Toxicology and Applied Pharmacology 273 (2013) 464–476

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

Physiologically-based pharmacokinetic model for Fentanyl in support of the development of Provisional Advisory Levels

Harish Shankaran [a,*], Femi Adeshina [b], Justin G. Teeguarden [c]

[a] Computational Biology and Bioinformatics Group, Pacific Northwest National Laboratory, Richland, WA 99352, USA
[b] National Homeland Security Research Center, United States Environmental Protection Agency, Washington, DC 20460, USA
[c] Systems Toxicology Group, Pacific Northwest National Laboratory, Richland, WA 99352, USA

ARTICLE INFO

Article history:
Received 12 January 2013
Revised 23 April 2013
Accepted 11 May 2013
Available online 31 May 2013

Keywords:
Computational modeling
Inhalation
Oral transmucosal
Anesthetic
Route-to-route extrapolation
Risk assessment

ABSTRACT

Provisional Advisory Levels (PALs) are tiered exposure limits for toxic chemicals in air and drinking water that are developed to assist in emergency responses. Physiologically-based pharmacokinetic (PBPK) modeling can support this process by enabling extrapolations across doses, and exposure routes, thereby addressing gaps in the available toxicity data. Here, we describe the development of a PBPK model for Fentanyl – a synthetic opioid used clinically for pain management – to support the establishment of PALs. Starting from an existing model for intravenous Fentanyl, we first optimized distribution and clearance parameters using several additional IV datasets. We then calibrated the model using pharmacokinetic data for various formulations, and determined the absorbed fraction, *F*, and time taken for the absorbed amount to reach 90% of its final value, *t90*. For aerosolized pulmonary Fentanyl, $F = 1$ and t90 < 1 min indicating complete and rapid absorption. The *F* value ranged from 0.35 to 0.74 for oral and various transmucosal routes. Oral Fentanyl was absorbed the slowest (t90 ~ 300 min); the absorption of intranasal Fentanyl was relatively rapid (t90 ~ 20–40 min); and the various oral transmucosal routes had intermediate absorption rates (t90 ~ 160–300 min). Based on these results, for inhalation exposures, we assumed that all of the Fentanyl inhaled from the air during each breath directly, and instantaneously enters the arterial circulation. We present model predictions of Fentanyl blood concentrations in oral and inhalation scenarios relevant for PAL development, and provide an analytical expression that can be used to extrapolate between oral and inhalation routes for the derivation of PALs.

Published by Elsevier Inc.

Introduction

In response to the Homeland Security Presidential Directives (HSPD) 8 for National Emergency Preparedness the US Environmental Protection Agency's (EPA) National Homeland Security Center is developing Provisional Advisory Levels (PALs) for toxic industrial chemicals, pesticides and chemical warfare agents in air and drinking water (Adeshina et al., 2009). PALs are temporary values that are intended to be used at the discretion of risk managers during emergency situations to assist decisions for evacuation, re-entry and infrastructure use. Specifically, PALs are threshold inhalation and oral exposure levels for the general public, and are derived for assumed continuous 24-hour, 30-day, 90-day and 2-year exposure durations. For each of these exposure periods the objective is to identify three PAL levels (PAL 1, PAL 2 and PAL 3) that vary in the severity of toxic effects. Hence, for each priority chemical the EPA seeks to develop 24 distinct PAL values (12 each for drinking water and inhalation exposures) based on available data and chemical-specific information (Young et al., 2009). The overview of the Standing Operating Procedure for developing PALs (Young et al., 2009), and details of PAL derivation for specific chemicals have been previously published (Glass et al., 2009; Goldhaber et al., 2009; Marshall et al., 2009).

The PAL development process involves several steps including the identification of a chemical specific critical effect, selection of quantitative points of departure (POD) and exposure duration adjustments and extrapolation (Young et al., 2009). A key challenge in the PAL process is the lack of appropriate human toxicity data for each route of exposure, and for the various exposure durations of interest. Some of these challenges are currently overcome via the use of uncertainty factors for: i) interspecies differences, ii) intraspecies variability and iii) short-term to long-term exposure adjustments. Further, exposure duration adjustments based on Haber's rule ($C \times t = k$ where C = concentration, t = time and k = a constant) or related exponential relationships ($C^n \times t = k$ where n is a chemical specific exponent; Miller et al., 2000; ten Berge et al., 1986) are applied in instances where the data involves discontinuous exposures or a different exposure duration than what is desired (Glass et al., 2009; Goldhaber et al., 2009; Marshall et al., 2009; Young et al., 2009).

* Corresponding author at: Computational Biology and Bioinformatics Group, Pacific Northwest National Laboratory, PO Box 999, MS J4-33, Richland, WA 99352, USA. Fax: +1 509 371 7637.
E-mail address: harish.shankaran@pnnl.gov (H. Shankaran).

0041-008X/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.taap.2013.05.024

Rigorous approaches that enable quantitative extrapolation across species, exposure routes and durations, while taking into account the specific pharmacokinetic (PK) properties of a chemical are expected to be valuable in the PAL development process. In this regard, computational approaches such as physiologically based pharmacokinetic (PBPK) modeling are a promising means to fill gaps in the available toxicity data, and to reduce or identify key areas of uncertainty. PBPK models are a quantitative means to relate the external dose of a chemical in air or water to internal or target tissue concentrations. They do so by accounting for the specific PK properties of a chemical (absorption, distribution, metabolism and elimination), and are well-suited for the kinds of extrapolations necessary in the PAL development process. However, in order to develop and apply a PBPK model in this context we need chemical-specific PK parameters, and experimental datasets for calibration and validation of the model for the specific routes of interest (oral and inhalation). Fentanyl (CAS Reg. No. 437-38-7) is a chemical on the PAL priority list that meets these criteria, and can thus be used as an example to illustrate the application of PBPK modeling to support the PAL process.

Fentanyl, commercially available as Fentanyl citrate salt, is a highly potent synthetic opioid used clinically as an anesthetic and for the treatment of acute and chronic pain (Modesti et al., 2006; Peng and Sandler, 1999; Scott et al., 1991; Waara-Wolleat et al., 2006). It exerts its anesthetic and analgesic effects by binding to the μ-opioid receptor, and is metabolized primarily in the liver by cytochrome P450 3A4 (CYP3A4) (Labroo et al., 1997). The metabolites do not have pharmacologic activity and are excreted mainly by the kidney (Grape et al., 2010). Fentanyl is highly lipophilic (octanol:water partition coefficient of ~800:1), and hence is easily absorbed by tissues. Various Fentanyl formulations including intravenous (IV), oral, aerosolized pulmonary (AP), intranasal (IN), transdermal patches, and a variety of oral transmucosal formulations have been developed for clinical use (Grape et al., 2010). Several human PK datasets are available for these modes of drug delivery, with studies involving time course measurements of Fentanyl concentrations in either arterial or venous blood following administration of the compound.

The Fentanyl blood concentration appears to be a relevant metric to assess the pharmacodynamic (PD) effects of the compound with the concentrations that elicit particular clinical effects being reasonably well documented (Kharasch et al., 2004a). For instance, a Fentanyl concentration of 1–3 ng/mL is required for the treatment of acute pain (Peng and Sandler, 1999). The half-maximal concentration (EC_{50}) for changes in the electroencephalogram (EEG) spectral edge frequency is 8 ng/mL (Scott and Stanski, 1987). The EC_{50} for respiratory effects is 3, 3.5 and 6 ng/mL, respectively, for depression of carbon dioxide responsiveness, respiratory rate, and minute volume (Cartwright et al., 1983; Mildh et al., 2001). Concentrations less than 1 ng/mL have been reported to elicit significant miosis (changes in pupil diameter) (Kharasch et al., 2004a).

Our objective here is to develop a human PBPK model for Fentanyl that would enable prediction of blood and tissue concentrations following oral and inhalation exposures. Such a model would enable extrapolation across routes based on biologically active internal concentrations. We note that while human dose-response data are available for oral and oral transmucosal exposures [e.g. (Goldstein-Dresner et al., 1991; Lind et al., 1991; Stanley et al., 1989; Streisand et al., 1989, 1991, 1998; Wheeler et al., 2002, 2004)] enabling the determination of a POD for the oral route, no such data exist for inhalation exposure thereby preventing the direct derivation of a POD for this route. Given POD values derived from experimental data for a specific route (e.g. oral) and exposure duration, a calibrated PBPK model would enable us to generate equivalent toxicity levels for other routes (e.g. inhalation) and durations in the PAL matrix corresponding to the same internal exposure (blood concentration). Here, we develop and calibrate a Fentanyl PBPK model, and use it to derive analytical expressions for the extrapolation of oral toxicity data to equivalent inhalation exposures.

Methods

General approach

There is an extensive set of human PK data (blood concentration profiles) available for various Fentanyl formulations collected in studies that involve a broad range of study subjects (surgery vs. healthy volunteers, young vs. old, broad range of body weights etc.) and dosing protocols. Our objective here is to develop a model with a single set of parameter values that is most consistent with all of the available data. Toward this end, we used maximum likelihood estimation to obtain point estimates for parameter values that yield the best consensus fit to multiple human datasets. We then generated predictions for oral and inhalation exposures using this single optimum parameter set.

We adopted a step-wise approach to model calibration. We first optimized parameters governing Fentanyl distribution and clearance using IV datasets alone. We chose a subset of 5 parameters for optimization based on a sensitivity analysis. We used a subset of the IV datasets for parameter optimization, and the rest for model testing. Following this step, we calibrated the absorption parameters for various Fentanyl formulations related to oral and inhalation exposures.

For these calibrations we kept the organ volumes, blood flows, partition coefficients and clearance fixed at values obtained following IV optimization.

We tabulated the absorbed fraction, and absorption rate for various Fentanyl formulations, and chose the appropriate values that would be the most health-protective for oral and inhalation exposures. These values were then used to simulate Fentanyl blood concentrations during PAL relevant exposure scenarios. Finally, to examine the effects of inter individual variability on Fentanyl PK, we performed Monte Carlo simulations where we varied the model parameters around the values obtained following model calibration. These simulations were performed for continuous inhalation exposures.

All model simulations, sensitivity analysis and optimization were performed using acslX (Aegis Technologies, Hustsville, AL). The model code will be made available upon request. Detailed methods for each of the model development steps are provided below.

PBPK model structure and governing equations. Bjorkman and co-workers have published PBPK models for simulating Fentanyl blood and tissue concentrations following IV administration of the compound in rats and humans (Bjorkman, 2003; Bjorkman et al., 1990, 1993, 1994, 1998). Here we use the model in (Bjorkman, 2003) (herein we refer to this as the "Bjorkman model") as a starting point to develop a human PBPK model for the oral and inhalation routes. The Bjorkman model is a 13-compartment perfusion-limited model with explicit representation of arterial and venous blood compartments (Fig. 1). Clearance is assumed to occur only in the liver. The remaining tissue compartments are lung, brain, heart, kidneys, skin, gut, muscle, carcass, fat, and a lumped "pancreas + spleen" compartment. The Bjorkman model was constructed solely for simulating IV exposures. We extended the model by incorporating uptake routes for several other Fentanyl formulations (see Table 1) relevant to oral and inhalation exposures (Fig. 1).

The equations for the Fentanyl model, in general, are consistent with standard perfusion-limited PBPK modeling practice (see Supplementary Material for the complete set of model equations). We address some of the non-standard features here. Note that in the model, the lungs in addition to receiving the flow from the venous blood are also perfused by the bronchial arteries (Fig. 1). The equation for the rate of change of the Fentanyl amount in the lungs is thus expressed as follows: $dALU/dt = QV \times CV + QLU \times CA - QC \times CLU/PLU$, where ALU (mg) is the amount of Fentanyl in the lungs; QV (L/min) is the flow from the veins to the lung; QLU (L/min) is the bronchial arterial flow to the lungs; QC is the cardiac output (L/min); CV, CA, and CLU are the Fentanyl