[**Original Research**]

Use of Transdermal Fentanyl and Elevated Gamma-glutamyl Transpeptidase Levels Are Associated with Increased Total Daily Dose of Opioid

Tomoyoshi MIYAMOTO,[*1, *2] Masanori FUJITANI,[*1] Shigekatsu HATANAKA,[*3] Yuichi KOIZUMI,[*1] and Atsufumi KAWABATA[*2]

[*1] Department of Pharmacy, Seichokai Fuchu Hospital
[*2] Laboratory of Pharmacology and Pathophysiology, Faculty of Pharmacy, Kindai University
[*3] Department of Clinical Laboratory, Seichokai Fuchu Hospital

(Accepted July 20, 2020)

Abstract: Some patients require high doses of opioids for pain relief. Chronic administration of opioids causes adverse events such as opioid-induced hyperalgesia and analgesic tolerance. However, factors influencing eventual daily dose of opioids are unknown. We investigated whether eventual daily doses of opioids for cancer pain and chronic pain management would be associated with the use of different types of opioids or clinical test values. This was a retrospective study of 406 patients who received transdermal fentanyl, oral oxycodone, and oral morphine at a single institution. Patients treated with different opioids were divided into two groups according to eventual daily doses of opioids, namely a high-dose (≥ 120 mg/day morphine conversion) and a low-dose group (< 120 mg/day), and opioid use patterns or biological measures were compared between the two groups. Data were analyzed to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). Patients who received cumulative doses of transdermal fentanyl ≥ 1,440 mg or showed γ-glutamyl transpeptidase (γ-GTP) levels of ≥ 63 IU/L had significantly rapid increase in the probability of high-dose opioid use. Multivariate analysis showed that the fentanyl cumulative doses ≥ 1,440 mg (adjusted HRs, 2.94; 95% CIs, 1.51–5.71, $p = 0.001$) and γ-GTP levels ≥ 63 IU/L (adjusted HRs, 1.99; 95% CIs, 1.12–3.54, $p = 0.019$) were significantly associated with high-dose opioid use. This study shows that overall high dose fentanyl use and elevated liver-related enzymes are associated with increased daily doses of opioids. These results may help identifying patients who have a high risk for escalated opioid use.

Key words: fentanyl, analgesic tolerance, opioid, liver enzyme, pain management

INTRODUCTION

The opioid dose required for effective pain management varies from person to person, even among individuals whose pain originates from similar afflictions[1]. Therefore, some patients require high doses of opioids for pain relief and are at higher risk for developing negative side effects including death[2, 3]. Furthermore, high dose opioid administration causes analgesic tolerance[4, 5] and opioid-induced hyperalgesia[6]. For example, individuals who undergo surgery and are administered high-doses of opioids tend to have higher rates of post-operative opioid use[5, 7]. Preclinical studies confirm that fentanyl produces analgesic tolerance in rodents in a dose-dependent manner[8]. On the other hand, it is known that methadone is an effective analgesic for patients who have difficulty with pain management and are resistant to morphine, oxycodone, or fentanyl[9–11]. Opioid-resistant individuals are difficult to identify without first exposing them to treatment and can result in unwanted and adverse side effects. To date, few studies have been done to better understand the many factors that affect individual differences in opioid sensitivity. Therefore, the present study was performed to ask whether different opioid regimens for pain management and laboratory test values would be associated with eventual increase in daily opioid doses.

Correspondence Author: Tomoyoshi Miyamoto, Department of Pharmacy, Seichokai Fuchu Hospital, 1–10–17, Hiko-cho, Izumi, Osaka 594–0076, Japan
E-mail: miyamoto.tomoyoshi@gmail.com

MATERIALS AND METHODS

1. Patient characteristics and design

This was a cohort study that retrospectively investigated the opioid choice (dose per day and length of use) for patients on an opioid regimen for 4 years between April 1, 2014 to March 31, 2018. Inclusion criteria for patient participation were as follows: A starting opioid dose of less than 30 mg/day (morphine conversion), opioid treatment periods of 7 days or more, and fully available laboratory test values including gamma-glutamyl transpeptidase (γ-GTP) and alkaline phosphatase (ALP). Of 406 patients, 151 were excluded from

the study due to the following reasons: 19 individuals received an initial opioid dose ≥ 30 mg/day (morphine conversion), 73 individuals received opioids for less than 7 days, and 59 individuals lacked data on γ-GTP and ALP. The remaining 255 patients were included in the present study. The most common cancer types in our total sample were hematopoietic cancer, rectal/colon cancer, pancreatic cancer, and stomach cancer. Other carcinomas included ovary, thyroid, and unknown cancer. Nine non-cancer patients (including those with gonarthrosis and disc herniation) were also included. The route of administration of the different opioids varied such that fentanyl was administered transdermally while oxycodone and morphine were given orally. The conversion dose was calculated with the equivalent of 0.3 mg/day (12.5 μg/h) of transdermal fentanyl, 20 mg/day of oxycodone, and 30 mg/day of morphine. In this study, patients requiring 120 mg/day or more of morphine equivalent were defined as the high-dose group[12]. For the total opioid dose, the total dose administered up to the day on which 120 mg of morphine-equivalent opioid was administered per day, and the total dose during the observation period were examined. The numerical rating scale (NRS) evaluated by nurses was investigated for the maximum value within 2 weeks after the start of administration of the maximum opioid dose and the maximum value staying in hospital. Nonsteroidal anti-inflammatory drugs and pregabalin use within 30 days of opioid administration (maximum dose) were monitored. Patients were also monitored for alendronate administration 30 days before and after maximum dose of opioid administration. Patients were also screened for bone metastasis as comorbidity. Laboratory evaluations for all patients included analysis of albumin (Alb), C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-GTP, total bilirubin (T-Bil), ALP, creatinine kinase (CK), serum creatinine (Cr), and lactate dehydrogenase (LDH). The average value taken within 2 weeks of maximum dose of opioid administration was used as a correlate. The values obtained at this time point were used to calculate the ratio of CRP to Alb and used as an indicator of general nutritional status. The albumin bilirubin (ALBI) value was used to evaluate liver dysfunction. ALBI score was calculated by the following formula[13]: ALBI score = ($\log_{10}$ bilirubin × 0.66) + (albumin × 0.085), where bilirubin is in μmol/L and albumin in g/L. Patient characteristics are summarized in Table 1. This research was approved by the Ethics Committee of Seichokai Fuchu Hospital (Approval No.2018008).

Table 1 Characteristics of the patients

	No of patients n = 255	%
Age		
Age < 72[a]	122	48
Age ≥ 72[a]	133	52
Sex		
Female	107	42
Male	148	58
Disease		
Hematologic malignancy	59	23
Rectum / colon	44	17
Pancreas	28	11
Stomach	27	11
Pulmonology	25	10
Liver	14	5
Esophagus	11	4
Urinary tract	11	4
Biliary tract	7	3
Breast	7	3
Prostate	6	2
Others	7	3
No cancer	9	4
Starting dose opioid		
Fentanyl	46	18
Morphine	20	8
Oxycodone	189	74
Maximum dose opioid		
Fentanyl	128	50
Morphine	16	6
Oxycodone	111	44
Pain control		
after the start of maximum opioid dose		
NRS < 8[a]	59	49
NRS ≥ 8[a]	62	51
in admission		
NRS < 7[a]	65	46
NRS ≥ 7[a]	76	54
Related factors		
NSAIDs	151	59
Pregabalin	29	11
Alendronate	20	8
Bone metastasis	44	17
Liver metastasis	56	22

[a] Median.

2. Statistical analysis

Spearman's rank correlation coefficient was used to study correlations of continuous variables that do not show a normal distribution. The Kruskal-Wallis test and Steel-Dwass method were used to compare three or more continuous variables not showing normality. Using the receiver operating characteristic curve (ROC) and variable of a high daily dose of opioid (> 120 mg), we selected optimal cut-off values for opioid dose, age, γ-GTP and ALP that provided the closest "perfect classification" point, and then divided our patients into two groups. In the univariate analysis, comparisons of categorical variables were performed using the Cox proportional hazards regression model. A multivariate Cox proportional hazards regression analysis was performed on factors considered to be important in the univariate analysis that is, variables with a p value < 0.05 in the log-rank test. Collinearity was examined with a variance inflation factor (VIF). The variable we used for all multivariate analysis was VIF < 5. The results obtained were described as hazard ratios (HRs) and 95% confidence intervals (CIs). A p value < 0.05 was defined as being statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University,

Saitama, Japan)[14], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria version 3.5.2). More precisely, it is a modified version of R commander (version 2.5-1) designed to easily execute statistical functions frequently used in biostatistics.

RESULTS

1. Drug use distribution among cancer types

The most commonly administered opioid was the transdermal fentanyl, followed by sustained-release oxycodone and then sustained-release morphine. Figure 1 shows a comparison of opioid doses for each cancer type and no significant differences were found across these conditions. Figure 2 shows a comparison of opioid doses by type. There were no differences in opioid dose per day for the opioid type selected at the initiation of treatment. However, the type of opioids at maximal doses had significant effect on eventual daily opioid doses; i.e. patients who received transdermal fentanyl at maximal doses ultimately required significantly higher opioid doses than ones receiving morphine and oxycodone at maximal doses. Further, the cumulative doses of transdermal fentanyl ≥ 1,440 mg, but not those of oxycodone ≥ 720 mg, were significantly associated with rapid increase in daily opioid doses (Fig. 3).

2. Correlation between laboratory data and opioid dose

Table 2 shows the correlation between daily escalation maximum dose of opioid and laboratory data (including CRP/Alb ratio and ALBI score). γ-GTP, ALP, and age were significantly associated with escalation of opioid use. However, CRP/Alb ratio and ALBI score did not correlate with opioid use.

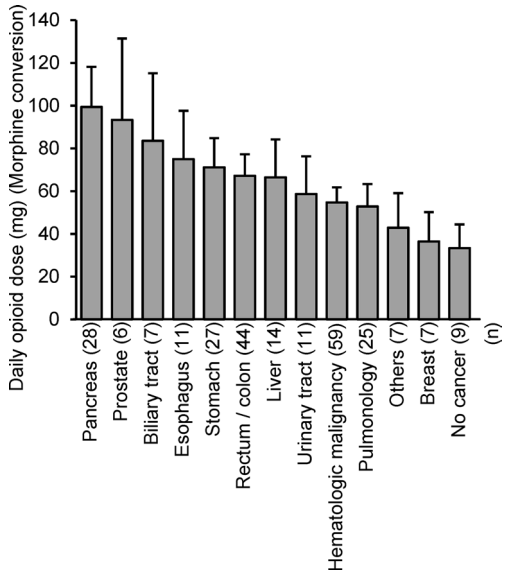

Fig. 1 Comparison of opioid dosage for various cancer types. Data show the mean with S.E.M.

3. Factors associated with high dose opioid administration

Table 3 shows the association of high dose opioids for age, sex, γ-GTP, ALP, NRS, pregabalin or NSAIDs use, bone metastasis, liver metastasis and total opioid dose. The optimal cut-off value was calculated by ROC analysis. Univariable Cox regression on the patient characteristics showed that γ-GTP ≥ 63 IU/L, ALP ≥ 341 IU/mL, and total fentanyl ≥ 1,440 mg were significantly associated with high dose opioid use. However, NSAIDs, pregabalin and alendronate use, liver metastases, bone metastases and NRS were not associated with the time-dependent increase in opioids. In addition, no patient was treated with nerve block. Figure 3 shows the time course of the rate of high dose administration after the start of opioid administration. The total opioid dose in (C) and (D) indicates the total dose administered up to the day on which 120 mg morphine equivalent opioid was administered per day. The total opioid dose in (E) and (F) indicates the total dose during the observation period. γ-GTP ≥ 63 IU/L (HRs: 2.8, 95% CIs: 1.61–4.87, $p < 0.001$) was associated with patients requiring high doses of opioids. And it was suggested that oral oxycodone and transdermal fentanyl have different dose-dependent increase rates of opioids (HRs: 3.68, 95% CIs: 1.96–6.93, $p < 0.001$). By multivariate Cox proportional hazard regression analysis, γ-GTP ≥ 63 IU/L (adjusted HRs: 1.99; 95% CIs: 1.12–3.54; $p = 0.018$) was significantly independent factors requiring high doses of opioids (Table 3) and it was suggested that oral oxycodone and transdermal fentanyl have different dose-dependent increase rates of opioids (adjusted HRs: 2.94; 95% CIs: 1.51–5.71; $p = 0.001$). We did not select ALP as a factor for multivariate analysis because of the high correlation between γ-GTP and ALP.

DISCUSSION

This study was a retrospective cohort study using a single-site patient database, investigating the maximum dose, days of administration, and patient characteristics

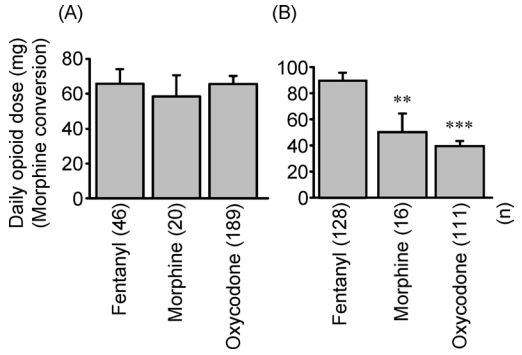

Fig. 2 Comparison of maximal opioid doses in patients receiving fentanyl, morphine, and oxycodone. (A) Opioid type selected at the start. (B) Type of opioid selected at maximum dose. Data show the mean with S.E.M. $^{***}p < 0.001$, $^{**}p < 0.01$ versus Fentanyl group. (Steel-Dwass test).

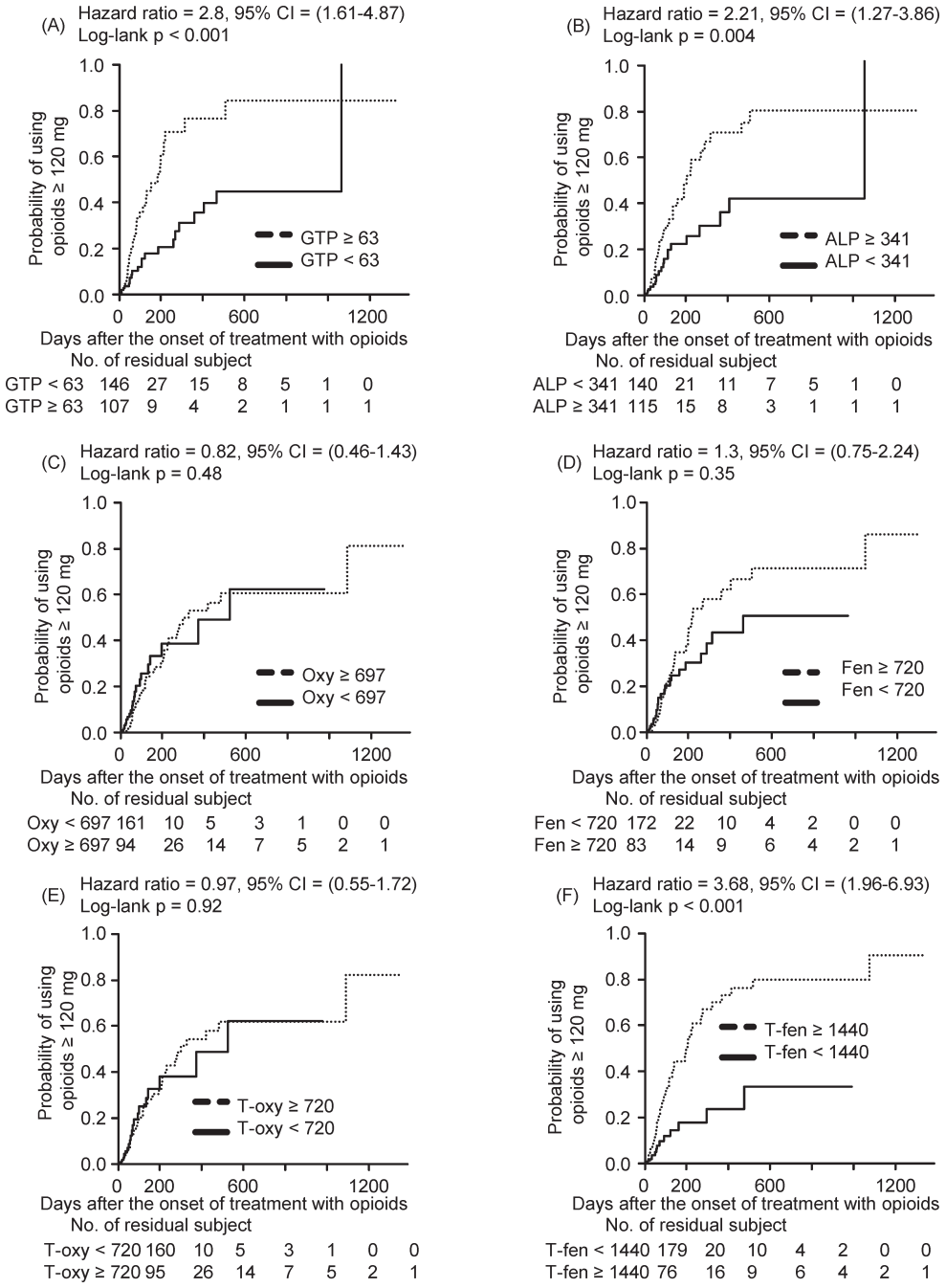

Fig. 3 Kaplan-Meier curves for the probability of using high doses of opioids in association with various cut-off values calculated by receiver operating characteristic (ROC) analysis for patients after the onset of opioid treatment. (A) γ-GTP (GTP); (B) ALP; (C) Total oxycodone dose (Oxy) until 120 mg/day is administered; (D) Total fentanyl dose (Fen) until 120 mg/day is administered; (E) Total oxycodone dose (T-oxy); (F) Total fentanyl dose (T-fen).

after starting opioid administration. Patients with high γ-GTP and higher total fentanyl exposure were associated with continued high opioid doses.

Previous studies have reported that individuals with breast cancer, albumin levels, ALT, and especially men and the elderly, are at high risk for necessitating higher doses of transdermal fentanyl when switching from oxycodone[15]. However, studies investigating escalation history and specific patient characteristics, specifically among those with cancer, are still lacking. Although the absorption rate of transdermal fentanyl may vary depending on the type of cancer[16], our study revealed no effect of cancer type warranting different opioid dosing. However, this study also used opioids other than fentanyl and there was no effect of cancer type among the other opioids investigated. Plasma concentration of fentanyl after transdermal administration varies greatly among individuals and is also affected by individual character-

istics such as smoking[17]. Some studies suggest that the unstable pharmacokinetics of transdermal fentanyl lead to inadequate pain management and an escalation in use[18]. On the other hand, switching from transdermal fentanyl to oral oxycodone may improve pain management[18]. The analgesic effect of opioids is reduced by neuropathic pain[19, 20]. However, the necessary opioid dose for pain alleviation was not affected by pregabalin administration.

Animal experiments suggest that liver injury can cause hyperalgesia[21]. Cholestasis causes itching due to an increase in endogenous opioid peptides[22]. Endogenous opioids may be associated with analgesic tolerance[23]. Therefore, patients with high γ-GTP are more likely to develop analgesic tolerance and may be associated with higher opioid doses. The pharmacokinetics of fentanyl in patients with cirrhosis are not different from normal patients[24]. Furthermore, there was no correlation between the ALBI score, an indicator of liver function, and opioid dose, suggesting that elevated γ-GTP may affect opioid dose independently of changes in liver function. In addition, the large number of patients who used fentanyl in the high-dose opioid group in this study (43 patients: 81%) also suggests that ALBI and opioid dose were not correlated. The patient's liver metastasis did not affect the opioid dose. γ-GTP and ALP are highly specific for diseases related to biliary epithelial disorders such as primary biliary cholangitis and intrahepatic cholangiocarcinoma[25]. Therefore, this study suggested a relationship between bile duct epithelial disorder and opioid dose. In addition, the median ALP (Median [Range], non-bone metastasis; bone metastasis, 310 [104, 4,830]; 345 [142, 1,300]; $p = 0.38$) was less associated with bone metastasis in this study. The nutritional index CRP/Alb ratio was not correlated with the opioid dose, and the patient's nutritional status did not affect the opioid dose. The limitation of this study was a single-center, retrospective study with a small number of cases and in particular, few patients were treated with morphine. Additionally, some patients had no recorded NRS. The examination frequency of patients was not constant. The opioid choice might not necessarily be influenced by physicians' preference or patient convenience. Opioids prescribed outside the hospital were not investigated. The number of cases varied depending on the type of cancer. Evaluation of bone metastases was not performed in some patients.

Table 2 Spearman's rank correlation between laboratory data and daily escalation maximum dose of opioid (morphine conversion)

	Correlation coefficient	p	n
Age	−0.21	< 0.001	255
Weight	−0.09	0.17	238
Albumin	−0.04	0.58	251
CRP	0.09	0.15	248
AST	0.05	0.38	255
ALT	0.08	0.23	255
γ-GTP	0.18	0.003	255
T-Bil	0.01	0.90	252
ALP	0.17	0.005	255
CK	−0.05	0.45	245
Cr	−0.09	0.17	254
LDH	0.04	0.50	253
CRP/Alb	0.09	0.16	248
ALBI score	0.02	0.79	249

Table 3 Factors characteristic of patients with opioid doses of 120 mg / day or more

			Dose ≥ 120 mg/day			
n = 255	Yes		Univariate analysis		Multivariate analysis	
Factor	n/n_{total}	%	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age < 73[a]	20/53	38	0.86 (0.49–1.5)	0.59		
Male	33/53	62	1.65 (0.94–2.87)	0.08		
γ-GTP ≥ 63[b] IU/L	31/53	58	2.80 (1.61–4.87)	< 0.001	1.99 (1.12–3.54)	0.018
ALP ≥ 341[b] IU/mL	33/53	62	2.21 (1.27–3.86)	0.005		
Fentanyl ≥ 720[b] mg	27/53	51	1.30 (0.75–2.24)	0.35		
Morphine ≥ 100[b] mg	4/53	8	0.82 (0.46–1.43)	0.48		
Oxycodone ≥ 697[b] mg	31/53	58	0.90 (0.32–2.51)	0.84		
Total fentanyl ≥ 1440[b] mg	40/53	75	3.68 (1.96–6.93)	< 0.001	2.94 (1.51–5.71)	0.001
Total morphine ≥ 100[b] mg	6/53	11	0.97 (0.55–1.72)	0.92		
Total oxycodone ≥ 720[b] mg	33/53	62	1.32 (0.56–3.11)	0.52	1.30 (0.74–2.30)	0.37
NRS after the start of maximum opioid dose ≥ 8[c]	18/29	62	1.13 (0.52–2.44)	0.76		
NRS in admission ≥ 7[c]	20/27	74	2.06 (0.86–4.92)	0.10		
NSAIDs	28/53	53	0.90 (0.52–1.55)	0.69		
Pregabalin	9/53	17	0.88 (0.43–1.83)	0.74		
Alendronate	6/53	11	1.34 (0.56–3.21)	0.51		
Bone metastasis	11/53	21	1.25 (0.64–2.45)	0.52		
Liver metastasis	11/53	21	1.01 (0.52–1.97)	0.97		

Dose ≥ 120 mg/day; Patients who used more than 120 mg/day (morphine equivalent) opioids. [a] Median, [b] Optimal cut-off value calculated by receiver operating characteristic (ROC) analysis, [c] NRS after the start of maximum opioid dose group and NRS in admission group were analyzed in 121 or 141 patients.

Taken together, the present study suggests that individuals who receive transdermal fentanyl at high doses are more likely to escalate their opioid use over time. This indicates that fentanyl is more susceptible to analgesic tolerance than is oxycodone and less effective in pain management. Additionally, individuals with elevated γ-GTP may be more likely to develop analgesic tolerance and therefore require higher levels of administration, putting them at greater risk for negative health outcomes. Finally, we believe that clinical pharmacists may recognize and utilize these results in daily clinical practice.

Conflict of interest: No competing financial interests exist.

REFERENCES

1) Pico L, Hernot S, Nègre I, et al. Peroperative titration of morphine improves immediate postoperative analgesia after total hip arthroplasty. Can. J. Anaesth. 2000; 47: 309–314.
2) Gomes T, Mamdani MM, Dhalla IA, et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch. Intern. Med. 2011; 171: 686–691.
3) Bohnert ASB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011; 305: 1315–1321.
4) Angst MS, Koppert W, Pahl I, et al. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain 2003; 106: 49–57.
5) Chia YY, Liu K, Wang JJ, et al. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can. J. Anaesth. 1999; 46: 872–877.
6) Fletcher D and Martinez V. Opioid-induced hyperalgesia in patients after surgery: A systematic review and a meta-analysis. Br. J. Anaesth. 2014; 112: 991–1004.
7) Kim D, Lim H-S, Kim M-J, et al. High-dose intraoperative remifentanil infusion increases early postoperative analgesic consumption: A prospective, randomized, double-blind controlled study. J. Anesth. 2018; 32: 886–892.
8) Sirohi S, Dighe SV, Walker EA, et al. The analgesic efficacy of fentanyl: Relationship to tolerance and mu-opioid receptor regulation. Pharmacol. Biochem. Behav. 2008; 91: 115–120.
9) Scholes CF, Gonty N, and Trotman IF. Methadone titration in opioid-resistant cancer pain. Eur. J. Cancer Care 1999; 8: 26–29.
10) Mercadante S, Casuccio A, Fulfaro F, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: A prospective study. J. Clin. Oncol. 2001; 19: 2898–2904.
11) Sugiyama Y, Sakamoto N, Ohsawa M, et al. A retrospective study on the effectiveness of switching to oral methadone for relieving severe cancer-related neuropathic pain and limiting adjuvant analgesic use in Japan. J. Palliat. Med. 2016; 19: 1051–1059.
12) Franklin GM, Mai J, Turner J, et al. Bending the prescription opioid dosing and mortality curves: Impact of the Washington State opioid dosing guideline. Am. J. Ind. Med. 2012; 55: 325–331.
13) Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: A new evidence-based approach—the ALBI grade. J. Clin. Oncol. 2015; 33: 550–558.
14) Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant. 2013; 48: 452–458.
15) Kanbayashi Y, Hosokawa T, Okamoto K, et al. Factors predicting requirement of high-dose transdermal fentanyl in opioid switching from oral morphine or oxycodone in patients with cancer pain. Clin. J. Pain 2011; 27: 664–667.
16) Solassol I, Caumette L, Bressolle F, et al. Inter- and intra-individual variability in transdermal fentanyl absorption in cancer pain patients. Oncol. Rep. 2005; 14: 1029–1036.
17) Kuip EJM, Oldenmenger WH, Thijs-Visser MF, et al. Effects of smoking and body mass index on the exposure of fentanyl in patients with cancer. PLoS One 2018; 13: e0198289.
18) Ravera E, Di Santo S, Bosco R, et al. Controlled-release oxycodone tablets after transdermal-based opioid therapy in patients with cancer and non-cancer pain. Aging Clin. Exp. Res. 2011; 23: 328–332.
19) Kohno T, Ji R-R, Ito N, et al. Peripheral axonal injury results in reduced mu opioid receptor pre- and post-synaptic action in the spinal cord. Pain 2005; 117: 77–87.
20) Rashid MH, Inoue M, Toda K, et al. Loss of peripheral morphine analgesia contributes to the reduced effectiveness of systemic morphine in neuropathic pain. J. Pharmacol. Exp. Ther. 2004; 309: 380–387.
21) Belghiti M, Estévez-Herrera J, Giménez-Garzó C, et al. Potentiation of the transient receptor potential vanilloid 1 channel contributes to pruritogenesis in a rat model of liver disease. J. Biol. Chem. 2013; 288: 9675–9685.
22) Thornton JR, Dean H, and Losowsky MS. Is ascites caused by impaired hepatic inactivation of blood borne endogenous opioid peptides? Gut 1988; 29: 1167–1172.
23) Neyama H, Dozono N, and Ueda H. NR2A-NMDA receptor blockade reverses the lack of morphine analgesia without affecting chronic pain status in a fibromyalgia-like mouse model. J. Pharmacol. Exp. Ther. 2020; 373: 103–112.
24) Haberer JP, Schoeffler P, Couderc E, et al. Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. Br. J Anaesth. 1982; 54: 1267–1270.
25) Kinoshita M, Kubo S, Tanaka S, et al. The association between non-alcoholic steatohepatitis and intrahepatic cholangiocarcinoma: A hospital based case-control study. J. Surg. Oncol. 2016; 113: 779–783.