Computers in Biology and Medicine 73 (2016) 141–146

Contents lists available at ScienceDirect

Computers in Biology and Medicine

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

Transition modeling of neuropsychiatric impairment in HIV

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ARTICLE INFO

Article history:
Received 17 January 2016
Received in revised form
29 March 2016
Accepted 14 April 2016

Keywords:
Neuropsychiatric impairment
Efavirenz
Continuous time Markov model
NONMEM
Monte Carlo simulation
Duration of NPI

ABSTRACT

Few studies have reported analyses of neuropsychiatric impairment (NPI) data from HIV patients, in a real world clinical setting with the aim of establishing association between anti-retroviral drug concentrations and NPI development and resolution. No study has modeled the effect of efavirenz exposure beyond the pre-steady state period on the frequency and duration of NPI. The data used consists of 196 HIV patients whose efavirenz pharmacokinetic parameters were previously determined. Neuropsychiatric evaluation was done at baseline, week 2 and week 12. Patients were classified into NORMAL and NPI states. The duration of NPI was further classified as transient (NPI at week 2 but not at week 12), persistent (NPI at week 2 and 12) and delayed (NPI at week 12 but not at week 2). The proportion of patients in each duration category out of the total NPI patients was calculated. A continuous time Markov model was developed in NONMEM 7.3 and used to describe the relationship between efavirenz exposure and the duration of NPI. Monte Carlo simulations with the model were used to describe the effect of efavirenz dose reduction from 600 mg to 400 mg on the duration of NPI. The model adequately described the data. The influence of efavirenz exposure on the rate of development of NPI decayed with a half-life of 8.4 days. Efavirenz dose reduction to 400 mg significantly reduces the duration of NPI, but has no impact on delayed NPI symptoms or efficacy.

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1. Introduction

Neurological and psychiatric disorders are among the most prevalent comorbidities in patients undergoing treatment for human immunodeficiency virus (HIV) leading to significant impairment of functional capacity, quality of life and survival [1,2]. The etiology of these disorders is highly varied, ranging from substance abuse, preexisting psychiatric disease, toxicity of certain regimens of the anti-retroviral therapy, opportunistic infection of the central nervous system (CNS) or HIV infection itself [3–5]. In most cases there is more than one cause at a time in an individual. In order to address these neuropsychiatric complications, it is important to establish the etiology. Unfortunately, CNS side effects of highly active anti-retroviral therapy (HAART) and neurological complications of HIV infections overlap significantly in terms of symptoms, thus complicating diagnosis and subsequent management.

The ART regimen, efavirenz is widely reported to cause CNS toxicity [6]. This toxicity presents with mild and transient symptoms but severe and persistent episodes have been reported. The incidence of NPI is higher in patients with a history of psychiatric impairment [7,8].

Few studies have reported analyses of neuropsychiatric impairment (NPI) data from HIV aimed at establishing association between as anti-retroviral drug such an efavirenz concentrations and NPI [9–11]. These studies aimed at establishing statistical associations between risk of NPI and efavirenz concentration cutoffs among HIV patients who did not have NPI at baseline. However, these do not reflect reality in that the inclusion and exclusion criteria eliminate potential causes of NPIs and, therefore, interaction between different etiological factors is not considered. A pragmatic approach to obtaining data that reflects real world clinical setting is to relax entry criteria to include subjects with some history of NPI and subsequently in the analysis of the data collected. To date, not many studies have analyzed NPIs in such a study setting. Mukonzo and colleagues used descriptive and summary statistics to describe the association between frequency of NPI symptoms and genetic, demographic and pharmacokinetic factors [12]. Whereas they sought to establish a link between efavirenz pharmacokinetics and the NPI symptoms observed during therapy, the approach used in the analysis did not take into consideration the baseline NPI status and therefore presents a risk

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http://dx.doi.org/10.1016/j.compbiomed.2016.04.011
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of bias in the analysis. In addition, the approach did not characterize the exposure response relationship adequately. Pharmacokinetic/pharmacodynamic modeling is a more suitable method for characterizing exposure–response relationship so as to maximize the amount of knowledge obtained from an experiment and enable prediction beyond conditions that have been studied [13]. This is particularly important if the outcome of interest is an adverse effect (AE) like NPI for which the design of dose-response studies may not be practical.

Patients with NPI symptoms at baseline may experience persistence or resolution of the symptoms upon initiation of efavirenz. Likewise, those without symptoms at baseline may or may not develop NPI symptoms. A Markov process can be used to characterize the probability of development or resolution of NPI symptoms upon initiation of efavirenz therapy, and the factors influencing these probabilities. Thus, this investigation was undertaken to characterize the development and resolution of NPI symptoms during HIV therapy with efavirenz in order to gain an understanding of the process and the factors that modulate it.

2. Methods

2.1. Discrete versus continuous time Markov models

A sequence of discrete valued random variables is said to be a Markov chain, if only the present value of a random variable is needed to determine the immediate future value of the random variable. The discrete values are referred to as states and occupy a finite space. The transition between states is a random process itself and can be modeled with a discrete time Markov model [14]. Thus a discrete time Markov model is primarily characterized by "states" and "transition probabilities". The covariate dependence of transition probabilities can be analyzed using logistic functions [15]. We previously utilized a discrete time Markov model to characterize NPIs in the efavirenz pre-steady state period of treatment [16]. Only two observations time points were utilized and the description of outcomes was limited to only the frequency of NPI. However, it is important to describe NPI across the entire treatment period and also characterize the impact of treatment on the duration and time of onset of NPI. When an adverse effect (AE) such as NPI occurs during drug therapy, understanding the AE process over the duration of drug therapy is important. Dividing the process into pre-steady state and steady state in an attempt to provide a quantitative understanding of the adverse effect process may result in information loss and yields only fragmented knowledge. The intent of understanding the full course of the AE such as NPI should inform the type of transition model developed, discrete versus continuous transition time model. In addition, a discrete time Markov modeling method would require uniform observation intervals, yet most clinical data, even with in a research setting often has non-uniform intervals between observations.

A continuous time Markov model can solve these limitations. For a continuous time Markov process, both the future state and the time left in the current state depend on the current state. The states are still discrete and are finite in number. However, state occupancy time occupies continuous space. The probability of staying in a particular state decays exponentially and is directly proportional to the rate (intensity) of transition from that state. Covariate factors, including drug exposure, can affect the transition intensities [17]. A continuous time Markov model is capable of utilizing data with non-uniform observation intervals because time variation is built into the model via transition intensities. Here, we utilize a continuous time Markov model to describe NPI beyond pre-steady state using observations that are not equally spaced. First, we describe in this section the data used in this investigation, followed by a description of the pharmacokinetic model, pharmacokinetic/pharmacodynamic model development, model validation (predictive performance), and the application of the model.

2.2. The data

The data was collected in 2008 to 2009 and consists of newly diagnosed anti-retroviral therapy (ART) naïve HIV patients with ($n=138$) and without ($n=58$) tuberculosis co-infection attending the HIV/TB or HIV clinic at Mulago and Butabika National referral Hospitals in Kampala, Uganda. At baseline, the participants had a mean age of 33.8 with standard deviation (SD) of 7.2 years, mean weight of 53.6 (SD=10.1) kg, mean CD4 of 97.2 (SD=77.4), and mean log10 viral load of 4.95 (SD=0.71).

The participants were initiated on ART containing efavirenz 600 mg daily in combination with zidovudine and lamivudine. Blood samples for genotyping were collected at baseline while those for the pharmacokinetic analysis were collected between 11 and 18 h post efavirenz-dosing at baseline and on subsequent visits for 6 months. Neuropsychological evaluation for sleep disorders (insomnia, vivid dreams, and sleep-walking) and hallucinations (visual, auditory, and tactile) was performed at baseline week 2 and week 12. The study was approved by institutional review boards of Mulago and Butabika hospitals and the Uganda National Council for Science and Technology [12].

Participants could experience none, one or more than one neuropsychiatric symptoms. At each evaluation, the patients were classified as NPI (coded as 1) if a participant reported at least one of the symptoms, or NORMAL (coded as 0) if the participant did not report any symptom. The assessment was carried out using an interviewer administered questionnaire. Insomnia was categorized as mild (failure to sleep within 15 min), moderate (failure to sleep in 1 h), and severe (failure to sleep for more than 1 h). Other sleep disorders and hallucinations were assessed as "yes" or "no" as declared by the participants. A summary of the symptoms at the different observation times is shown in Table 1. The duration of NPI after initiation of ART was further categorized as transient (NPI only at week 2), persistent (NPI at both week 2 and 12) and delayed (NPI only at week 12). The proportion of patients in each duration category was calculated. The neuropsychiatric assessment was administered by a trained psychiatric nurse under the supervision of a physician. Details about the procedure and methods of data collection were reported elsewhere [12].

2.3. Pharmacokinetic model development

A previously developed full covariate one compartment model with first order absorption and elimination was used to describe efavirenz pharmacokinetic (PK). Absorption rate constant (KA), apparent clearance (CL/F), relative bioavailability (F1) and apparent

Table 1
A summary of the observed symptoms at the observation times.

Symptoms ($n=196$)	Baseline (Week 0)	Week 2	Week 12
Sleep disorders (n)			
Insomnia	27	55	18
Vivid dreams	11	113	31
Sleep walking	9	11	3
Hallucinations (n)			
Audio	3	47	11
Visual	0	34	3
Tactile	0	4	1
Total Aggregated NPI (n)			
	39	126	41

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