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Title Page

Comparison of a novel methadone rotation method with other commonly used methods

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Abstract

Objectives

To compare a novel method of methadone rotation used in a Specialist Palliative Care Inpatient Unit (SPCU) in Cork, Ireland, with rapid titration methods using Perth and Brisbane Protocols, as well as the Edmonton method of methadone rotation.

Methods

A retrospective chart review was performed in March – June 2022. All patients who completed rotation to methadone during 2018 – 2019 in the SPCU were included. 2018- 2019 was selected to study a population not affected by the coronavirus pandemic. Oral Morphine Equivalent (OME) was calculated using the opioid conversion chart. From the OME, the expected daily methadone dose was calculated using the Perth, Brisbane and Edmonton methods. These figures were then compared directly with the actual methadone doses achieved using our dosing schedule.

Results

Comparison of the expected doses using the Perth and Brisbane rapid titration protocols and stable daily dose achieved revealed that the stable methadone dose was significantly lower than both rapid titration protocols ($p=<0.0001$) and ($p=0.0035$, respectively). However, comparison of the expected dose using the Edmonton method and dose achieved did not determine any significant difference ($p=0.7602$).

Conclusions

This is the first evaluation of a novel Irish method of methadone rotation and demonstrates a lower overall daily methadone doses compared with established protocols.

Background

Methadone is a strong opioid medication with action predominantly at the μ opioid receptor. It is used to treat complex pain poorly responsive to other opioid medications[1] and treat neuropathic pain through NMDA receptor inhibition[2, 3]. It is safe in renal impairment and is relatively inexpensive[4, 5].

Methadone has complex pharmacokinetics including a variable half-life. It can take days to reach a stable plasma concentration [1, 5]. Clinicians should consider potential drug interactions and risk of QTc prolongation[4].

There is no universally accepted conversion ratio. The Palliative Care Formulary (PCF) states when switching from morphine to methadone the eventual 24-hour dose is typically 5-10 times smaller than the morphine dose, and sometimes 20-30 times smaller[1, 6]. Previous ratios have overestimated the dose of methadone leading to the development of unwanted side effects [7].

The PCF recommends *stop and PRN* (Morley Makin), where the pre-rotation opioid (PRO) is discontinued and PRN doses of methadone are used to establish the required methadone dose[1]. Other methods include rapid titration, which involves conversion of the patient's previous 24-hour opioid use or oral morphine equivalent (OME) to a target methadone dose, with the patient's PRO ceased and methadone started immediately. The equianalgesic dose is calculated using the 'Perth' Protocol ratio[8]. The 'Brisbane Protocol' is a modified version of the Perth Protocol, with more conservative conversion ratios [9]. The Edmonton method, otherwise known as the 3-day switch method, involves reducing the OME by thirty-three percent daily over 3 days, while commencing an equianalgesic dose of methadone. An equianalgesic titration dose ratio of 10:1 (morphine: methadone) is used for OME <1000mg [7].

Marymount University Hospital and Hospice favours a gradual substitution of methadone for PRO, starting at a methadone dose of 2-2.5mg twice daily with the PRO reduced by approximately 20% of the previous 24-hour dose of opioid use. This is continued over several days with the methadone dose being increased daily in increments of 2-2.5mg twice daily and daily reduction of the PRO by 20% of the original dose.

Aim

This paper compares the method of methadone rotation used in our specialist palliative care inpatient unit (SPCU) with established Perth [8], Brisbane[9] and Edmonton[7] methods.

Methods

Approval was sought and obtained from the local ethics committee. A retrospective chart review was performed in March – June 2022. All patients who completed rotation to methadone from another opioid during 2018 – 2019 in the SPCU were included in the study. The years 2018 – 2019 chosen with a view to study a population who were not affected by the coronavirus pandemic, as this had a significant impact on the number of admissions to hospice. Inclusion and exclusion criteria are as follows (Figure 1):

Inclusion Criteria:

- Patients over 18 years of age who were rotated to methadone from another opioid during 2018- 2019 in the SPCU.

Exclusion Criteria:

- Methadone use as adjunct and initial use as adjunct before rotation to methadone.
- Poor tolerance of methadone resulting in discontinuation before stable dose is achieved.
- Use in conjunction with another primary opioid and full rotation not completed.
- Charts not accessible.

Two reviewers assessed medical charts. Data collected included demographics, admission length, diagnosis, opioid requirement in the 24 hours prior to rotation, presence of opioid toxicity during time to achieve stable dose, documentation of opioid-sparing interventions (interventional procedure and radiotherapy) within the previous month, final stable daily methadone dose achieved, length of time to achieve stable daily methadone dose (defined as a dose that was stable for 5 days or until death/discharge). Data was anonymized and stored on a password protected computer.

OME was calculated using Marymount University Hospice and Hospital's opioid conversion chart (Appendix 1). From the OME, the expected daily methadone dose was calculated using Perth, Brisbane and Edmonton methods. These figures were then compared directly with the actual methadone doses achieved using Marymount's dosing schedule. For this study, we used a ratio of 2:1 for SC:PO methadone[1, 10]. Doses were compared by paired t-tests, applying a 5% level of significance, using SAS® software (version 9.4).

Results

Twenty-eight patients were included in the analysis. 46% were female and 54% were male. 71% were admitted from home, 25% were admitted from hospital and 4% were admitted from residential care. Mean admission length was 46 days (9-138). 96% had a cancer diagnosis, one patient had a dementia diagnosis.

25% received radiotherapy within the month prior to rotation. One patient received a pain intervention during rotation and 11% had an intervention in the month prior to rotation. During the rotation, 61% of patients developed opioid toxicity.

The mean OME was 131mg (SD=108). The mean stable daily methadone dose achieved was 12.6mg (SD=6.7). The mean time to achieve a stable daily methadone dose was 7.1 days (SD=3.7). Comparison data of expected daily methadone doses calculated using the pre-rotation OME are presented in Table 1. Direct comparison of the expected doses using the Perth and Brisbane rapid titration protocols and stable daily dose achieved in our review revealed that the stable methadone dose was significantly lower than both rapid titration protocols ($p=<0.0001$) and ($p=0.0035$, respectively). However, comparison of the expected dose using the Edmonton method and daily methadone doses achieved and did not determine any significant difference ($p=0.7602$).

Table 1. Comparison of expected methadone doses by conversion protocol

	OME, *mg*	Stable Daily Methadone Dose (Marymount Novel Method), *mg*	Perth Protocol, *mg*	Brisbane Protocol, *mg*	Edmonton Method, *mg*
Mean (SD)	131	12.6 (6.7)	26.5 (14.8)	17.3 (7.9)	13.1 (10.3)
Median (range)	100 (4-360)	12.0 (2.0-25.0)	26.5 (1.0-68.0)	16.5 (1.0-34.0)	10.0 (0.0-36.0)
Difference of predicted dose to stable methadone dose achieved (SD)			13.9 (11.9)	4.6 (7.7)	0.5 (9.2)
***t*-statistic**			-6.17	-3.20	-0.30
***p*-value**			<0.0001	0.0035	0.7602

n=28. OME, oral morphine equivalent.

Discussion

This is the first time that an Irish method of methadone rotation in use for several decades in an established SPCU has been evaluated against international protocols. Results show that a gradual dosing schedule with slow titration leads to significantly lower overall doses than may be achieved with rapid titration with Brisbane (27%) and Perth (52%) conversion ratios. The European Association for Palliative Care guideline on the use of opioid analgesics refrained from commenting on methadone conversion ratios due to the variability of ratios previously published and the complex pharmacology of methadone[11]. Previous opioid dose conversion tables may overestimate the dose of methadone required and lower doses than suggested may be safe and effective[7, 12, 13], this is supported by the results of our study.

We found no significant difference between our method and Edmonton. McLean and Twomey's systematic review reported no basis for using a rapid conversion method in preference to the Edmonton method[12]. Moksnes *et al* also favoured the Edmonton method over a rapid stop and go titration at the conclusion of their randomised control trial[14]. Our method is similar to Edmonton but uses a more gradual titration period with close observation for dose-limiting toxicity.

61 % of patients had documentation of opioid toxicity during methadone rotation. This resulted in a dose-reduction and longer time to achieve stable dose. This reinforces the need for inpatient rotation under a specialist service. It is worth noting that the mean length of time to achieve a stable dose was 7.1 days on our review, with a mean admission length of 46 days. Further prospective evaluation of our method versus Edmonton could examine rates of

toxicity/ side effects and associated length of stay. Of note, there were no reports of respiratory depression and naloxone was not administered.

McPherson *et al* compiled an expert consensus paper for methadone use in the hospice and palliative care setting[9]. They recommend different conversion ratios based on OME without adjusting the dose for 5-7 days and not by increments >5mg/day. They suggest that more aggressive titration may be possible with oversight by clinical experts in an inpatient setting[15]. Conversion ratios vary based on numerous factors, such as individual patient factors[4, 12, 15], previous opioid use, with higher conversion ratios suggested for higher doses of opioid use[4].

Limitations

Limitations include the retrospective and unblinded nature of the study, and small sample size. Some paper records of patients selected for screening were not accessible to us at the time of review. It is unknown whether these patients were prescribed methadone as an adjunct or fully rotated to methadone. This affected our sample size.

We selected patients from the pre-pandemic era as the pandemic affected the volume and type of SPCU admissions. However, this era predated the introduction of standardised clinician and patient-rated symptom scores. A small number of patients who developed toxicity during rotation to methadone and were excluded from analysis. These factors may limit the generalisability of the findings.

Conclusion

This study describes a new method of methadone rotation. When we compare expected doses of methadone by conversion protocol, lower final doses of methadone were achieved using our method compared with Brisbane and Perth protocols. There was no difference in final doses between our method and Edmonton. Lower stable effective doses of methadone may reduce the potential for adverse effects in patients with palliative care needs, potentially improving their quality of life.

Ethical approval

Ethical approval granted from Cork Research Ethics Committee, University College Cork.

Contributorship statement

Project design and implementation performed by EC, NDB and AL. Eligible participants identified by MF. Data collection performed by EC, NDB. Statistics were performed by MC. Manuscript drafted by EC. Manuscript review and revisions were conducted by EC, NDB, FOC, MF, MC, MM, MJOL, FK, AL. EC is the guarantor.

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Competing Interests

No conflicting interests to declare.

Data Sharing Statement

Not applicable.

Figure 1. Flowchart depicting selection of patients included

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