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ORIGINAL RESEARCH

Opioid rotation in patients initiated on oxycodone or morphine: a register study

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Purpose: Strong opioids are recommended for the treatment of moderate to severe pain. However, some patients do not achieve a successful treatment outcome due to intolerable adverse events and/or inadequate analgesia, thus may benefit from switching to another opioid, a procedure known as "opioid rotation." The type of opioid at treatment initiation may influence the risk of opioid rotation and the objective of this study was to assess such rotation after treatment initiation with two alternative treatments, controlled-release (CR) oxycodone versus CR morphine in patients suffering from non-cancer pain.

Method: The study reported here was a real-life study based on Swedish register data: the Prescribed Drug, National Patient, and Cause of Death registers. The captured data cover the entire Swedish population treated in specialist care. A statistical analysis plan was agreed and signed before data were accessed.

Results: Data from 50,223 cases were included in the analyses. The risk of rotation was 19% higher in patients initiating treatment with morphine compared with oxycodone (hazard ratio 1.19; 95% confidence interval 1.11–1.27; $P < 0.001$), after adjusting for such baseline variables that were both significantly correlated with the outcome variable (time to rotation) and significantly different between the groups; age at index date, osteoarthritis and number of pain-related drugs.

Conclusion: Patients with non-cancer pain who initiated treatment with CR morphine had a higher risk of opioid rotation than patients initiated with CR oxycodone.

Keywords: nationwide data, Sweden, drug rotation, non-cancer pain

Introduction

Opioid analgesics are effective in the management of pain relief. Strong opioids such as oxycodone and morphine are recommended for the treatment of moderate to severe pain. Strong opioids are classified as step 3 medications in the World Health Organization (WHO) ladder for cancer pain management.[1–3] In national and international guidelines for the treatment of chronic non-cancer pain, treatment with strong opioids is recommended when other analgesics have been unsuccessful.[4]

Opioid rotation is discussed as an alternative mainly to avoid development of tolerance, but also when intolerable adverse effects or inadequate analgesia despite dose increases arise.[5–8] Despite the lack of randomized studies to support the effectiveness of the approach, opioid rotation is generally accepted as clinical practice in such cases[9] and guidelines for the strategy have been developed.[10,11]

The pharmacokinetic profiles of morphine and oxycodone differ in that the oral bioavailability of oxycodone is higher than that of morphine[12,13] and morphine has

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active metabolites that may accumulate and lead to an increased risk of adverse events and toxicity.[14–16] The clinical relevance of these differences poses a challenging question, and is as yet unresolved in the available randomized trials.

However, results from a US health care claims-database study on the risk of opioid rotation has shown that non-cancer pain patients treated with controlled-release (CR) morphine or transdermal fentanyl were more disposed to opioid rotation than patients treated with CR oxycodone. The corresponding analyses in cancer patients showed no such differences.[17] As register studies always have caveats, we wanted to find out if the results of the US study could be reproduced. In Sweden, the availability of national health care registers offers unique opportunities to perform research on the general population on a nationwide basis, as the registers cover total data for Sweden.

Thus, the objective of our study was to assess opioid rotation after treatment initiation with CR oxycodone versus CR morphine in patients suffering from non-cancer pain using Swedish register data.

Methods

This was a real-life study based on Swedish register data. The study was approved by the regional ethics review board in Gothenburg and performed according to the World Medical Association's Declaration of Helsinki.

National health care registers

Data on prescribed and dispensed pharmaceuticals at Swedish pharmacies were obtained from the Swedish Prescribed Drug Register, which contains information such as patient age, sex, and personal identification number, as well as information about dispensed products. All drugs are classified according to the Anatomical Therapeutic Chemical classification system.[18] Information about hospital inpatient and outpatient health care was extracted from the Swedish National Patient Register and included patient age, sex, personal identification number, length of hospitalization, consulting visits, dates of admission and discharge, and *International Classification of Diseases*, tenth revision (ICD-10) diagnoses.[19] Information on the date of a patient's death was obtained from the Cause of Death Register. Information from the registers was linked by each patient's unique ten-digit personal identification number. All registers are held at the Swedish National Board of Health and Welfare (NBHW).

Study population

Inclusion and exclusion criteria

Patients eligible for the study should have been dispensed either CR oxycodone or CR morphine at the pharmacy for the first time between January 1, 2006 and December 31, 2008, and diagnosed according to the definitions later in this paper at a hospital visit the year preceding start of treatment. This means that patients diagnosed within the Swedish primary health care system and with no contact with the hospital or specialist care, were not included, since no register encompasses the entire Swedish primary health care system. The date of the first dispensation of CR oxycodone or CR morphine was denoted as the "index" date. To ensure that the patients were naive to strong opioids, no dispensation of any strong opioid was allowed during the 6-month period preceding the index date (pretreatment). Patients were excluded from the study if, at the index date, they were dispensed CR oxycodone tablets of 40 mg or stronger or CR morphine tablets of 60 mg or stronger. These patients were excluded since they were not considered naive to strong opioids as had probably initiated the treatment earlier – for example, while hospitalized.

Population

The population was defined by the ICD-10 diagnosis codes registered in the National Patient Register any time during the year preceding the index date. Diagnoses were selected that possibly could have been indications for opioid use; for example fibromyalgia, low back pain, other spinal pain (excluding low back pain but including neck pain), osteoarthritis, other musculoskeletal pain, or neuropathic pain (a list of all diagnoses is presented in Online supplement A). Patients who before the index date had also been registered with a cancer diagnosis were excluded from the population. If a patient had a cancer diagnosis registered after the index date, the patient was included in the study until the date of the cancer diagnosis, since it was assumed a cancer diagnosis would change the treatment strategy.

Study procedure

A statistical analysis plan was developed and approved by the sponsor, the statistician and the responsible scientist at Nordic Health Economics before the data extracted from the registers were accessed. In the statistical analysis plan, definitions as well as analyses were predefined.

Data extraction

Data were extracted from the Prescribed Drug Register then linked to the National Patient and Cause of Death registers

using personal identification numbers. Extraction and linkage of data were performed by the Department of Statistics, Monitoring and Evaluation at the NBHW. All data were anonymized by the NBHW before analyses were performed.

Opioid rotation

Opioid rotation was identified as the first dispensation of any other strong CR opioid or strong immediate-release (IR) opioid, except IR oxycodone in the CR oxycodone group and IR morphine in the CR morphine group. Dispensation of any weak opioid that was not dispensed during the 6-month pretreatment period was also defined as a rotation, since such a therapy change could be due to dissatisfaction with treatment. This time point had to occur within 3.5 months following the last dispensation of the study medication. Patients were followed until the first change in treatment strategy. All opioids considered are listed in Online supplement B.

Censoring

"Censoring" was defined as: date of death; date of the last dispensation of CR oxycodone/CR morphine plus the number of days 25 mg/50 mg daily would last (however, if the last dispensation was within the first month following the index date, the daily dose was assumed to be 10 mg/20 mg daily); if more than 6 months had passed between two dispensations of the study medication, the treatment was considered discontinued and the former of the two dispensations plus the number of days the treatment would last according to the doses just mentioned was set as the censoring date; and a maximum of 3.5 months from the last dispensation.

Concomitant and pain-related medication

The number of concomitant drugs was used as a proxy for comorbidity and analyzed by registering the total number of drugs dispensed, including dietary supplements and nutrient solutions, during the 6-month pretreatment period.[20] In addition, a separate analysis of the number of pain-related drugs dispensed during pretreatment was performed (a list of all pain-related drugs is presented in Online supplement C). Each substance was counted as one concomitant drug.

Statistical analysis

For comparison between the CR oxycodone and CR morphine groups, the Mann–Whitney *U*-test was used for continuous variables and Fisher's exact test for dichotomous variables.

Patients were followed for 1 year from the index date. Time to opioid rotation was assessed as the number of days between the date of each patient's index date and the date of rotation. Treatment stop was treated as the censoring date. All analyses of time to opioid rotation between the two groups were performed with Poisson regression models adjusted for all measured variables significantly correlated with the outcome variable (time to opioid rotation) and significantly different between the groups (oxycodone versus morphine). The time variable in the model was analyzed with a break point 30 days after the index date to achieve a better estimate of updated time in the study. The unadjusted and adjusted hazard ratios (HRs) including 95% confidence intervals (CIs) were calculated from Poisson regression models. The HRs for age in the Poisson regression models were given for 10 years' change.

Programming of all statistical analyses was performed using SAS® (v 9.2; SAS Institute, Cary, NC, USA). All significance tests were two-sided and conducted at a 0.05 significance level.

Results

Patient characteristics

The dataset included 50,223 patients, 44,917 (89.4%) of whom initiated treatment with CR oxycodone and 5306 (10.6%) with CR morphine. In the oxycodone group, there were 6265 (13.9%) patients rotating and the corresponding number in the morphine group was 983 (18.5%).

The baseline characteristics are shown in Table 1. Oxycodone patients were younger at the index date (mean ± standard deviation: 65.9 ± 16.9 versus 70.9 ± 15.5) and had a lower number of concomitant (9.0 ± 5.4 versus 11.0 ± 5.7) as well as pain-related (2.4 ± 1.4 versus 2.6 ± 1.4) drugs compared with morphine patients during the 6-month pretreatment period. The proportion of patients with a diagnosis of low back pain and osteoarthritis was higher in the oxycodone group, while patients with a diagnosis of fibromyalgia or neuropathic pain were more common in the morphine group.

Baseline predictors

The baseline predictors of time from the index date to opioid rotation during the first year after the index date were analyzed for oxycodone and morphine together (Table 2). The significant predictors were age at index date, sex, osteoarthritis, other musculoskeletal pain, and number of pain-related drugs. For every 10-year increase in age, the risk of rotation was 3% lower, and among patients 65 years or older the risk was 13% lower. In addition, female sex was associated with 8% higher risk of rotation. Further, osteoarthritis was associated with

Table 1 Baseline characteristics of patients in the controlled-release oxycodone and controlled-release morphine groups

Baseline characteristics	Oxycodone (n = 44,917)	Morphine (n = 5306)	*P*
Age (years), mean ± SD	65.9 ± 16.9	70.9 ± 15.5	<0.001
Age category (%)			<0.001
<65 years	42.1	30.1	
≥65 years	57.9	69.9	
Sex (%)			0.18
Male	40.3	39.3	
Female	59.7	60.7	
Non-cancer diagnoses (%)[a]			
Fibromyalgia	10.9	15.5	<0.001
Low back pain	22.5	19.1	<0.001
Other spinal pain[b]	2.4	2.5	0.55
Osteoarthritis	46.8	38.3	<0.001
Other musculoskeletal pain	32.6	33.0	0.58
Neuropathic pain	25.3	35.8	<0.001
Concomitant drugs[c] (n), mean ± SD	9.0 ± 5.4	11.0 ± 5.7	<0.001
Pain-related drugs (n), mean ± SD	2.4 ± 1.4	2.6 ± 1.4	<0.001

Notes: [a]Patients could have >1 diagnosis; [b]excluding low back pain and including neck pain; [c]as a proxy for comorbidity.
Abbreviation: SD, standard deviation.

5% higher risk and other musculoskeletal pain with 8% lower risk of rotation. Finally, for every additional pain-related drug dispensed, the risk of rotation was 8% lower.

Risk of opioid rotation

Initiation with CR morphine was associated with a 14% higher risk of opioid rotation compared with CR oxycodone (HR 1.14, 95% CI 1.07–1.22, $P < 0.001$). The baseline variables that were significantly different between the oxycodone and the morphine groups as well as significant predictors for time to rotation were age at index date, osteoarthritis, and number of pain-related drugs. Using a multivariate Poisson regression model adjusting for these three variables, the risk of opioid rotation was 19% higher in the morphine group (HR 1.19, 95% CI 1.11–1.27, $P < 0.001$).

Table 2 Baseline predictors of time from index date to opioid rotation during the first year after index date for oxycodone and morphine together

Predictor	Hazard ratio (95% CI)	*P*
Age at index date (by 10 years)[a]	0.97 (0.95–0.98)	<0.001
Age category at index date (<65/≥65 years)	0.87 (0.83–0.91)	<0.001
Sex (1 = male, 2 = female)	1.08 (1.03–1.14)	<0.01
Non-cancer diagnoses		
Fibromyalgia	1.01 (0.95–1.08)	0.67
Low back pain	0.99 (0.93–1.04)	0.59
Other spinal pain[b]	1.03 (0.90–1.19)	0.63
Osteoarthritis	1.05 (1.00–1.11)	<0.05
Other musculoskeletal pain	0.92 (0.87–0.96)	<0.001
Neuropathic pain	0.98 (0.93–1.03)	0.37
Concomitant drugs (n)[c,d]	1.00 (0.99–1.00)	0.30
Pain-related drugs (n)[d]	0.92 (0.91–0.94)	<0.001

Notes: [a]For every 10-year increase in age, there could be a lower risk, higher risk, or no risk; [b]excluding low back and including neck pain; [c]as a proxy for comorbidity; [d]for every extra drug, there could be a lower risk, higher risk, or no risk.
Abbreviation: CI, confidence interval.

Discussion

This real-life study, based on observational data from Swedish national registers, assessed opioid rotation in non-cancer patients initiated on treatment with CR oxycodone or CR morphine. The analyses included a comprehensive dataset with a large study population of 50,223 patients, of whom 44,917 began treatment with oxycodone and 5306 with morphine.

Our findings show that non-cancer patients initiating treatment with CR morphine rotate more often than those beginning with CR oxycodone. The adjusted result showed that the risk of rotation was 19% higher in the morphine group than in the oxycodone group.

Patients in the morphine group were older and had a higher number of concomitant as well as pain-related drugs during the 6-month pretreatment period, compared with the oxycodone group. In terms of potential indications for treatment, more patients in the morphine group had fibromyalgia and neuropathic pain, while low back pain and osteoarthritis were more common in the oxycodone group.

Influence of the results of age, osteoarthritis, and number of pain-related drugs were controlled for in the analysis, as these baseline variables were not only different between the groups but also predictors for time to rotation. Concomitant medication was used as a proxy for comorbidity to assess the general burden of illness. Such medication was more common in the morphine group, but was not found to be a predictor of outcome. However, there may be other aspects to the general health status of the patients other than the number of drugs taken, and the lack of detailed information in this regard is a limitation of the study. Conversely, it is not intuitively clear in what direction a potential difference in the general burden of illness between the groups would go. Would more diseased patients be more or less likely to undergo opioid rotation? The answer would probably be "more likely" if the diseases were causing pain, but perhaps "less likely" if they were not painful, such as in the case of hypertension and hypercholesterolemia.

The concomitant use of pain drugs was handled as a separate variable and was adjusted for in the analysis. The results showed that for every additional pain-related drug dispensed during the 6-month pretreatment period, the risk of opioid rotation was lower. A possible explanation for this is that the more pain-related drugs a patient had during this period, the fewer options he/she had to change to if rotating pain therapy after initiation with a strong opioid (CR oxycodone or CR morphine).

Pain is a subjective sensation not easy to define,[21] thus is difficult to compare between individuals. There are no standard doses for treatment with opioid drugs. Therefore, the goal is to find individual doses that relieve each patient's pain.[3] Patients who are opioid naive or have moderate previous opioid exposure should start with a low dose, which should then be titrated slowly to minimize the risk of adverse events.[6] In this kind of study, the challenge is to find a dose that could be used for all patients in a particular population or even doses for different subgroups within the populations. The doses used for the calculations of treatment stop in the present study were chosen to reflect clinical practice in Sweden when a maintenance dose has been achieved. In Sweden, opioids are generally prescribed at lower doses compared with in other parts of the world, particularly in non-cancer pain patients. The choice of doses might have affected the length of treatment, as higher doses would have resulted in shorter treatment durations and vice versa. Since patients need to adapt to these kinds of drugs, the oxycodone and morphine doses were assumed lower during the first month of treatment initiation (10 mg and 20 mg, respectively) than during maintenance treatment (25 mg and 50 mg).

As with all register-based studies, the analyses were confined to data available in the registers and limitations of this study include lack of information on the reason for the initial choice of treatment and why patients switched therapy. The former may be due to differences in the characteristics of the patients not evident from data in the registers. However, the size of the patient population should have countered this problem, unless Swedish specialist doctors systematically make similar choices all over the country.

Interestingly, our results support the results of the previous study on 1896 non-cancer pain patients in the USA, in which the risk to rotate was reported to be 64% lower in the CR oxycodone group than in the CR morphine (HR = 0.36, 95% CI 0.27–0.47, $P < 0.01$).[17] This means that the risk of rotating was 178% higher in the morphine group (HR for CR morphine compared with CR oxycodone = 2.78). Our results showed a more moderate difference between the two drugs (19%), but the findings were still similar to those of Berger et al in that they indicated an increased risk to rotate for those initiated with CR morphine compared with those with CR oxycodone. The reason for this difference remains speculative, but it lends further support to the notion that the more favorable pharmacokinetic profile of oxycodone provides clinical advantages over morphine in everyday health care practice.

Conclusion

Patients with non-cancer pain initiated on treatment with CR morphine had 19% higher risk of opioid rotation than patients initiated with CR oxycodone in a nationwide Swedish population.

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The statistical analyses were carried out by Aldina Pivodic at Statistiska Konsultgruppen in Gothenburg, Sweden.

Author contributions

All authors contributed to the design of the study and the interpretation of data. Lisa Ericson and Ingela Björholt drafted the manuscript and all coauthors revised it critically for intellectual content. All authors approved the final version of the manuscript for publication.

Disclosure

Peter Dahm has been periodically engaged as a lecturer and has participated in clinical studies funded by different pharmaceutical companies, including Mundipharma. Nordic Health Economics is an independent research and consultancy group carrying out projects funded by companies, county councils, public authorities, and academic institutions. Anneli Ambring was employed at Nordic Health Economics when the study was carried out. The authors declare no other conflicts of interest in relation to this work.

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Supplementary materials

Online supplement A Non-cancer pain diagnoses

Fibromyalgia
M79.0, M79.1, M79.6, M79.7, R52.1, R52.2, R52.9
Low back pain
M40, M41, M42, M43, M45, M46, M47.9K, M48.0K, M48.4K, M48.8K, M49.5, M51.0, M51.0K, M51.1, M51.1K, M51.2, M51.3, M51.8, M51.9, M53.2, M53.3, M53.8, M53.9, M54.3, M54.4, M54.5, M54.8, M54.9, M80.0K, M84.0K, M84.1K, M84.2K, M96.0K, M96.1K, M96.6K, M99.1K
Other spinal pain (excluding low back pain but including neck pain)
M48.0A, M48.09, M48.4A, M48.4J, M48.8A, M48.8J, M50, M51.0J, M51.1J, M53.0, M53.1, M54.2, M54.6, M80.0J, M80.0A, M84.0A, M84.0J, M84.1A, M84.1J, M84.2A, M84.2J, M95.3, M95.4, M96.0A, M96.0J, M96.1A, M96.1J, M96.6A, M96.6J, M99.1A, M99.1J
Osteoarthritis
L40.5, M00–M03, M05–M09, M11, M13, M15–M19, M25.0, M25.5, M36, M84.1B–M84.1H, M96.0B–M96.0H
Other musculoskeletal pain
M00–M99 (except the codes already mentioned)
Neuropathic pain
E10–E14, E85, G00–G99, B02.2

Online supplement B Strong and weak opioids

ATC code	Substance
Strong opioids	
N02AA01	Morphine
N02AA03	Hydromorphone
N02AA05	Oxycodone
N02AA51	Bupivacaine hydrochloride + morphine hydrochloride
N02AA55	Oxycodone + naloxone
N02AB	Ketobemidone, meperidine, fentanyl
N02AE	Buprenorphine
N02AF	Nalbuphine
N02AG	Opioids in combination with antispasmodics
N07BC02	Methadone
Weak opioids	
M01AE51	Ibuprofen + codeine
N02AA59	Codeine + acetaminophen or acetylsalicylic acid and caffeine
N02AC04	Dextropropoxyphene
N02AX02	Tramadol
N02BE51	Acetaminophen + codeine
R05DA04	Codeine

Abbreviation: ATC, Anatomical Therapeutic Chemical.

Online supplement C Pain-related drugs

ATC code	Substance
Corticosteroids	
H02AB01	Betamethasone
H02AB06	Prednisolone
Analgesics	
M01A	Non-steroidal anti-inflammatory drugs
M02A	Topical products for joint and muscular pain
N02A	Opioids
N02B	Other analgesics and antipyretics
N07BC02	Methadone
R05DA04	Codeine
Muscle relaxants, centrally acting agents	
M03BB03	Chlorzoxazone
M03BC01	Orphenadrine
M03BC51	Orphenadrine + acetaminophen
M03BX01	Baclofen
Local anesthetics	
N01BB02	Lidocaine
N01BB20	Lidocaine + prilocaine
N01BX04	Capsaicin
Antiepileptics	
N03AF01	Carbamazepine
N03AF02	Oxcarbazepine
N03AX09	Lamotrigine
N03AX12	Gabapentin
N03AX16	Pregabalin
Antipsychotics	
N05AA02	Levomepromazine
Antidepressants	
N06AA04	Clomipramine
N06AA09	Amitriptyline
N06AA10	Nortriptyline
N06AB04	Citalopram
N06AX11	Mirtazapine
N06AX16	Venlafaxine
N06AX21	Duloxetine

Abbreviation: ATC, Anatomical Therapeutic Chemical.