Construction of a Risk Prediction Model of Extended Release Oxycodone Tablet-Induced Nausea and Clarification of Predictive Factors

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INTRODUCTION

Nausea, a typical adverse event associated with opioids, has been reported to occur in up to 40% of patients.1 Dopamine receptor antagonists and antihistamines are used for opioid-induced nausea and vomiting (OINV), and prophylactic antiemetics are sometimes used in Japan. However, some reports have denied the prophylactic effect, which is not recommended in the guidelines.2,3 The unnecessary use of dopamine receptor antagonists can lead to adverse events such as extrapyramidal symptoms. OINV might lead to poor compliance. Thus, for effective antiemetic therapy, it is important to identify high-risk patients who need antiemetics and reveal effective antiemetics.

Previous studies have outlined the risk factors for OINV, including female sex,4 age <50 years, nonsmokers, gastrointestinal cancer,4 and lung cancer.5 In clinical practice, patients often have multiple risk factors. Nonetheless, there is insufficient information on the risk of nausea due to the combination of risk factors.

The decision tree (DT) model is a prediction/discrimination model. By using this flow chart-like model, users can easily estimate the risk of events by considering the mutual relationship due to the combination of multiple factors. Therefore, the DT model can be applied to estimate the risk of adverse drug reactions.

Previously, we successfully constructed risk prediction models of vancomycin-induced nephrotoxicity and ganciclovir-induced neutropenia.6,7 In this study, we performed logistic regression analysis to clarify the risk factors for nausea when extended-release oxycodone (ER-OXY) is administered. Furthermore, we constructed a DT model to estimate the risk of oxycodone-induced nausea by combining multiple factors.

PATIENTS AND METHODS

Patients and Survey Items In this retrospective study conducted at Hokkaido University Hospital, patients ≥18 years of age who newly received ER-OXY for cancer pain between April 2015 and March 2018 were enrolled. New prescriptions of ER-OXY were confirmed from electronic medical records, including information from other hospitals. The evaluation period was 1 week after ER-OXY initiation.

The exclusion criteria were as follows: (a) undergoing surgery, discharge, and death during the evaluation period; (b) changes to the administration route or opioid type for reasons other than nausea and vomiting; (c) switching from other regularly scheduled strong opioids; (d) presence of nausea or vomiting at the start of ER-OXY; and (e) missing data. The survey items were selected by referring to previous studies (Supplementary Table).

We examined the records of doctors, nurses, and pharmacists from electronic medical records for confirmed records of nausea and vomiting. The occurrence of nausea was determined as grade 1 or higher based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Additionally, vomiting was evaluated based on CTCAE grade

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Cramer’s V value

analyses were performed using JMP 14® software (SAS Institute, Cary, NC, U.S.A.).

**Decision Tree Analysis** According to the chi-squared automatic interaction detection (CHAID) algorithm, a DT model predicting nausea was constructed. The dependent and independent variables were the same as those in logistic regression analysis. The procedure of CHAID algorithm was as follows: (1) constructing multiple 2×2 contingency tables between dependent and independent variables; (2) the most significant independent variable in a chi-squared test was selected; (3) branching of the tree; (4) repeating of the aforementioned steps; and (5) stop branching when the criteria were achieved. The stop criteria of the branches were (1) parent nodes ≤20 subjects or child nodes ≤10 subjects and (2) no significant differences among the independent variables. DT analysis was performed using SPSS Decision Trees Version 25 (IBM, Tokyo, Japan).

**Ethics** This study was conducted in accordance with the guidelines for the care of human studies. The ethics committee of Hokkaido University Hospital approved the study protocol (No. 019-0236).

**RESULTS**

**Patient Backgrounds** From April 2015 to March 2018, 537 patients started ER-OXY for cancer pain at Hokkaido University Hospital, of which 267 were included (Fig. 1). Nausea was observed in 30.3% (81/267) of the patients. The backgrounds of patients with and without nausea differed in terms of sex and gynecologic cancer (Table 1). Vomiting was observed in 7.5% (20/267) of patients. Patients who experienced vomiting “without nausea” were included in the non-nausea group. This is because 5 patients did not develop nausea despite suddenly vomiting due to irritability of the upper gastrointestinal tract from the pharynx, such as patients with head and neck cancer who received radiation therapy.

**Logistic Regression Analysis** Univariate analysis results revealed that age <50 years, sex, number of rescue doses >21, gynecological cancer, head and neck cancer, and non-steroidal anti-inflammatory drugs (NSAIDs) use were associated with p-values <0.1 (Table 2). Upper gastrointestinal cancer and multiple cancers were excluded because few cases were included in the analysis. Strong correlations were observed for “sex and gynecologic cancer,” “sex and head and neck cancer,” and “head and neck cancer and NSAID use,” with Cramer’s V of 0.411, 0.259, and 0.487, respectively. Therefore, age, sex, number of rescue doses during the evaluation period, and NSAID use were applied to multivariate analysis. Sex (female) was extracted as an independent factor affecting nausea in multivariate analysis (odds ratio, 1.98; Table 2).

**Construction of a Model to Estimate the Incidence Proportion of Nausea Using DT Analysis** In the DT model, the tree was divided into two levels, and three subgroups and two risk factors were extracted. Sex (female) was extracted as the most relevant factor associated with nausea. The incidence proportion of nausea in females and males was 42.5 and 25.1%, respectively. Age <50 years was extracted as the second risk factor in women. The incidence proportion of nausea among patients <50 years old and those ≥50 years old in the female subgroup was 66.7 and 36.9%, respectively.

The incidence proportion of nausea among patients <50 years old and those ≥50 years old in the male subgroup was 32% (8/25) and 24.1% (39/162), respectively. In the male subgroup, age <50 years was not extracted as a risk factor.

**DISCUSSION**

In this study, we investigated the risk of ER-OXY-induced nausea and constructed a risk prediction model using the CHAID algorithm.

Patients who experienced vomiting “without nausea” were included in the non-nausea group in our study. However, some studies evaluated vomiting without nausea as OINV. Similar to our study, some studies evaluated nausea by the presence of nausea and numeric rating scale. These data indicate that the standard definition of OINV is not well established. Vomiting is a different event from nausea, as evidenced by the fact that patients with achalasia or Zenker diverticulum may regurgitate undigested food without nausea. The occurrence of vomiting without nausea was observed in five cases in this study, all of which were associated with radiation therapy (data not shown). The cause of protruding vomiting, including sudden vomiting due to dietary stimulation, was considered to be more affected by the irritability of the head and neck and upper gastrointestinal tract associated...
with radiation therapy than with opioids. Thus, we consider that our definition of occurrence of nausea is reasonable.

In logistic regression analysis, univariate analysis showed that six variables were potentially associated with the occurrence of nausea ($p < 0.1$). Strong correlations were observed for “sex and gynecologic cancer,” “sex and head and neck cancer,” and “head and neck cancer and NSAIDs use.” Sex is considered to have a large effect on nausea based on previous reports.\(^3,5,13\) Gynecologic cancers and head and neck cancers were excluded from multivariate analysis to eliminate multicollinearity because they were strongly correlated with sex. In multivariate analysis, only sex was extracted as an independent factor affecting nausea. Similar to this study, previous studies reported that females are at a risk for OINV.\(^3,5,13\)

As with logistic regression analysis, sex was extracted as the strongest factor in the DT model. Female sex and young age are considered risk factors for postoperative nausea and vomiting (PONV) and chemotherapy-induced nausea and vomiting (CINV).\(^14,15\) Whether menstrual cycle and estrogen are risk factors for PONV remains controversial.\(^16\) Estrogen has been reported to increase the number and sensitivity of dopamine receptors.\(^17\) In our DT model, age was extracted

### Table 1. Comparison of Patient Characteristics between Those with and without Nausea

| Description | With nausea $n = 81$ | Without nausea $n = 186$ | $p$-Value |
|-------------|----------------------|--------------------------|-----------|
| Age, (years), median (range) | 62 (30–85) | 66 (20–92) | 0.052\(^a\) |
| Age $<$50, n (%) | 19 (23.46) | 22 (11.83) | 0.015\(^a\) |
| Sex (female), n (%) | 34 (41.98) | 46 (24.73) | 0.005\(^a\) |
| Serum albumin (g/dL), median (range) | 3.6 (1.4–4.7) | 3.6 (1.8–4.8) | 0.881\(^a\) |
| Serum calcium (mg/dL), median (range) | 9.6 (8.6–13.3) | 9.5 (8.1–13.4) | 0.069\(^a\) |
| PS $\leq 2$, n (%) | 74 (91.36) | 174 (93.55) | 0.522\(^a\) |
| Brain metastasis, n (%) | 3 (3.70) | 10 (5.38) | 0.760\(^a\) |
| Ascites, n (%) | 1 (1.23) | 6 (3.23) | 0.679\(^a\) |
| Ileus, n (%) | 3 (3.70) | 4 (2.15) | 0.437\(^a\) |
| BSC, n (%) | 72 (88.89) | 169 (90.86) | 0.617\(^a\) |
| Cancer chemotherapy, n (%) | 35 (43.21) | 98 (52.69) | 0.154\(^a\) |
| Radiation therapy, n (%) | 41 (50.62) | 96 (51.61) | 0.881\(^a\) |
| Drinker, n (%) | 43 (53.09) | 113 (60.75) | 0.243\(^a\) |
| Smoker, n (%) | 31 (38.27) | 68 (36.56) | 0.790\(^a\) |
| Switching from weak opioids (tramadol, codeine), n (%) | 19 (23.46) | 43 (23.12) | 0.952\(^a\) |
| Prior strong opioid rescue dose, n (%) | 16 (19.75) | 25 (13.44) | 0.188\(^a\) |
| Initial daily dose of oxycodone (mg), median (range) | 10 (5–30) | 10 (5–40) | 0.197\(^a\) |
| Number of rescue dose, median (range) | 6 (0–43) | 6 (0–41) | 0.264\(^a\) |
| Increase dose of oxycodone, n (%) | 36 (44.44) | 67 (36.02) | 0.194\(^a\) |
| Type of cancer, n (%) | | | |
| Lung | 16 (19.75) | 36 (19.35) | 0.940\(^a\) |
| Upper gastrointestinal | 0 (0) | 3 (1.61) | 0.556\(^a\) |
| Lower gastrointestinal | 1 (1.23) | 1 (0.54) | 0.516\(^a\) |
| Gynecologic | 12 (14.81) | 6 (3.23) | 0.001\(^a\) |
| Urologic | 2 (2.47) | 9 (4.84) | 0.513\(^a\) |
| Breast | 2 (2.47) | 3 (1.61) | 0.641\(^a\) |
| Liver, gallbladder, pancreas | 6 (7.41) | 18 (9.68) | 0.551\(^a\) |
| Hematologic | 3 (3.70) | 7 (3.76) | 1.000\(^a\) |
| Head and neck | 25 (30.86) | 80 (43.01) | 0.062\(^a\) |
| Multiple primary | 0 (0) | 2 (1.08) | 1.000\(^a\) |
| Skin | 1 (1.23) | 3 (1.61) | 1.000\(^a\) |
| Prostate | 1 (1.23) | 1 (0.54) | 0.516\(^a\) |
| Occult primary | 4 (4.94) | 6 (3.23) | 0.497\(^a\) |
| Others | 8 (9.88) | 11 (5.91) | 0.247\(^a\) |
| Concomitant medications, n (%) | | | |
| Prochlorperazine | 42 (51.85) | 79 (42.47) | 0.157\(^a\) |
| Antiemetic drug (other than prochlorperazine) | 7 (8.64) | 11 (5.91) | 0.414\(^a\) |
| Steroids | 4 (4.94) | 15 (8.06) | 0.361\(^a\) |
| Benzodiazepine | 13 (16.05) | 22 (11.83) | 0.347\(^a\) |
| NSAIDs | 40 (49.38) | 70 (37.63) | 0.073\(^a\) |
| H2 blocker | 6 (7.41) | 13 (6.99) | 0.903\(^a\) |
| PPI | 44 (54.32) | 85 (45.7) | 0.195\(^a\) |
| Hypnotic (other than benzodiazepine) | 10 (12.35) | 26 (13.98) | 0.720\(^a\) |
| Pregabalin | 12 (14.81) | 21 (11.29) | 0.421\(^a\) |
| Antihistamine | 6 (7.41) | 8 (4.30) | 0.370\(^a\) |

\(^{a}\) Chi-square test, \(^{b}\) Fisher’s exact test, \(^{c}\) Mann–Whitney U-test. *$p < 0.05$ was considered statistically significant. PS, performance status; BSC, best supportive care; NSAIDs, nonsteroidal anti-inflammatory drugs; H2, histamine H2-receptor blockers; PPIs, proton pump inhibitors.
as a risk factor in the female subgroup but not in the male subgroup. Fifty years is the approximate age of menopause in women, and female hormone levels may affect nausea. In logistic regression analysis, age < 50 years had a high odds ratio (2.05), but there was no significant difference. Young individuals may also be affected by nausea, as young age is a risk factor for PONV and CINV. These findings suggest that women aged < 50 years may be at an increased risk of nausea.

Cancer chemotherapy did not affect ER-OXY-induced nausea, which is consistent with a previous report. Typi- 

Table 2. Univariate and Multivariable Analyses of Risk Factors for Nausea

| Risk Factor                                      | Univariate Analysis OR (CI) | 95% CI     | p-Value | Multivariate Analysis OR (CI) | 95% CI     | p-Value |
|--------------------------------------------------|----------------------------|------------|---------|-------------------------------|------------|---------|
| Age, (years) < 50                               | 2.28 (1.15–4.51)           | 0.019**    | 2.05 (1.00–4.20)              | 0.051      |         |
| Sex (female)                                    | 2.20 (0.26–3.83)           | 0.005**    | 1.98 (1.12–3.50)              | 0.019**    |         |
| Serum albumin ≤ 2.5 (g/dL)                      | 1.85 (1.27–4.09)           | 0.138      |         |                               |            |         |
| Serum calcium < 10.1 (mg/dL)                    | 1.56 (0.79–3.04)           | 0.198      |         |                               |            |         |
| PS ≤ 2                                          | 0.73 (0.28–2.03)           | 0.529      |         |                               |            |         |
| Brain metastasis                                | 0.68 (0.15–2.28)           | 0.550      |         |                               |            |         |
| Ascites                                         | 0.38 (0.02–2.24)           | 0.316      |         |                               |            |         |
| Ileus                                           | 1.75 (0.34–8.11)           | 0.479      |         |                               |            |         |
| BSC                                             | 1.24 (0.51–2.86)           | 0.621      |         |                               |            |         |
| Cancer chemotherapy                            | 0.68 (0.40–1.15)           | 0.154      |         |                               |            |         |
| Radiation therapy                               | 0.96 (0.57–1.62)           | 0.881      |         |                               |            |         |
| Drinker                                         | 0.73 (0.43–1.24)           | 0.244      |         |                               |            |         |
| Smoker                                          | 1.08 (0.62–1.84)           | 0.790      |         |                               |            |         |
| Switching from weak opioids (tramadol, codeine), n (%) | 1.02 (0.54–1.87)       | 0.952      |         |                               |            |         |
| Prior strong opioid rescue dose                 | 1.61 (0.79–3.19)           | 0.124      |         |                               |            |         |
| Initial daily dose of oxycodone ≤ 10 mg          | 0.56 (0.25–1.30)           | 0.174      |         |                               |            |         |
| Number of rescue doses ≤ 21                     | 0.45 (0.21–0.98)           | 0.046**    | 0.52 (0.23–1.19)              | 0.122      |         |
| Increase dose of oxycodone                      | 1.42 (0.83–2.42)           | 0.196      |         |                               |            |         |
| Type of cancer                                  |                           |            |         |                               |            |         |
| Lung                                            | 1.03 (0.52–1.95)           | 0.940      |         |                               |            |         |
| Upper gastrointestinal                          |                           |            |         |                               |            |         |
| Lower gastrointestinal                          | 2.31 (0.09–58.91)          | 0.561      |         |                               |            |         |
| Gynecologic                                     | 5.22 (1.95–15.49)          | 0.001      |         |                               |            |         |
| Urologic                                        | 0.50 (0.07–1.99)           | 0.348      |         |                               |            |         |
| Breast                                          | 1.54 (0.20–9.49)           | 0.643      |         |                               |            |         |
| Liver, gallbladder, pancreas                    | 0.75 (0.26–1.86)           | 0.544      |         |                               |            |         |
| Hematologic                                     | 0.98 (0.21–3.64)           | 0.981      |         |                               |            |         |
| Head and neck                                   | 0.59 (0.34–1.02)           | 0.059      |         |                               |            |         |
| Multiple primary                                |                           |            |         |                               |            |         |
| Skin                                            | 0.76 (0.04–6.06)           | 0.812      |         |                               |            |         |
| Prostate                                        | 2.31 (0.09–58.91)          | 0.561      |         |                               |            |         |
| Occult primary                                  | 1.56 (0.39–5.61)           | 0.508      |         |                               |            |         |
| Others                                          | 1.74 (0.65–4.48)           | 0.260      |         |                               |            |         |
| Concomitant medications                         |                           |            |         |                               |            |         |
| Prochlorperazine                                | 1.46 (0.86–2.47)           | 0.158      |         |                               |            |         |
| Antiemetic drug (other than prochlorperazine)   | 1.50 (0.54–3.97)           | 0.424      |         |                               |            |         |
| Steroids                                        | 0.59 (0.19–1.84)           | 0.346      |         |                               |            |         |
| Benzodiazepine                                  | 1.43 (0.66–2.96)           | 0.355      |         |                               |            |         |
| NSAIDs                                          | 1.62 (0.95–2.74)           | 0.074*     | 1.62 (0.94–2.82)              | 0.084      |         |
| H2 blocker                                      | 1.06 (0.36–2.80)           | 0.903      |         |                               |            |         |
| PPI                                             | 1.41 (0.84–2.39)           | 0.195      |         |                               |            |         |
| Hypnotic (other than benzodiazepine)             | 0.87 (0.38–1.84)           | 0.718      |         |                               |            |         |
| Pregabalin                                      | 1.37 (0.62–2.89)           | 0.428      |         |                               |            |         |
| Antihistamine                                   | 1.78 (0.57–5.29)           | 0.309      |         |                               |            |         |

*p-Values < 0.1 were included in the multiple logistic regression analysis. **p-Values < 0.05 were considered statistically significant. CI, confidence interval; OR, odds ratio; PS, performance status; BSC, best supportive care; NSAIDs, nonsteroidal anti-inflammatory drugs; H2 blocker, histamine H2-receptor blockers; PPIs, proton pump inhibitors.

Typically, prophylactic antiemetics are administered based on the emetic risk of cancer chemotherapy. Yamada et al. reported that cancer chemotherapy during opioid initiation suppresses OINV. They also considered that neurokinin 1 receptor antagonists (NK1 antagonists), 5-hydroxytryptamine-3 receptor antagonists (5-HT3 antagonists), and steroids might be effective against OINV. In this study, chemotherapy was not significantly different in the development of nausea, but the odds ratio was less than 1. It is possible that the various antiemetics contained in the chemotherapy regimen are also effective.
against OINV. It is necessary to examine the prophylactic antiemetics used in combination in detail.

Dopamine action via the opioid μ receptor expressed in the chemoreceptor trigger zone (CTZ) and histamine action via the opioid μ receptor expressed in the vestibular organs are known mechanisms of OINV.2) Not limited to OINV, nausea is known to be associated with four neurotransmitter pathways from the cerebral cortex, CTZ, vestibular organs, and various peripheral organs to the vomiting center.19) Besides dopamine and histamine, stimulation is transmitted via various neurotransmitters, including serotonin, acetylcholine, and substance P.

In this study, neither logistic regression analysis nor DT model analysis showed that prochlorperazine had a nausea-suppressive effect. Opioid use is considered a major factor in PONV. However, droperidol, a dopamine receptor antagonist, has been reported to be ineffective in suppressing PONV.20) Serotonin antagonists have been reported to be effective in suppressing PONV. Prochlorperazine did not have a nausea-suppressive effect. This might be explained by the fact that multiple neurotransmitters, such as serotonin, might be involved in OINV besides dopamine and histamine. As mentioned previously herein, initiating opioids during chemotherapy could alleviate OINV. OINV might also be suppressed by a combination of NK1 antagonists, 5-HT3 antagonists, and steroids, such as chemotherapy prophylaxis.

The prophylactic administration of antiemetics to opioid-naive patients is associated with no evidence of sufficient efficacy and not recommended in various guidelines.2,21) The effect of suppressing OINV might not be detected owing to the low incidence of OINV when the patients are not limited. Female patients under 50 years of age were found to be at high risk, so it is important to carefully monitor these patients for nausea and to have antiemetics readily available.

Although it is known that female sex and young age are risk factors for OINV,4,10) by employing a DT model, our study provided new findings that age <50 years is a particularly strong risk factor for ER-OXY-induced nausea in women. By applying our DT model to clinical practice, clinicians and pharmacists can easily estimate the risk of nausea. Since this was a retrospective observational study conducted in a single center, there are certain limitations to the generalization of the study results. Further research is required to validate our DT model by performing a multi-center study.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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