Safe Treatment with Oral Methotrexate – A Shared Responsibility Demanding a Shared Solution?

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IMSN Networking for Safety in Cancer Care
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Introduction

- Low dose oral and sub-cutaneous methotrexate is indicated for a variety of autoimmune conditions

- Safe & effective when taken at the correct dose and frequency, and when appropriately monitored

- Taken once weekly - an unusual dose frequency

- Errors can arise during or as a result of prescribing, dispensing, administration and monitoring processes
Medication incidents associated with low-dose methotrexate

- Severe harm and death as a result of neutropaenic episodes & toxicities

- Root cause analysis indicates increased frequency of administration as primary cause of morbidity

- Others contributing factors:
  - Availability of more than 1 strength of tablet leading to 4-fold overdose risk
  - Absence of prescriber clarity
  - Lapses
  - Non-adherence to monitoring guidelines

- Epidemiology of incidents
A Case of Methotrexate Death in Ireland (2000)

- Inadvertent daily prescription of methotrexate caused the death of a 74-year-old man.
- Dermatologist prescribed 15mg once weekly to treat a chronic skin condition.
- However, a note by the consultant was not interpreted correctly by staff in the hospital where the patient was in long-term care and the wrong dosage amount was entered on the ward's prescription chart.
- Patient got 15mg daily and continued for 9 days until a nurse reported that the patient had a sore throat and some difficulties with swallowing.
- Blood tests confirmed bone marrow suppression with the patient becoming seriously ill. He was transferred to an acute but died four days later.
- An autopsy revealed that he died of bronchial pneumonia as a consequence of bone marrow suppression due to methotrexate toxicity.
Safety initiatives (UK)

Following the death of a patient in Cambridgeshire, an Inquiry was published (July 2000) which had far-reaching impact on practice.
Current Guidance (Ireland)

1. Methotrexate Safe Dispensing Policy - Pharmaceutical Society of Ireland Practice

   Notice issued to all community pharmacies in 2008, available on the PSI web site.

2. Irish Medication Safety Network Alert on Methotrexate May 2010

   Notice published on IMSN web site.
Safety Initiatives in 2011

1. HSE Medication Safety Programme Plan 2011 (October 2010)
   • Establish an audit to assure compliance with safe practice guidance on oral methotrexate for non-cancer treatment (arthritis and psoriasis) in the community

2. Proposal by IMSN (March 2011) to the Department of Health Medication Safety Forum that in order to prevent errors due to mix-ups of the 10mg and 2.5mg tablets,
   • Irish Medicines Board should withdraw the licence for 10mg strength methotrexate tablets OR
   • Primary Care Reimbursement Scheme should withdraw reimbursement from the 10mg strength
IMSN Guidance May 2010

To Doctors, Nurses, Pharmacists, Pharmaceutical Technicians

1. Prescribe, dispense and administer oral methotrexate ONCE WEEKLY (usual dose range 7.5mg – 20mg orally once weekly), specifying the day of the week.

2. Specify the number of tablets (“10mg, i.e. 4 x 2.5mg tablets”) to be taken per dose.

3. Ensure that the patient understands their therapy, including dose and frequency, when and where monitoring will be carried out, the signs and symptoms of toxicity and what to do should they occur.
To Doctors, Nurses, Pharmacists, Pharmaceutical Technicians

4. Folic acid 5mg once weekly orally can reduce mucositis and gastrointestinal side effects. It should be administered on a different day of the week to methotrexate.

5. Ensure that you are aware of contra-indications and cautions, symptoms of adverse reactions and toxicity associated with methotrexate, the appropriate monitoring to carry out and potential interactions with other drugs, e.g. NSAIDs.
PSI Practice Notice: Safe Dispensing of Methotrexate 2008

- Ten-point guidance
- 2.5mg only to be stocked
- Specify day of administration on label
- Awareness of symptoms of toxicity
- Ensure patient can distinguish between folic acid tablets and methotrexate tablets
Background to study

- In Service Plan 2011 based on IHI safety driver principles (ensure safe process for management of high-risk medications)
- Incorporate IMSN request to remove 10mg strength from PCRS list of reimbursable medicines raises many issues
  - Implications for legacy stocks, further errors
  - Is there enough evidence that this is the solution to the problem?
  - Unsure of existing safe practice initiatives around methotrexate in community pharmacies
  - Legal implications, company involvement etc.
  - Were withdrawal to be undertaken, what effect would this have on patients? If any?
- Focus audit on primary care dispensing to determine baseline practice and attitudes
Demographics of Oral Methotrexate Use

- Interrogation of PCRS database (Dr. Kath Bennett, HRB Centre for Primary Care Research)
- 11,434 DPS & GMS patients in Ireland taking oral methotrexate (Nov 2010 data)
  - 7,032 (62%) on 2.5mg alone
  - 3,218 (28%) on 10mg alone
  - 1,184 (10%) on a combination of 10mg and 2.5mg
- 38% of patients taking 10mg tablets in Ireland compares to 8% on average in UK audits.
Postulated reasons for dispensing of 10mg strength

- Prescriber instructions or absence of same?
- Patient preferences?
- Pharmacist preference?
- Lack of awareness of risks and potential side-effects?
- Lack of guidance (GPs)
- Lack of awareness of guidance (pharmacists)?
- Practicability of guidance re storage of 2.5mg only
- Lack of audit?
Aims of audit

1. To assist the decision-making process at a national level regarding steps to optimise safety for patients on low-dose methotrexate

2. To obtain information on:
   - Local policies wrt storage dispensing and labelling of methotrexate
   - Perceptions around risks
   - Measures in place to guard against daily instead of weekly dosing
   - Indication, dose of methotrexate and folic acid regimens
Audit methodology

- Development of audit form
  - 37 questions with check box format
  - 27 related to supply of methotrexate
  - 10 related to audit of last Rx dispensed
  - Sphinx® software (Dr. Ian Callanan, HSE National Clinical Audit Lead.)

- Sampling method
  - PSI list of registered pharmacists
  - Random selection generated using www.random.org
  - Hospitals excluded
  - N=498 as denominator
### National Community Pharmacy Audit of Methotrexate 2011

1. What is the name of the dispensing software installed on your dispensary system?
   - ○ Cliniscript
   - ○ McLernon
   - ○ Other

2. Is there a WRITTEN Methotrexate Safe Supply Protocol in place in your pharmacy?
   - ○ Yes
   - ○ No
   - ○ Don’t know

3. Are you aware of the PSI Safe Practice on the Supply of Methotrexate 2008 guidelines?
   - ○ Yes
   - ○ No

4. What strength methotrexate tablets do you currently stock?
   - ○ 2.5mg only
   - ○ 10mg only
   - ○ Both strengths

5. If both strengths are stocked, are they distinguishable in shape?
   - ○ Yes
   - ○ No

6. Do you have special storage arrangement in place for oral methotrexate?
   - ○ Yes
   - ○ No

If no strength of tablet is indicated on a prescription for methotrexate i.e. weekly dose only indicated, how do you usually decide what strength methotrexate tablets to provide?

<table>
<thead>
<tr>
<th>Yes for new Rx only</th>
<th>Yes in all Rx</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>
Ten Minutes for Patient Safety

You can help inform policy on safe use of oral Methotrexate by responding to this survey

Dear Supervising Pharmacist,

There are over 11,000 patients taking oral methotrexate in Ireland, mostly for non-cancer indications. Safe use of oral methotrexate is an issue of concern because of its toxicity in overdose.

The Patient Safety First initiative is a collaborative established to help implement the recommendations of Building a Culture of Patient Safety, the Report of the Commission on Patient Safety and Quality Assurance (2008). A Medication Safety Forum was set up by the Department of Health & Children to address patient safety issues to do with all aspects of medication use. Among the collaborating organisations are the Irish Medication Safety Network (IMSN), the PSI, the IMB, the HSE, and the IPU. The safe use of oral methotrexate is a key project for the Medication Safety Forum and its members. As part of a patient safety initiative to enhance the safe use of this medicine, we are carrying out a survey to gain an understanding of the current use of Methotrexate in Ireland.
Results – Response rate

- Questionnaires posted to supervising pharmacists 31\textsuperscript{st} July
- 2 week turnaround requested
- 233 responses as of September 5\textsuperscript{th} (47%)
- No information on respondent demographics
  - Superintendent vs. supervising vs. employee
  - Age, education etc.
- Independent vs. multiples unknown
Results – Policy adherence

- Awareness of PSI Safe Practice Policy

- Written policy in 45.1% of pharmacies; None in 49.4%
Results – Methotrexate strength

- Two-thirds of pharmacies stock both strengths
- 37.4% tablets not distinguishable by shape
- No special storage arrangements in 62%
Results – Last Rx dispensed

- RA indication in 75% of prescriptions
- 15mg weekly most common dose
- 54% GMS patients
- 15% 10mg alone, 17% both strengths dispensed
- 85.4% on 5mg folic acid regimen
  - Day or days not stated in 66%
Labelling with day of the week

21. Day of the week stated on the prescription that methotrexate to be taken?

<table>
<thead>
<tr>
<th>Day</th>
<th>No.</th>
<th>% cit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non response</td>
<td>13</td>
<td>5.6%</td>
</tr>
<tr>
<td>Monday</td>
<td>14</td>
<td>6.0%</td>
</tr>
<tr>
<td>Tues</td>
<td>11</td>
<td>4.7%</td>
</tr>
<tr>
<td>Wed</td>
<td>33</td>
<td>14.2%</td>
</tr>
<tr>
<td>Thur</td>
<td>7</td>
<td>3.0%</td>
</tr>
<tr>
<td>Fri</td>
<td>18</td>
<td>7.7%</td>
</tr>
<tr>
<td>Sat</td>
<td>6</td>
<td>2.6%</td>
</tr>
<tr>
<td>Sun</td>
<td>4</td>
<td>1.7%</td>
</tr>
<tr>
<td>Not stated</td>
<td>127</td>
<td>54.5%</td>
</tr>
<tr>
<td>Total</td>
<td>233</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

12. Do you include the day of administration on the label?

Mean = 1.45, Std deviation = 0.50

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>123</td>
<td>101</td>
<td>233</td>
</tr>
</tbody>
</table>

52.8% Yes
43.3% No
3.9% Non response
Decision re choice of strength

- 30% provide strength previously dispensed
- 63% ask clarity from patient or carer
- 50% would check with prescriber, 33% would not
- 63% do not refer to patient monitoring booklet
- 42% indicated they would not dispense the strength(s) resulting in the least number of tablets

*Significant non-response rate for this question*
Clinical monitoring outcomes

- Respondents asked about monitoring booklets – 92% no or don’t know
  
  ![Graph 1: Did the patient have a monitoring booklet?](image1)

- Checking adherence to monitoring ~30% do
  
  ![Graph 2: Do you normally check if methotrexate patients are having regular blood monitoring tests?](image2)

- 28% check patient awareness of signs of methotrexate toxicity (29% do not & 38% do so occasionally)

- 60% of staff are unaware or unsure of signs

- PILs routine as are easy-to-open bottles
Perceptions re withdrawal of 10mg strength

- 30% of respondents stated that patients expressed preference for 10mg strength

- 56% indicated that withdrawal of 10mg strength would add safety benefits

- 20% indicated there may be risks associated with withdrawal

- 15% definitely willing to ask patients to participate in further assessment
  - 10% No, 51% could try asking them
Implications & Recommendations

- PSI policy revisions and re-launch
  - Include more specific methotrexate toxicities
  - Labelling instructions: visual examples
  - Special storage measures – visual examples
  - Communication of revised safe practice recommendations
  - Follow-up audit to assess adherence

- Pharmacies
  - Specific education for compliance with guidance for all staff
  - Prescribers, pharmacists, pharmacy staff and patients

- Initiatives with Prescribers
  - Recommendations re prescribing 2.5mg strength
  - 54% of patients must have their hospital prescription transcribed by their GP so as to obtain supply on PCRS
Prescribing of Methotrexate

- Rheumatology accounts for 80% of Irish patients on Methotrexate, an estimated 9,147 patients).
- There are 47 consultant rheumatologists in the State, of which 32 have public hospital appointments and 15 are private sector only.
- Assuming that all patients see a rheumatologist, this means each consultant takes care of 195 methotrexate patients on average.

- There are 13 referral centres for public patients
  - Dublin/Mid-Leinster - 4 Centres with 10 consultants
  - Dublin/North East - 4 Centres with 11 consultants
  - South - 3 Centres with 8 consultants
  - West - 2 Centres with 3 consultants

- 15 private-only consultants operate out of 13 locations
  - 6 South, 4 Dublin/Mid-Leinster, 4 West, 1 Dublin/North-East
Harm from Methotrexate in Ireland

Two national sources of data

1. Data collected by the National Poisons Information Service in relation to calls about Methotrexate ingestion

2. Data collated by State Claims Agency from the Clinical Indemnity Scheme (2004-2010) from incident reports submitted by hospitals to the STARSWeb database.
132 enquiries about Methotrexate, in relation to 88 adult patients.
- Of these 58 cases were therapeutic errors that had actually led to overdose.
- Information on actual dose ingested available for 22 of these cases
- Average ingested dose was 46mg (range 5mg – 160mg).

There were also 11 cases of accidental ingestion by children aged 1-5
- average dose of 17.5mg (range 2.5mg-50mg)
State Claims Agency Data from the Clinical Indemnity Scheme (2004-2010)

Incident reports submitted by hospitals to the STARSWeb database:

- 128 incident reports involving Methotrexate
- 20 incidents related to daily versus weekly dosing errors
- 18 near miss cases of incorrect prescribing daily rather than weekly discovered by healthcare personnel before dispensing and the prescription amended.
Three Cases of Harm reported to State Claims Agency

1. Patient prescribed 2.5 mg TDS rather than 7.5mg weekly. The patient had received 5 doses before the error was noted and was monitored by blood tests. The patient suffered no lasting ill-effects.

2. Patient prescribed 7.5 mg daily rather than 7.5mg weekly. Patient received 4 doses (30mg in 4 days) before the error was noted. The patient had a very stormy 4 month hospitalisation with marrow depression but survived.

3. Patient death from neutropaenic sepsis after continuing methotrexate while on chemotherapy for a cancer.
Patient already taking 20mg Methotrexate per week for long-standing rheumatoid arthritis started on chemotherapy for a newly-diagnosed metastatic cancer.

Patient continued his methotrexate regime though started on Gemcycabine and Cisplatin chemotherapy in a day case setting.

Patient took Methotrexate 60mg in 3 doses within 15 days of chemotherapy.

21 days after the chemotherapy date, he was admitted to hospital with a respiratory tract infection, feeling weak and unable to cope at home. Blood tests were done and patient was started on IV broad spectrum antibiotics.
Case Study: Methotrexate Death

- Depleted WCC was noted. However a chart note stated “continue routine meds”
- Patient was given another 20mg dose of Methotrexate the next day
- On the following day it was realised that the patient had inadvertently been continued on Methotrexate and the prescription was discontinued.
- However, the patient remained very ill, ventilated, and on platelets in ICU with persisting severe neutropenia and ultimately died on Day 11 after the final dose of methotrexate had been given.
Comparison with England and Wales

- Since launch of the NPSA guidance (2004), 90 incidents per year for a population of 53 million people, 11.5 times the population of Ireland.
- Given a similar incident rate, we might expect to receive eight Methotrexate incident reports per year in Ireland.
- We are actually experiencing 31 reports per year, four times more than the UK.
Difference between NHS and Irish situation

- Since the issuing of the NPSA Guidance in July 2004, Shared Care Protocols have been implemented throughout the NHS
- Local compliance (of pharmacies, GPs and hospitals) with the guidance is regularly audited with results fed back to the stakeholders in newsletters and other communications.
Northern Ireland Guidance

- “Guidance for Improving the Safe Use of Oral Methotrexate in Primary Care: Information for GPs and Community Pharmacists” *Northern Area Prescribing Forum December 2006*

- “Oral methotrexate Dermatology/ Gastroenterology/ Neurology/ Ophthalmology/ Respiratory/ Rheumatology Shared Care Guideline” *October 2008*
  

- “Shared Care Guideline for Sub-Cutaneous Methotrexate NIHSSB Interface Pharmacist Network for Specialist Medicines *June 2011*
Follow-up: Pharmacy

- Present audit results to PSI Pharmacy Practice Development Committee,
- Recommendations for revised guidance to community pharmacies
  - Show examples of safe storage measures
  - Labelling instructions: TALL MAN lettering for day of week
  - Computer alerts from vendors
  - Record of diagnosis in patient profile
  - Recording of OTC medicines in patient profile
  - Safe handling of Methotrexate as an oral anticancer medicine
Consultation with rheumatologists has begun.

Next step is obtain prescribing protocols from prescribing centres and compare.

Gastroenterologists & dermatologists consultation also

Follow up with the ICGP to discuss possible guidance for GP’s
Follow-up – whole system

- Qualitative assessment of patients’ attitudes to withdrawal of 10mg strength
- Evaluation of current practice in 13 rheumatology public referral centres
  - Use of monitoring booklets
  - Local shared care guidelines
  - Prescribing & monitoring protocols
- Develop a short on-line educational resource for prescribers and pharmacists
  - Narrated presentation/on-line completion of exercises
- Consensus on national documentation
  - PIL, monitoring booklet and monitoring guidelines
  - Shared Care Protocol
Conclusions

- Work to date has identified a number of improvement strategies to be implemented in community pharmacies.
- Widespread lack of awareness of policy indicates that more attention needs to be paid to communicating policies to target audiences.
- The audit indicates that the safety issues are broader than the issue of whether or not to withdraw reimbursement status from the 10mg tablet strength.
- UK experience points to the introduction of Shared Care Protocols to maximise safety and minimise harm.
- Consultants, GPs, Pharmacists, and the HSE have a shared responsibility to enhance safety.
- This can best be achieved though the introduction of shared care protocols.
Acknowledgements

Audit
- Participating pharmacists
- Pharmaceutical Society of Ireland
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- Dr Kath Bennett, Senior Lecturer in Pharmaco-epidemiology & Statistics, TCD

Incident Data:
- State Claims Agency
- National Poisons Information Centre