detector[e] and a Hewlett Packard Reporting Integrator Model HP3390A.[f] The wave length was set at 305 nm. A Beckman Ultrasphere OCTYL 4.6 mm × 15 cm column was used with a solvent system of CH_3CN:0.01M KH_2PO_4/0.005M heptane sulfonate (15:85), adjusted to a pH of 3.0. Flow rate was 1.5 mL/min, providing MTX retention times of 5–8 minutes, and triamterene (internal standard) retention times of 12–17 minutes. One set of standards (0, 0.0044, 0.0066, 0.011, 0.022, 0.055, 0.11, 0.22, 0.33, 0.44, 0.55, 0.77, and 1.1 µmol/L) and controls (0.022, 0.11, and 0.55 µmol/L) for plasma were run with each group of patient samples. Chromatograms of the pre-MTX dose samples did not contain any interfering peaks or components, indicating that concomitant medications did not affect the assay. Leucovorin was evaluated for assay interference, and also did not interfere with the MTX assay.

Table 1. Patient Characteristics

CHARACTERISTIC	MEAN (SD)	RANGE
Age (y)	32 (12)	21–61
Weight (kg)	81.0 (21.6)	49.4–143.7
Body surface area (m^2)	1.93 (0.29)	1.47–2.77
Methotrexate dosage		
(mg/kg)	0.20 (0.05)	0.10–0.30
(mg/m^2)	7.9 (1.1)	5.4–10.2

PHARMACOKINETIC ANALYSIS

AUC from zero to infinity ($AUC_{0-\infty}$) was determined using linear trapezoidal estimation of the area from time of dosing to T_{max}, log-linear trapezoidal estimation of the area from peak concentration to the time of last measurable concentration, and extrapolation of the area from the last measurable concentration to infinity by dividing the last concentration by the elimination rate constant (K_e) calculated for each curve. Other noncompartmental pharmacokinetic parameters analyzed included C_{max}, T_{max}, K_e, terminal half-life ($t^1/_2$), and relative bioavailability.

STATISTICAL ANALYSIS

ANOVA was performed using the General Linear Models procedure of Statistical Analysis Systems.[g] The statistical model included factors accounting for sequence, subjects nested in sequence, period effect, and treatment. All main effects were tested against the residual error (MSE) from the ANOVA. A two one-sided test was used to calculate 90 percent confidence intervals.[13]

Results

Thirty-two patients were screened for participation in this study. Two did not meet the study eligibility criteria (uncontrolled high blood pressure, hepatitis); another two elected not to participate. Of the remaining 28 patients, 22 completed both parts of the study. Reasons for not completing the study included difficult venous access in 2 patients, out-of-state move by 1 patient, and 3 cancellations by the principal investigator because preliminary evaluation of data indicated sufficient statistical power with 22 data sets.

Of the 22 patients (11 men, 11 women) completing the study, 21 had psoriasis and 1 had cancer; mean age was 32 years (range 21–61). All patients received a standardized dose of MTX 15 mg, which resulted in a two- to threefold dosage difference among patients when normalized to body surface area or body weight, respectively (Table 1). Eleven subjects received Mylan's MTX product first. Con-

[a]Lederle lot #229-417, yellow/scored.
[b]Mylan lot #2S007K, peach/scored.
[c]Burroughs Wellcome lot #7N3091.

[d]Waters Associates, Milford, MA.
[e]ABI Analytical, Ramsey, NJ.
[f]Hewlett Packard, Pittsburgh, PA.
[g]SAS Institute, SAS Circle, Cary, NC.

current medications included oral contraceptives (7 women), topical steroids (2 patients), gemfibrozil and verapamil (1), and enalapril and fluphenazine (1). These medications were taken at the same dosages and schedules during both phases of the study.

BIOEQUIVALENCE PARAMETERS

ANOVA showed no period, treatment, or sequence effect. MTX concentrations in the 36- and 48-hour blood samples were generally below the lower limit of assay quantitation. Therefore, the bioavailability parameters were obtained from the 0–24 hour samples only. Bioavailability results are summarized in Table 2. No significant differences were detected in the rate or extent of MTX absorption. The mean $AUC_{0-\infty}$, C_{max}, T_{max}, K_e, and $t^1/_2$ did not differ significantly between the two MTX products. The 90 percent confidence intervals for the test (Mylan)/reference (Lederle) ratios for all parameters except T_{max} were within the required 80–120 percent range, thus establishing bioequivalence. The mean difference in T_{max} was 0.2 hour (12 min), which has no statistical or clinical significance.

Figure 1 depicts the mean MTX plasma concentrations measured for each product. The relative bioavailability of Mylan MTX to Lederle MTX was 99.2 percent. The standard deviation of each concentration was large, indicating considerable interpatient variability. A threefold range of AUC and C_{max} values was seen with both products. Normalizing the parameters to weight or body surface area did not alter the variability.

ADVERSE REACTIONS

Mild-to-moderate headache was reported by five patients: three patients experienced headaches with the first treatment course, one patient with the second course, and one with both courses. The incidence was evenly distributed between the MTX products. Headaches were treated with acetaminophen and were thought to result from caffeine and/or activity restriction rather than to MTX. One patient also reported mild nausea after taking leucovorin during her first MTX course. No change in clinical laboratory values were noted during the study.

Discussion

In order for systemically absorbed generic drug products to receive marketing approval from the Food and Drug Administration (FDA), bioequivalence of the generic to the innovator's or brand-name product must be shown. The products must contain the identical amounts of the identical active drug ingredient in the same dosage form and also meet compendial or applicable standards of the identity, strength, quality, and purity. In addition, the rate and extent of absorption cannot show a significant difference when administered at the same molar dose as the brand-name product under similar conditions. Generally, differences of less than 20 percent in the mean AUC between generic and brand-name products are acceptable.[14] The 20 percent difference allows for interpatient variability and uncontrollable variance factors, and minimizes the potential for differences in clinical response.

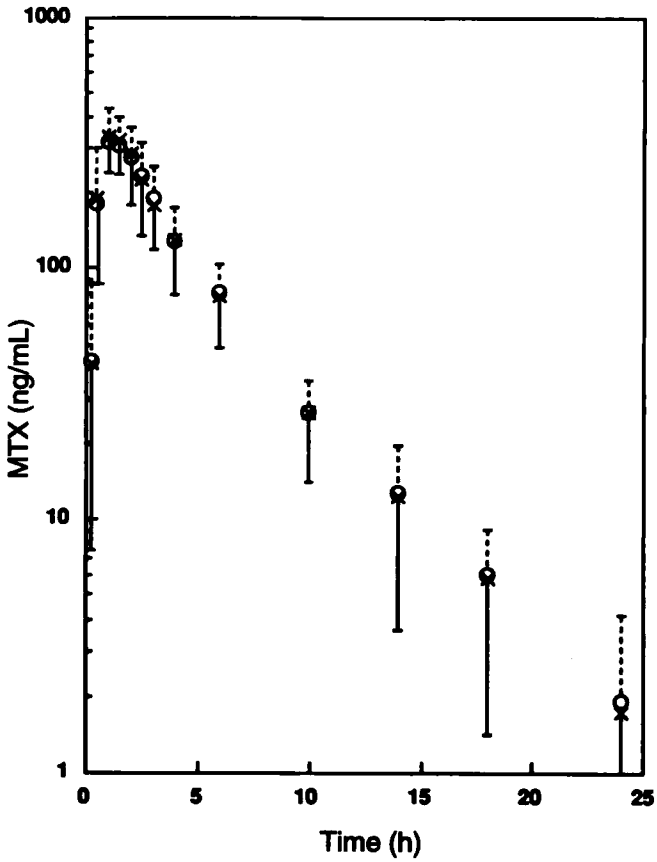

Figure 1. Mean (SD) methotrexate plasma concentrations after Mylan tablets (×) and Lederle tablets (o). MTX = methotrexate.

Table 2. Methotrexate Bioequivalence Parameters[a]

PARAMETER	METHOTREXATE PRODUCT		MEAN % RATIOS	% CONFIDENCE INTERVALS[b]	
	MYLAN	LEDERLE		LOWER	UPPER
AUC_{0-24} (μmol•h/L)	2.98 (0.86)	3.00 (0.78)	99.3	93.9	104.7
$AUC_{0-\infty}$ (μmol•h/L)	3.02 (0.86)	3.04 (0.78)	99.2	93.8	104.6
C_{max} (μmol/L)	0.80 (0.18)	0.81 (0.23)	98.5	91.3	105.6
T_{max} (h)	1.2 (0.4)	1.4 (0.5)	86.7	69.5	103.8
K_e (h-1)	0.21 (0.06)	0.21 (0.04)	1.025	97.2	107.8
$t^1/_2$ (h)	3.6 (1.3)	3.6 (1.0)	1.019	95.5	108.3

AUC = area under the curve; C_{max} = peak concentration; K_e = elimination rate constant; $t^1/_2$ = terminal half-life; T_{max} = time to peak concentration.
[a]Mean (SD).
[b]Two one-sided confidence interval (90 percent) for the test (Mylan)/reference (Lederle) ratios.

The Mylan generic MTX tablets used in this study produced absorption parameters comparable to those of the industry standard (Lederle tablets) and well within the 20 percent allowed by the FDA. In fact, the difference between the mean $AUC_{0-\infty}$ of the Mylan generic and the Lederle MTX product was <1 percent. Mean C_{max} and T_{max} differences between the two products were <2 percent and 14 percent, respectively. T_{max} exceeded the lower bound of the 90 percent confidence intervals; however, T_{max} is an insensitive and variable parameter. The larger difference is probably caused by the dependence of T_{max} on blood sampling times. Other than the initial 15-minute sample, blood samples were obtained at 30-minute intervals during the absorption phase. The mean difference in T_{max} was small, however, and of no statistical or clinical relevance.

A threefold range of AUC, C_{max}, and T_{max} values was observed for both products. This interpatient variability is consistent with other reports in the literature.[12,15-18] Normalization of the parameters to weight (kg) or body surface area (m^2) did not greatly reduce the variability. This is similar to results published by Kearney et al., who found no correlation between doses administered and plasma concentrations obtained from 11 children receiving MTX 9.1–24.5 mg/m^2/wk.[12] Uniform dosages of MTX are unlikely to produce predictable MTX plasma concentrations. However, the crossover nature of our study should have minimized the effect this variability had on the comparison of the two products, as the participants served as their own controls.

The use of actual patients with psoriasis or cancer in this bioequivalence study offers the potential advantage of deriving data specific for the populations using this medication. Another advantage of this study is the relatively large sample size and the prolonged blood sampling time compared with other MTX bioavailability studies.

Both products were well-tolerated with no significant adverse effects reported during this single-dose, crossover study. Because inactive ingredients may differ between the products, the potential does exist for a patient to react to one product and not the other. This occurs only rarely, and usually is associated with the coloring dye.

This study was conducted under controlled, fasting conditions. Food and other medications that affect the gastrointestinal tract may interfere with MTX absorption.[19-22] Because the tablets are immediate-release and lack special coatings, these factors should affect the generic and brand-name MTX products in a similar manner.

The Mylan MTX product is bioequivalent to Lederle MTX tablets, providing a reliable substitution option to healthcare professionals and patients. ≃

References

1. **Jonsson OG, Kamen BA.** Methotrexate and childhood leukemia. *Cancer Invest* 1991;9:53-60.
2. **Roenigk HH, Auerbach R, Mailbach HI, Weinstein GD.** Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988;19:145-56.
3. **Weinblatt WE, Weissman BN, Holdsworth DE, Fraser PA, Maier GL, Falchuk KR, et al.** Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis: 84-month update. *Arthritis Rheum* 1992;35:129-37.
4. **Jeurissen MEC, Boerbooms AMTh, van de Putte LBA, Doesburg WH, Lemmens AM.** Influence of methotrexate and azathioprine on radiologic progression in rheumatoid arthritis: a randomized, double-blind study. *Ann Intern Med* 1991;114:999-1004.
5. **Guss S, Portnoy J.** Methotrexate treatment of severe asthma in children. *Pediatrics* 1992;89:635-9.
6. **Mullarkey MF, Lammert JK, Blumenstein BA.** Long-term methotrexate treatment in corticosteroid-dependent asthma. *Ann Intern Med* 1990;112:577-81.
7. **Meyer MC.** The therapeutic equivalence of drug products—a second look. Monograph. Knoxville: University of Tennessee Center for the Health Sciences, 1985.
8. **Strom BL.** Generic drug substitution revisited. *N Engl J Med* 1987;316:1456-62.
9. **Koch-Weser J.** Bioavailability of drugs (first of two parts). *N Engl J Med* 1974;291:233-7.
10. **Koch-Weser J.** Bioavailability of drugs (second of two parts). *N Engl J Med* 1974;291:503-6.
11. **Craft AW, Rankin A, Aherne W.** Methotrexate absorption in children with acute lymphoblastic leukemia. *Cancer Treat Rep* 1981;65(suppl 1):77-81.
12. **Kearney PJ, Light PA, Preece A, Mott MG.** Unpredictable serum levels after oral methotrexate in children with acute lymphoblastic leukaemia. *Cancer Chemother Pharmacol* 1979;3:117-20.
13. **Schuirmann DJ.** A comparison of the two one-sided test procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987;15:657-80.
14. **Nightingale SL, Morrison JC.** Generic drugs and the prescribing physician. *JAMA* 1987;258:1200-4.
15. **Balis FM, Savitch JL, Bleyer WA.** Pharmacokinetics of oral methotrexate in children. *Cancer Res* 1983;43:2342-5.
16. **Campbell MA, Perrier DG, Dorr RT, Alberts DS, Finley PR.** Methotrexate: bioavailability and pharmacokinetics. *Cancer Treat Rep* 1985;69:833-8.
17. **Teresi ME, Crom WR, Choi KE, Mirro J, Evans WE.** Methotrexate bioavailability after oral and intramuscular administration in children. *J Pediatr* 1987;110:788-92.
18. **Herman RA, Veng-Pedersen P, Hoffman J, Koehnke R, Furst DE.** Pharmacokinetics of low dose methotrexate in rheumatoid arthritis. *J Pharm Sci* 1989;78:165-71.
19. **Pearson ADJ, Craft AW, Eastham EJ, Aherne GW, Littleton P, Pearson GL, et al.** Small intestinal transit time affects methotrexate absorption in children with acute lymphoblastic leukemia. *Cancer Chemother Pharmacol* 1985;14:211-5.
20. **Pinkerton CR, Glasgow JFT, Welshman SG, Bridges JM.** Can food influence the absorption of methotrexate in children with acute lymphoblastic leukemia? *Lancet* 1980;1:944-6.
21. **Oguey D, Kolliker F, Gerber NJ, Reichen J.** Effect of food on the bioavailability of low-dose methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 1992;35:611-4.
22. **Evans WE, Christensen ML.** Drug interactions with methotrexate. *J Rheumatol* 1985;12(suppl 12):15-20.

EXTRACTO

OBJETIVO: Comparar la bioequivalencia del fármaco metotrexato (MTX) genérico (Mylan) con el de marca (Lederle).

DISENO: Estudio aleatorio cruzado utilizando dosis sencilla.

ESCENARIO: Centro de investigación clínica localizado en un hospital universitario.

PACIENTES: Hombres y mujeres mayores de 21 años de edad con diagnóstico de cáncer o soriasis.

METODOLOGIA: Dos períodos de estudio de un día para otro fueron programados con por lo menos una semana pero no más de dos semanas de separación. Cada período consistió de 10 horas de ayuno antes y 4 horas después de una dosis de 15 mg de MTX (seis tabletas de 2.5 mg). Se obtuvieron muestras de sangre durante 48 horas. Concentraciones en plasma de MTX se determinaron utilizando un ensayo de HPLC. El área bajo la curva se calculó usando el método de trapezoide logarítmico.

RESULTADOS: Un total de 22 pacientes (21 con soriasis, 1 con cáncer del colon) entre las edades de 23 y 61 completaron ambos períodos de estudio. Los valores promedio para C_{max}, T_{max}, $AUC_{0-\infty}$ fueron 0.80 µmol/L, 1.2 horas, 3.0 µmol•h/L para el fármaco genérico, y 0.81 µmol/L, 1.4 horas, 3.0 µmol•h/L para el fármaco de marca. La normalización de

los datos de acuerdo a peso o área superficial del cuerpo no afectó la variabilidad entre pacientes. La biodisponibilidad relativa de MTX genérico fue 99.2 por ciento. La rapidez y la cantidad de absorción no fueron significativamente diferentes y los intérvalos de confianza estuvieron dentro de los requeridos por la Administración Federal de Alimentos y Drogas (80–120 por ciento).

CONCLUSIONES: La tableta de MTX de Mylan es bioequivalente a la tableta de MTX de Lederle.

HOMERO A. MONSANTO

RESUME

OBJECTIF: Comparer la bioéquivalence de deux formulations de méthotrexate (MTX) en comprimés: MTX générique (Mylan) et le produit original fabriqué par la compagnie pharmaceutique Lederle.

DEVIS EXPERIMENTAL: Etude randomisée, en chassé-croisé, avec administration d'une dose unique.

LIEU DE L'ETUDE: Centre de recherche clinique (CRC) d'un hôpital universitaire.

PATIENTS: Hommes et femmes d'au moins 21 ans souffrant d'une néoplasie ou de psoriasis.

METHODOLOGIE: L'étude s'est deroulée la nuit, au CRC, en deux portions, qui devaient être séparées d'au moins une semaine et d'au plus deux semaines. Chacune des parties comportait 10 heures de jeûne avant l'administration de 15 mg de MTX à raison de 6 comprimés de 2.5 mg, et 4 heures de jeûne après la prise du médicament. Des prélèvements sanguins ont été recueillis sur une période de 48 heures. Les concentrations plasmatiques de MTX ont été mesurées par HPLC. La surface sous la courbe ($AUC_{0-\infty}$) a été calculée par une méthode logarithmique-trapézoïdale.

RESULTATS: Vingt-deux patients (21 avec psoriasis, 1 avec cancer du colon) âgés de 23 à 61 ans ont complété les deux portions de l'étude. Les valeurs moyenne de C_{max}, T_{max}, et $AUC_{0-\infty}$ étaient de 0.80 µmol/L, 1.2 heures, 3.0 µmol•h/L pour les comprimés de MTX de Mylan, et de 0.81 µmol/L, 1.4 heures, 3.0 µmol•h/L pour les comprimés de MTX de Lederle, respectivement. La normalisation des résultats en fonction du poids ou de la surface corporelle n'a pas diminué l'importance des variations interindividuelles. La biodisponibilité du MTX générique était de 99.2 pour cent. Le taux et le degré d'absorption n'étaient pas significativement différents et les intervalles de confiance se situaient à l'intérieur des limites acceptées par la "Food and Drug Administration" américaine, soit de 80 à 120 pour cent.

CONCLUSIONS: Les comprimés de MTX de Mylan sont bioéquivalents au produit de la compagnie Lederle.

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