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SUMMARY

Background
Methotrexate (MTX) is administered subcutaneously to Crohn's Disease (CD) patients. There are very few studies evaluating the use of oral (PO) MTX in CD. A drug and its pharmaceutical alternative are equivalent (bioequivalence) when the bioavailability of the alternative falls within 80–125% of the bioavailability of the standard (US Food and Drug Administration - FDA).

Aim
To compare the pharmacokinetic (PK) profiles of PO and subcutaneous (SC) MTX in CD patients to determine the bioequivalence of these two routes.

Methods
Eleven patients received a PO and an SC MTX dose (25 mg) separated by one week over a two-week interval. Blood samples were collected at specified times over a 24-h period for each patient on two separate days. MTX plasma levels were obtained using sensitive mass spectrometry. Areas under the curve (AUC) were compared between the two routes.

Results
The mean AUC values were 3375 ng/mL × h (PO MTX) and 3985 ng/mL × h (SC MTX). The mean AUC ratio (PO/SC) was 0.86 (0.62–1.08). This correlates with a relative PO bioavailability of 86% in comparison to SC. The 90% confidence interval for the mean AUC (PO/SC) ratio is (0.785, 0.929). There were no adverse events.

Conclusions
The mean MTX AUC (PO/SC) in these patients falls outside the 90% confidence interval for the bioequivalence limit. SC MTX is more bioavailable than PO MTX; however, the mean relative MTX bioavailability (PO/SC) nearly met the FDA bioequivalence standard and PO MTX could be proposed in responders who would prefer this route.

INTRODUCTION

Crohn's Disease is an incurable chronic inflammatory condition that can involve any part of the gastrointestinal tract. The inflammation of CD follows a discontinuous course along the gut's length and may involve all its layers, from mucosa to serosa. CD affects 400 000–600 000 individuals in North America with an increasing annual incidence.[1] Its course is punctuated by periods of exacerbation and remission.

Since the first published use of methotrexate (MTX), a dihydrofolate reductase inhibitor, in CD by Kozarek in 1989,[2] MTX has been shown to be an effective treatment for the induction and maintenance of remission in this patient population.[3, 4] However, such randomised controlled studies have only evaluated the parenteral administration of MTX; there has been ongoing debate about the relative oral (PO) absorption of this drug in CD patients. Smaller nonrandomised studies have reported conflicting data regarding the bioavailability of PO vs. parenterally administered MTX in CD patients.[5, 6]

Orally administered MTX is effective for treating cutaneous lupus erythematosus, sarcoidosis and rheumatoid arthritis (RA).[7–9] Furthermore, frequent intramuscular (IM)/subcutaneous (SC) injections have been associated with peripheral nerve injury, local irritation, pain, bleeding, fibrosis, abscess, gangrene and contractures.[10] There may also be increased costs and inconvenience for the patient with this mode of drug administration. Patients typically prefer oral therapy over parenteral therapy. Therefore, the PO administration of MTX may be preferred for patients with CD over injections if proven to be bioequivalent. Currently, there are no recommendations regarding the PO administration of MTX in CD.

Bioavailability refers to the rate and extent to which a drug is absorbed and becomes available in the systemic circulation. Bioequivalence refers to the equivalent release of the same drug substance from two or more drug formulations as well as the equivalent rate and extent of absorption from these formulations. According to the US Food and Drug Administration, 'if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted for that drug product.'[11]

The aim of this study was to compare the pharmacokinetic profiles (PK) of PO and SC MTX in patients with CD to determine the bioequivalence of these two routes of administration.

MATERIALS AND METHODS

Patients

This single centre, nonrandomised, bioequivalence study was carried out in London, Ontario, Canada. Recruitment of patients took place from March 2009 to August 2011. Eligible patients were at least 18 years of age with a history of CD who were starting on MTX therapy. Patients receiving concurrent corticosteroids ($n = 4$) were eligible for this study. Patients were excluded from the study for the following reasons: use of MTX within 4 weeks of study enrolment; pre-existing hepatic, pulmonary or renal dysfunction; known pregnancy or ongoing breast-feeding; history of cancer, erythrocyte macrocytosis or high alcohol consumption or MTX hypersensitivity. Written informed consent was obtained from each patient. The study protocol was approved by the University of Western Ontario Health Sciences Research Ethics Board (15765).

Procedure

Patients were screened for eligibility 2 weeks prior to enrolment. Each patient underwent oesophagogastroduodenoscopy (EGD) to rule out upper gastrointestinal tract CD involvement. All EGDs were normal. Body weight and routine blood tests (blood count, biochemistries, liver enzymes and creatinine) were measured for each patient. All female patients were screened for pregnancy with a urine pregnancy test. Demographic data, including CD-related medications and disease activity (assessed using the Crohn's Disease Activity Index - CDAI) were collected for each patient. Each patient participated in two separate Pk analyses (PO MTX and SC MTX). Each analysis occurred over the course of one study day separated by one week's duration as per the standard MTX dosing interval. Patients were instructed to take nothing by mouth the morning of their 2 study days. During each study day, patients randomly received either a PO or a SC 25 mg dose of MTX. The dose of MTX was selected based on the standard practice carried out at London Health Sciences Centre (LHSC) for CD patients. Plasma collections at 10 prespecified time-points measured in hours (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10) were obtained for MTX plasma concentrations. MTX plasma concentrations were measured using a sensitive mass spectrometer. Patients were monitored clinically for signs of MTX intolerance (hypersensitivity reaction, gastrointestinal upset).

Pharmacokinetic analysis

Pharmacokinetic (Pk) analysis was performed by the noncompartmental method. PK parameters collected

included the following: maximum plasma drug concentration (Cmax); time to the maximum plasma drug concentration (tmax); total drug exposure estimated by the area of under the plasma concentration-time curve (AUC); and the drug half-life (t1/2). The AUC of PO and SC MTX for each patient was calculated using the trapezoidal rule (numerical integration) and represents the bioavailability of MTX administered either orally or subcutaneously. The relative bioavailability (the fraction of an administered dose of unchanged drug that reaches the systemic circulation compared to the standard of care) of oral MTX was calculated by determining the ratio of AUC_{po} to AUC_{sc}, assuming 100% bioavailability of SC MTX.

Statistical analysis

Data are presented as the arithmetic mean. PK data for PO and SC MTX were compared using a two-one-sided-tests procedure suggested by Schuirmann.[12] Consider μ_{PO} and μ_{SC} to be the population mean AUCs of PO and SC respectively. The bioequivalence of PO and SC can be tested using the following statistical hypotheses: H_0: $\mu_{PO}/\mu_{SC} \leq \theta_1$ or $\mu_{PO}/\mu_{SC} \geq \theta_2$ vs. H_A: $\theta_1 \leq \mu_{PO}/\mu_{SC} < \theta_2$. The null hypothesis ($H_0$) states that μ_{PO} and μ_{SC} are not equivalent and the alternative hypothesis (H_A) states that μ_{PO} and μ_{SC} are equivalent. As recommended by the FDA (2001), the AUC was log-transformed using natural logarithms. The 90% CI for the difference in the means of the log AUCs was calculated and then antilog transformed to obtain the 90% CI of the ratio of the mean AUCs between PO and SC.

RESULTS

Twelve CD patients were enrolled in this study. Their baseline characteristics are highlighted in Table 1. One patient was withdrawn from the protocol on the day of the first Pk analysis due to meeting one of the exclusion criteria (high alcohol consumption) on re-assessment. The PK analyses for the remaining 11 patients are summarised in Table S2 (published online).

The mean bioavailability of PO MTX and SC MTX was 3375.0 ng/cc × h ± 1143 and 3985.4 ng/cc × h ± 1556.7 respectively (Figure 1). The mean maximum concentrations were 955 ng/mL (PO) and 1163.6 ng/mL (SC). The times to maximum concentration were 1.4 h (PO) and 0.6 h (SC). The mean

Table 1 | Baseline characteristics

| Patient	Sex	Race	Age	Disease duration (years)	Intestinal involvement	Concomitant medications	CDAI score	Previous intestinal resection	Laboratory values
1	M	Caucasian	53	5	Colon	Asacol 1.2g BID	61	No resections	Wbc 7.8, Hb 136, plts 299, ALT 15, AST 16
2	M	Caucasian	29	3	Colon	Nil	55	No resections	Wbc 8.1, Hb 161, plts 213, ALT 18, AST 22
3	F	Caucasian	52	17	Colon	Pentasa 500mg BID	28	No resections	Wbc 7.8, Hb 126, plts 390, ALT 16, AST 30
4	M	Caucasian	43	4	Colon	Budesonide 6mg daily	49	No resections	Wbc 8.6, Hb 145, plts 336, ALT 16, AST 16
5	F	Caucasian	34	0.75	Colon	Nil	96	No resections	Wbc 8.1, Hb 114, plts 245, ALT 17, AST 12
6	M	Caucasian	28	7	Terminal ileum	Prednisone 40mg daily	122	No resections	Wbc 13.6, Hb 140, plts 291, ALT 12, AST 17
7	F	Caucasian	56	40	Ileum and Colon	Prednisone 15mg daily	229	Small bowel resections	Wbc 6.7, Hb 136, plts 236, ALT 16, AST 20
8	M	Caucasian	29	14	Ileum	Remicaide 5mg/kg q8w	264	Ileal resection	Wbc 7.7, Hb 131, plts 276, ALT 32, AST 24
9	F	Caucasian	56	9	Colon		34	No resections	Wbc 8.6, Hb 136, plts 273, ALT 17, AST 16
10	F	Caucasian	56	7	Ileum and colon	Budesonide 9mg daily	6	Ileal resection	Wbc 7.7, Hb 146, plts 320, ALT 19, AST 19
11	F	Caucasian	47	21	Ileum and colon	Nil	24	Ileocecal resection	Wbc 7.7, Hb 131, plts 276, ALT 32, AST 24

CDAI, Crohn's disease activity index; Wbc, white blood cells; Hb, haemoglobin; plts, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
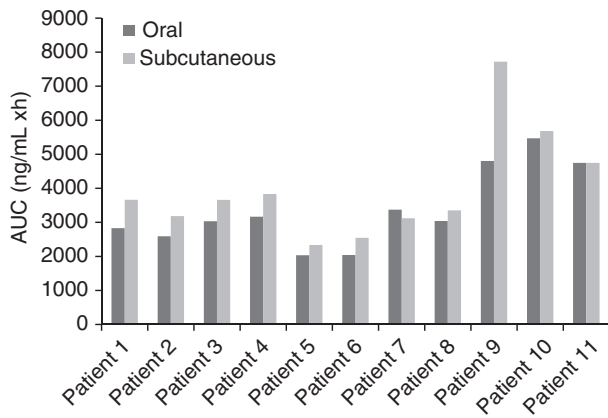
Figure 1 | The area under the curve (AUC) of PO (dark bar) vs. SC (light bar) MTX in 11 patients with Crohn's disease. AUC represents the bioavailability expressed as a rate of orally and subcutaneously administered methotrexate.

half-lives were 2.6 h (PO) and 2.9 h (SC). This is consistent with values quoted in the literature. The mean relative bioavailability (PO/SC) was 0.86 ± 0.1. This correlates with a mean relative PO bioavailability of 86% in comparison to SC MTX with a range of 62–108% (Figure 2). There were no adverse events.

According to the 80/125 rule proposed by FDA,[13, 14] if the 90% confidence interval (CI) of the ratio of the averages of AUCs for two treatments (PO and SC)
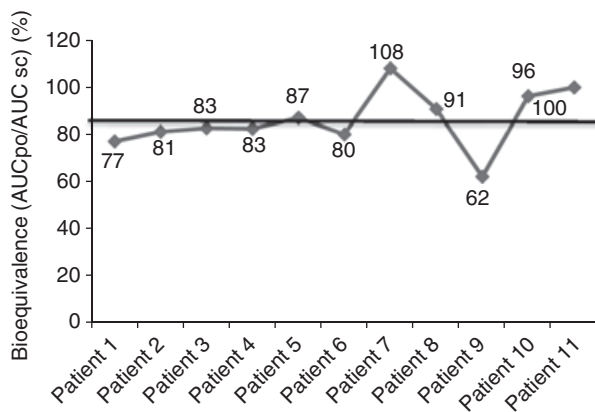
Figure 2 | The relative bioavailability (the diamonded grey line) of PO MTX vs. SC MTX in 11 patients with Crohn's disease. The Food and Drug Administration (FDA) require a minimum relative bioavailability of 80% for two drugs (or routes of administration) to be considered bioequivalent. The mean relative bioavailability of the 11 study patients is represented by the black line.

entirely falls in a bioequivalence limit (0.8, 1.25), then bioequivalence can be concluded. In our study, the 90% confidence interval for the mean AUC (PO/SC) ratio is (0.785, 0.929).

DISCUSSION

The mean relative bioavailability of PO MTX to SC MTX is 0.86 in this study population. On average, there is a 14% reduction in the bioavailability of PO compared with SC MTX. This could be accounted for by presystemic metabolism (first-pass effect) as well as possible insufficient absorption time, relating to the interpatient variability in gut motility.[15] Furthermore, competing intraluminal reactions such as PO MTX hydrolysis by gastric acids, digestive enzymes and luminal microflora could contribute to the reduced bioavailability.[15] The 90% confidence interval for the mean AUC (PO/SC) ratio (0.785, 0.929) falls just outside the range of the 80/125 rule proposed by the FDA; therefore, the statistical bioequivalence of these two routes cannot be concluded.[13, 14] However, it should be noted that even though there is a statistically significant difference between the bioavailability of PO and SC MTX, this may not translate to a clinically significant difference with respect to overall MTX exposure.

A similar mean relative bioavailability of PO vs. SC MTX was seen in a Pk study in non-CD patients.[16] Jundt et al. examined the relative PO bioavailability of MTX in comparison to parenterally administered MTX in 12 RA patients. They found that the relative PO bioavailability of MTX was 0.85 when administered by tablet in comparison to parenteral administration. Furthermore, there is evidence to support the use of oral MTX in RA patients despite the fact that the PO vs. SC bioavailabilities are not identical.[17, 18]

With respect to the CD patient population, earlier studies examining the efficacy of MTX as a treatment for CD evaluated the parenteral administration of this drug.[2–4] It has been hypothesised that the reasoning behind the exclusive evaluation of this route in the CD population was due to the following: (i) limited oral bioavailability relative to parenteral bioavailability; (ii) greater interpatient variability in drug exposure with oral administration.[5] More recent studies by Kurnik et al. and Stephens et al. fail to support these assumptions.

Stephens et al. conducted a PK analysis of PO and SC MTX in a CD paediatric population.[5] They found that the relative bioavailability of PO vs. SC MTX was high (0.84) and concluded that the dose rather than the route

of administration was the most important factor influencing bioavailability. Similarly, they found that the interpatient variability is no more an issue in PO dosing than in SC dosing.

A similar study in an adult CD population by Kurnik *et al.* found a slightly lower mean relative PO bioavailability of 0.74.[6] This may have been due to the lower and variable doses of MTX used in that study compared with the current study which used the same 25 mg dose in all patients.

The current study is the first of its kind to conduct PK analyses in CD patients at the point of MTX initiation. Previously referenced studies have analysed the bioavailability of SC and PO MTX in patients who had been on therapy for several weeks to months. Despite their findings, Stephens *et al.* questioned whether or not the high relative bioavailability of PO MTX was limited to patients who were chronically on the medication. The current study confirms that the relative PO bioavailability of MTX at its initiation appears to be similar to that seen in patients who have been on the drug for a prolonged period of time.

Therefore, the current study adds to this emerging body of literature supporting the relative comparability of PO and SC MTX in CD patients. Similarly to the above mentioned studies, it highlights the lack of evidence to support the avoidance of PO MTX in CD patients.

It should be noted that the majority of the patient population in this study was in remission. This study did not examine the effect of MTX on disease activity or the effect of disease activity on MTX bioavailability. Patients with small bowel and colonic resections were included in this study (5/12). Four of the five patients had limited ileal resections while one patient had several small bowel resections where the amount of bowel removed could not be quantified. MTX is a highly specific substrate for the proton-coupled folate transporter, that is maximally expressed in the duodenum and jejunum.[19] Within our patient population, these areas were not affected by disease or surgery. Thus methotrexate absorption may be different in CD patients with an altered duodenum or jejunum by surgery or inflammation.

Also, the patient population is this study were fasting up until the time of PO MTX consumption and up to two hours after the medication was ingested. Patients in clinical practice will likely not be fasting and this could possibly change the absorption of MTX if orally administered.

CONCLUSIONS

Further study to determine the cause of interpatient drug bioavailability variability in CD, particularly in the setting of active disease or significant upper GI involvement, is needed to more fully determine the overall bioavailability and clinical dosing strategies. Nevertheless, at least when CD is in remission, our data suggest that it may be reasonable to offer PO MTX to patients requiring the drug, particularly in cases where compliance may be compromised by a parenteral route of administration.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Pharmacokinetic analysis of PO vs. SC MTX in 8 patients with Crohn's disease.

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