METHOTREXATE USE IN
PAEDIATRIC RHEUMATOLOGY
Information for health professionals

CLINICAL DRUG INFORMATION
Methotrexate is a structural analogue of folic acid. It competitively inhibits binding of dihydrofolate acid to the enzyme dihydrofolate reductase. The amount of intracellular folinic acid (the active metabolite of dihydrofolic acid) is thereby decreased, and intracellular metabolic pathways dependent on folinic acid affected. Purine and pyrimidine metabolism are two such pathways. Whilst these pathways are considered important, the exact mechanism of action of methotrexate in these conditions remains unclear.

Low-dose methotrexate is therapeutic in various disorders eg. rheumatology, gastroenterology, and dermatology. It is used to treat a wide range of childhood rheumatological conditions including: Juvenile Idiopathic Arthritis (JIA), Juvenile Dermatomyositis, Vasculitis, Uveitis, Systemic Lupus Erythematosus, Localised Scleroderma, Systemic Sclerosis and Sarcoidosis.

Methotrexate is the first-choice second-line agent to treat JIA, with up to 75% of JIA patients in recent registries having used methotrexate at some time in their disease course.¹

LICENSE
Oral and intravenous methotrexate are NOT licensed for JIA.

Pre-filled, pre-dosed methotrexate syringes; metoject® (Medac) for subcutaneous (sc) use are licensed for JIA in those over three years of age for polyarticular forms of JIA who have not responded to Non-Steroidal Anti-Inflammatory Drugs (NSAID’s)². These syringes have a reduced volume (50mg/ml) of drug resulting in a smaller syringe. Also these commercially available syringes have a pre-attached needle, making them safer; decreasing the risk of accidental spillage. While the drug is licensed for children over three years of age with JIA, it is often prescribed for those under this age and for other conditions due to the lack of other available licensed medications.

Methotrexate is only given as a ONCE WEEKLY dose, whether oral, subcutaneous or in rare instances; intravenously. It is good practice to administer the same day each week for safety purposes and to promote concordance.

SAFETY
The National Patient Safety Association (NPSA, 2006³) ‘Methotrexate Treatment alert’ highlighted errors with incorrect Methotrexate dosing. They recommend families are advised of the dose and frequency, and given written information. Young people and families should be supplied with a methotrexate information sheet (copies available from BSPAR⁴), receive a blood monitoring booklet (either a local trust approved monitoring card or NPSA monitoring booklet) and an appropriate teaching package (if to be taught to self administer). Clinicians should be aware that
whilst the National Patient Safety Agency (NPSA)\(^3\) has issued a Patient Safety Alert specifically relating to improving compliance with oral methotrexate guidelines, the principles apply equally to other modes of administration.

**PRE-TREATMENT CONSIDERATION/TESTING**
Before commencing methotrexate the following should be checked:
- Full blood count (FBC)
- ESR and CRP
- Liver transaminase levels (Aspartate Aminotransferase (AST) and/or Alanine Aminotransferase (ALT))
- Serum creatinine
- Varicella immunity status
  - If negative, consider pre-treatment vaccination if systemic immunosuppression can be delayed
- Measles status
  - If negative, consider pre-treatment vaccination if systemic immunosuppression can be delayed

In addition:
- Ensure family know attending for regular blood tests is a requirement to receiving methotrexate
- Confirm who will be prescribing the methotrexate
- Confirm who will be administering the methotrexate
- If commencing subcutaneous therapy, ensure good shared care is initiated with the injections set up locally and support in place (if appropriate)
- Consider teaching the family how to administer their own injections, if the family are happy with this and suitable for teaching
- Consideration of life styles issues such as alcohol consumption and the importance of contraception whilst taking methotrexate of both females and males, and for 6 months after methotrexate cessation

**CONTRAINDICATIONS**
**Absolute:**
Active bacterial infection, active TB, active herpes-zoster infection, active life-threatening fungal infections, acute hepatitis B or C, planning (or in) pregnancy, breastfeeding

**Relative:**
Chronic hepatitis B or C, hepatic disease, renal disease

**DRUG INTERACTIONS**
Please see current British National Formulary for Children (BNFC)\(^5\) and metoject® (Medac) Summary of Product Characteristics (SPC)\(^2\) for further information.

**POTENTIAL SIDE EFFECTS**
These must be explained to the patient and parents/carers before commencing methotrexate therapy. The incidence of serious side effects with methotrexate used for the above indications are very low, however, please check with the BNFC\(^5\) and SPC\(^2\) for specific effects, and these should be reported with a yellow card.

**Frequently occurring side effects:**
1) Nausea, vomiting and anorexia. Nausea, vomiting and particularly anticipatory nausea, are more common\(^6,7\) and often underestimated problems in children. Although anti-emetics are often used, their effects on patients are variable and rarely stop anticipatory nausea. Anticipatory
nausea often affects the child for the whole day that their injection is due. The sickness felt is real, and this must be emphasised to them, and to their families. Anticipatory nausea and vomiting associated with weekly methotrexate is often not present at the beginning of treatment, but increases with duration of therapy.

Suggested strategies to overcome these troublesome side-effects include:

- Anti-emetics given before and after the dose of methotrexate, and sometimes for the following day
- Increasing the dose of folic acid
- Administering at night
- Changing the route of administration
- Referral to specialist support eg. Clinical Nurse Specialist (CNS), child psychology.

2) Post dosing reaction – feeling ‘unwell’ for 24 hours after their methotrexate

3) Mouth ulceration: minor mouth ulceration may be treated with increased doses of folic acid

4) Injection site reaction (if given by subcutaneous injection): usually mild e.g. erythema, pruritis

5) Hepatotoxicity – irreversible liver damage in children receiving methotrexate for rheumatological conditions has not been reported. Transient elevation of liver enzymes however, is common.

Other potential side effects could include; rashes, bone marrow suppression and altered liver function blood tests (see below under monitoring). Fertility concerns, lymphoma risk and pulmonary disease are much less of an issue than in adult practice.

**DOSAGE /ADMINISTRATION**

Usual starting dose: **10-15mg/m² once weekly**. Maximum dose (BNFC): 25mg/m² once weekly

Although Appendix D of the NICE Technology Appraisal for Biological therapies (2002) states that ‘patients must have had adequate trials of methotrexate (defined as at least 3 months at a dosage of parenteral methotrexate of 20mg/m² weekly unless significant toxicity limits the dose tolerated’ there is no evidence that doses greater than 15mg/m² are more effective.

Methotrexate can be administered subcutaneously, orally, intravenously and intramuscularly. The dose is not altered by route of administration. The first two routes are the usual modes of administration. Subcutaneous administration achieves higher bioavailability than oral administration and less gastrointestinal upset, particularly at higher doses. If tolerated, subcutaneous administration is therefore preferable as first line compared to oral. Intramuscular administration is more painful than subcutaneous and should not be used. If the patient has venous access methotrexate may also be given by this route, in this case the dose should be given by a slow bolus injection.

**DISPOSAL**

A purple topped cytotoxic sharps bin must be used for any Metoject syringes and a purple lidded waste bin for any syringes or ancilliary items used.

**FORMULATIONS**

Subcutaneous route:

Use of pre-filled commercially available licensed syringes (metoject®, Medac) is best practice:

- They are licensed, whereas hospital prepared syringes of methotrexate are not
• They are safer than hospital prepared syringes as they have a pre-attached needle, thus reducing the risk of spillage.
• The volume is lower, thus less medication is injected at a time and therefore preferred by the child/young person.
• A home package of care can be established supported by the manufacturing company with provision of ancillary items, and a delivery/waste collection service can be provided.
  ○ NOTE; if the injections are delivered to the patient’s home, they have a reduced cost as VAT is not included.
• The syringes do not require refrigeration and have a long shelf life.
• The use of these syringes is endorsed by the RCN 2013.

Metoject® (medac) is available in pre-filled syringes in strength of 50mg/ml. They come in gradients of 2.5mg at a starting dose of 7.5mg. With this in mind, doses should be increased or decreased in steps of 2.5mg.

Oral route:
1. Tablets: 2.5mg and 10mg
   • It is good practice to prescribe single tablet strength to avoid patient confusion.
   • 10mg tablets are not available from all community pharmacies following NPSA recommendations.
   • If the child is struggling with 2.5mg tablets obtained in the community, alternative hospital prescribing of 10mg tablets may help.
2. Oral solution: 10mg in 5mls or 10mg in 1ml (manufactured specials). Other strengths may be available. To avoid potential dosage errors it is recommended that only the 10mg/5ml solution should be prescribed.

Intravenous route:
Give as a slow bolus (with Sodium Chloride 0.9% and following manufacturer’s recommendations).
Use local IV guidelines especially when using central lines (high pressure generated by 1ml syringes (pre filled) may damage lines).

FOLIC ACID
Usual dose: 5mg orally weekly (given on a different day to the weekly methotrexate dose) or 1mg orally daily.

Whilst there is evidence for the use of folic acid to ameliorate adverse effects of methotrexate in adults, there is no supporting evidence for the paediatric population. Folic acid may be given, either when initiating methotrexate treatment, or in response to adverse effects (e.g. nausea, mouth ulcers).

MONITORING
Regular blood test monitoring is accepted on a consensus basis, with recognition that early detection of signs of toxicity (through blood test monitoring) is likely to reduce the risk of serious adverse effects. However, evidence to this effect has proved elusive. In the British Isles, monitoring practice varies significantly, particularly between larger and smaller centres.

Accepting the paucity of evidence, the following recommendations are consensus-based:
- After starting methotrexate centres across the UK monitor FBC and LFT’s from as frequently as two weekly to monthly, depending on the individual patient.
- After this, the Full Blood Count and liver transaminase (Aspartate Aminotransferase (AST) and/or Alanine Aminotransferase (ALT)) levels at 2-4 monthly intervals.
- Serum Creatinine at 6 monthly intervals.
Interpreting blood-monitoring results is challenging and evidence guiding intervention lacking. Raised liver transaminases encountered during monitoring may be the result of factors other than methotrexate \(^2\), often being caused by intercurrent infection \(^9\). Needlessly withholding doses of methotrexate is likely to decrease disease control. Therefore intervention must take into consideration the likeliest cause of the blood test result abnormality and balance risks. The following recommendations are largely consensus based;

<table>
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<tr>
<th>Monitoring Parameter</th>
<th>Action</th>
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<tr>
<td>AST or ALT &gt;3-times upper limit of normal reference range, or unexplained fall in albumin</td>
<td>Consider omitting methotrexate and repeating blood test. May necessitate dose reduction, or rarely discontinuation. Avoid abrupt cessation as may result in disease flare. Consider other more common causes for abnormal blood test results</td>
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<td>WCC &lt;3.0x10^9/l (or steadily falling)</td>
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<td>Neutrophils &lt;1.5x10^9/l (or steadily falling)</td>
<td>Consider omitting methotrexate whilst investigating cause</td>
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<td>Lymphocytes &lt;0.5x10^9/l (or steadily falling)</td>
<td>Consult paediatric nephrologist. May necessitate dose reduction, or rarely discontinuation</td>
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<td>New or worsening unexplained dyspnoea or cough</td>
<td>Patient must be reviewed by medical team prior to continuing with methotrexate</td>
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<td>Rising creatinine (falling creatinine clearance)</td>
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<tr>
<td>Rash or unexplained bruising, temperature above 38.5°C or chicken pox contact or suspected chicken pox infection</td>
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**VACCINATIONS**

- Live Vaccines: Children and young people receiving methotrexate should not receive any live vaccines (e.g. MMR, Varicella, BCG, and Yellow Fever).
- Inactivated vaccines: these should be given according to the normal immunization schedule (including HPV), however methotrexate treatment may lower the level of immunity achieved.
- Children receiving methotrexate are ‘immunosuppressed’ and should receive annual influenza immunization. They may also benefit from special vaccinations formulated in response to particular threats (e.g. H1N1). See Department of Health “Immunisation against infectious disease” for current advice.

In patients receiving methotrexate exposed to varicella (in whom immunity is uncertain), passive immunisation should be provided using VZIG or oral aciclovir. Patients developing chickenpox or shingles should be treated with acyclovir and have their methotrexate withheld until the patient has recovered. See Department of Health “Immunisation against infectious disease” for current advice.

**FERTILITY/PREGNANCY/BREAST-FEEDING**

Embryotoxicity and teratogenicity have been documented, and methotrexate should therefore be avoided in young people either contemplating pregnancy, or sexually active and not using reliable methods of contraception \(^{16}\). Sexual health should always be addressed before starting methotrexate and if the child is too young to be addressed directly, this should be revisited once the child matures. These issues **must** be discussed prior to commencing methotrexate treatment.

Health professionals should be aware that methotrexate can cause embryotoxicity and teratogenicity, and they should avoid handling of it if they are concerned.

**PERSONAL PROTECTIVE EQUIPMENT**

-Good hand washing practices are essential.
-As with giving any subcutaneous therapy, the use of gloves by health professionals should be standard practice, however if the young person is administering their own injection, gloves are unnecessary.

-NO Personal Protective Equipment, such as goggles, armlets and aprons are necessary when giving low dose prefilled syringes for rheumatological conditions as advised by the RCN 2013\textsuperscript{13}. This is supported by the paper by Wong et al (2009) who deliberately contaminated skin with low dose methotrexate and found no adverse effects\textsuperscript{17}.

-Universal precautions, such as good hand washing and gloves are recommended for the handling of body fluids by health professionals as standard.

-Spillage kits are NOT required when using a pre-filled pre-dosed methotrexate syringe, such as metoject®.

**TEACHING**

The RCN guidance (2013)\textsuperscript{13} advocates that NO specialist teaching, including practical assessment is required for healthcare practitioners, apart from the ability to safely give subcutaneous therapies and know reasons for use and possible side effects.

It is recognized as good clinical practice that patients and carers receive comprehensive teaching about the treatment including contra-indications, risks and side-effects. Ideally teaching families how to administer their own methotrexate increases independence. For home administration of subcutaneous methotrexate, a training plan ensuring clear understanding of the associated process and responsibilities is necessary. A robust, risk-assessed system in which the paediatric rheumatology specialist nurse plays a key role is required to fulfill these requirements\textsuperscript{18}.

**REFERENCES**

1. Becker, ML. Role of methotrexate in juvenile idiopathic arthritis: where we have been and where we are going. Int.J.Clin.Rheumatol. 2013 8(1):123-135


5. www.bnfc.org (accessed March 2013)


FURTHER READING

AUTHORS
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