Retrospective Study

Gastrointestinal Adverse Events in Hospitalized Patients Following Orthopedic Surgery: Tapentadol Immediate Release Versus Oxycodone Immediate Release

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Background: Tapentadol has relatively less effect on μ-opioid receptors compared with other opioids. This has the potential to reduce the occurrence of gastrointestinal (GI) adverse drug events (ADEs).

Objectives: To compare the GI ADEs during hospitalization between tapentadol immediate release (IR) and oxycodone IR following orthopedic surgeries.

Study Design: Retrospective cohort study.

Setting: A major metropolitan tertiary referral hospital in Australia.

Methods: Data for adult orthopedic surgery patients receiving postoperative tapentadol IR or oxycodone IR during hospitalization between January 1, 2018 and June 30, 2019, were collected from electronic medical records. The primary outcome was the occurrence of postoperative GI ADEs occurring during hospitalization. This was defined as a composite of nausea, vomiting, or constipation.

Results: The study cohort included 199 patients. Of these, 99 patients received tapentadol IR and 100 patients received oxycodone IR for postoperative pain during hospitalization. The mean age was 66 ± 12 years, and 111 patients (56%) were women. There was no significant difference between groups on the occurrence of GI ADEs (53% in oxycodone group and 51% in tapentadol group, difference 2%, 95% confidence interval [CI], –11% to 16%; $P = 0.777$). After adjusting for potential confounders, the use of tapentadol IR was not associated with a significant reduction of GI ADEs (odds ratio, 0.62; 95% CI, 0.32–1.20; $P = 0.154$).

Limitations: This was a single-center study and should be extrapolated with caution. As this was a retrospective study, the accuracy and availability of data were dependent on documentation in electronic medical records.

Conclusions: Tapentadol IR is associated with similar GI ADE occurrence compared with oxycodone IR in patients with orthopedic postoperative pain during hospitalization.

Key words: Opioid analgesics, tapentadol, oxycodone, orthopedic procedures, postoperative pain, acute pain, gastrointestinal adverse drug events, opioid-induced adverse drug events

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Postoperative pain is common after orthopedic surgeries. When postoperative pain is severe, opioids are indicated during hospitalization (1). Current guidelines recommend immediate release (IR) orally administered opioids as part of multimodal analgesia for these patients (1). However, opioids are not without risk and are associated with serious adverse drug events (ADEs) (2). In postoperative

hospitalized patients, gastrointestinal (GI) ADEs are among the most commonly reported opioid-induced ADEs (2). These primarily include constipation, nausea, and vomiting.

Opioid-induced constipation occurs owing to stimulation of mechanoreceptors and chemoreceptors in the GI tract. Activation of μ-opioid receptors (MOR) and κ-opioid receptors causes delayed gastric emptying time, slower small intestinal and colonic transit, increased fluid absorption from the intestinal content, and increased sphincter tone (3). In addition, immobility after common orthopedic surgeries such as hip or knee arthroplasty, contributes to postoperative constipation. Other opioid-induced GI ADEs such as nausea and vomiting are mediated via stimulation of receptors in the chemoreceptor trigger zone, the vestibular apparatus, and the GI tract (4).

Epidemiologic studies have shown that oxycodone is one of the most commonly used oral opioids for postoperative pain (5). However, there is interest in the use of alternative opioids such as tapentadol because it has a different mechanism of action. Tapentadol is an MOR agonist and norepinephrine reuptake inhibitor (6). Unlike traditional opioids, the affinity of tapentadol for MOR is 50-fold lower than morphine, but the analgesic potency of tapentadol is only 2 to 3 times lower (6). It is possible that this mechanistic difference would result in a decreased incidence of postoperative GI ADEs.

A recent meta-analysis evaluated 8 randomized controlled trials comparing tapentadol IR to oxycodone IR for acute pain (7). The lowest dose (50 mg) of tapentadol was associated with a lower relative risk (RR) of GI ADEs such as nausea (RR, 0.60), vomiting (RR, 0.39), and constipation (RR, 0.44) compared with oxycodone (10 mg) (7). However, only 2 small trials included in the meta-analysis were conducted in patients who had orthopedic surgery (8,9). Neither of these studies showed a reduction in GI ADEs with tapentadol use. One of these studies was in patients who underwent outpatient arthroscopic shoulder surgeries, which cannot be extrapolated to hospitalized patients. In addition, the stringent patient selection criteria used in these trials may not be generalizable to the real-world setting.

The aim of this study was to determine if tapentadol IR is associated with a lower incidence of GI ADEs after orthopedic surgery in hospitalized patients compared with oxycodone IR. We hypothesized that tapentadol IR would be associated with lower GI ADEs.

Methods

Study Design and Setting

This was a retrospective cohort study conducted in a 950-bed, tertiary referral teaching hospital in Sydney, Australia. The study was approved by the Sydney Local Health District Human Research Ethics Committee (Protocol No. X18-0419). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline was followed to develop and report this study (10). There was no institutional protocol in place for use of postoperative oxycodone IR or tapentadol IR. Thus opioid selection was based on prescriber preference.

Study Aim

The following Participants Intervention Comparator Outcome (PICO) question was evaluated: in orthopedic postoperative patients (P), is there a difference between tapentadol IR (I) and oxycodone IR (C) with regard to GI ADEs during hospitalization (O)?

Patient Selection

An electronic medical record query was used to obtain a list of patients admitted between January 1, 2018 and June 30, 2019, who received tapentadol IR or oxycodone IR after orthopedic surgery. Patients were included if they received only one of these orally administered IR opioids during admission, did not receive other IR opioids, and did not receive sustained-release forms of these opioids. Patients in each treatment group (oxycodone or tapentadol) were selected randomly using a random number generator to minimize selection bias. Patients were excluded if they were younger than 18 years of age, had a history of cancer, renal impairment (creatinine clearance <30 mL/min), liver disease, history of opioid use disorder (as documented in the medical record), or transferred to a nonorthopedic unit.

Study Variables and Data Collection

The following variables were collected: patient demographics (age, gender), surgical procedures, prehospital analgesia (i.e., home medications), perioperative analgesia, postoperative analgesia, and ADEs. Information regarding rescue laxatives and antiemetics were collected as part of our assessment of ADEs. Study data were collected from electronic medical records. Paper-based medical records were accessed if documentation in the electronic medical records were incomplete. All data were collected using REDCap (Research Electronic Data Capture; Vanderbilt University, Nashville, TN), which is a secure, web-based software platform

designed to support data capture for research studies (11). All data were collected by one investigator and double-checked for accuracy by a second investigator.

Study Outcomes and Definitions

The primary outcome measure was GI ADEs occurring postoperatively during hospitalization. GI ADEs were defined as a composite of constipation or nausea/vomiting. This was based on a previous systematic review comparing oxycodone IR and tapentadol IR that these GI ADEs were common (7). For our study, a patient was considered to have constipation if the occurrence of constipation was documented in the medical record, or there was no bowel movement for more than 3 days, or the patient was given a rescue stimulant or osmotic laxative. Rescue agents are used for the treatment of constipation per hospital protocols. In our study cohort, all patients were given docusate sodium for prophylaxis. A patient was considered to have nausea/vomiting if the occurrence was documented in the medical record or an antiemetic was used for treatment of nausea. Antiemetic therapy was not used prophylactically at the institution.

Secondary outcomes included (1) occurrence of other ADEs such as pruritus, dizziness, dysphoria/hallucinations, respiratory depression, or death. These were selected based on previous systematic reviews pertaining to this topic (7). (2) Postoperative opioid consumption reported as oral morphine milligram equivalent (MME) based on recommended conversion factors from the Australian and New Zealand College of Anesthetists (12).

Sample Size Estimate

The sample size estimate was based on an absolute difference in GI ADEs of 20%. This was considered to be clinically meaningful by the investigators. Based on previous studies, we assumed a baseline estimate of GI ADEs with oxycodone IR to be 70% (7). Assuming a change of GI ADEs from 70% to 50%, power of 80%, and 2-sided α of 0.05, we estimated that 93 patients would be required in each group.

Data Analyses

Categorical variables, including the primary outcome of GI ADEs, were reported as percentages and compared between groups using the Fisher exact test. Continuous variables were reported as means with standard deviation or medians with interquartile ranges (IQR) as appropriate. The Student t-test was used to compare normally distributed continuous variables, whereas the Wilcoxon rank-sum test was used to compare non-normally distributed variables. Because there were no missing data, imputation was not needed.

A logistic regression analysis was conducted for the primary outcome to adjust for potential confounders. Based on clinical experience, the investigator team considered age, gender, type of surgery, and extent of postoperative opioid consumption as potential confounders. Thus these variables were added to the model. The model was checked for linearity in the log-odds for continuous variables, collinearity, interactions, and goodness-of-fit. Based on an evaluation of linearity in the log-odds for MME, this variable was dichotomized (< 100 mg, ≥100 mg) for the regression analysis. A 2-tailed α of 0.05 was considered to be statistically significant. All analyses were conducted with the statistical software STATA, version 16.0 (StataCorp, College Station, TX).

Results

Study Cohort

There were 237 patients during the study period who met inclusion criteria. After excluding patients, 199 patients (99 in tapentadol group and 100 in oxycodone group) were included in the study cohort. The flow of patient selection and reasons for exclusion are shown in Fig. 1. The mean age of patients was 66 ± 12 years, and the majority of patients were women (n = 111, 56%). The types of orthopedic surgeries were total knee arthroplasty (n = 91, 46%), total hip arthroplasty (n = 63, 32%), shoulder surgery (n = 26, 13%), and other (n = 19, 10%). Prior to hospitalization, there were 22 (11%) patients who were taking opioids. All of these patients were taking less than 50 mg MME per day, which is considered to be a low-risk cutoff value (13). Median length of stay was 4 days (IQR, 3–5 days) in both groups. All patients were prescribed tapentadol 50 to 100 mg or oxycodone 2.5 to 10 mg as needed for pain in the tapentadol and oxycodone groups, respectively. This dose comparison is similar to the titration strategy used in some clinical trials (7). Baseline comparisons between the oxycodone and tapentadol groups are reported in Table 1. Overall, the groups were similar except for a few variables. Patients in the tapentadol group were older, more likely to be women, more likely to undergo total hip arthroplasty, and less likely to have shoulder surgery (Table 1).

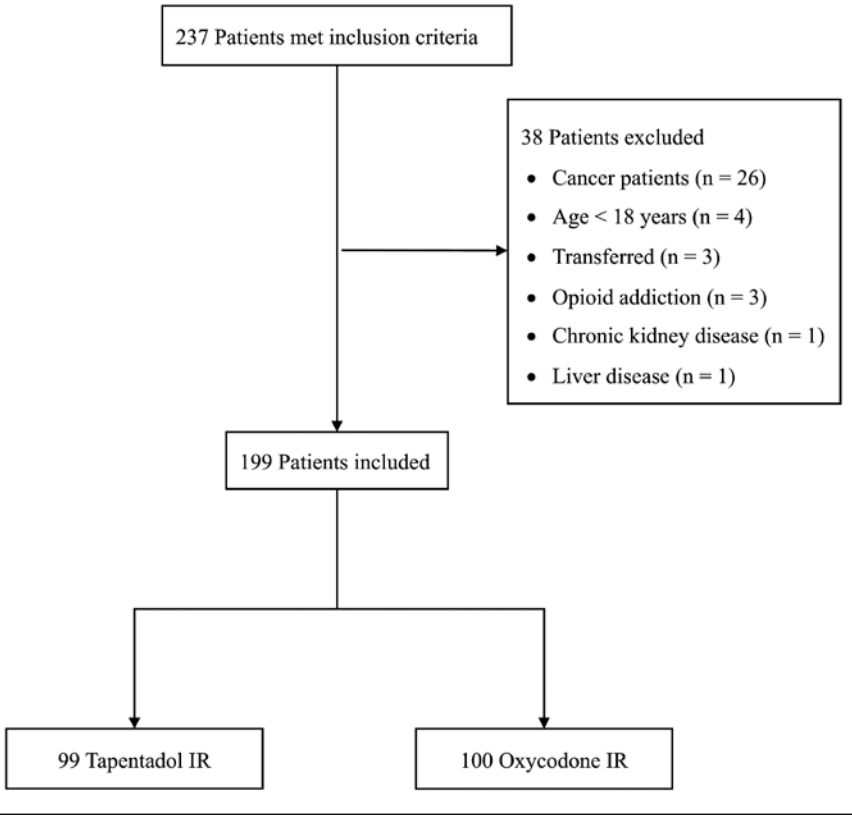

Fig. 1. *Flow diagram of patient selection.*

ADEs

GI ADEs occurred in 51% (n = 50) of patients in the tapentadol group and 53% (n = 53) in the oxycodone group (difference 2%, 95% confidence interval [CI], –11% to 16%; *P* = 0.777). After adjusting for potential confounders (Table 2), the use of tapentadol was not associated with a significant reduction of GI ADEs (odds ratio [OR] 0.62; 95% CI, 0.32–1.20; *P* = 0.154). The Hosmer-Lemeshow goodness-of-fit test showed that the model fit the data well (*P* = 0.445). Individual ADEs are reported in Table 3. ADEs such as dizziness, dysphoria/hallucinations, respiratory depression, or death were not reported during hospitalization.

Opioid Consumption

The total median amount of tapentadol received postoperatively in the tapentadol group was 300 mg (IQR 150–500 mg) [dose/day 75 mg (IQR, 33–125 mg)]. The total median amount of oxycodone received postoperatively in the oxycodone group was 50 mg (IQR, 23–95 mg) [dose/day 16 mg (IQR, 8–24 mg)]. The total median postoperative oral MME was 95 mg (IQR, 45–165 mg) in the tapentadol group and 75 mg (IQR, 41–150 mg) in oxycodone group (*P* = 0.184). The total median postoperative oral MME per day was 25 mg (IQR, 11–40 mg) in the tapentadol group and 23 mg (IQR, 13–35 mg) in the oxycodone group (*P* = 0.531). The types of postoperative analgesia used other than study drugs are reported in Table 1. There did not appear to be a significant difference in terms of other analgesics used between the groups.

Discussion

To our knowledge, this is the first real-world study to compare GI ADEs between tapentadol IR and oxycodone IR in orthopedic patients with postoperative acute pain during hospitalization. The key finding was that GI ADEs were similar between groups. It highlights that the relative decreased effect of tapentadol on MORs may not translate into less GI ADEs in this particular patient population.

A previous systematic review and meta-analysis showed that tapentadol IR had similar analgesic effect but was associated with less GI ADEs compared with oxycodone IR (7). The difference in findings between our study and previous studies may be attributed to a number of reasons. First, in our study, docusate sodium was used for all patients postoperatively as prophylaxis for constipation. Such prophylaxis was not used in the aforementioned clinical trials in the systematic review. It is possible that the mild stool softening effect of docusate sodium could have blunted differences in the occurrence of constipation between groups. Second, the patient population included in our study is not representative of the population from the meta-analysis. For example, only 2 of the previous studies were conducted in patients with orthopedic surgery (8,9). Regional anesthesia used after orthopedic procedures reduces opioid requirements (14), which could mini-

mize the opioid-related GI effects, especially if opioid consumption is lower. It is possible that patients with other procedures, such as those with abdominal surgeries who have a greater propensity for postoperative GI ADEs, may benefit more from tapentadol IR (15). Third, the average age of patients was 66 years in our cohort, which was older than patients in previous clinical trials whose average ages were 40 to 50 years (9,16-19). In general, older patients are more likely to suffer from constipation (2). Intuitively, we would expect these patients to benefit from MOR sparing effects. However, we were unable to show an effect even in this population. Finally, our study had less stringent selection criteria and is more representative of real-world practice than clinical trials. For example, we were less stringent with regard to limiting the sample based on comorbidities, medication history, intraoperative, regional, or perioperative analgesia.

As shown in the recent systematic review (7), 2 previous studies have compared oxycodone IR and tapentadol IR in orthopedic surgery patients (8,9). In one of these trials (8) involving patients (n = 330) with total hip replacement surgery, there was no significant difference between occurrence of nausea (OR, 1.38; 95% CI, 0.72–2.62), vomiting (OR, 0.44; 95% CI, 0.16–1.21), or constipation (OR, 0.80; 95% CI, 0.38–1.69) between the oxycodone IR (10 mg) and tapentadol IR (50 mg) groups. Interestingly, our postoperative opioid consumption was lower. In the trial by Viscusi et al (8), the median daily opioid consumption ranged from 133 to 300 mg (50 and 100 mg dose study arms) in the tapentadol group and was 43 mg in the oxycodone group. In our study, the median daily opioid consumption was 95 mg for tapentadol and 16 mg for oxycodone. Thus we would expect that lower opioid consumption would result in even less GI ADEs.

The second trial was conducted in patients (n = 378) with outpatient arthroscopic shoulder surgery. There was no significant difference between occurrence of nausea (OR, 1.07; 95% CI, 0.68–1.67) or constipation (OR, 0.61; 95% CI, 0.34–1.08) between oxycodone IR (5–10 mg) and tapentadol IR (50–100 mg) groups. Interestingly, vomiting was greater with tapentadol IR (OR, 1.84; 95% CI, 1.09–3.08). However, the wide range of the CI suggests that this was not a robust finding. Because this was conducted in patients with outpatient surgery, we did not consider this to be necessarily comparable to our study cohort.

There were some important baseline differences between groups in our study cohort. Patients in the ta-

Table 1. *Baseline characteristics.*

Variable	Tapentadol (n = 99)	Oxycodone (n = 100)	*P* Value
Age, years, mean (SD)	70.4 (10.5)	62.2 (12.8)	<0.001
Gender, female, n (%)	62 (62.6)	49 (49.0)	0.064
Surgery type			
THA, n (%)	39 (39.4)	24 (24.0)	0.023
TKA, n (%)	49 (49.5)	42 (42.0)	0.321
Shoulder repair, n (%)	7 (7.1)	19 (19.0)	0.019
Other, n (%)	4 (4.0)	15 (15.0)	0.014
Medical history			
Obstructive sleep apnea, n (%)	12 (12.1)	7 (7.0)	0.238
Prehospital analgesia			
Paracetamol, n (%)	17 (17.2)	13 (13.0)	0.435
NASIDs, n (%)	10 (10.1)	8 (8.0)	0.631
Opioid, n (%)	14 (14.1)	8 (8.0)	0.183
Pregabalin, n (%)	4 (4.0)	7 (7.0)	0.537
Carbamazepine, n (%)	1 (1.0)	1 (1.0)	1.000
Perioperative intrathecal analgesia			
None, n (%)	46 (46.5)	59 (59.0)	0.089
Morphine, n (%)	52 (52.5)	38 (38.0)	0.047
Fentanyl, n (%)	0 (0.0)	2 (2.0)	0.497
Pethidine, n (%)	1 (1.0)	1 (1.0)	1.000
Perioperative regional analgesia			
None, n (%)	57 (57.6)	54 (54.0)	0.669
Single-shot adductor canal block, n (%)	13 (13.1)	21 (21.0)	0.187
Single-shot femoral nerve block, n (%)	4 (4.0)	6 (6.0)	0.748
Continuous adductor canal infusion, n (%)	25 (25.3)	19 (19.0)	0.310
Postoperative patient-controlled analgesia			
None, n (%)	39 (39.4)	32 (32.0)	0.302
Morphine, n (%)	1 (1.0)	2 (2.0)	1.000
Fentanyl, n (%)	42 (42.4)	43 (43.0)	1.000
Oxycodone, n (%)	17 (17.2)	23 (23.0)	0.377
Postoperative analgesia			
Paracetamol, n (%)	99 (100.0)	100 (100.0)	1.000
NSAIDs, n (%)	66 (66.7)	54 (54.0)	0.082
Opioid (other than target drugs), n (%)	15 (15.2)	22 (22.0)	0.274
Pregabalin, n (%)	7 (7.1)	9 (9.0)	0.795
Carbamazepine, n (%)	1 (1.0)	0 (0.0)	0.497
Ketamine, n (%)	1 (1.0)	0 (0.0)	0.497

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Table 2. *Logistic regression analysis for GI ADEs.*

	OR	95% CI	*P* Value
Group			
Oxycodone	Reference	Reference	Reference
Tapentadol	0.62	0.32–1.20	0.154
Sum of opioid consumption (MME)			
<100 mg	Reference	Reference	Reference
≥100 mg	2.83	1.54–5.21	0.001
Age (years)	1.02	0.99–1.04	0.232
Gender			
Male	Reference	Reference	Reference
Female	2.30	1.26–4.21	0.007
Type of surgery			
THA	Reference	Reference	Reference
TKA	0.82	0.41–1.64	0.574
Shoulder repair	0.75	0.27–2.05	0.572
Other	0.79	0.26–2.43	0.684

MME (dichotomized as <100 vs. ≥100 mg).
Abbreviations: THA, total hip arthroplasty; TKA, total knee arthroplasty

Table 3. *ADEs.*

	Tapentadol (n = 99)	Oxycodone (n = 100)	*P* Value
Constipation, n (%)	40 (40.4)	43 (43.0)	0.774
Nausea/vomiting, n (%)	21 (21.2)	21 (21.0)	1.000
Pruritus, n (%)	1 (1.0)	2 (2.0)	1.000

pentadol group were older, more likely to be women, and more likely to undergo total hip arthroplasty. These characteristics are important confounders for GI ADEs. Age is a well-known risk factor for constipation (2). Women also have been shown to have an increased risk (1.5–1.8 times) of postoperative nausea and vomiting, which may be related to hormonal effects (2,20). Patients with total hip arthroplasty are expected to receive a greater amount of opioids compared with shoulder surgery, which would increase risk for GI ADEs. However, after adjusting for these variables in the logistic regression analysis, we did not find a reduction in GI ADEs with tapentadol IR. Our model was consistent with previous literature that shows an increased risk for GI ADEs in women and with higher opioid consumption.

There were a few limitations in our study. The study was conducted in one referral hospital in Australia and should be extrapolated with caution to other centers or countries. As this was a retrospective study, the accuracy of data depended on documentation and accuracy in medical records. However, as opioids are controlled substances with strict documentation requirements at our institution, we are confident in the accuracy of data obtained from the medical record. It is possible that all bowel movements were not captured by nursing documentation. However, we believe this risk is low given that these patients tend to be immobile and require nursing assistance for bowel care. Some patients in the study received patient-controlled analgesia in the immediate postoperative setting prior to initiation of study drugs. The amount of opioids consumed from this treatment modality was not available. Thus postoperative MMEs reported do not include this quantity. We did not collect information pertaining to pain control (i.e., pain scores) as these were not consistently documented. Also, pain control was not the focus of this investigation. There is no evidence from trials that tapentadol provides superior pain relief to oxycodone (7).

Conclusions

In postoperative orthopedic surgery patients, GI ADEs occurred to a similar extent between patients given tapentadol IR or oxycodone IR during hospitalization. There was also no significant difference with regard to other ADEs or postoperative opioid consumption. However, these results need to be replicated in clinical trials. Future studies should also investigate the patient population that may benefit most from the use of tapentadol for postoperative pain.

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