Methotrexate and patient harm: an analysis of notifications involving oral methotrexate in Australia 2010 to 2019

Key Messages

- Methotrexate is a high-risk medicine
- Since 2010 there have been 28 notifications involving pharmacists and methotrexate
- In this cohort, seven deaths and nine patients required presentation to hospital
- All deaths were preventable
- Errors with dose administration aids and labelling responsible for majority of errors
- Identifying trends in notifications can help to highlight risk and protect the public

Numerous notifications about oral methotrexate (MTX) have been recorded since inception of the National Scheme and establishment of the Pharmacy Board of Australia (PharmBA) in 2010. The PharmBA recently commissioned the Research Unit of the Australian Health Practitioner Regulation Agency (Ahpra) to undertake an analysis of notifications involving oral MTX. This document is the summary of findings from that analysis. The analysis was prompted by recommendations from the Coroner's Court of Victoria which asked the PharmBA and others to improve public safety in this area. [1] The recommendations came from a 2018 inquest into a death caused by oral MTX poisoning, where a pharmacist identified an error with the dose and frequency of a prescription for a patient with psoriatic arthritis, contacted the prescriber, yet felt compelled to supply the MTX, even though they were of the professional opinion that it was inappropriate. The supply of MTX for this patient tragically lead to a death that was preventable.

Background

When dosed and administered appropriately, oral MTX is considered safe and effective. Low-dose MTX for indications such as rheumatoid arthritis, psoriasis and inflammatory bowel diseases is typically administered orally weekly as opposed to high-dose MTX for cancer treatment where doses are more likely to be intermittent daily either orally or as an injectable. Internationally, low dose oral MTX has been associated with high rates of harm and death. [2] A study of medication errors reported to the United States Food and Drug Administration between 1997 and 2001 identified 106 errors involving MTX, including 25 deaths and 48 serious adverse outcomes. [3] Factors influencing errors were confusion about once-weekly dosing (30%) and other errors in dosing (22%) being the most commonly reported errors. Errors were attributed to the prescriber (37%), the patient (20%), dispensing (19%) and administration by a health professional (17%). An Australian study of medication errors in the National Coronial Information System database, identified 22 deaths linked to MTX between 2000 and 2014, including seven cases of incorrect daily dosing. [4] That study did not distinguish between oral and intravenous MTX. The objective of the current analysis of MTX notifications commission by the PharmBA, was to better understand the underlying issues influencing the dispensing and supply of oral MTX, which lead to poor outcomes and ultimately the notifications.

Approach

To undertake this work, regulatory data related to notifications (complaints) about pharmacists involved in the dispensing of methotrexate between 1 July 2010 and 30 June 2019 was examined. Data was obtained from Ahpra, the Queensland Office of the Health Ombudsman, the NSW Health Professional Councils Authority and the Pharmacy Council of NSW. Data was coded to identify

various domains such as the underlying issue, levels of harm to the patient, setting and whether the patient died. Patient harm was classified using a modified National Coordinating Council for Medication Error Reporting and Prevention Taxonomy of Medication Errors. [5]

Findings

From 1 July 2010 to 30 June 2019 there were 28 notifications about 26 pharmacists that covered 23 incidents involving oral MTX across Australia. All notifications were about pharmacists working in community practice. The largest sources of notifications were from patients or patient representatives (50%) and non-treating health practitioners (19%), (Table 1). There were seven (30%) deaths from 23 incidents, and a further nine (39%) patients required attendance or stay in hospital (Table 2). Dosage administration aids (DAAs) being packed with once-daily dosing in error for weekly dosing (54%) as well as problems with labelling (29%) featured prominently. Failing to resolve prescribing MTX errors, dispensing MTX in error and inadequate counselling all featured as underlying issues (Table 3). Many of the labelling errors involved no label on the primary bottle containing MTX, or no directions or wrong direction being provided. A description of each mislabelling is provided in Table 4.

Discussion

Medicine safety was announced as a *National Health Priority Area* for Australia in 2019. [6] Internationally, this follows the 2017 announcement from the World Health Organization on the *Global Patient Safety Challenge of Medication Without Harm*. [7] Additionally, Ahpra and all National Boards that regulate health practitioners, including the PharmBA, recently received policy directives from The Council of Australian Governments (COAG) Health Council. These directives stating that Ahpra and the National Boards must act in the interests of public protection and patient safety in regulatory decision making. [8] Considerable work goes on in the background to realise these important initiatives and directives, which highlight the importance of medicine safety and strive to limit patient harm from all medicines including oral MTX.

How do these errors, some fatal, continue to persist? It is unlikely because there is a lack of guidance or practice standards. Key documents exist, such as the PharmBA *Guidelines for dispensing of medicines [9], Pharmaceutical Defence Limited (PDL) Guide to good dispensing [10], the Pharmaceutical Society of Australia (PSA) Dispensing practice guidelines [11], and the PSA Guidelines for pharmacists providing dose administration aid service (DAA).* [12] Regarding cytotoxic or hazardous medicines, the PSA DAA guidance advises that clear benefit of patient adherence must be weighed against risks when contemplating packing a cytotoxic agent in a DAA.

The PharmBA has also published case studies involving oral MTX on its website, provided information about the hazard of dispensing MTX in its newsletters and communicated with stakeholders and professional bodies on the topic.

In reviewing these cases, half of all errors involved a failure in packing or checking of DAAs. Pharmacists, including proprietors of pharmacies must ask themselves, what quality control provisions are in place to avoid once-weekly MTX being inadvertently packed once-daily? Oral cytotoxic medicines, including methotrexate, must be packed separately to a patients' other medicines. [13] Consideration must be given to what solutions could mitigate error in this hazardous process.

Labelling is a core professional and legal requirement performed by pharmacists when dispensing medicines. Appropriate labelling of medicines is always important and is even more so for medicines such as MTX with a narrow therapeutic index, which have the possibility to cause lethal toxicity if directions for the patient are absent, ambiguous or incorrect on the primary container. A cytotoxic medication, such as MTX, also requires an ancillary label. [14]

Failure to 'gatekeep' prescription errors was the root cause for two incidents that each led to a Coronial investigation. [1, 15] In both cases, the patient was prescribed and dispensed MTX daily instead of weekly. Pharmacist scope of practice includes denial of supply, if their professional judgment is that the medicine or prescribed dose or frequency is unsafe for the patient, irrespective of instruction from the prescriber to dispense.

The number of notifications about MTX is unlikely to reflect the true extent of errors. The actual number of errors and patient harm from MTX is likely to be considerably more than that reported here. Furthermore, a limitation of this work is that the analysis did not include prescriber errors with oral MTX.

While all notifications were about pharmacists working in community pharmacy, this does not preclude the possibility that errors with oral MTX may have occurred in hospital pharmacies during this period. As hospitals have governance systems for errors and complaints, it is possible complaints would be made to the hospital rather than Ahpra or other jurisdictional regulators and thus not captured in these data. Noteworthy, is that it is commonplace in Australian hospital pharmacies for oral MTX to be stored in a dedicated cytotoxic location of the dispensary, reducing inappropriate drug selection, and also requiring two signing pharmacists to endorse patient supply, to further limit human error. It is possible such measures contributed to the absence of notifications involving hospital pharmacies and may provide insights to limit oral MTX errors in community practice.

Conclusion

It is likely that the extent of harm caused by inappropriate dispensing of oral MTX is greater than that captured by regulatory notifications. This analysis of national data over nearly a ten-year period, identified morbidity and mortality from inappropriate oral MTX dispensing. Incorrect once-daily packing of MTX, rather than weekly packing, was highlighted as a substantial problem, as was incorrect or absent labelling. While the number of notifications involving oral MTX was relatively low, the outcomes were frequently catastrophic. Pharmacists need to ensure their own processes and those of the pharmacy where they are practising support them to exercise their professional responsibilities in the safest way possible.

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Table 1: Complainant: source of notifications (1 July 2010 – 30 June 2019)

Source of notification	Number of MTX notifications	Percent of MTX notifications
Patient or patient representative	14	50
Non-treating practitioner	5	19
Hospital/treating practitioner	4	14
Prescriber	2	7
Government department	2	7
Aged care service	1	3
TOTAL	28	100

Table 2: Patient harm for each incident (1 July 2010 – 30 June 2019)

Harm	MTX-related incidents	Percent of MTX-related incidents
Death	7	30.5
ICU/CCU	2	8.5
Hospitalisation general ward	4	17.5
Longer hospital stay	1	4.5
Emergency department	2	8.5
Feeling unwell	1	4.5
None	6	26
TOTAL	23	100

Table 3: Underlying issue for each MTX-related notification (1 July 2010 – 30 June 2019)

Issue	MTX-related notifications	
	n	%
DAA packing– daily, not weekly	15	54
Labelling	8	29
Prescribing error –failure to resolve	2	7
DAA – other	1	3.5
Dispensed in error	1	3.5
Inadequate counselling	1	3.5
TOTAL	28	100

DAA: dosage administration aid

Table 4: Labelling errors of dispensed oral MTX (1 July 2010 – 30 June 2019)

Case	Labelling issue
1	No directions on the label of an old bottle of MTX that the patient decided to resume using after a long break
2	Bottle labelled ‘as directed’ – taken daily, not weekly
3	Box said ‘Take 10 tabs a week’ – script was ONE 10 mg tab/week
4	Box labelled for wrong patient and MTX bottle labelled correctly
5	Wrong patient name and address
6	Labelled box, not bottle
7	Wrong label – celecoxib one capsule twice daily
8	Wrong label – folic acid – correct name on outer box, incorrect name on MTX bottle

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