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A study of parenteral use of methotrexate in rheumatic conditions

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Summary

• This paper reports the findings of a small pragmatic study to compare the safety and efficacy of methotrexate administered by intramuscular and subcutaneous injection, and to teach patients to self-administer methotrexate by the subcutaneous route.

• Eight patients with rheumatic conditions, already receiving a stable weekly dose of methotrexate by intramuscular injection, were entered into this 13-week study.

• Serum levels of methotrexate were measured on six consecutive occasions: three whilst patients received intramuscular methotrexate and then three after switching to the subcutaneous route.

• Patients were taught to self-administer their methotrexate subcutaneously and were then discharged to perform this task at home.

• Levels of disease activity and psychological scores were measured at the start and end of the study. Satisfaction with self-administration and teaching of injection techniques were assessed at 13 weeks.

• Serum methotrexate levels were not significantly affected by the route of administration. All patients were able to perform self-injection safely and seven out of eight preferred self-administration at home.

• This small study demonstrates that there is no difference in the safety and efficacy of methotrexate given by either parenteral route. Patients were able to

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administer safely methotrexate subcutaneously. Self-administration reduced hospital visits, was more convenient for patients and improved patient satisfaction.

Keywords: injections, methotrexate, patient education, patient satisfaction, rheumatology, self-administration.

Introduction

Methotrexate (MTX), one of several disease-modifying anti-rheumatic drugs (DMARDs), is used to treat rheumatic diseases such as rheumatoid arthritis and psoriatic arthritis. It may be given orally or parenterally, although it is not licensed in the UK for the latter route of administration. Patients are usually prescribed oral MTX. However, where this is ineffective or poorly tolerated due to nausea and gastrointestinal upset (Consumers' Association, 1995), it may be given as a weekly intramuscular (IM) injection. Methotrexate may be better tolerated and more effective in this form (Brooks *et al*., 1990). It is not normal practice in rheumatology for MTX to be prescribed by subcutaneous (SC) injection except for paediatric patients (Wallace, 1998). Concerns about the safety of using parenteral MTX centre on its cytotoxic properties and the dangers associated with handling and spillage. In the UK professional guidelines exist for its safe administration and disposal (RCN, 1989; Royal Marsden Hospital NHS Trust, 1996a).

For some years a number of patients with a variety of rheumatic conditions attended rheumatology nurse-led clinics at a district general hospital on a weekly basis to receive IM injections of MTX. They had previously tried oral MTX but it proved either to be ineffective or poorly tolerated by this route, resulting in a change of administration to weekly IM injections. Their continued care in nurse-led clinics rather than in primary care was for several reasons: the general practitioner was unwilling for them to receive a cytotoxic drug in the health centre; district nurses were unwilling to administer the injections in patients' homes; or the consultant rheumatologists preferred hospital supervision by nurse specialists because of disease complexities. The question was asked whether some patients could be safely discharged to self-administer their own injections at home, with improved convenience for themselves and a reduction in hospital visits. In order to do this a switch from the IM route of administration to the SC route was considered.

Literature review

A literature review revealed that few studies have been undertaken to look at the safety and efficacy of the parenteral routes of injectable MTX. A study by Brooks *et al*. (1990) looked at the pharmacokinetics of administration by the two parenteral routes. This small study was of five patients with rheumatoid arthritis (RA) already taking MTX, but by which route was not disclosed. Each patient was randomly assigned to be given two injections either of IM MTX or SC MTX, at the same dose as their current MTX therapy, and a week apart. Serum MTX levels were measured at intervals ranging from time zero to 8 h post-injection. Peak concentration values varied between the routes of administration and between patients but was not shown to be statistically significant. No patients complained of any problems relating to the SC injection and most found it less painful than the IM route. The authors mention the advantages of self-administration of SC MTX at home and support its use.

A brief report by Zackheim (1992) describes how 10 dermatology patients were given SC MTX injections over a period of between 3 to 17 weeks. Six had previously been receiving IM MTX injections. It was found that SC injections were well tolerated, less painful, easier to administer and clinical response appeared to be similar to IM MTX. Zackheim notes that SC injections can be self-administered, which is an advantage to patients who would otherwise need to make weekly hospital visits for MTX administration.

A study by Jundt *et al*. (1993) compared the bioavailability of low dose MTX given by oral solution, oral tablet, SC route and IM route. Baseline serum concentrations of MTX were determined for 12 patients with RA who were already taking MTX weekly. Over three consecutive weekends the subjects were randomized to receive MTX either by oral solution, oral tablet or IM injection. In an extension to the study six subjects returned to receive their MTX as an SC injection. Serum MTX concentration was measured at intervals from a quarter of an hour post-injection to 24 h post-injection. The results indicated that there was no significant difference between the bioavailability of MTX with either the SC or the IM routes of injection, and that these two routes of injection are interchangeable. The biovailability of the tablets was found to be lower than the injection and the authors suggest that adjustments should be made to

dosages when changing patients from oral to parenteral administration.

A report by Wallace (1998) that looked at the use of MTX in childhood rheumatic diseases, notes that children are prescribed higher doses of MTX than adults. The SC route is preferred as absorption is better, few gastrointestinal side-effects occur, and considerable savings occur when parents (and/or teenagers) are taught to self-administer SC MTX at home, compared with the cost of tablets.

This was reflected in a retrospective study of SC MTX vs. oral MTX in RA and juvenile rheumatoid arthritis (JRA) by Ostrov *et al.* (1998) that demonstrated that SC MTX was more cost-effective than oral MTX. Fifty-two patients, 16 with JRA and 36 with RA had received oral MTX followed by SC MTX for at least 3 months each. The results showed that 73% of patients were switched from oral to SC injection due to lack of efficacy. Efficacy improved in 65% after the switch and 79% were able to self-administer SC MTX. Moreover, the cost of switching the route of administration to SC MTX saved $676 000 annually for a population of 1000 RA and JRA patients.

Another retrospective study by Arthur *et al.* (1999), from the University of British Columbia, describes the safety, efficacy and practicality of self-administration of MTX or gold by the IM route. Forty patients, with RA and psoriatic arthritis (PSA), were selected to self-administer their injections. Twenty were receiving gold, 17 were receiving MTX and three were receiving both drugs. They or a partner were taught IM self-injection techniques and were assessed at baseline and every 3 months thereafter. Compliance was measured by self-report, regular monitoring of adherence, drug supply requirements and attendance at clinic appointments. Patient satisfaction with self-injection was assessed by questionnaire. The authors conclude that self- injection is convenient for patients in terms of time-saving and costs. Clinic visits were reduced from a mean of every 2 weeks to every 12th week, indicating substantial savings for the health care system. Some problems with non-compliance were identified relating to monitoring or injection schedules. The authors highlight the importance of patient education to prevent serious adverse outcomes.

In conclusion, the studies by Brooks *et al.* (1990) and Jundt *et al.* (1993) involved only single parenteral doses of MTX, small sample sizes and did not look at efficacy or patient satisfaction. The study by Zackheim (1992) used a small group of dermatology patients. Therefore, no conclusive evidence can be drawn from these three studies. Brooks *et al.* (1990) state that there is no significant difference between the two parenteral routes of administration. Jundt *et al.* (1993) concur with this opinion and state that the two routes of administration are interchangeable. Ostrov *et al.* (1998) found that the efficacy of MTX was increased after switching from the oral to the parenteral route. The general opinion appears to be that self-administration at home is practical compared with clinic attendance. The advantages noted by Brooks *et al.* (1990), Zackheim (1992) and Arthur *et al.* (1999) relate to time-saving and cost. The cost savings arising from a switch to parenteral MTX from the oral route are also noted by Wallace (1998) and Ostrov *et al.* (1998).

The paucity of studies into the efficacy and safety of parenteral MTX is noted by Arthur *et al.* (1999) and reinforces the suggestion by Wallace (1998) that appropriate investigations could optimize the dosage, frequency of administration and route of delivery of this treatment.

Design of the study

This was a comparative, descriptive study with both qualitative and quantitative aspects. There were two aims to the study: to determine whether SC MTX is as safe and effective as IM MTX and whether patients could safely self-inject SC MTX at home. The objectives of the study were to compare blood levels of MTX whilst patients received MTX by each route, to assess the impact of changing from IM to SC on disease activity, to teach patients to safely administer their own injections by the SC route and to gauge patient satisfaction with self-administration of SC MTX.

Sample selection

Patients were enrolled from those already receiving IM MTX for a variety of rheumatic disorders, and who had been on a stable dose for a least 1 month. The study had been approved by the regional health service ethics committee. All participants received written information and written consent was obtained.

Research Instruments

An open-ended questionnaire format was used to gain qualitative data about symptoms of increased disease activity from this heterogeneous group. The measures of disease activity used were tender and swollen joint counts, duration of early morning stiffness (EMS), pain and fatigue visual analogue scales (VAS), erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and in the case of one subject creatinine phosphokinase (CPK).

Patients were asked to complete both the Stanford Health Assessment Questionnaire (HAQ) (Fries *et al.*, 1980) and the Hospital Anxiety and Depression Scale (HAD) (Snaith & Taylor, 1985). At the end of the study additional questionnaires were used to determine patient satisfaction and any problems relating to the self-administration of SC MTX.

Data collection

Data were collected in five stages.

STAGE 1

Participants were requested to write down what happened to them when their arthritis was better and also when it was worse. These qualitative data were used to ensure that measurements of disease activity were specific for each participant within this small heterogeneous population, and that the activity of symptoms relevant to their particular disease could be measured.

STAGE 2 (3 WEEKS)

Patients were assessed by one of the nurse specialists (VA) for baseline parameters of disease activity as described above. Further data recorded at baseline included age, gender, rheumatic condition, disease duration and length of time on IM MTX. For 3 consecutive weeks methotrexate was administered by IM injection by the clinical nurse specialists and blood was taken, 1 h after each injection, for measurement of MTX levels.

STAGE 3 (3 WEEKS)

The route of MTX administration was switched to SC injection, which was administered as specified in the *Manual of Clinical Nursing Procedures* (Royal Marsden Hospital NHS Trust, 1996b). For 3 consecutive weeks the injections were given by the clinical nurse specialists and on each occasion blood was taken, 1 h post-injection, for measurement of MTX levels.

At each visit during this stage participants were taught, by the two nurse specialists (VA and DH), to self-administer SC injections. Comprehensible written information sheets, based on a question and answer format, about the injection technique, disposal of used syringes and how to deal with any spillage of MTX, were given to each participant. These assisted in the teaching process and provided participants with a reminder when they undertook the procedure at home.

Before the study commenced, discussions had taken place with the hospital pharmacist to ensure that MTX injections could be provided in 2-ml Luer lock syringes. It had been observed that sometimes the needle can be pulled off the end of the syringe when the needle guard is removed and also that patients with poor hand function could more easily grasp a wider syringe then the pen-type syringe that is more commonly used for SC injections. It was anticipated that 2-ml Luer lock syringes would avoid any problems. Syringes with needles already attached could not be provided as the sterility of the drug could not be guaranteed by the hospital pharmacy.

STAGE 4 (3 WEEKS)

Participants self-administered their MTX subcutaneously under the supervision of the nurse specialists at the hospital for 3 consecutive weeks. This was to ensure that the procedure was carried out in a sterile and safe manner. They were assessed regarding their ability to safely self-administer the injections and also the safe storage of their injections at home. These needed to be stored in a refrigerator and care taken that they were not accessible to children. Three pre-filled syringes in a lockable box, needles, alcohol swabs and a sharps disposal box were provided and participants were discharged for a month. They were advised to use the rheumatology telephone helpline number should they encounter any problems with self-administration between hospital visits.

STAGE 5 (4 WEEKS)

Participants self-administered their MTX by the SC route at home for 3 consecutive weeks. They then returned to the nurse-led clinics to collect further injections, for the clinical nurse specialist to review their self-administration technique, and for safety monitoring of their MTX therapy. Monitoring for safety was done at weeks 1, 4, 9 and 13. Disease activity was measured at this hospital visit for comparison against the baseline parameters.

Results

STAGE 1

The qualitative data gained from the open-ended questionnaire reflected the views of the individual participants. The use of an open-ended question asking about 'What happens when your arthritis is better and when it is worse?' permitted participants to express their experience freely. The measurement of health status in rheumatic

conditions, such as RA, can be difficult as symptoms vary considerably between patients. It is important therefore to understand the patient's perspective (Ryan, 1998).

Content analysis of the qualitative data obtained from Stage 1 revealed that pain, fatigue, joint swelling, stiffness, loss of function, immobility and depression were all factors related to increased disease activity for this group. These symptoms are commonly exhibited by patients with rheumatic disease and it was decided therefore to adopt the disease activity and outcome measures recommended by the OMERACT Committee (1993), namely the number of tender and swollen joints, visual analogue scale for pain, and functional status using the HAQ (Fries *et al.*, 1980). Physician and patient global assessment, acute phase reactants and radiological damage were excluded as not being useful for this study. Other measures used in addition were the duration of early morning stiffness (EMS), fatigue, anxiety and depression using the HAD questionnaire (Snaith & Taylor, 1985).

STAGE 2

Demographic data

Thirteen patients were invited to participate in the study. Five were receiving their IM MTX in primary care settings and eight were receiving their treatment at the nurse-led hospital clinics. The five from primary care were contacted by telephone, given an explanation of the study, and invited to participate. All declined, preferring to remain in primary care for the following reasons: one participant preferred to have the injection at home given by her husband, two were given it by the nurse as it was 'too far to come to the hospital', two others said that 'their hands were too bad to give the injection themselves'.

Of the eight participants who entered the study, two were male and six were female. Disease characteristics, disease duration, age range and length of time on MTX are shown in Table 1.

Serum levels of MTX

Analysis of weekly serum levels of MTX were undertaken by the biochemistry department using routine assays. As shown in Table 2, these varied within individuals each week and also between the two routes of administration, even although blood was taken strictly at 1 hour post-injection. There was no significant difference in blood serum levels between IM and SC MTX injections. Brooks *et al.* (1990) found slightly different MTX serum levels in their study of IM MTX vs. SC MTX and they list the possible factors that may influence this as being: change of

Table 1 Demographic data

Participant No.	Gender	Age (yr)	Disease	Disease duration (months)	Duration IM/MTX (months)	Dose (mg)	Stable dose (months)
01	M	55	PSA	48	15	7.5	2
02	F	52	WG	30	13	22.5	16
03	F	36	RA	72	6	15	1
04	F	49	PMS	72	5	7.5	5
05	F	58	RA	364	11	12.5	4
06	F	50	RA	132	19	15	11
07	F	38	RA	62	5	10	2
08	M	55	PSA	312	75	25	48

RA = rheumatoid arthritis; WG = Wegener's granulomatosis; PSA = psoriatic arthritis; PMS = polymyositis.

Table 2 Weekly and mean serum methotrexate levels (mmol L^{-1})

Participant No.	Week 1	Week 2	Week 3	Mean IM	Week 4	Week 5	Week 6	Mean SC
01	0.5	0.55	0.67	0.57	0.44	0.44	0.38	0.42
02	1.1	1.5	0.97	1.19	1.59	1.35	1.75	1.56
03	0.01	0.54	0.47	0.34	0.55	0.48	0.59	0.54
04	0.35	0.6	0.29	0.41	0.51	0.75	0.27	0.51
05	0.85	0.83	0.69	0.79	0.76	0.48	0.64	0.62
06	0.66	0.58	0.92	0.72	1.05	0.99	0.81	0.95
07	0.75	0.81	0.55	0.7	0.67	0.78	0.84	0.76
08	1.65	1.8	1.8	1.05	1.5	1.32	0.88	1.07

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