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Slow drug delivery decreased total body clearance and altered bioavailability of immediate- and controlled-release oxycodone formulations

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Abstract

Oxycodone is a commonly used analgesic with a large body of pharmacokinetic data from various immediate-release or controlled-release formulations, under different administration routes, and in diverse populations. Longer terminal half-lives from extravascular administration as compared to IV administration have been attributed to flip-flop pharmacokinetics with the rate constant of absorption slower than elimination. However, PK parameters from the extravascular studies showed faster absorption than elimination. Sustained release formulations guided by the flip-flop concept produced mixed outcomes in formulation development and clinical studies. This research aims to develop a mechanistic knowledge of oxycodone ADME, and provide a consistent interpretation of diverging results and insight to guide further extended release development and optimize the clinical use of oxycodone. PK data of oxycodone in human studies were collected from literature and digitized. The PK data were analyzed using a new PK model with Weibull function to describe time-varying drug releases/ oral absorption, and elimination dependent upon drug input to the portal vein. The new and traditional PK models were coded in NONMEM. Sensitivity analyses were conducted to address the relationship between rates of drug release/absorption and PK profiles plus terminal half-lives. Traditional PK model could not be applied consistently to describe drug absorption and elimination of oxycodone. Errors were forced on absorption, elimination, or both parameters when IV and PO profiles were fitted separately. The new mechanistic PK model with Weibull function on absorption and slower total body clearance caused by slower absorption adequately describes the complex interplay between oxycodone absorption and elimination in vivo. Terminal phase of oxycodone PK profile was shown to reflect slower total body drug clearance due to slower drug release/absorption from oral formulations. Mechanistic PK models with Weibull absorption functions, and release rate-dependent saturable total body clearance well described the diverging oxycodone absorption and elimination kinetics in the literature. It showed no actual drug absorption during the terminal phase, but slower drug clearance caused by slower release/absorption producing the appearance of flip-flop and offered new insight for the development of modified release formulations and clinical use of oxycodone.

Abbreviations

ADME, absorption, distribution, metabolism and excretion; AUC, area under the curve; BID, twice (two times) a day; $CL_{intrinsic}$, in vivo intrinsic clearance; CL, total body clearance; C_{max}, the maximum plasma concentration; CR, controlled-release;

CYP, cytochrome P450 enzymes; ER, extended-release; *F*, bioavailability; FOCEI, first-order conditional estimation with the INTERACTION; i.m., intramuscularly; i.n., intranasally; i.v., intravenously; IR, immediate-release; IV, intravenously; L, liter; NONMEM, nonlinear mixed effect model; OFV, objective function value; PK, pharmacokinetics; PO, orally; QD, once a day; Q_h, the drug input rate into the blood flow feeding into clearance organ (portal liver blood flow for IV administration); *Q*, intercompartment clearance; RV, residual variability; s.c., subcutaneously; SE, standard error; $t_{1/2}$, terminal half-life; USA, United States of America; V/F, apparent volume of distribution; VPC, visual predictive check.

Introduction

Oxycodone (14-hydroxy-7,8-dihydrocodeinone) is one of the most studied and widely used analgesics (Ross and Smith 1997; Smith 2008). It has been administered intravenously (i.v.) (Takala et al. 1997; Kokki et al. 2004; Hao et al. 2014; Kokubun et al. 2014), intramuscularly (i.m.) (Kokki et al. 2004), intranasally (i.n.) (Takala et al. 1997; Dale et al. 2002), subcutaneously (s.c.) (Kokubun et al. 2014), bucally (Kokki et al. 2004), rectally (Tegon et al. 2009; Li et al. 2011), epidurally (Kokki et al. 2014), and orally (Mandema et al. 1996; Bass et al. 2012; Mundin et al. 2012; Kim et al. 2015) using immediate release (IR) solutions and immediate- and controlled-release tablets to diverse disease populations for the treatment of acute, and chronic nonmalignant pain and cancer pain (Hanks et al. 2001; Radbruch and Nauck 2002; Lux et al. 2014; Mehta et al. 2014; Stessel et al. 2014; Poelaert et al. 2015).

Oxycodone has been shown to have consistent pharmacokinetic properties and pharmacologic activities in diverse ethnic populations of Caucasians, Japanese, and Chinese (Hao et al. 2014; Kokubun et al. 2014). Oxycodone is relatively well absorbed after oral administration, and commercially available IR and ER formulations have a bioavailability of 40–80% (Mandema et al. 1996; Bass et al. 2012; Mundin et al. 2012; Kim et al. 2015). The sublingual bioavailability of oxycodone is less than 20% at normal pH (Al-Ghananeem et al. 2006). The mean bioavailability of intranasal oxycodone is 46%, but there is wide interindividual variability from 16% to 100% (Lofwall et al. 2012). Approximately, 40% of oxycodone is bound to plasma proteins *in vitro* (Vallejo et al. 2011). Approximately, 99% of oxycodone is distributed outside the plasma compartment, as reflected by the large volume of distribution of oxycodone (2–3 L/kg). The main known metabolic pathways of oxycodone are through *O*-demethylation to oxymorphone via CYP2D6 and through *N*-demethylation to noroxycodone via CYP 3A4 (Lalovic et al. 2006; Gronlund et al. 2011; Naito et al. 2013; Soderberg Lofdal et al. 2013). Oxycodone itself is the major contributor to the analgesic effect following oxycodone administration. Although two of the metabolites, in particular oxymorphone, have higher affinities for the μ-receptors, their contribution to the overall analgesic effect is insignificant (Trescot et al. 2008). Total plasma clearance of oxycodone in adults is 0.7–1 L/min, which is consistent with intermediate hepatic extraction and a moderate first-pass effect. The T1/2 is about 2–3 h after i.v. administration, about 3 h after IR solution and about 8 h after controlled-release (CR) oxycodone (Mandema et al. 1996; Kokki et al. 2004; Bass et al. 2012).

Though a large body of pharmacokinetics data have been accumulated and effectively advanced the knowledge of pharmacokinetic disposition of oxycodone, gaps remain in the explanation of the diverging pharmacokinetic parameter values derived from IV and PO administration of oxycodone solutions, and between distinct PK parameters derived from oral administration of IR and ER formulations. Among these, one particular problem stands out on how to correctly disentangle oxycodone oral absorption from its elimination. Compared to IV administration, longer half-lives of oxycodone following PO administration has been attributed to flip-flop kinetics in which the rate of oxycodone oral absorption is slower than that of elimination, however, PK parameters derived from IR and ER pharmacokinetic profiles showed the absorption rate constant is much faster than the elimination rate constant contradicting the traditional concept of flip-flop kinetics. In addition, the pharmacokinetic parameters by traditional noncompartment and compartment modeling from IV and various PO administrations varied significantly and sometimes were against common pharmacological understanding (especially discordant apparent volume of distribution and apparent total body clearance). Furthermore, guided by the flip-flop concept, efforts to slow oxycodone release, which have been the mainstay for BID and QD sustained release formulations, produced somewhat mixed outcomes in formulations development and clinical studies (Mandema et al. 1996; Bass et al. 2012; Mundin et al. 2012; Kim et al. 2015). The purpose of this investigation is to survey the existing literature and develop a consistent mechanistic model for

the divergent pharmacokinetics of oxycodone after IV and PO administration of IR and ER formulations; and provides new insight into oxycodone disposition and a consistent framework of oxycodone ADME to guide further extended release development and optimize the clinical use of oxycodone.

Materials and Methods

Oxycodone plasma concentration–time data

Plasma oxycodone concentration–time data were obtained from eight manuscripts (Mandema et al. 1996; Takala et al. 1997; Kokki et al. 2004; Bass et al. 2012; Mundin et al. 2012; Hao et al. 2014; Kokubun et al. 2014; Kim et al. 2015). The data covered a wide dose range from 5 to 20 mg following IV and extravascular administration using immediate and modified release formulations under fasted and fed conditions. Table 1 summarizes the doses, types of formulations and routes of administration for each study.

All the manuscripts were either obtained in digital pdf format or scanned from paper copies into pdf formatted files. The electronic plasma concentration–time profile were then digitized using UN-SCAN-IT Graph Digitizing Software version 6.0 (Silk Scientific Inc., Orem, UT) software to obtain the plasma concentration and time data.

Noncompartmental PK analyses

Plasma concentration–time data of oxycodone were analyzed using noncompartmental PK methodology with Phoenix WinNonlin (CERTARA, Princeton, NJ). The Cmax was the highest concentrations based on the plasma concentration–time data, while the AUC were calculated using trapezoidal rules. PK parameters of V/F, CL/F, T1/2, and etc. were estimated based on the standard nonparametric methodology in WinNonlin.

Compartmental PK analyses

Compartmental model PK analyses were performed in nonlinear mixed-effect model (NONMEM), version 7.2 (ICON Development Solutions, Hanover, MD). One-compartment model was parameterized in Ka, CL, and V using ADVAN2, TRANS2 routine, while two-compartment model was parameterized in K_a, CL, Q, V2, and V3 using ADVAN4 and TRANS4 routine in NONMEM.

Weibull function is frequently applied to the analysis of dissolution and release studies of drug formulations (Gomez-Mantilla et al. 2013, 2014; Tan et al. 2013). The success of Weibull functions in describing drug release from oral formulations have been shown to capture concentration gradients near the releasing boundaries of the Euclidian matrix (Kosmidis and Argyrakis 2003), as well as adequately describe the fractal kinetics behavior associated with the fractal geometry of the dissolution environment. In addition, due to its versatile and flexible forms, Weibull function has been used numerically to describe complex plasma concentration–time profiles of oral absorption of drugs (Vk 1987; Zhou 2003). To describe the convex ascending oxycodone plasma concentration–time profile prior to C_{max}, a time-varying Weibull function was introduced to describe time-varying absorption rate constant as follows:

$$f(x;\lambda,k)=\begin{cases}\frac{k}{\lambda}\left(\frac{x}{\lambda}\right)^{k-1}e^{-(x/\lambda)^k} & x\geq 0,\\ 0 & x<0,\end{cases} \quad (1)$$

The absorption rate defined by Weibull absorption was coded in NONMEM as follows:

Table 1. Summary of clinical studies included in meta-analysis.

Study number	Dose	Type of formulation	Route of administration
1. Hao et al. (2014)	2.5, 5 and 10 mg	Oxycodone hydrochloride solution	IV
2. Mandema et al. (1996)	20 mg	IR solution and CR tablet	PO
3. Kokki et al. (2004)	0.1 mg/kg	Oxycodone hydrochloride solution	IV, intramuscularly, and buccally
4. Bass et al. (2012)	5, 10, and 15 mg	An immediate-release oxycodone hydrochloride formulation (IRO-A) and marketed oxycodone hydrochloride (IRO) tablets	PO
5. Takala et al. (1997)	0.05 mg/kg	Oxycodone hydrochloride solution	IV and intranasal
6. Kokubun et al. (2014)	5 mg	Oxycodone hydrochloride solution	IV
7. Mundin et al. (2012)	20 mg	Slow, median, and fast dissolution formulations of tablets	PO
8. Kim et al. (2015)	10 and 20 mg	IR and CR	PO

IV, intravenously; PO, orally; IR, immediate-release; CR, controlled-release; IRO, marketed oxycodone hydrochloride (IRO) tablets; IRO-A, An immediate-release oxycodone hydrochloride formulation.

ALPHA = THETA(1) × EXP(ETA(1)); where $\theta 1$ is the rate constants (λ) of Weibull distribution
BETA = THETA(2) × EXP(ETA(2)); where $\theta 2$ is the Weibull shape (κ) of Weibull distribution
KA = BETA/ALPHA ×(TIME/ALPHA) ×(BETA-1) × EXP(−1 × (TIME/ALPHA) × BETA)

Though it not easy to ascribe the physical interpretation of the Weibull shape (k) and rate constants (lamda), one can draw analogy of drug release as a function changing with time (such as release rate increases, decreases, or not change with time) and also associated with a shape distribution.

The concept that the total body drug clearance is function of its intrinsic clearance rate and blood flow delivering drug to the clearance organ was first introduced by Pang and Rowland (1977) using the well-stirred tank model as:

$$CL = \frac{CL_{intrinsic*Q_h}}{CL_{instrinsic+Q_h}} \quad (2)$$

where CL is the observed total body clearance, $CL_{intrinsic}$ is the intrinsic clearance defined as V_m/K_m of metabolic rate of Michaelis–Menten kinetics, Q_h is the drug input rate into the blood flow feeding into clearance organ (portal liver blood flow for IV administration for metabolism). Total body clearance as defined by Equation (2) has been successfully applied to classify drugs into two categories of high and low extraction ratios. And it has been shown in theory and practice that total body clearance of drugs with high extraction ratio is limited by the rate of blood flow feeding into the clearance organ of liver or kidney, while the total body clearance of drugs with low extraction ratio is determined by its intrinsic clearance. As for drugs with mild to moderate intrinsic clearance, its total body clearance is defined by equation (2). For intravenously administered oxycodone, $CL_{intrinsic}$ of oxycodone can be estimated based on observed total body clearance (CL_{total}) and liver blood flow Q_h of 84 L/h. When oxycodone was administered orally in IR or ER formulations, the drug release rates from the formulations may be slower than rate of portal liver blood flow and thus reduce the drug input rate to liver. Therefore, the total body clearance for orally administered oxycodone would be determined by the drug release rate from the IR or ER formulations and the intrinsic oxycodone clearance defined by equation (2).

Since there is no reason to suppose route of oxycodone administration would change it intrinsic distribution and clearance properties. A single set of PK parameters of intrinsic oxycodone clearance, oxycodone volume of distribution and rate of distribution were employed to simultaneously fitting of oxycodone plasma concentration-time profile following IV and PO administrations of IR and ER formulations. The absorption-related PK parameters of bioavailability (F), first-order absorption rate constant, or time-varying Weibull absorption rate constants and formulation-dependent drug release rate Q_h were estimated based on the oxycodone plasma concentration–time data following IR or ER administration.

To assess the robustness of parameter estimates of absorption-related oxycodone PK characteristics, PK analyses were conducted using plasma concentration–time data following PO administration of IR and ER formulations without data from IV administration. In addition, the model developed using the data from IV administration and PO administration of IR and ER formulations were used to analyze separate oxycodone PK data from separate source modified release efforts.

Comparison of structural models was based on the objective function value (OFV) and goodness-of-fit criteria. A value of $P < 0.001$, representing a decrease in OFV of >10.83, was considered statistically significant. Selection criteria during the model development process were based on goodness-of-fit plots, changes in the OFV, residual distributions, and parameter estimates and their relative SE values.

Results

Noncompartmental and traditional one compartmental analysis

Mean plasma concentration–time data of oxycodone following oral administration of immediate and sustained release formulations at 5–20 mg and intranasal administration at 6.7 mg were shown in Figure 1. After reaching the peak concentration of C_{max}, the oxycodone plasma concentrations followed a monoexponential decline. The terminal phases of the plasma concentration–time profiles had distinct half-lives with PO administration of immediate-release (IR) and controlled-release (CR) or with intranasal administration. These data were analyzed using noncompartmental and traditional compartmental analyses by way of one-compartment model with first-order rate constants. The results from noncompartmental and traditional compartmental analyses were tabulated in Tables 2, 3, together with the PK parameter values reported from the original manuscripts.

Consistent with original literature, both noncompartmental and compartmental analyses for different doses and formulations resulted in significantly distinct sets of PK parameters. Though PK profiles were adequately described by different set of PK parameters, it is difficult to relate the PK parameters to the underlying ADME processes. The wide range of apparent volume distribu-

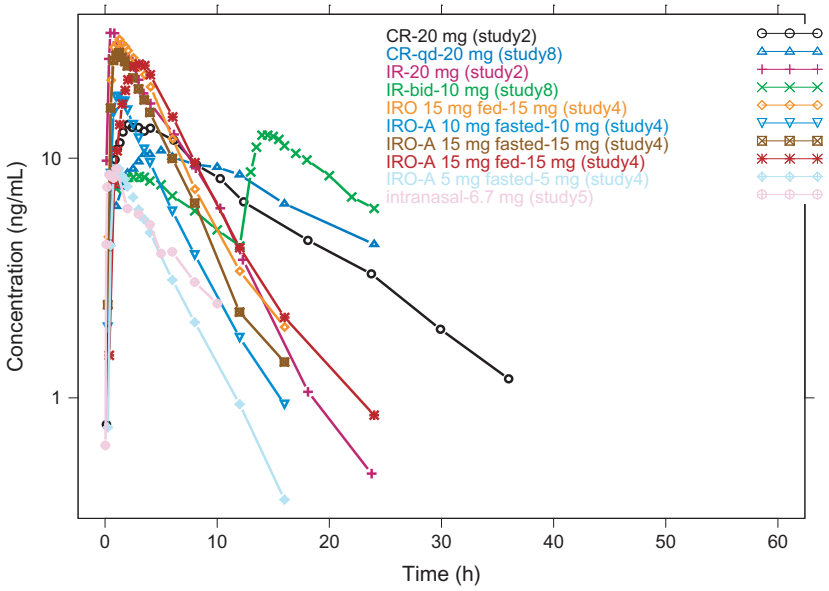

Figure 1. Mean plasma concentration–time profile of oxycodone from different doses, different types of formulations, and different routes of extravascular administration.

Table 2. PK parameter estimates from noncompartmental analyses.

Study	Dose (mg)	Formulation/route	$t_{1/2}$ (h)		V_z/F (L)	CL/F (L/h)	
			Estimated	Reported		Estimated	Reported
2	20	CR	8.42	7.99 ± 2.96	1097.62	90.37	
2	20	IR	3.70	3.21 ± 0.87	539.86	101.16	
4	5	IRO-A 5 mg fasted	3.24	3.24	479.12	102.40	105.48
4	10	IRO-A 10 mg fasted	3.72	3.38	544.84	101.41	104.7
4	15	IRO 15 mg fed	3.47	3.57	397.43	79.45	96.5
4	15	IRO-A 15 mg fasted	3.25	3.71	459.23	97.80	81.5
4	15	IRO-A 15 mg fed	5.25	3.74	603.92	79.66	79.3
5	6.7	Intranasal	5.58		794.83	98.72	114.2
8	10	IR-bid	8.81		676.62	106.48	112.26
8	20	CR-qd	12.82		1415.98	76.59	121.08

$t_{1/2}$, terminal half-life; V_z/F, terminal volume of distribution; CL/*F*, apparent total body clearance; CR, controlled-release; IR, immediate-release; IRO, marketed oxycodone hydrochloride (IRO) tablets; IRO-A, An immediate-release oxycodone hydrochloride formulation; bid, twice daily; qd, once daily.

tion from 397.43 to 1415.98 L based on noncompartmental analysis or from 28.1 to 1521 L based on one-compartment analysis, and relatively narrow range of apparent total body clearance from 74 to 120 L/h suggested disproportional effect on oxycodone intrinsic distribution and intrinsic elimination parameters (ratio of apparent volume of distribution and apparent clearance (CL/*F*)/(V/*F*) = CL/*V* should be consistent regardless of *F*). It is particularly perplexing that different route of drug delivery and different rate of oral delivery from IR to ER would change the intrinsic distribution and elimination of oxycodone, against the common pharmacology understanding that drug distribution and elimination are intrinsic to the molecule and agnostic to the path on which it arrives into the blood circulation.

Two-compartment analyses of the IV data to assess the intrinsic oxycodone distribution and total body clearance

Plasma concentration–time data following intravenous administration of oxycodone at 2.5, 5, and 10 mg in Chinese; at 5 mg in Japanese; at 0.05 mg/kg in adult Caucasians; and at 0.1 mg/kg in Caucasian Children from

Table 3. PK parameter estimates from one-compartment analyses.

Study	Dose (mg)	Formulation/route	K_a (1/h)	V/F (L)	CL/F (L)
2	20	CR	0.70	1120.3	88.8
2	20	IR	2.99	540.6	102.6
4	5	IRO-A 5 mg fasted	0.24	114.7	102.7
4	10	IRO-A 10 mg fasted	0.22	97.2	101.4
4	15	IRO-A 15 mg fasted	0.23	102.0	98.5
4	15	IRO-A 15 mg fed	0.19	203.6	82.1
4	15	IRO 15 mg fed	0.22	76.1	79.2
5	6.7	Intranasal	0.15	28.1	105.4
8	10	IR-bid	0.08	73.3	77.4
8	20	CR-qd	0.61	1521.9	73.5

K_a, absorption rate constant; *V/F*, apparent volume of distribution; CL/F, apparent total body clearance; CR, controlled-release; IR, immediate-release; IRO, marketed oxycodone hydrochloride (IRO) tablets; IRO-A, An immediate-release oxycodone hydrochloride formulation; bid, twice daily; qd, once daily.

studies 1, 3, 5, and 6 (Takala et al. 1997; Kokki et al. 2004; Hao et al. 2014; Kokubun et al. 2014) and goodness of fit of the two-compartment analyses of the IV data to assess the intrinsic oxycodone distribution and clearance. Solid lines: observed data; dotted lines: model predicted data were shown in Figure 2. The IV oxycodone PK profiles followed a biphasic decline and were adequately described by a two-compartment structure model, and a single set of intrinsic PK parameters across a wide dose range in diverse populations (Table 4). Consistent with known oxycodone ADME characteristics, larger volume of distribution from peripheral compartment as compared to volume of distribution from central compartment (105 vs. 39.2 L) and larger intercompartment clearance as compared to total body clearance (199 vs. 39.8 L/h) suggest that oxycodone is rapidly and extensively distributed into tissue following intravenous administration. In addition, high in vivo intrinsic clearance ($CL_{intrinsic}$) of 75.8 L/h estimated from the modeling is consistent with its moderate hepatic extraction and first-pass effect.

Two-compartment analyses with first-order absorption rate constant and saturable elimination affected by slower drug input to portal vein

The plasma concentration–time data following both IV and PO administration of oxycodone IR and CR formulations from studies 2 and 8 (Mandema et al. 1996; Kim et al. 2015) were analyzed simultaneously using a two-compartment model with first-order absorption rate constant and saturable elimination affected by slower drug input to portal vein defined by Equation 2 and common set of PK parameters on oxycodone distribution. The results from the analyses were shown in Table 5, and the goodness of fit of the model was shown in Figure 3.

As shown in Figure 3, the model with input rate-dependent clearance provided good fit of both the absorption and the terminal phases of IV and PO profiles of IR and CR formulations with distinct half-lives.

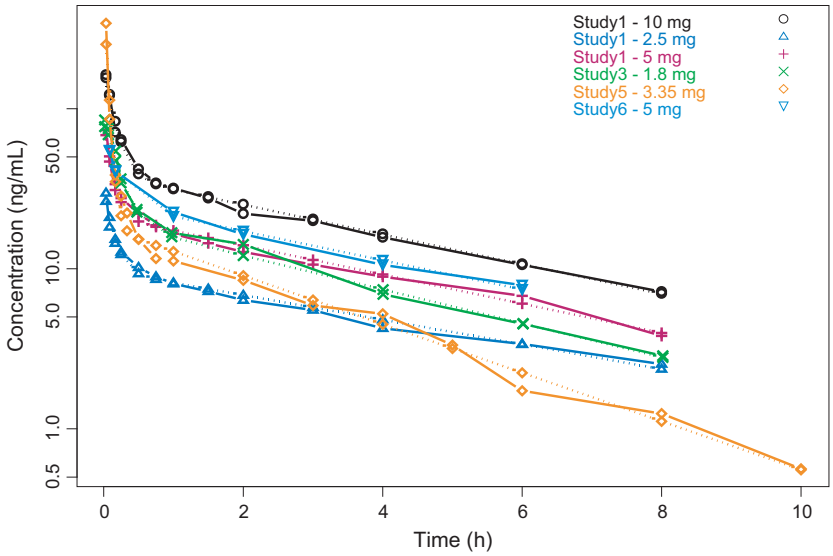

Figure 2. Mean plasma concentration–time profile of oxycodone from different doses under IV administration and goodness of fit of the two-compartment analyses of the IV data to assess the intrinsic oxycodone distribution and clearance. Solid lines, observed data; dotted lines, model predicted data.

Table 4. Intrinsic oxycodone PK parameter estimates from IV administration.

PK parameters	Mean	90% CI[1]
V2 (L)	39.2	(22.3, 64.6)
V3 (L)	105	(73.4, 143.9)
Q (L/h)	199	(89.3, 356.2)
$CL_{intrinsic}$ (L/h)	75.8	(49.4, 108.3)
Q_h (L/h)	84 FIXED	
CL (L/h)	39.8	

CI, confident interval; V2, volume of distribution of central compartment; V3, volume of distribution of peripheral compartment; *Q*, intercompartment clearance; $CL_{intrinsic}$, in vivo intrinsic clearance; Q_h, the drug input rate into the blood flow feeding into clearance organ (portal liver blood flow for IV administration), CL, clearance defined by Equate 2.

[1]Nonparametric 90% CI (5–95 percentiles) from the 100 bootstrap.

Two-compartment analyses with Weibull absorption and saturable total body elimination affected by slower drug input to portal vein

The plasma concentration–time data following both IV and PO administration of oxycodone IR formulations from study 4 (Bass et al. 2012) were initially analyzed simultaneously using a two-compartment model with first-order absorption rate constant and saturable elimination affected by slower drug input to portal vein (Fig. 4). The model provided good fit of the terminal phases of IV and PO profiles. However, this model did not well characterize the absorption phases of different formulations. A time-varying Weibull function was introduced to describe time-varying profiles. The results from the analyses were shown in Table 6, and the goodness of fit of the model was shown in Figure 4.

As shown in Figure 4, the model with Weibull distribution improved the model fit during the absorption phase of oxycodone PK profile over the constant rate of absorption, while input rate-dependent total body clearance provided good fit of the terminal phase of IV and PO profiles of IR and CR formulation with distinct half-lives.

Two-compartment analyses with Weibull absorption and saturable elimination affected by slower drug input to portal vein under intranasal administration

The oxycodone plasma concentration following intranasal administration from study 5 (Takala et al. 1997) (shown in Fig. 1) were analyzed using a two-compartment model with Weibull absorption and saturable elimination affected by slower drug input to portal vein and common set of PK parameters on oxycodone distribution based on IV data. The results from the analyses were shown in Table 6, and the goodness of fit of the model was shown in Figure 5. Again, the model provided good fit of both the intranasal absorption and the terminal phase of intranasal PK profile.

Sensitivity analysis using one-compartment analyses with saturable elimination affected by slower drug input to portal vein in the absence of IV Data

The robustness of Weibull absorption and saturable elimination affected by slower drug input into portal vein was further assessed using the plasma concentration–time data following PO administration of oxycodone IR and ER formulations in the absence of the IV data. In lieu of oxycodone PK profile following IV administration, visual inspection of the semilog oxycodone concentration–time profile following PO administration of IR and ER formulations suggested a one-compartment model is adequate to describe the oxycodone plasma concentration–time profile. Thus, the oral oxycodone PK profiles from study 2 (Mandema et al. 1996) were analyzed simultaneously using a one-compartment model with a first-order absorption rate and saturable elimination affected by slower drug input to portal vein and common set of PK parameters on oxycodone distribution. The results from the analyses were shown in Table 7, and the goodness of fit of the model was shown in Figure 6.

Table 5. PK parameter estimates from two-compartment analyses with first-order absorption rate constant and saturable elimination affected by slower drug inputs to portal vein.

Study	Formulation/route	V2 (L)	V3 (L)	*Q* (L/h)	$CL_{intrinsic}$ (L/h)	KA (1/h)	Q_h (L/h)	F1	CL (L/h)
	IV	39	105	199	75.8		84		39.8
2	CR/PO					0.348	22.7	20.4%	17.5
2	IR/PO					1.34	54.7	33.6%	31.8
8	CR (qd)/PO					0.477	7.4	9.0%	6.7
8	Commercial IR (bid)/PO					0.886	12.3	13.9%	10.6

V2, volume of distribution of central compartment; V3, volume of distribution of peripheral compartment; *Q*, intercompartment clearance; $CL_{intrinsic}$, in vivo intrinsic clearance; K_a, absorption rate constant; Q_h, the drug input rate into the blood flow feeding into clearance organ (portal liver blood flow for IV administration); F1, bioavailability; CL, clearance defined by Equation 2; IV, intravenous; CR, controlled-release; PO, orally; IR, immediate-release; qd, once daily; bid, twice daily.

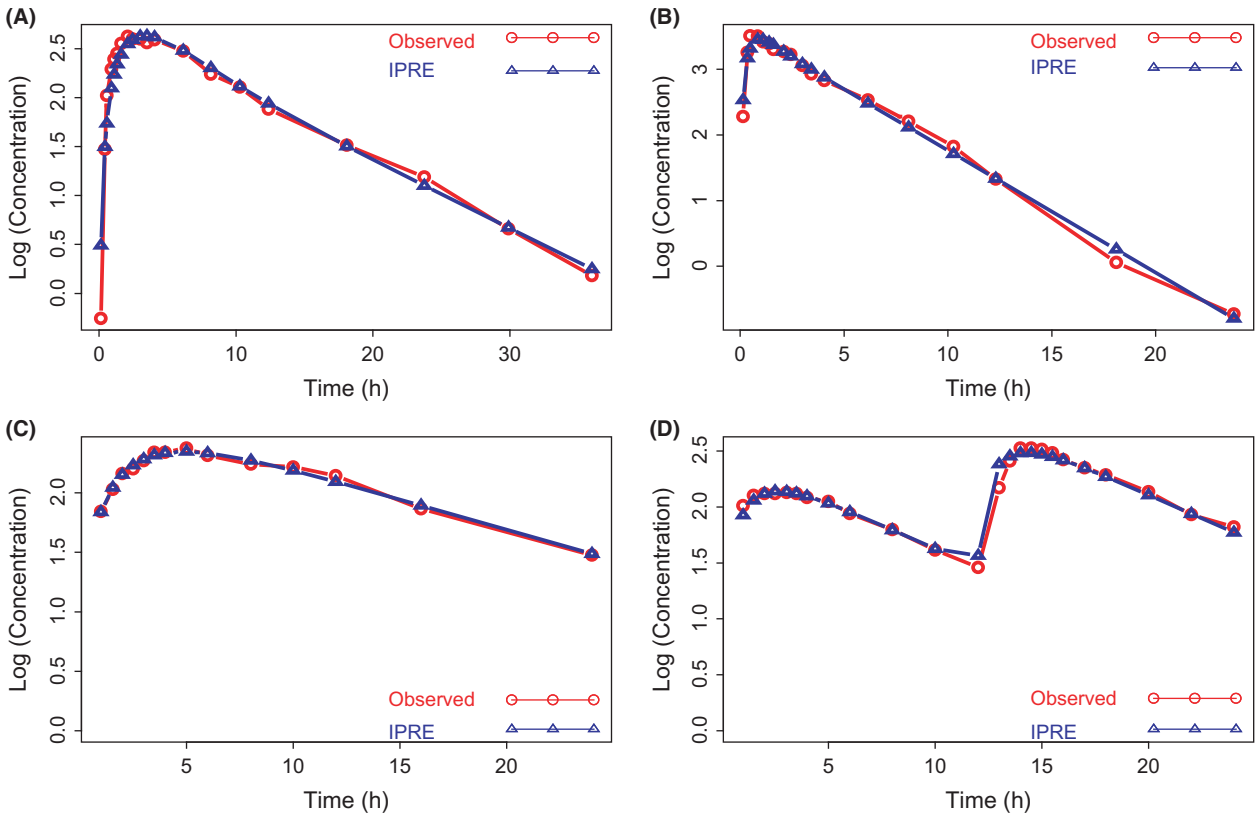

Figure 3. Goodness of fit of the two-compartment analyses with first-order absorption rate constant and saturable elimination affected by slower drug input to portal vein for (A) controlled-release formulation from study 2, (B) immediate-release formulation from study 2, (C) once-a-day CR tablets from study 8, and (D) commercial products (bid) from study 8. Observed, observed concentrations; IPRE, model predicted concentrations.

As shown in Figure 6, the model with input rate-dependent total body clearance provided good model fit of orally administered oxycodone PK profile. The results derived from the oral data without IV data were similar to those derived with both IV and oral data. Further, though the apparent volume of distribution following IR administration has increased due to confounding F, the magnitude of change in V/F and apparent total body clearance CL/F following ER administration was 40% and 18%, respectively, tracking the 38% and 14% change estimated from with the IV data. In addition, the model developed based on oxycodone IV and PO administration of IR and ER formulations provided adequate fit of oxycodone PK profiles from separate sources of modified release efforts.

Discussion

Oxycodone is a drug with moderately high total body clearance of ~34–47 L/h (in comparison of 86 L/h liver blood flow) following a bolus IV dose (Kalso 2005). Interestingly, when oxycodone was administered in a slow intravenous infusion of ~1 mg/h to Japanese patients, its total body clearance decreased from ~34 L/h following a bolus intravenous injection to 24.3 L/h indicating that oxycodone total body clearance following intravenous administration is sensitive to its input rate to blood (Kokubun et al. 2014). Assuming a typical liver blood flow of 86 L/h, the intrinsic hepatic clearance of oxycodone is estimated to be 76 L/h using equation 2. With these typical values, slower intravenous infusion regimen may be designed to exploit the decreased oxycodone total body clearance with slow infusion rate to maximize the oxycodone plasma exposure and associated benefit and outcome for patients under intensive care in clinics.

Though intravenously administered bolus oxycodone behaved consistently across wide dose ranges and in diverse populations with dose proportional exposure and consistent distribution and elimination characteristics (Table 2 in results), there is considerable variability in oral oxycodone bioavailability reported in the literature, depending on the formulations tested. The findings of this research offer a new mechanistic explanation of the large variability in oxycodone oral bioavailability. For

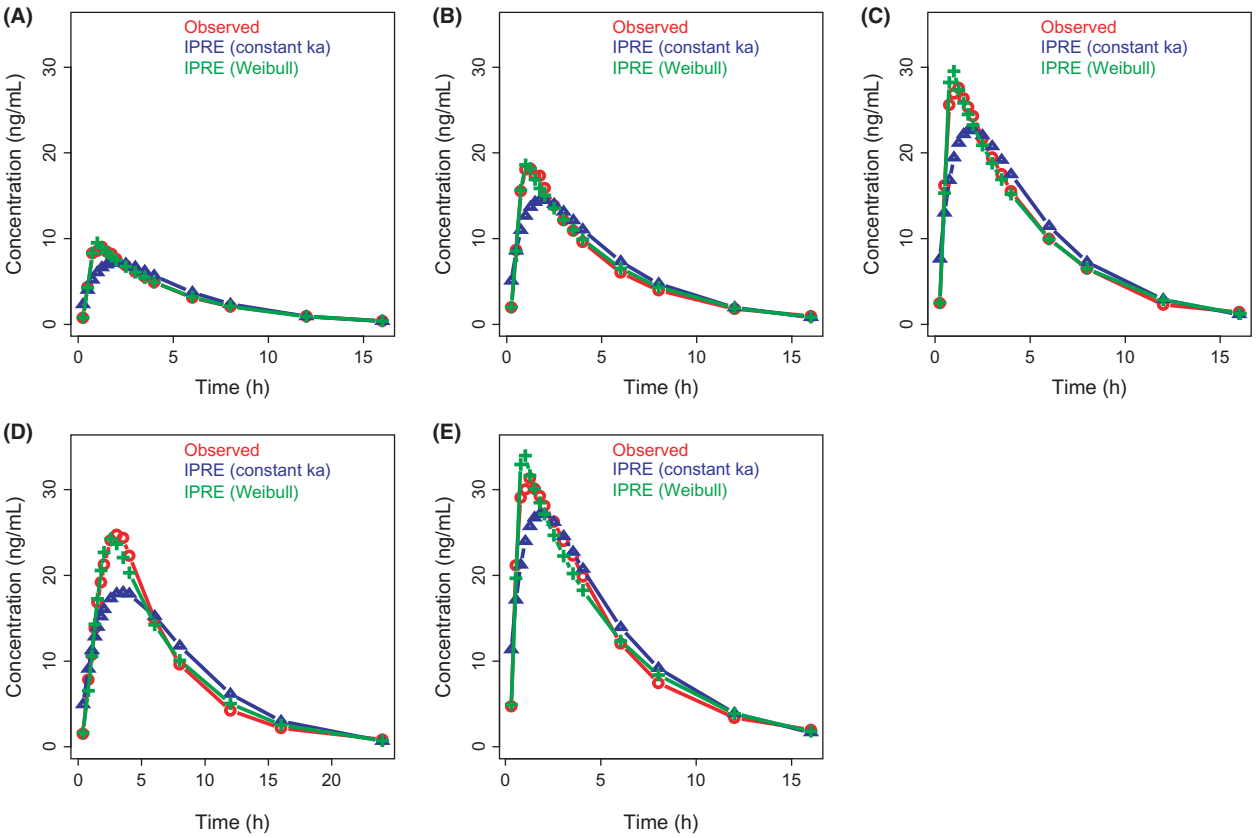

Figure 4. Goodness of fit of the two-compartment analyses with first-order absorption rate constant or Weibull absorption and saturable elimination affected by slower drug input to portal vein for (A) IRO-A 5 mg fasted data, (B) IRO-A 10 mg fasted data, (C) IRO-A 15 mg fasted data, (D) IRO-A 15 mg fed data, (E) IRO 15 mg fed data. Observed, observed concentrations; IPRE (k_a constant), model predicted concentrations with first-order absorption rate constant; IPRE (Weibull), model predicted concentrations with Weibull absorption.

Table 6. PK parameter estimates from two-compartment analyses with Weibull absorption and saturable elimination affected by slower drug inputs to portal vein.

Study	Formulation/route	V2 (L)	V3 (L)	Q (L/h)	$CL_{intrinsic}$ (L/h)	λ	κ	Q_h (L/h)	F1 (%)	CL (L/h)
	IV	39	105	199	75.8			84		39.8
5	Intranasal					0.465	1.92	21.4	29.9	16.7
4	IRO-A 5 mg fasted					0.878	3.64	31.0	34.9	22.0
4	IRO-A 10 mg fasted					0.958	3.2	32.7	37.0	22.8
4	IRO-A 15 mg fasted					0.806	3.86	29.5	35.1	21.2
4	IRO-A 15 mg fed					2.21	2.68	26.6	40.1	19.7
4	IRO 15 mg fed					0.833	4.03	26.6	39.7	19.7

V2, volume of distribution of central compartment; V3, volume of distribution of peripheral compartment; Q, intercompartment clearance; $CL_{intrinsic}$, in vivo intrinsic clearance; λ, λ factor of Weibull distribution; κ, κ factor of Weibull distribution; Q_h, the drug input rate into the blood flow feeding into clearance organ (portal liver blood flow for IV administration), F1, bioavailability; CL, clearance defined by Equation 2; IV, intravenous; IRO, marketed oxycodone hydrochloride (IRO) tablets; IRO-A, An immediate-release oxycodone hydrochloride formulation.

drug like oxycodone with high intrinsic clearance and high liver extraction ratio, its total body clearance is largely determined by the blood flow feeding into the metabolic enzymes. When the rate of drug release from oral formulations is much slower than the intrinsic oxycodone clearance rate, the total body clearance of oxycodone is largely determined by the slow drug release rate from the formulations. Therefore, different IR and ER formulations with distinct oxycodone release rates will cause different oxycodone total body clearance and significantly affect

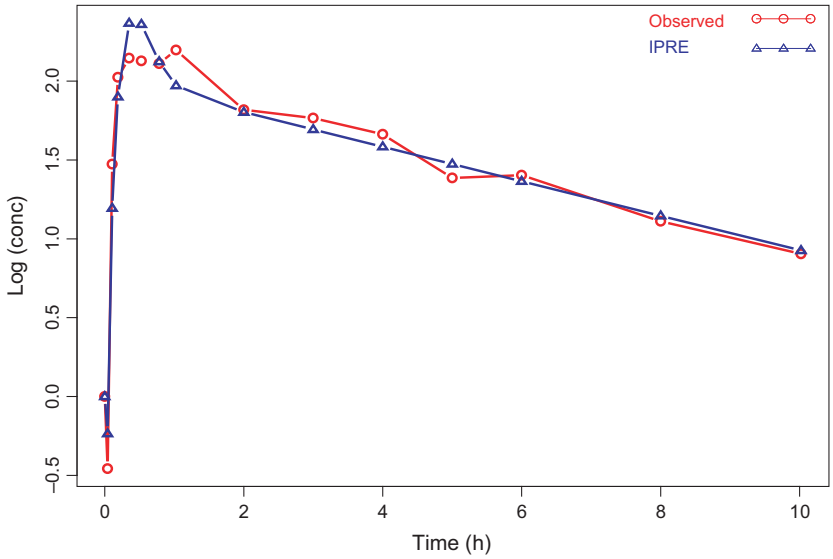

Figure 5. Goodness of fit of the two-compartment analyses with Weibull absorption and saturable elimination affected by slower drug input to portal vein under intranasal administration. Observed, observed concentrations; IPRE, model predicted concentrations.

Table 7. PK parameter estimates from sensitivity analysis.

	IR	CR
KA (1/h)	2.99	0.698
V (L)	541	541
CL (L/h)	103	42.8
F1 (CR/IR)	1	48.3%

K_a, absorption rate constant; *V*, volume of distribution; CL, clearance; F1, relative bioavailability to IR formulation; IR, immediate-release; CR, controlled-release.

the first-pass extraction and bioavailability of oxycodone (Table 5, 6, and 7 in the results).

There was also considerable variation in the apparent volume of distribution and apparent total body clearance reported in the literature (Table 1). The lack of concordance between the changes in apparent volume of distribution and apparent total body clearance were most puzzling and contradicted the traditional pharmacokinetic concept that route of drug administration should only affect a drug's systemic bioavailability, but not affect its intrinsic distribution and dispositional characteristics. The findings of this research offer new insight into this incongruence and provide a new and consistent mechanistic explanation on the discordant effect of different routes of oxycodone delivery on its apparent volume of distribution and apparent total body clearance. The slower drug release rates from different IR and ER oral formulations and intranasal administrations causes slower effective oxycodone blood input rate and results in slower oxycodone total body clearance. In addition to the different extent of first-pass effect caused by slower oxycodone release from IR or ER oral formulations and intranasal administration, the slower oxycodone release also affected the fraction of dose absorbed and complicated the eventual systemic bioavailability of oxycodone. While the route and rates of oxycodone delivery does not affect its distribution characteristics, the route and rate do affect the denominator, but NOT the nominator on the estimation of apparent volume distribution in V/F. However, route and rate of oxycodone delivery directly changes oxycodone total body clearance rate and indirectly affect the fraction of oxycodone absorbed (Table 2), as such the total effect would be on both the nominator and denominator in estimation of apparent total body clearance in CL/F; consequently, apparent volume of distribution would become disparate from the apparent total body clearance estimation by traditional noncompartmental analyses and one-compartment analyses (Table 1).

Furthermore, different terminal half-lives from different oral formulations had been traditionally attributed to flip-flop kinetics, that is, slower oral absorption reflected the terminal half-lives rather than the different oxycodone total body clearance as a result of slower absorption. However, upon closer examination, the rate of oxycodone oral absorption based on noncompartmental or one-compartment analysis have invariably yielded a more rapid absorption rate constant than the elimination rate constant (Table 1). Based on the findings of this research, the slower oxycodone input to liver portal vein affected slower oxycodone total body clearance, but did not affect oxycodone distribution causing a shallower slope of

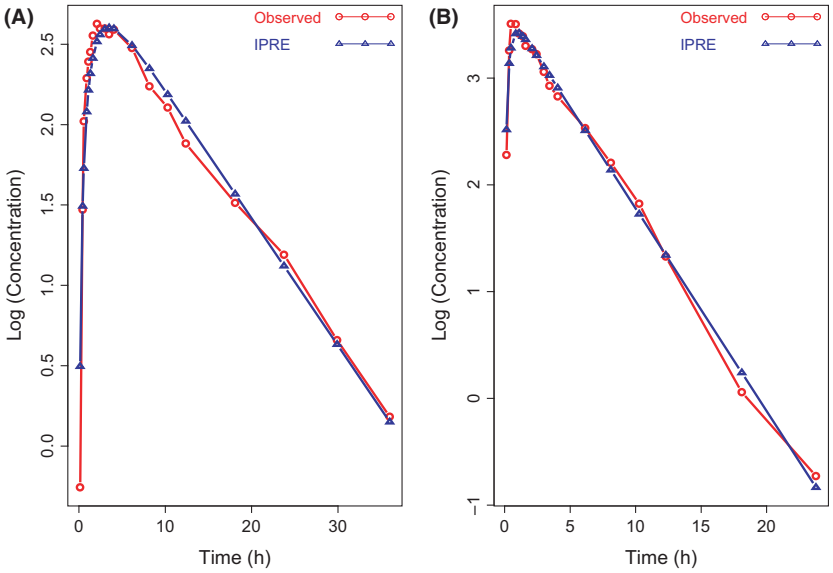

Figure 6. Goodness of fit of sensitivity analysis using one-compartment analyses with saturable elimination affected by slower drug input to portal vein in the absence of IV data for (A) controlled-release formulation from study 2, (B) immediate-release formulation from study 2. Observed, observed concentrations; IPRE, model predicted concentrations.

terminal elimination phase (kel) by way of CL/V. Thus, the terminal phase of oxycodone PK profile is a direct result of slower oxycodone total body clearance which is caused by slower oxycodone release. Though the rate of oral oxycodone absorption in modified release formulations and extravascular delivery is still much faster than the rate of oxycodone total body clearance and would be not reflected in its terminal phase of oxycodone PK profile, the longer terminal elimination phase would actually reflect its slower total body clearance as a result of the slower oxycodone absorption.

Oral absorption of oxycodone is rapid, as reflected by large rate constant from the one- and two-compartment model analyses. The first-order release and oral absorption is a reasonable approximation with a rapid ascending oxycodone plasma concentration–time profile for IR and certain ER formulations (Table 2 and Fig. 2) when oxycodone release is fast. However, when the rate of oxycodone release is modified and oxycodone is taken with food, the resulting convex and/or sigmoid plasma concentration–time during the absorption phase was better described with a time-varying Weibull absorption rate function (Fig. 3). The Weibull function appeared to capture the dynamic time-varying nature of oxycodone better than the first-order release with a constant rate, and more likely reflected the physical dissolution and physiological conditions of GI track.

The insights from this research shed new light on the strategy of modified release oxycodone development. In the past, efforts have been directed to delay and slow oxycodone release in proximal intestine and increase distal intestinal absorption of oxycodone. However, findings from this research indicate that distal intestinal absorption of oxycodone is poor and slow. Compared to IR oxycodone, the elevation in plasma concentration of oxycodone following Cmax by modified release formulations is a product of slower oxycodone total body clearance and decreasing oxycodone absorption. Rather than delaying release of oxycodone, optimization may be achieved by modifying the rate of oxycodone release in proximal intestine to maximize the fraction of oxycodone absorbed while slowing oxycodone total body clearance.

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Author Contributions

Participated in research design: **Li, Sun, Palmisano, Zhou.**

Contributed new reagents or analytic tools: **N/A.**

Performed data analysis: **Li, Zhou.**

Wrote or contributed to the writing of the manuscript: **Li, Sun, Palmisano, Zhou.**

Disclosures

None declared.

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