What is the clinical significance of the interaction between methotrexate and penicillins?

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Background

Methotrexate is an immunomodulatory drug used for a number of conditions including rheumatoid arthritis, cancer, and psoriasis. Its use may be associated with a number of serious side effects, including blood dyscrasias, liver cirrhosis and pulmonary toxicity1.

Penicillins are a widely used group of broad spectrum antibiotics which may interact with methotrexate1. The interaction does not, however, appear on the Summary of Product Characteristics for methotrexate2. Many patients who are taking methotrexate will also require antibacterial therapy with penicillins at some point in their lives3.

Answer

Mechanism

Methotrexate is cleared by the kidneys, through tubular secretions and glomerular filtration4. Penicillins are weak acids which are capable of competing with methotrexate within the tubules of the kidney, leading to reduced tubular secretion and therefore retention of methotrexate. Increased levels can in turn predispose to toxicity5. Evidence for this mechanism is mostly limited to animal studies and human case reports5,6,7 and its existence has also been disputed3,8. Penicillins do not appear to interfere with the glomerular filtration aspect of methotrexate clearance.

Onset of methotrexate toxicity following initiation of a penicillin may be delayed4.

Evidence

Amoxicillin

One case report describes a 16 year old given high dose methotrexate IV for osteogenic sarcoma. Co-administration of amoxicillin resulted in a 56% reduction in excretion of methotrexate, leading to a prolonged increase in methotrexate levels. The patient suffered from toxicity consisting of nausea, vomiting, renal failure, myelosuppression, fever, and dermatologic abnormalities8,9.

A case series reported by Lim et al looked at patients who had suffered from methotrexate-induced pancytopenia. One of the patients included (who was taking a dose of 10mg weekly methotrexate) had initiated a course of amoxicillin on the day of admission to hospital with symptoms of sepsis, malaena, and mucositis. The patient died due to a colonic haemorrhage. The authors of the paper do not attribute the development of pancytopenia to an interaction, but a follow-up letter to the authors suggests this may be a cause6,10,11.

Oral amoxicillin for 7 days was given to a patient taking a 7.5mg weekly dose of methotrexate. The patient developed neutropenia and thrombocytopenia, which was thought to be due to reduced methotrexate clearance. The patient died despite folinic acid rescue therapy. The patient was also given IV flucloxacillin, and IV benzylpenicillin8,12.

Neutropenia and thrombocytopenia were also observed in a patient who was prescribed co-amoxiclav (amoxicillin and clavulanic acid) alongside methotrexate for psoriasis8,12.
Flucloxacillin
A patient receiving methotrexate 5mg weekly for rheumatoid arthritis suffered suspected methotrexate-induced pneumonitis following a course of flucloxacillin. This prompted the authors to conduct a study in 10 patients with RA who were given flucloxacillin, which suggested no clinically significant pharmacokinetic effect on methotrexate levels. This small study is limited by the fact that it looks only at pharmacokinetic factors, and the small number of patients recruited to the study, all of whom were being treated for rheumatoid arthritis. A patient administered both flucloxacillin and piperacillin IV died as a result of neutropenia and thrombocytopenia thought to be due to methotrexate toxicity. The patient’s dose of methotrexate was 2.5mg three times a week which was being given for psoriasis.

Phenoxymethylpenicillin
A patient receiving 50mg IV methotrexate weekly for dermatomyositis experienced toxicity (including leukopenia, thrombocytopenia, deranged LFTs, and skin ulcerations) within a week of initiation of starting phenoxymethylpenicillin. The patient was treated with folinic acid and fluid replacement. This patient had also been coprescribed furosemide. Attribution of the cause of toxicity is postulated to be due to the interaction between both penicillin and furosemide, although it is acknowledged that the patient had also received his dose of methotrexate two days earlier than scheduled, which could have been a contributory factor.

Antipseudomonal penicillins
A 50 year old female being treated with an intrathecal high dose methotrexate-containing regime for Burkitt’s lymphoma experienced a prolonged increase in methotrexate levels which resolved only on discontinuation of piperacillin/tazobactam. During a later cycle of the methotrexate-containing chemotherapy regimen, Piperacillin/tazobactam was not administered, and methotrexate levels reduced. A 67% reduction in methotrexate clearance was observed in a patient receiving a high dose IV course of methotrexate for chronic myeloid leukaemia. The patient required prolonged folinic acid rescue.

Risk Factors:
Not all patients who use penicillins concurrently with methotrexate are affected by this interaction. So far, there is no way of predicting who it may occur in, as current available evidence does not suggest any strong risk factors for developing the interaction. Reports of symptomatic interactions are not limited to high dose methotrexate therapy. Theoretically, patients with a degree of existing renal impairment may be more susceptible to the interaction.

Management
Patients who require a penicillin antibiotic whilst taking methotrexate therapy should be closely monitored for the duration of the treatment. One resource suggests measuring platelets and white cell counts twice weekly for two weeks. If methotrexate toxicity is suspected, methotrexate levels should be performed, and folinic acid rescue should be available where required. Another resource suggests considering a dose reduction and monitoring serum methotrexate levels. Patients should be counselled to look out for adverse effects of methotrexate such as sore throat, infection, leukopenia, thrombocytopenia, and skin ulcerations.

Summary
The evidence for an interaction between methotrexate and penicillins is limited to case reports and animal studies. So far, there is no conclusive evidence that any particular patient group is more at risk of an interaction occurring, and it does not appear to be dose related.
If concurrent use of methotrexate and a penicillin is required, patients should be carefully monitored during treatment. Monitoring may include measuring platelets and blood counts twice weekly for two weeks, with methotrexate levels being taken if the patient becomes symptomatic.

**Limitations**

There have been no large, controlled studies in humans to determine the mechanism or clinical effect of this potential interaction, so information is mainly limited to animal studies and case reports. This makes it difficult to estimate incidence and likelihood of the interaction. Only evidence relating to UK licensed penicillin antibiotics have been included in this Q&A.

**Quality Assurance**

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**Search strategy**

**Embase**

METHOTREXATE/it [it=Drug Interaction]; AND [*AMOXICILLIN/ OR *AMOXICILLIN PLUS CLAVULANIC ACID/ OR *AMPICILLIN/ OR *BENZATHINE PENICILLIN/ OR *BENZATHINE PENICILLIN V/ OR *FLUCLOXACILLIN/ OR *PENICILLIN G/ OR *PENICILLIN V/ OR *PIPERACILLIN/ OR *TICARCILLIN/]

**Medline**

*METHOTREXATE/ AND [*PENICILLIN G/ OR PENICILLIN V.af OR *FLOXACILLIN/ OR TEMOCILLIN.af; OR *AMOXICILLIN/ OR *AMPICILLIN/ OR *AMOXICILLIN-POTASSIUM CLAVULANATE COMBINATION/ OR CO-FLUAMPICIL.af OR *PIPERACILLIN/ OR *TICARCILLIN/ OR PIVMECILLINAM.af;]

In-house database/ resources

eBNF 66

Micromedex

Medicines Complete

**References**


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