# Improving the **S**afety of **M**ethotrexate therapy: **A**ssessing **R**isks and **T**oxicity (SMART)

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## Background and objectives

A recent case of a severe methotrexate (MTX) intoxication in our hospital revealed weak points in the process of MTX therapy management. MTX is well known as a high risk drug and a frequent cause of drug related morbidity. Therefore the objective was to redesign the process in order to improve the **s**afety of **m**ethotrexate **t**herapy by **a**ssessing **r**isks and **t**oxicity (SMART).
The aims of the SMART project were:
(1) to identify risk factors in our process of MTX prescribing and dispensing.
(2) to implement a safety checking procedure in MTX prescribing and dispensing to avoid inappropriate prescribing and to detect toxicity at an early stage.

## Methods

(1) An in-depth analysis of the case mentioned above and a literature search were performed to identify risk factors contributing to MTX toxicity. Important risks in our management of MTX therapy could be identified: daily instead of weekly prescription, subcutaneous instead of oral administration, potential drug-drug-interactions, lack of knowledge in health care professionals about signs and symptoms of MTX toxicity and inadequate therapy monitoring.
(2) To address the identified risks the process was completely redesigned:
- A checklist was elaborated regarding discrepancies in the patient's file (dosage and route of administration, indication), laboratory values influencing MTX pharmacokinetics or representing early signs of toxicity, unspecific clinical symptoms (diarrhoea, cough etc.), and concomitant medication (with focus on potential drug-drug-interactions [pDDI]).
- In case of concerns about the appropriateness of MTX prescription the physician is informed by the clinical pharmacist in a standardised written form (or in urgent cases orally).
- The MTX dose is dispensed to the ward in an individual package with the patient's name and an information leaflet about signs of toxicity and the correct therapy monitoring in order to increase health care professionals' knowledge and awareness concerning these issues at the point of care.

## Results

The new standardised procedure was implemented in August 2009. Since then the hospital pharmacy dispensed 144 doses of methotrexate for 54 different patients.
72% of treated patients were female. Age ranged from 43 to 91 years. Causes of admission were eclectic and in most of the cases probably not connected to MTX-therapy.
The main indications for MTX-therapy were rheumatoid arthritis, psoriasis, rheumatic polymyalgia and vasculitis. Half of MTX-doses were administered by mouth with dosages between 5 and 25 mg and the other 50% followed a subcutaneous administration with dosages from 7.5 to 25 mg. During their hospital stay 17 patients received MTX only once, 32 had a repeated prescription.
The findings of the validation process are displayed in figure 1.

## Conclusion

Standardised pharmaceutical validation of MTX prescriptions in hospital is useful since more than 50% of all prescriptions at hospital admission needed to be modified or clarified. A close pharmaceutical follow-up and monitoring of repeated MTX prescriptions during hospital stay helps to detect drug related problems at a very early stage and can contribute to avoid clinically significant adverse outcomes.
Discussions with physicians and nurses about the results of MTX prescribing validation confirmed their need for information about MTX-drug-interactions and early signs of possible toxicity.
Our SMART procedure seems to be suitable to detect MTX associated risks and to improve the awareness of risk factors in health care professionals.

Table 1: laboratory monitoring during MTX-therapy

| Laboratory monitoring | | |
|---|---|---|
| **Parameter** | **Normal range** | **Deviation ⇨ indicator for …** |
| **RENAL VALUES** | | |
| Creatinin clearance | > 60 ml/min | ↓ ⇨ ↑ MTX serum concentration |
| **LIVER** | | |
| ASAT & ALAT | < 50 U/l | ↑ ⇨ hepatotoxicity |
| **PROTEIN** | | |
| Albumin | 35-52 g/l | ↓ ⇨ ↓ MTX binding → ↑ free MTX serum concentration |
| **HAEMATOLOGIC** | | |
| Leucocytes | 3.6-10.5 * 10 9 /l | ↓ ⇨ myelosuppression |
| Thrombocytes | 160-370 * 10 9 /l | ↓ ⇨ myelosuppression |

Table 3: Selected potential drug-drug interactions (pDDI)

| pDDI | |
|---|---|
| **Active agent** | **Mechanism & Effect of interaction** |
| **HIGHLY RELEVANT** | |
| Live vaccine | ↑ risk for infections |
| Leflunomide | Mechanism unknown, ↑ risk for hepatotoxicity& myelosuppression |
| Cotrimoxazole | Synergistic anti-folate effect , ↑ serum-concentration of MTX ⇨ ↑ toxicity |
| Triamteren | See above |
| NSAID | ↓ renal blood flow ⇨ ↓ MTX-Clearance ⇨↑ serum-concentration of MTX ⇨ ↑ toxicity |
| Penicillin-like antibiotics | ↓ renal secretion of MTX ⇨ ↑ serum-concentration of MTX ⇨ ↑ toxicity |
| **MODERATLY RELEVANT** | |
| Proton pump inhibitors (PPI) | ↓ MTX-Clearance⇨ ↑ serum-concentration of MTX ⇨ ↑ toxicity |
| Metamizole | ↑ risk of agranulocytosis |
| Amiodarone | Unknown , ↑ risk for toxicity |
| Ciclosporin | Inhibits oxidation in the inactive metabolite ⇨ ↑ serum-concentration of MTX ⇨ ↑ toxicity |
| Probenecid | See PPI |
| Pyrimethamine | Unknown , ↑ risk of myelosuppression |

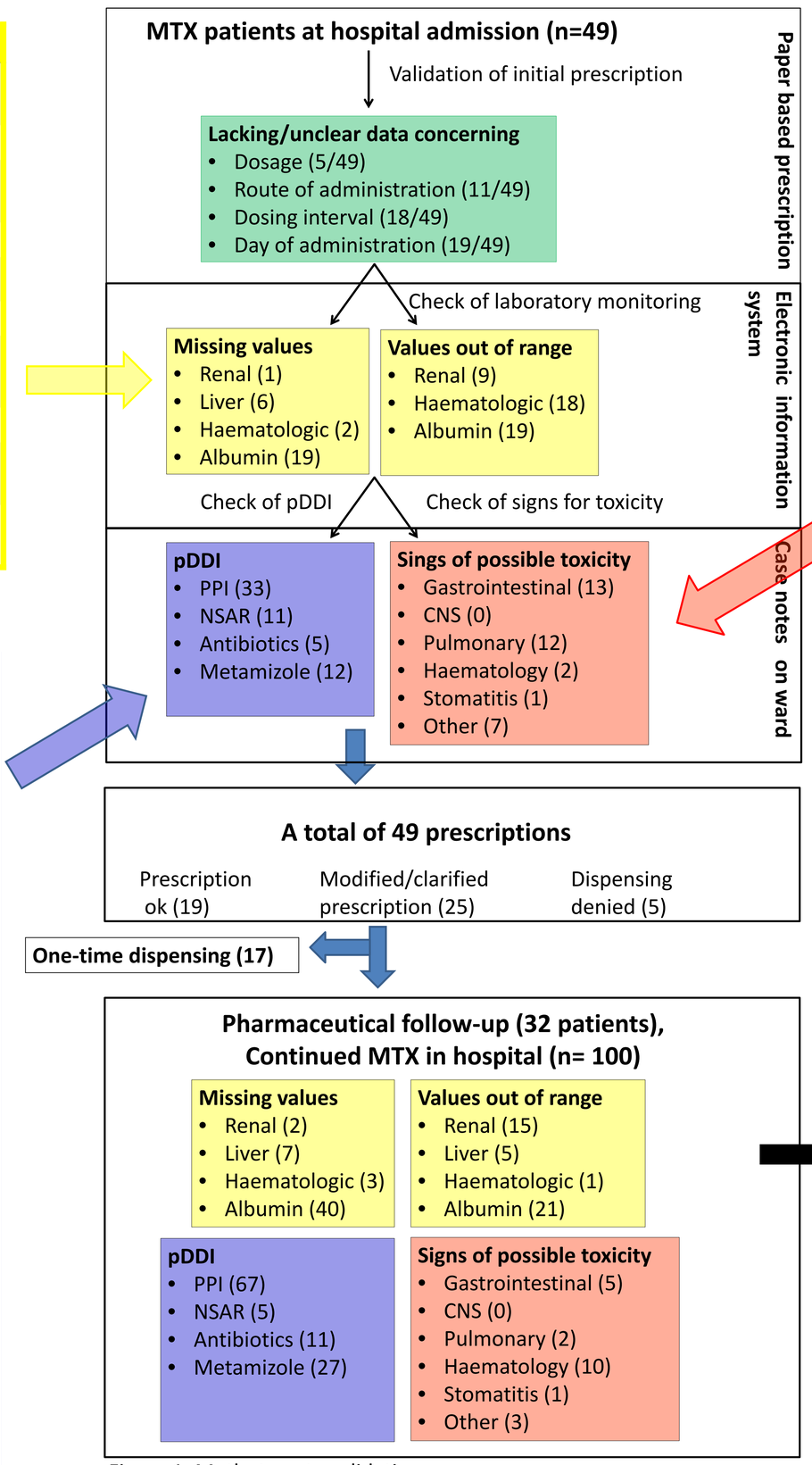
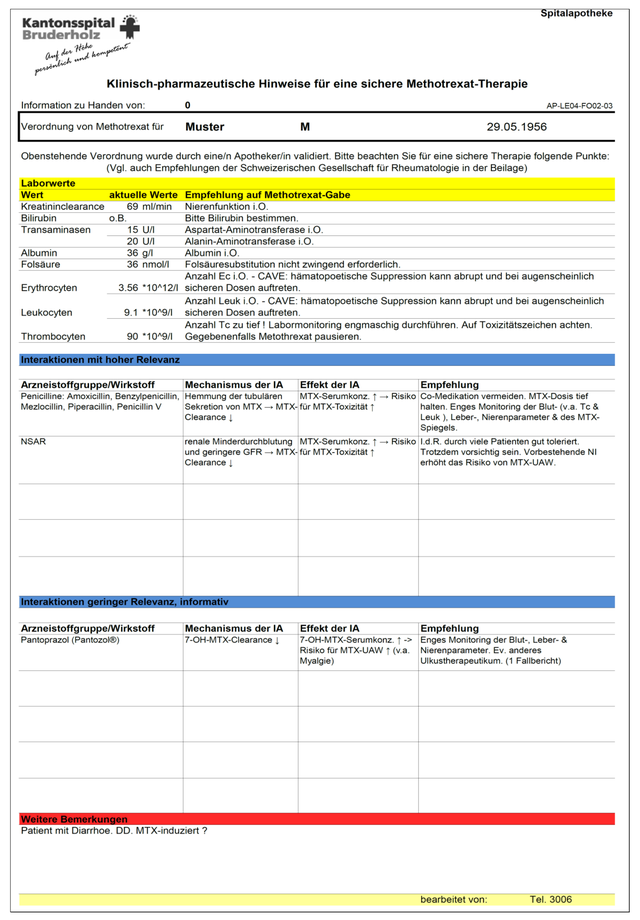



Figure 1: Methotrexate validation process

Table 2: Signs of methotrexate toxicity

| Signs of MTX-Toxicity |
|---|
| Type and frequency of MTX-toxicity are generally reliable to the duration of treatment and administered dose. Nevertheless signs of toxicity were observed through all doses and at any point in therapy. |
| **Gastrointestinal:** nausea, abdominal pain, diarrhoea, pancreatitis<br>**Central nervous system (CNS):** headache, fatigue<br>**Pulmonary:** cough, pneumonitis, dyspnoea<br>**Haematology:** neutropenia, thrombocytopenia, myelosuppression<br>**Stomatitis**<br>**Other:** rash/pruritus, hair loss, weight loss, fever |



Kantonsspital Bruderholz — Spitalapotheke

**Klinisch-pharmazeutische Hinweise für eine sichere Methotrexat-Therapie**

Information zu Handen von: 0 AP-LE04-FO02-03

Verordnung von Methotrexat für **Muster** **M** 29.05.1956

Obenstehende Verordnung wurde durch eine/n Apotheker/in validiert. Bitte beachten Sie für eine sichere Therapie folgende Punkte:
(Vgl. auch Empfehlungen der Schweizerischen Gesellschaft für Rheumatologie in der Beilage)

**Laborwerte**

| Wert | aktuelle Werte | Empfehlung auf Methotrexat-Gabe |
|---|---|---|
| Kreatininclearance | 69 ml/min | Nierenfunktion i.O. |
| Bilirubin | o.B. | Bitte Bilirubin bestimmen. |
| Transaminasen | 15 U/l | Aspartat-Aminotransferase i.O. |
| | 20 U/l | Alanin-Aminotransferase i.O. |
| Albumin | 36 g/l | Albumin i.O. |
| Folsäure | 36 nmol/l | Folsäuresubstitution nicht zwingend erforderlich. |
| Erythrocyten | 3.56 *10^12/l | Anzahl Ec i.O. - CAVE: hämatopoetische Suppression kann abrupt und bei augenscheinlich sicheren Dosen auftreten. |
| Leukocyten | 9.1 *10^9/l | Anzahl Leuk i.O. - CAVE: hämatopoetische Suppression kann abrupt und bei augenscheinlich sicheren Dosen auftreten. |
| Thrombocyten | 90 *10^9/l | Anzahl Tc zu tief ! Labormonitoring engmaschig durchführen. Auf Toxizitätszeichen achten. Gegebenenfalls Metothrexat pausieren. |

**Interaktionen mit hoher Relevanz**

| Arzneistoffgruppe/Wirkstoff | Mechanismus der IA | Effekt der IA | Empfehlung |
|---|---|---|---|
| Penicilline: Amoxicillin, Benzylpenicillin, Mezlocillin, Piperacillin, Penicillin V | Hemmung der tubulären Sekretion von MTX → MTX-Clearance ↓ | MTX-Serumkonz. ↑ → Risiko für MTX-Toxizität ↑ | Co-Medikation vermeiden. MTX-Dosis tief halten. Enges Monitoring der Blut- (v.a. Tc & Leuk ), Leber-, Nierenparameter & des MTX-Spiegels. |
| NSAR | renale Minderdurchblutung und geringere GFR → MTX-Clearance ↓ | MTX-Serumkonz. ↑ → Risiko für MTX-Toxizität ↑ | I.d.R. durch viele Patienten gut toleriert. Trotzdem vorsichtig sein. Vorbestehende NI erhöht das Risiko von MTX-UAW. |

**Interaktionen geringer Relevanz, informativ**

| Arzneistoffgruppe/Wirkstoff | Mechanismus der IA | Effekt der IA | Empfehlung |
|---|---|---|---|
| Pantoprazol (Pantozol®) | 7-OH-MTX-Clearance ↓ | 7-OH-MTX-Serumkonz. ↑ -> Risiko für MTX-UAW ↑ (v.a. Myalgie) | Enges Monitoring der Blut-, Leber- & Nierenparameter. Ev. anderes Ulkustherapeutikum. (1 Fallbericht) |

**Weitere Bemerkungen**
Patient mit Diarrhoe. DD. MTX-induziert ?

bearbeitet von: Tel. 3006

Figure 2: Pharmaceutical MTX-Information for the physician

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