Methotrexate

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What is methotrexate?

Methotrexate is a medication used in low doses to treat inflammatory skin conditions such as psoriasis and eczema/dermatitis. It is also prescribed for rheumatoid arthritis, psoriatic arthritis, and increasingly, other inflammatory and autoimmune disorders (off-label). In much higher doses, it is used as a chemotherapy agent for leukaemia and some other forms of cancer.

Which skin diseases respond to methotrexate?

Methotrexate has been used in the treatment of moderate to severe psoriasis for many years. It is now used in suitable patients that have other extensive or troublesome skin conditions. These include:

- Atopic dermatitis
- Pityriasis rubra pilaris
- Pompholyx and other forms of chronic hand dermatitis
- Pityriasis lichenoides (PLC) and pityriasis lichenoides et varioliformis acuta (PLEVA)
- Chronic spontaneous urticaria
- Immunobullous diseases such as bullous pemphigoid and pemphigus
- Morphoea (localised scleroderma)
- Cutaneous lupus erythematosus

Methotrexate is used in adults and in children over 3 years of age.

How quickly does the skin condition improve on methotrexate?

For responding skin diseases, methotrexate usually shows some benefit within 6 to 8 weeks. Maximum effects are generally achieved within 5 to 6 months, depending on dose escalation. In chronic plaque psoriasis, about 50–70% of patients see a good result (a reduction in PASI score of 75%).

How does methotrexate work?

There are several mechanisms that may explain the effect of low-dose methotrexate in skin diseases.

- Methotrexate has anti-inflammatory properties, through increasing intracellular adenosine, a purine nucleoside.
- Methotrexate has immune modulatory effects. It reduces the homing of T cells to the skin, reduces oxidative inflammation in other immune cells (neutrophils/monocytes), and alters immune signals sent between cells (inhibits cytokine release from monocyte/macrophages and decreases TNF-α, IL-10, IL-12).
- At higher (anti-cancer) doses, methotrexate acts more as an antimetabolite. This means it reduces the speed that skin cells proliferate, because it antagonises the B vitamin, folic acid. It reduces pyrimidines, purines and methylation of DNA.

Contraindications to methotrexate and precautions in its use

Avoid methotrexate in pregnancy

Methotrexate is TGA and FDA pregnancy category X. At high dosages, methotrexate is known to cause miscarriage and/or stillbirth, especially in the first 3 months of pregnancy. There is also a concern regards the risk of lower dosage methotrexate affecting functional development in the later stages of pregnancy. It is therefore recommended that pregnant women do not take methotrexate, and women of childbearing age should not become pregnant while taking methotrexate. Adequate contraceptive measures are necessary during therapy. Consult your doctor before considering pregnancy.

Avoid methotrexate when breastfeeding

The amount of methotrexate excreted in breast milk is likely to be small. It is unclear how much would be absorbed by a nursing baby. However, the precautionary approach is to limit or avoid breast feeding in mothers being treated with methotrexate.

Is there a risk if the father is on methotrexate?

For many years men were advised not to father children while they were on methotrexate and for at least 3 months afterwards, because methotrexate had been reported to cause a reduction in sperm count. The current expert view is that the risks are very low, and this precautionary approach is not necessary.

Other health concerns

Care should be taken prescribing methotrexate in patients with low blood counts (anaemia, leukopenia, thrombocytopenia). It maybe unsuitable for patients with severe liver disease.

It should be taken with caution by patients with significant liver or kidney disease, infections, obesity or diabetes (ie metabolic syndrome).

Illness can increase the levels of methotrexate

Dehydration from fever, vomiting, diarrhoea, or decreased fluid intake may increase levels of methotrexate. Excessive thirst may be a symptom of dehydration. Notify your doctor if these symptoms develop before you take the next dose of methotrexate.

Dehydration or any other reason for reduced kidney function may prevent normal excretion of methotrexate resulting in toxic accumulation of the medication. The excessive methotrexate can in turn damage the kidneys further.

Avoid alcohol while on methotrexate

Alcoholic beverages (including beer and wine) may increase some of the side effects, including the chance of liver damage, and should be restricted to less than 20 mg/day (1–2 standard drinks/day; 10–14 drinks/week).

See guidelines of The Alcohol Drug Association of New Zealand, The Alcohol Advisory Council of New Zealand (ALAC) on safe drinking.

Patients who need surgery

The expert view is that methotrexate does not need to be stopped for any surgery.

How to take methotrexate

Methotrexate is available as 2.5 mg and 10 mg tablets, and as a solution for injection. Take care not to mix up the 2.5 mg and 10 mg-sized tablets — you might end up taking an overdose, or too little.

Most people are prescribed tablets. The most common dose is 15 mg each week, but it varies from 2.5 mg to 30 mg each week depending on kidney function, side effects experienced, and efficacy in treating the skin disease. The doctor may decide to start with a very low dose such as 2.5 to 5 mg and then gradually build it up to the full dose over several weeks. An initial lower dose should be used if there is reduced renal function (kidney disease), in patients with lower body weight, or in older patients (> 75 years of age).

Methotrexate is taken weekly, rather than daily.

This is different from most medications. The importance of this weekly schedule cannot be stressed enough; it is best if a specific day of the week is nominated (eg Monday) on the prescription. On the specified day of the week, the methotrexate can be taken either as a single dose, or split into 2 to 3 smaller doses.

If methotrexate tablets cause nausea, your doctor may recommend splitting the dose, taking it after meals or at bedtime on two days a week.

If oral treatment causes too many gastrointestinal side effects, once weekly subcutaneous injection may be tried.

Taking methotrexate more often, or changing the dose schedule may result in serious side effects. If doses are taken too often, notify your doctor at once.

Tests before starting methotrexate

Pre-treatment laboratory tests usually include a full blood count with differential (CBC), kidney function tests (creatinine), liver function tests, HbA1c (a test for diabetes), and lipids.

Hepatitis B and C serology, HIV and varicella (chickenpox) serology and tuberculosis testing (QuantiFERON®-TB Gold) may be considered in populations at risk of these infections. Pretreatment FibroScan®/liver biopsy is rarely necessary, but may be considered if there is existing liver disease or high risk of liver disease.

Consider measuring trough level polyglutamed methotrexate as a measure of 1) compliance and 2) whether a dose adjustment is necessary.

P3NP collagen testing

In some regions, a blood test measuring type 3 procollagen amino terminal propeptide (P3NP collagen) may be requested in adults aged 20–70 years before treatment with methotrexate, and repeated every 3 to 6 months while on methotrexate.

P3NP collagen measurement can be used to assess hepatic fibrosis in patients with psoriasis on long term methotrexate. Three elevated levels over a 1-year period may indicate liver damage; however P3NP may be elevated in a variety of conditions, including:

- Myocardial infarction (heart attack)
- Trauma (injury)
- Hypertension (high blood pressure)
- Heart disease
- Liver disease for other reasons
- Inflammatory arthritis

P3NP testing in childhood is less reliable, as normal growth leads to higher P3NP collagen levels.

Transient elastography scan

A liver ultrasound scan using transient elastography (FibroScan®) measures the stiffness of the liver and may reveal fibrosis or cirrhosis. If the result is in the normal range, it is very unlikely that methotrexate is causing liver fibrosis (i.e a normal scan is a negative predictor of liver damage).

Liver biopsy

It may occasionally be necessary to take a small specimen of liver tissue with a needle (liver biopsy). Liver biopsy findings may be reported using Roenigk classification:

- Class 1: normal or mild fatty change
- Class 2: more severe fatty change and portal tract inflammation
- Class 3: fibrosis
- Class 4: cirrhosis.

Side effects of methotrexate

Side effects can occur at any time during treatment with methotrexate, but are most common in the first few weeks. Folic acid supplements may be prescribed, as they are thought to reduce some of the side effects of methotrexate. There is still some debate as to the best dose and timing of folic acid. Current expert recommendation is to take 5 mg once a week, eg on a Friday (Monday for methotrexate, Friday for folic acid).

If the side effects described below or other problems trouble you, or should you develop any signs of infection or unusual bleeding, notify your doctor promptly and before your next dose of methotrexate is due.

Gastrointestinal side effects

The most common side effects of methotrexate are loss of appetite, nausea and diarrhoea, and affect about one in 12 patients. These side effects are usually temporary, but changes in dose and/or supplemental folic acid tablets may be helpful. If you have gastroenteritis (stomach upset), do not take methotrexate until you have recovered. Mouth ulcers or diffuse stomatitis are uncommon at normal dermatological doses.

Blood count abnormalities

An overdose of methotrexate or deficiency of the vitamin folic acid may result in anaemia (decreased haemoglobin), leucopaenia (reduced white cell count, risking serious infections), and thrombocytopenia (low platelet count, resulting in bruising and bleeding). Methotrexate should not be taken unless the blood count is normal or near-normal prior to the next dose. Low blood counts are more likely in people with kidney disease, with existing haematological disorders, or when taking other medications (particularly sulfonamides).

Liver toxicity

Methotrexate is stored by the liver. Transaminase liver enzyme levels may rise for a few days after treatment but they quickly return to normal. It's best to do blood tests at least 5 days after a dose, or just prior to the next dose.

Long term therapy may be associated with scarring (fibrosis or cirrhosis) of the liver. This is more commonly due to other reasons such as fatty liver, diabetes, hyperlipidaemia, and obesity (ie metabolic syndrome), but can also develop from viral hepatitis and alcohol.

Lung disease

Methotrexate can rarely cause a lung reaction similar to pneumonia called acute pneumonitis or interstitial pneumonia. The symptoms are usually fever, cough (often dry and hacking), and shortness of breath. Should you develop such symptoms, stop taking methotrexate and notify your doctor promptly. A chest X-ray may reveal diffuse white patches.

Slowly progressive lung fibrosis or bronchiolitis obliterans associated with methotrexate is rare. Eosinophilic pneumonia is also reported. As with acute pneumonitis, chronic lung disease usually affects patients with rheumatoid arthritis on methotrexate.

Serious infections

Although uncommon, methotrexate may rarely result in reactivation of tuberculosis or opportunistic bacterial, fungal or viral infections. Shingles (herpes zoster infection) and cold sores (herpes simplex) may be more severe in those taking

methotrexate. It is unwise to take methotrexate if there is significant immunodeficiency, untreated tuberculosis or untreated HIV infection.

Overdose

If an accidental overdose occurs, folinic acid injections may be necessary. The antidote should be given as early as possible.

Cutaneous side effects of methotrexate

Methotrexate may rarely causes skin problems.

- Photosensitivity (sunburn): as a general precaution, cover up and use sunscreens when outdoors. Concurrent phototherapy, if recommended by your dermatologist, is safe but should be undertaken cautiously with a slow build-up in treatment time.
- Ulceration of skin and mucous membranes (especially in overdose)
- Diffuse hair loss: this is rare, and usually occurs in the setting of high cancer-treatment doses.

Other side effects

Some patients taking methotrexate have headaches, dizzinesss, fatigue and mood changes, especially when first starting on methotrexate. Nausea, confusion or headache can also rarely be due to hyponatraemia (sodium imbalance).

Refer to datasheets and prescribing information for a full list of risks and side effects.

Drug interactions with methotrexate

Several medications may increase side effects or decrease the effectiveness of methotrexate or the other drug. Tell your doctor all the medicines you are taking, whether they are prescription or non-prescription medicines. If you are having an operation with a general anaesthetic, tell the anaesthetist you are on methotrexate. It is not necessary to stop methotrexate for an operation, but always discuss this with your surgeon.

Do not begin or change the dosage of any medicine without first checking with your doctor. This is especially true of antibiotics and anti-inflammatory agents.

Like methotrexate, antibiotics that contain the drug trimethoprim or sulfonamides (eg cotrimoxazole) antagonise folate. Taking them at the same time as methotrexate could increase the toxicity. Penicillins, minocycline and ciprofloxacin may also increase methotrexate toxicity.

Aspirin and aspirin-like drugs (nonsteroidal anti-inflammatories) may reduce how much methotrexate is eliminated by the kidneys. This could potentially result in a toxic build-up of methotrexate in the blood stream. Anti-inflammatories can often be taken safely but you should have regular blood tests if you start these medicines or others, as advised by your doctor. Alternatively, you could take paracetamol (acetominophen), as this does not interfere with methotrexate. Do not take excessive paracetamol, as this can cause liver damage.

Other drugs that may increase methotrexate toxicity include barbiturates, proton pump inhibitors (pantoprazole, omeprazole, esomeprazole, lansoprazole, rabeprazole), colchicine, dipyridamol, phenytoin, sulfonylureas, frusemide/furosemide and thiazide diuretics. Ask your doctor's advice if you take any of these medicines.

Vaccination on methotrexate

Vaccines (live and/or killed) may be less effective in those taking methotrexate, so it is best if you are fully immunised before starting methotrexate. If this is not possible, a double dose of the vaccine may be required.

Killed vaccines are safe and are often advisable to reduce the impact of infection – arrange annual influenza vaccination.

There is on-going debate as to the risks of live vaccination in patients taking methotrexate. Many dermatologists believe the benefits of vaccination far outweigh the increased risk, with the possible exception of yellow fever vaccination. Discuss vaccination with your doctor/travel physician. See Immunisation in immunosuppressed dermatology patients.

Safety measures on methotrexate

Methotrexate should be kept out of the reach of children. Do not give this medication to other people. Dispose of the injected form of methotrexate in appropriate sharps containers.

Close monitoring, ie medical supervision of patients on methotrexate is essential. It is important that you carry out your doctor's instructions faithfully and promptly report any side effects or symptoms you may develop to him or her.

Related information

References:

- Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. Journal of the American Academy of Dermatology. Volume 61, Issue 3, September 2009, Pages 451-485 doi:10.1016/j.jaad.2009.03.027
- Shen S, O'Brien T, Yap LM, Prince HM, McCormack CJ. The use of methotrexate in dermatology: a review. Australas J Dermatol. 2012 Feb;53(1):1-18. doi: 10.1111/j.1440-0960.2011.00839.x. Epub 2011 Dec 29.

On DermNet NZ:

- Psoriasis
- Psoriatic arthritis
- Monitoring immune-modulating drugs used in dermatology
- Immunisation in immunosuppressed dermatology patients
- Tuberculosis screening for patients prescribed immunosuppressing drugs

Other websites:

- Consumer medicine information and data sheets – Medsafe
- Drugs, Herbs and Supplements – MedlinePlus
- Methotrexate – British Association of Dermatologists
- Nonalcoholic fatty liver disease fibrosis score, online calculator
- Methotrexate – SafeRx

Note:

The New Zealand approved datasheet is the official source of information for this prescription medicine, including approved uses and risk information. Check the New Zealand datasheet on the Medsafe website.