Pharm Res (2012) 29:2555–2564
DOI 10.1007/s11095-012-0786-5

RESEARCH PAPER

Pharmacokinetic and Pharmacodynamic Modeling of Opioid-Induced Gastrointestinal Side Effects in Patients Receiving Tapentadol IR and Oxycodone IR

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Received: 20 January 2012 / Accepted: 14 May 2012 / Published online: 23 May 2012

ABSTRACT

Purpose To understand the relationship between the risk of opioid-related gastrointestinal adverse effects (AEs) and exposure to tapentadol and oxycodone as well as its active metabolite, oxymorphone, using pharmacokinetic/pharmacodynamic models.

Methods The analysis was based on a study in patients with moderate-to-severe pain following bunionectomy. Population PK modeling was conducted to estimate population PK parameters for tapentadol, oxycodone, and oxymorphone. Time to AEs was analyzed using Cox proportional-hazards models.

Results Risk of nausea, vomiting, and constipation significantly increased with exposure to tapentadol or oxycodone/oxymorphone. However, elevated risk per drug exposure of AEs for tapentadol was ~3–4 times lower than that of oxycodone, while elevated AE risk per drug exposure of oxycodone was ~60 times lower than that for oxymorphone, consistent with reported *in vitro* receptor binding affinities for these compounds. Simulations show that AE incidence following administration of tapentadol IR is lower than that following oxycodone IR intake within the investigated range of analgesic noninferiority dose ratios.

Conclusions This PK/PD analysis supports the clinical findings of reduced nausea, vomiting and constipation reported by patients treated with tapentadol, compared to patients treated with oxycodone.

KEY WORDS oxycodone · pharmacodynamics · pharmacokinetics · side effects · tapentadol

INTRODUCTION

Current analgesic therapy is complicated by the side effects profile of opioids. Research indicates that avoidance of opioid-related side effects can lead to a reluctance for physicians to prescribe opioid treatment, and therefore contributes to unrelieved pain in patients (1–3). In addition, retrospective matched cohort studies found that patients experiencing opioid-related side effects had significantly increased median total hospital costs and median length of hospital stay compared with matched non-AE controls (4,5). Gastrointestinal (GI) side effects (e.g., nausea, vomiting, and constipation) are commonly associated with opioid treatment for pain based on a recent meta-analysis (6). Nausea and vomiting are reported to be the least desirable from the patients' perspective (7). A survey analysis demonstrated that nausea, vomiting, and constipation were the major determinants of opioid medication preference (8).

Electronic supplementary material The online version of this article (doi:10.1007/s11095-012-0786-5) contains supplementary material, which is available to authorized users.

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Oxycodone, a potent agonist of the μ- and possibly κ-opioid receptors, is a frequently prescribed oral opioid analgesic for treatment of moderate to severe pain (9,10). Oxycodone is primarily metabolized in the liver to noroxycodone via the enzyme cytochrome P450 3A4 (CYP3A4) and, to a lesser extent, to oxymorphone via CYP2D6 (9). The binding affinity of oxymorphone to μ-opioid receptor (MOR) is approximately 2.5–3 times higher than that of morphine (11,12), while the binding affinity of noroxycodone to MOR is only approximately 1/20 that of morphine (13).

Tapentadol is a new centrally active analgesic agent for the relief of moderate to severe pain. Analgesic efficacy of tapentadol is thought to be due to μ-opioid agonist activity and the inhibition of norepinephrine reuptake, evidenced by preclinical studies where tapentadol provided analgesia that was only two to three times less potent than morphine in rat models in spite of 50 times lower affinity to rat MOR compared to morphine (14). The binding affinity of tapentadol to human MOR is about 18 times lower than that of morphine (15). The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. However, none of the metabolites contributes to the analgesic activity. Tapentadol has been shown to exert potent analgesic effects in various pain models.

Patients who receive tapentadol have been observed to experience less opioid-related AEs when compared to oxycodone (16–20). A double-blind, placebo- and active-controlled, fixed-dose study was conducted to evaluate the efficacy and safety of tapentadol IR for the treatment of moderate-to-severe pain following bunionectomy (19). It was found that there was an increasing trend of adverse events at higher doses of tapentadol IR in this study, and the active comparator, 15-mg oxycodone HCl IR, appeared to have at least 17% higher incidence of nausea and/or vomiting compared to tapentadol IR arms even though it was shown that tapentadol IR 100 mg was non-inferior to oxycodone HCl IR 15 mg for efficacy comaprison (19). The pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation can help to capture the knowledge of the relationship between drug exposure and clinical responses, including side effects of drugs. We hypothesize that tapentadol has lower risk of MOR related side effects due to its dual mechanisms of action and its weaker receptor binding to MOR compared to other classical opioids such as oxycodone. The objectives of this analysis were: (1) to develop PK/PD models to understand the relationship between the risk of typical opioid-related GI side effects (nausea, vomiting, and constipation) and exposure to tapentadol, oxycodone, and its active metabolite, oxymorphone, (2) to identify potential risk factors that influence the risk of AEs following administration of tapentadol IR and oxycodone IR, and (3) to investigate the relationship between risk of the side effects and the binding affinities of these compounds to MOR. The AE profiles after receiving equianalgesic doses of tapentadol IR and oxycodone IR were compared using model-based simulations.

METHODS

Patients and Treatment

Approximately 600 patients with moderate-to-severe pain following bunionectomy were randomized to 5 treatment groups: tapentadol IR 50 mg, tapentadol IR 75 mg, tapentadol IR 100 mg, oxycodone HCl IR 15 mg, or placebo. Oxycodone HCl IR 15 mg was used as an active comparator. The study protocol was reviewed and approved by institutional review boards based on the Declaration of Helsinki and Good Clinical Practices, and written informed consent was obtained from each subject prior to participation in the study. Following randomization, patients were required to take study medication every 4 to 6 h during the double-blind period (72 h), regardless of pain level, except for Day 1, where the second dose of study medication could be administered, if needed, no sooner than 1 h after the first dose of study drug. Details of the study design of the clinical study can be found elsewhere (19).

Adverse events were reported by subjects throughout the study. All adverse events were documented in the Case Report Form with the following information: nature of the adverse event, time of first occurrence, severity, duration, countermeasures, outcome, and relationship to investigational product. Only treatment emergent adverse events that occurred during the double blind phase were investigated in this PK/PD analysis. For subjects who discontinued from the study, adverse events were collected up to 48 h after the last administration of study drug. These subjects were instructed to report any adverse event after ending their participation by calling the study site.

Population Pharmacokinetic Modeling

A total of 4 PK samples were drawn from each subject. Two blood samples were collected on Day 1 at approximately 1 and 3 h after the first study drug administration, and 2 samples were collected before (predose) and approximately 2 h after the third study drug administration on Day 2. Serum samples were analyzed using validated LC/MS/MS methods for tapentadol, oxycodone, and oxymorphone. The lower limits of quantification (LLOQ) of tapentadol, oxycodone, and oxymorphone were 0.15, 1.00, and 0.1 ng/mL, respectively. Concentration data below LLOQ were flagged in the dataset and not included in the analysis.

The PK data for tapentadol from this study were included in a population PK analysis of tapentadol using pooled

data from multiple Phase 1, 2, and 3 studies and published elsewhere (21). A two-compartment model was used to describe the PK of tapentadol IR following oral administration.

A joint population parent-metabolite PK model was developed to describe the disposition of oxycodone and oxymorphone. A one-compartment model with first-order absorption and first-order elimination was used to describe the PK of oxycodone (22). As an extension of the parent drug model, the PK of the metabolite (oxymorphone) was also described by a one-compartment model with first-order elimination. A first-order bio-transformation process was assumed for the conversion of oxycodone to oxymorphone. The joint PK model was parameterized in terms of a first-order absorption rate constant (KA), elimination rate constants for oxycodone and oxymorphone (K20 and K30, respectively), volume of distribution for oxycodone and oxymorphone (V2/F and V3, respectively), and formation rate constant for oxymorphone (K23). Non-linear mixed effects modeling of the sparse data was conducted using NONMEM® VI level 1.1 (ICON, Ellicott City, MD, USA) (23,24). Log-transformed oxycodone / oxymorphone serum concentrations were fitted using the First Order Conditional Estimation (FOCE) method without interaction. Inter-individual (IIV) variability for pharmacokinetic parameters was evaluated using an exponential error model. The magnitude of residual variability in the plasma concentrations was modeled using an additive error model in the log domain. The covariate effects on the oxycodone/oxymorphone PK were not explored since the main purpose of this PK modeling was to provide individual empirical Bayes estimates of PK parameters for subsequent PK/PD analysis.

PK/PD Modeling of GI Side Effects

The distribution of time to the first occurrence of an AE was characterized by a survival model through its hazard rate function ($h(t)$). Cox Proportional-hazards (PH) models were used to model the relationship between the risk of the AEs and the exposure to tapentadol, oxycodone, and oxymorphone, using the "survival" package in R 2.9.0 (25) as follows:

$$\log h_i(t) = \log h_0(t) + \beta_1 \bullet AUC_{Tapentadol,i} + \beta_2 \bullet SEX_i \quad (1)$$

$$\log h_i(t) = \log h_0(t) + \beta_1 \bullet AUC_{oxy} + \beta_2 \bullet AUC_{oxym} + \beta_3 \bullet SEX_i \quad (2)$$

where, $h_0(t)$ is the unspecified baseline hazard estimated by non-parametric approaches; $AUC_{tapentadol,i}$, $AUC_{oxy,i,}$ *and* $AUC_{oxym,i}$ are the individual daily area under the concentration curve (AUC) at steady state for tapentadol, oxycodone, and oxymorphone, respectively, for the ith subject; and SEX_i is the gender for the ith subject. The Cox PH regression model, the most widely applied survival analysis, leaves the baseline hazard unspecified and does not have parametric assumptions on the baseline hazard (26). The baseline hazard ($h_0(t)$) in Eqs. 1 and 2 represents the placebo effects when the drug exposure is 0. The individual steady-state AUC of tapentadol, oxycodone, and oxymorphone, was predicted based on the empirical Bayes estimates obtained from the final population PK models of tapentadol and oxycodone/oxymorphone, respectively.

Model Evaluation

The adequacy of the PK model in describing oxycodone and oxymorphone kinetics was evaluated based on goodness-of-fit criteria such as the agreement between the observed and model predicted concentration values; and the disappearance of patterns in conditional weighted residuals (CWRES) (27) plotted against predicted population concentrations, as well as against the time post the latest intake of the study medication. To evaluate the predictive performance of the final PK model, visual predictive checks (VPC) were performed on the concentration-time data (28). This method evaluates whether the majority (i.e. approximately 90%) of the observed concentrations fall within the 90% prediction interval simulated using the final PK model. Serum concentrations of oxycodone and oxymorphone in the study population were simulated 500 times using the data from the subjects that were used in the model development dataset. The 90% prediction intervals of the simulated data were compared visually to the observed data.

RESULTS

Patient Characteristics

A total of 603 patients were randomized (1:1:1:1:1) to 5 treatment arms of the study. Of those patients, 596 patients had PK samples and were included in the analysis: 120 patients in the placebo group, 118 in the tapentadol IR 50-mg group, 119 in the tapentadol IR 75-mg group, 116 in the tapentadol IR 100-mg group, and 123 in the oxycodone HCl IR 15-mg group. Patient characteristics for the study are presented in Table I. The average age of the subjects was around 44 years with a standard deviation (SD) of 14. The mean body mass index was approximately 28.2 kg/m^2 (SD=6). The mean baseline pain score was 7.0 (SD=1.86). The majority of the study population was women (87.4%). The incidence rate of the adverse event for the PK population is listed in Table II.

Table I Patient Characteristics

Characteristics	Median	Range	Mean	SD
Age (yr)	46	18–77	44.4	13.7
Body Weight (kg)	72.3	46.4–150	76.5	17.9
Body Mass Index (kg/m^2)	27.5	16.1–55	28.2	5.97
Baseline Pain Intensity [a]	7.0	4–10	6.97	1.86
Sex				
Men	75 (12.6%)			
Women	521 (87.4%)			
Treatment				
Placebo	120			
Tapentadol 50 mg	118			
Tapentadol 75 mg	119			
Tapentadol 100 mg	116			
Oxycodone 15 mg	123			

[a] 11-point numerical rating scale (NRS)

Population PK Model for Tapentadol

The population PK model for tapentadol has been published elsewhere (21). Briefly, a two-compartment model with zero-order release followed by first-order absorption and first-order elimination best described the PK of tapentadol IR following oral administration. The estimated apparent oral clearance (CL/F) and the apparent central volume of distribution after oral administration were 214 L/h (IIV[expressed as %CV]: 30%) and 1170 L (29%), respectively. Simulations demonstrated that hepatic function (as characterized by total bilirubin and total protein) may be considered a clinically relevant covariate.

Joint Population PK Model for Oxycodone and Oxymorphone

The PK of oxycodone and oxymorphone in patients with acute pain following bunionectomy was adequately described by a joint parent-metabolite model with first-order absorption and first-order elimination. The parameter estimates for the joint PK model are presented in Table III. The estimated value of KA, K20, and K30 were 3.05, 0.116, and 3.91 h^{-1}, respectively. The estimated volume of distribution of oxycodone (V2/F) was 1040 L. To avoid the identifiability issue for metabolite model, the volume of distribution of oxymorphone was fixed to the literature value, 3.08 L/kg (11,29), which was derived based on i.v. data. The estimated formation rate constant for oxymorphone (K23) was 0.0179 h^{-1}. The IIV of KA, V2/F, K20, and K23 were estimated at 130%, 27.6%, 18.8%, and 40.7% coefficient of variation, respectively. Additive error models were used to describe the residual variability for the log-transformed oxycodone and oxymorphone data and the variances were 0.156 and 0.181, respectively.

The goodness-of-fit plots of the final PK model indicate that population and individual predicted oxycodone and oxymorphone concentrations agreed well with observed concentrations, and the CWRES are randomly scattered across the range of population predictions and time, suggesting no bias or trends in the residual plots (Supplementary Figure 1). The VPC (Fig. 1) stratified by nominal sampling time-points was considered adequate for both oxycodone and oxymorphone because the majority of the observations fell within the 90% prediction interval. The VPC plots show that the joint parent-metabolite model predicted the oxycodone and oxymorphone concentration data in patients following bunionectomy well.

In addition, based on the parameter estimates of the joint parent-metabolite model for oxycodone and oxymorphone, the oral CL/F for oxycodone and the fraction of oxycodone that was metabolized to oxymorphone (calculated as K23/(K20 + K23)) were derived to be 139 L/h and 0.13, respectively. According to previously published PK/PD analyses and models, the oral CL/F value of oxycodone and the fraction of oxycodone that is transformed to oxymorphone are 110 L/h (22) and 0.11 ± 0.055 (13), respectively. The similarity between our estimated values and the literature reported values further reflects the adequacy of the joint parent-metabolite model for oxycodone and oxymorphone.

PK/PD Models for GI-Related AEs

Individual AUC values at each dose of tapentadol, and for oxycodone and oxymorphone are plotted in Supplementary Figure 2. Table IV describes the hazard ratio (HR) for risk factors in the multivariate Cox proportional hazards (PH)

Table II Adverse Events in the PK Patients During the Double-Blind Treatment Period

Adverse event, *n* (%)	Placebo (*n*=120)	Tapentadol IR 50 mg (*n*=118)	Tapentadol IR 75 mg (*n*=119)	Tapentadol IR 100 mg (*n*=116)	Oxycodone HCl IR 15 mg (*n*=123)
Nausea	16 (13)	42 (35)	44 (37)	56 (48)	84 (68)
Vomiting	3 (2.5)	22 (18)	24 (20)	36 (31)	52 (42)
Constipation	1 (1)	8 (7)	1 (1)	12 (10)	19 (15)

IR immediate release

Table III Parameter Estimates for the Joint Population Pharmacokinetic Model for Oxycodone and Oxymorphone (The Conditional Number of the Model Was 431, Indicating the Model Was Well-Conditioned, the Parameter Correlations were <0.75)

Parameter	Population mean (%SE)	Inter-individual variability, %CV (%SE)
KA (h^{-1})	3.05 (26.3)	130 (47.4)
V2/F (L)	1040 (4.3)	27.6 (25.2)
V3 (L/kg)	3.08 FIXED[a]	NA
K20(h^{-1})	0.116 (10.7)	18.8 (50.4)
K23 (h^{-1})	0.0179 (48.5)	40.7(22.9)
K30 (h^{-1})	3.91 (49.1)	NA
Additive Error (oxycodone)	0.156 (10.4)	NA
Additive Error (oxymorphone)	0.181 (8.8)	NA

KA first-order absorption rate constant, *K20 and K30* elimination rate constants for oxycodone and oxymorphone, respectively, *V2/F and V3* oral volume of distribution for oxycodone and oxymorphone, respectively, *K23* formation rate constant for oxymorphone, and *NA* not applicable

[a] The value was obtained from Prommer 2005 (29)

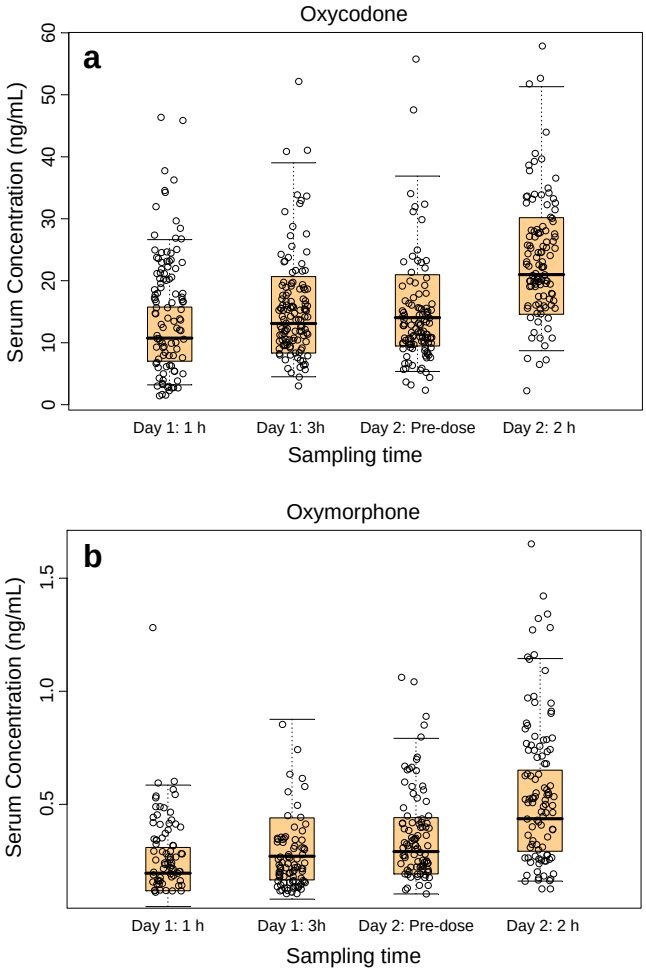

Fig. 1 Visual predictive check plots for the joint oxycodone (**a**) / oxymorphone (**b**) pharmacokinetic model. Box-plots represent predicted concentrations and circles represent observed concentrations. The bottom and top of the box are the 25th and 75th percentiles, respectively, and the band near the middle of the box is the median. The lower and upper ends of the whiskers of the box-plots represent the 5th and 95th percentiles, respectively.

models for constipation, nausea, and vomiting following administration of tapentadol IR. There is a statistically significant ($p<0.05$) association between risk of the GI-related AEs and the exposure to tapentadol. The risk of constipation, nausea, and vomiting increased 0.2%, 0.2%, and 0.3%, respectively, with 1 unit increase in AUC of tapentadol. In addition to exposure to tapentadol, gender was included in the models as a prognostic factor based on prior knowledge (30,31). Women tended to have higher risk of constipation (HR=1.41; $p=0.65$) and nausea (HR=3.21; $p=0.001$), although the gender effect on constipation was not statistically significant, probably due to the low incidence of constipation events in the bunionectomy population. No vomiting incidence was reported in the men following tapentadol exposure, while 82 women (26.8%) had vomiting following tapentadol exposure. This indicates a higher risk of vomiting in women compared to men, although the hazard ratio is not mathematically estimatable. The gender difference in GI AEs are commonly seen for opioids (30,31), and may not be related to the PK of tanpentadol and oxycodone since the PK of both compounds are similar in men and women (21,32).

The HR estimates for the risk factors in the Cox PH models for constipation, nausea, and vomiting following intake of oxycodone IR are presented in Table V. Exposures to oxycodone and oxymorphone following administration of oxycodone IR were associated with elevated risk of constipation, nausea, and vomiting. The risk of these 3 GI-related AEs increased 1% when the AUC of oxycodone increased by 1 unit. In addition, the risk of constipation, nausea, and vomiting increased 58% ($p=0.05$), 20% ($p=0.1$), and 40% ($p=0.02$), respectively, with 1 unit of increase in the AUC of oxymorphone. Like with tapentadol, gender was also found to be a significant risk factor for GI-related AEs following administration of oxycodone IR. Women had 2.2-, 5.6-, and 7.5-fold higher risk of constipation ($p=0.43$), nausea ($p=0.003$), and vomiting ($p=0.05$), respectively.

Overall, there was no evidence of violation of the proportional hazards assumptions, suggested by a p value of at least 0.26 for the global test of all the PK/PD models (33). Figure 2 shows that, for all the three GI-related AEs, the predicted event-free probability for the placebo, oxycodone, and tapentadol arms were comparable to the observed nonparametric Kaplan-Meier curves, indicating good predictive performance of the PK/PD models. The model predicted event-free probability for tapentadol also reasonably resembled the corresponding nonparametric Kaplan-Meier curves at different dose levels (Supplementary Figure 3). It should be noted that only one incidence of constipation was observed in 75 mg

Table IV Parameter Estimates of Multivariate Cox Proportional Hazards Models for Time to Constipation, Nausea, and Vomiting Following Administration of Tapentadol IR in Patients with Acute Pain after Bunionectomy

Prognostic factor	HR (95% CI)	P-value
Constipation		
AUC (ng.h/mL)	1.002 (1–1.004)	0.03
Gender (F *vs.* M)	1.41 (0.33–6.04)	0.65
Nausea		
AUC (ng.h/mL)	1.002 (1.001–1.003)	<0.0001
Gender (F *vs.* M)	3.21 (1.57–6.53)	0.0013
Vomiting		
AUC (ng.h/mL)	1.003 (1.002–1.003)	<0.0001
Gender (F *vs.* M)	NE[a]	NE[a]

Abbreviation: *AUC* AUC of tapentadol, *HR* hazard ratio, *F* female, *M* male

[a] NE: not estimatable as no vomiting observed in men in tapentadol arms of this study

tapentadol group, probably due to the small sample size and low event rate for this AE. In our exploratory analysis, different exposure metrics (e.g., average concentrations, AUC and Cmax after the 1st dose of study drugs, steady-state average concentrations, AUC, and Cmax, cumulative AUC up to dropout or censoring) have been tested and compared to assess the relationship between drug exposure and risk of the AEs. The steady-state AUC provided best model fit, and therefore was selected. In addition, more complex functions of exposure (e.g., nonlinear Emax model and interactions between oxycodone and oxymorphone) were also tested during the model fitting. However, the VPC plots suggest that the simple models (Eqs. 1 and 2) be sufficient to describe the observed data.

Table V Parameter Estimates of Multivariate Cox Proportional Hazards Models for Time to Constipation, Nausea, and Vomiting following Administration of Oxycodone IR in Patients with Acute Pain after Bunionectomy

Prognostic Factor	HR (95% CI)	P-value
Constipation		
AUCoxy (ng.h/mL)	1.01 (0.99–1.02)	0.34
AUCoxym (ng.h/mL)	1.58 (1–2.49)	0.05
Gender (F *vs.* M)	2.25 (0.3–16.9)	0.43
Nausea		
AUCoxy (ng.h/mL)	1.01 (1.005–1.02)	<0.0001
AUCoxym (ng.h/mL)	1.20 (0.96–1.50)	0.11
Gender (F *vs.* M)	5.55 (1.76–17.5)	0.003
Vomiting		
AUCoxy (ng.h/mL)	1.01 (1.00–1.02)	0.008
AUCoxym (ng.h/mL)	1.40 (1.07–1.83)	0.015
Gender (F *vs.* M)	7.52 (1.04–54.4)	0.046

AUCoxy AUC of oxycodone, *AUCoxym* AUC of oxymorphone, *HR* hazard ratio, *F* female, *M* male

Model-Based Simulations

The developed PK/PD models allow us to predict and compare the risk of GI-related AEs for tapentadol and oxycodone at different dose ratios. Simulations were performed to compare the event-free probability for the AEs following a 3-day treatment with tapentadol IR and oxycodone IR within the range of the noninferiority dose ratios from 4:1 to 7:1. A 15 mg dose was selected as the anchoring dose for oxycodone for the simulations. One thousand subjects (N=1000; men: women=1:1) were simulated using the estimated baseline hazard function for each AE. Figure 3 shows that tapentadol IR exhibits better GI-related AE profiles than oxycodone IR across the evaluated range of analgesic noninferiority dose ratios as a statistical superiority can be expected for nausea and vomiting (i.e., a clear separation in the temporal profiles of event-free probability), and a numeric improvement is predicted for constipation based on the simulations.

DISCUSSION

Classical opioids (i.e., oxycodone and morphine) provide analgesia through activation of μ-opioid receptors. However, binding with μ-opioid receptors can also be associated with unwanted effects such as nausea, vomiting, and decreased gastrointestinal motility (34,35). Tapentadol provides analgesic efficacy through two mechanisms of action: not only through MOR agonist activity, but also through its inhibitory effect on norepinephrine reuptake (14,15). In preclinical studies, the affinity of tapentadol to rat MOR was found to be approximately 50 times lower than that of morphine, but the *in vivo* analgesic potency of tapentadol was only two to three times lower than that of morphine in rat models (14), suggesting that tapentadol may have weaker μ-receptor related side effects than classical opioids at equianalgesic doses. This article is the first description of the quantitative relationship between the risk of GI-related AEs (constipation, nausea, and vomiting) and the exposure to tapentadol and oxycodone/oxymorphone in patients with acute pain after bunionectomy.

The opioid exposure was found to have dominating influence in determining postoperative GI-related side effects such as nausea and vomiting (36). The time-to-event PK/PD modeling showed that the risk of nausea, vomiting, and constipation significantly increased as the exposure to tapentadol or oxycodone/oxymorphone increased following bunionectomy. However, the increase in the AE risk per drug exposure appeared to be greater for oxycodone and oxymorphone compared with that for tapentadol. The time-to-event models can be used to compare the relative risk for tapentadol, oxycodone, and oxymorphone. However, in the absence of observed data

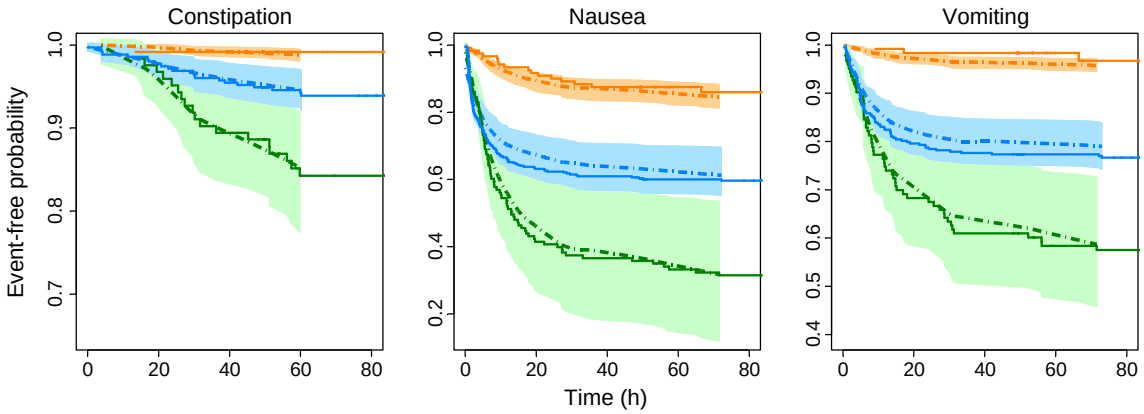

Fig. 2 Comparison of predicted event-free probability based on the PK/PD models to the observed event-free probability over time (Kaplan-Meier [KM] curves according to treatment). The orange, blue, and green solid lines are the observed KM curves for the placebo, tapentadol, and oxycodone arms, respectively; the orange, blue, and green dashed lines are the predicted event-free probability curves for the placebo, tapentadol, and oxycodone arms, respectively; the orange, blue, and green shaded areas represent the 95% confidence intervals for the placebo, tapentadol, and oxycodone treatment arms, respectively. The confidence intervals were constructed using the uncertainty (standard error) for the model parameters.

following oxycodone or oxymorphone exposure alone, the comparisons of relative hazards of tapentadol *versus* oxycodone and oxycodone *versus* oxymorphone could be difficult. To circumvent the problem, it is possible to scale oxycodone or oxymorphone concentrations by the relative *in vitro* potency of oxymorphone/oxycodone to calculate the

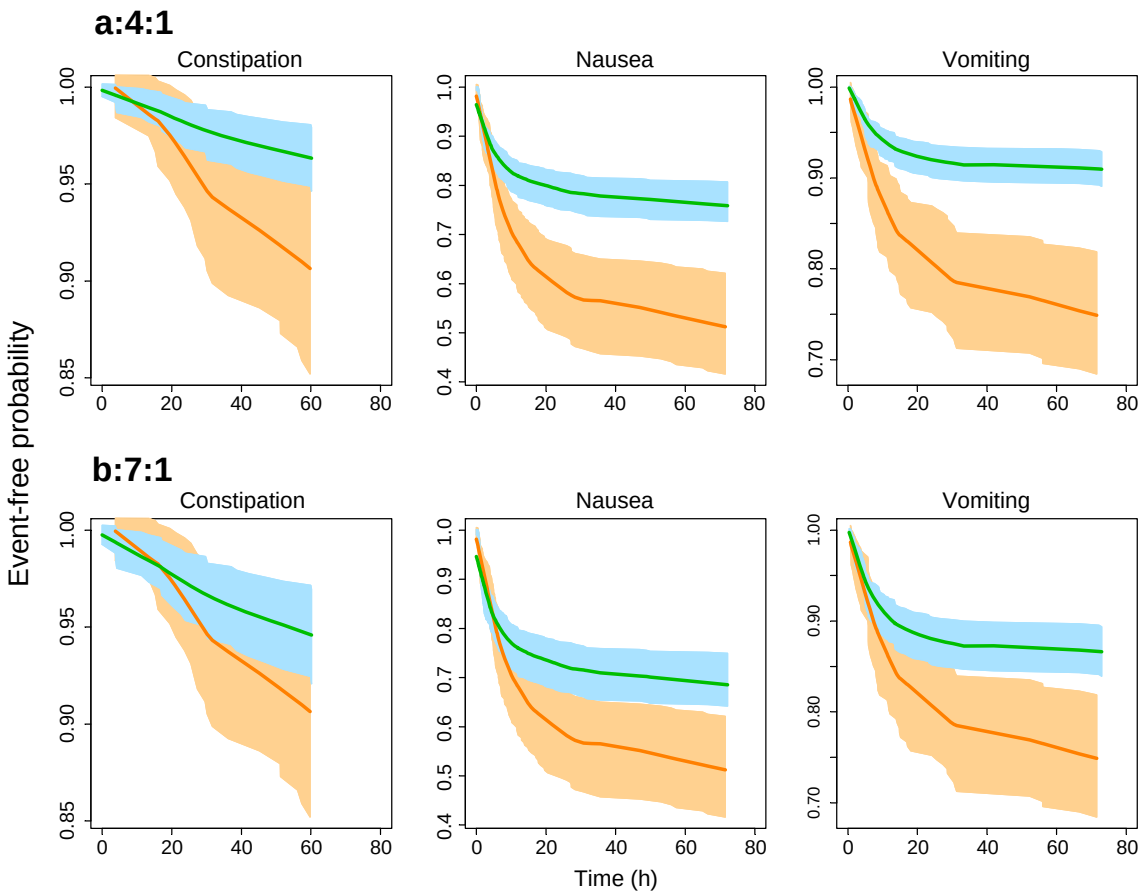

Fig. 3 The simulated event-free probability over time at noninferiority dose ratios of 4:1 (**a**) and 7:1 (**b**) based on the PK/PD models for the GI-related AEs. The orange line and shaded area represent the expected mean and 95% confidence interval, respectively, of the event-free probability for the AEs following administration of oxycodone IR. The blue line and shaded area represent the expected mean and 95% confidence interval, respectively, of the event-free probability for the AEs following administration of tapentadol IR.

oxycodone-equivalent AUC of oxymorphone or the oxymorphone-equivalent AUC of oxycodone to drive the separate hazard estimates for the parent and metabolite. If the relative potency of oxymorphone/oxycodone was set to 50, an average of the reported values (12,13,37), oxycodone showed 3- to 4-fold higher rate of increase in risk of the GI-related AEs in patients than tapentadol, while the elevated AE risk per oxymorphone exposure (i.e., AUC) for nausea, vomiting, and constipation in patients was shown to be approximately 60 times higher than the elevated risk of the GI-related AEs per oxycodone exposure. These findings are consistent with the results from preclinical *in vitro* receptor binding studies where the binding affinity to human MOR of tapentadol was found to be approximately 6 times lower than that of oxycodone (12,14), while the binding of oxymorphone to human MOR was approximately 40 to 65 times greater than that of oxycodone (12,13,37). Therefore, the PK/PD modeling of the GI-related AE risks based on the clinical study confirms the hypothesis that tapentadol has lower risk of MOR related side effects due to its weaker receptor binding to MOR compared to other classical opioids such as oxycodone. The comparative opioid pharmacology (i.e, relative binding affinity to MOR) has been suggested as an important factor in identifying risk of opioids (12). However, direct use of binding affinity for the opioid drugs provided only a limited success in predicting clinical potency and risk of these drugs (12). The present analysis indicates that PK/PD modeling and simulation can be an appropriate tool to integrate the preclinical (i.e., binding affinity) and clinical (i.e., drug exposure in humans) knowledge to understand clinical potency and risk of opioids, and thereby to support their appropriate uses.

Following administration of tapentadol IR and oxycodone IR, nausea and vomiting tended to have a quick onset, and majority of the AE incidences occurred during the first day of the study. For subjects who were in the tapentadol arms, very few new incidences were reported after approximately 15 h since the first dose, and the time to event curves of nausea and vomiting approached a plateau (Fig. 2), whereas for subjects in the oxycodone arm, a steady decline in the event-free probability for both nausea and vomiting was seen even up to 40 h. This finding might be explained by the longer half life of oxymorphone, leading to its accumulation to pharmacologically relevant concentrations. Compared to the half life of tapentadol (approximately 4 h (15)), the half lives of oxycodone and oxymorphone are approximately 3.5 h and 9 h following oral administration (13). Although the concentration levels of oxymorphone are generally low (e.g., 0.5–2 ng/mL), our PK/PD analysis suggests that it is a statistically significant factor affecting the AEs, and therefore could explain additional variability in the AE data after adjusting for oxycodone. Therefore, oxymorphone may play an important role in triggering GI-related AEs due to its higher receptor affinity to human MOR (13). The long half-life of oxymorphone may be responsible for the AE incidences observed at later times (e.g., 15–40 h) in the oxycodone arm (Fig. 2). However, due to lack of information for other active metabolites of oxycodone in the current data, the effect of oxymorphone could be partially confounded with the other metabolites. Therefore, further investigation is needed once the data for other oxycodone metabolites become available in the future.

Recent research suggests that following administration of a single 15-mg dose of oxycodone IR in 12 subjects, the central opioid effect of oxycodone (evaluated by pupil constriction) was governed by the parent drug, with a negligible contribution from its circulating metabolites (13). In addition, it has been shown that blocking the pathway of oxymorphone formation with quinidine in 10 healthy subjects who received a single dose of 20-mg controlled-released oxycodone did not attenuate the perceived pharmacodynamic effects, including opioid side effects, of oxycodone (38). The results of our analysis, however, suggest that the accumulation of oxymorphone following multiple doses of oral oxycodone may result in pharmacologically relevant concentrations. Furthermore, the limited sample size (N=10–12) used in previous single-dose studies may not provide sufficient statistical power to evaluate the effect of oxycodone metabolites as failures of model convergence and large confidence intervals were encountered when joint effects on pupil constriction of parent and metabolites were modeled (13), and only 1 out of 10 subjects reported nausea and vomiting in the latter study (38), whereas this analysis is based on a large double blinded study (N=596).

Unlike other medications, opioids do not have a ceiling effect (39). When patients have inadequate pain control or intolerable side effects, opioid rotation is an accepted clinical practice (40). A clinically meaningful comparison of adverse events for different opioid drugs should be made at equianalgesic doses that provide the same levels of analgesia. Comparison of efficacy between tapentadol and oxycodone has been performed in a wide range of clinical studies (16–20). Based on pain intensity and pain relief results from a Phase 2 study, an exploratory analysis suggested that the efficacy of tapentadol IR 50 mg was statistically similar to, but numerically slightly better than that provided by oxycodone IR 10 mg (16,17). Based on prespecified noninferiority analyses of two other Phase 3 studies, tapentadol IR 50 and 75 mg both provided statistically noninferior efficacy compared to that provided by oxycodone HCl IR 10 mg (18,20). In addition, a *post hoc* analysis of the efficacy data from the present Phase 3 clinical study showed that tapentadol IR 100 mg was noninferior to oxycodone HCl IR 15 mg (19). It is known that there is often a certain degree of variability in equianalgesic ratios for opioids (39). The data from these Phase 2/3 clinical studies suggest a possible range of variability in the noninferiority

ratio between tapentadol IR and oxycodone IR (i.e., from 4:1 to 7:1), depending on patient populations or disease conditions.

ACKNOWLEDGMENTS AND DISCLOSURES

All authors are employees of Janssen Research and Development. The analyses and studies described in this report were funded by Janssen Research and Development. Steven Xu is an adjunct assistant professor in the School of Public Health at the University of Medicine and Dentistry of New Jersey.

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