Levodopa in Parkinson's Disease: A Review of Population Pharmacokinetics/Pharmacodynamics Analysis

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ABSTRACT - Background*:* Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Although levodopa remains the single effective agent in the management of Parkinson's disease, the accurate determination of this optimal dosage is complicated by marked between-subject and between-occasion variability in this population. This review presents a synthesis of the population pharmacokinetic and pharmacodynamic models of levodopa described in Parkinson's disease. **METHODS:** A literature search was conducted from the PubMed database, from their inception through April 2016, using the following terms: levodopa, pharmacokinetic(s), pharmacodynamic(s) population, model(ling) and nonlinear mixed effect. Articles were excluded if they were not pertinent. References of all selected articles were also evaluated. **RESULTS***:* A total of 12 articles were finally retained. The following covariates were selected as interindividual variability factors: body weight, age, sex, creatinine clearance and levodopa dose. The clinical response versus effect site concentration relationship was described with different sigmoidal E_{max} models. Different pharmacodynamic effects were described: UPDRS, Tapping, Dyskinesia, CURSΣ and treatment response scale. **DISCUSSION:** This review allows us to realize interpretation of a patient's clinical picture and confirmed the appropriateness of the pharmacokinetic-pharmacodynamic modeling for levodopa. External evaluation of previous published models should be also continued to evaluate these previous studies. New pharmacokinetic and/or pharmacodynamic population modelling studies could be consider to improve future models and decrease variability, to better understand the evolution of patients with Parkinson's disease treated by levodopa.

INTRODUCTION

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease [1]. The disease is characterized by progressive degeneration of the dopaminergic nigrostriatal system and depletion of dopamine, which results in the core motor symptoms of bradykinesia, rigidity, tremor, and postural instability [2]. Parkinson's disease is a progressive neurodegenerative disease that affects approximately 1-2% of the population above 60 years of age [3]. The cardinal clinical manifestations of Parkinson's disease are resting tremor, rigidity, bradykinesia, and gait dysfunction. During the early stages of the disease, about 70% of patients may experience a slight tremor. Bradykinesia is described as a general reduction in spontaneous movement, and can cause difficulty with repetitive movements, such as finger tapping. Rigidity may cause stiffness of the limbs, neck, and trunk. In the 80s, the Movement Disorders Society has developed the Unified Parkinson's Disease Rating Scale (UPDRS) and in 2001, the MDS sponsored a critique of the UPDRS. The summary conclusions recommended the development of a new version of the UPDRS that would retain the strengths of the original scale, but especially incorporate a number of clinically pertinent PD-related problems poorly captured in the original version. Based on this critique, the MDS commissioned a revision of the scale, resulting in a new version: The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [4]. This scale provides an efficient and flexible means of monitoring Parkinson's disease-related disability and impairment, and has been used in

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studies of early, mild, moderate, and advanced disease with motor fluctuations. The MDS-UPDRS rates 65 items in comparison to 55 on the original UPDRS, 48 that had 0 to 4 options and 7 with yes/no responses. The total MDS-UPDRS scale comprises four components: Part I, Mentation; Part II, Activities of daily living; Part III, Motor; Part IV, Complication of therapy.

Facilitation of dopamine biosynthesis by administration of the precursor levodopa is one, and until now the most important, therapeutic principle in drug therapy of Parkinson's disease [5,6,7,8,9,10]. Levodopa is one of the effective agents in the management of Parkinson's disease [8,11,12] and reaches its effect site by crossing the blood-brain barrier. In brain tissues, levodopa is decarboylated to dopamine, which normally stored in presynaptic terminals of striatal neurons [5,13]. Unfortunately, after several years of treatment motor complications such as motor fluctuations and dyskinesias can arise [14, 15]. Risk and time to emergence of these motor complications vary substantially among patients for complex reasons, including both disease- and drug-related factors, particularly treatment with levodopa [16,17] . A previous review of studies of motor complications estimated that the risk of developing motor fluctuations and dyskinesias were both about 40% after 4–6 years of levodopa treatment [18]. However, most previous studies have been based on unrepresentative samples, with attendant selection biases [19,20]. Only two representatives, community-based incidence studies have examined the development of motor complications over time, both of which were small, only reported dyskinesias and one was retrospective [21,22]. An increased understanding of the levodopa plasma concentration-effect relationship could be valuable in the assessment of Parkinson's disease management [23,24,25,26].

This has created a need to examine more carefully the factors which influence the variability in levodopa pharmacokinetics and pharmacodynamics. After oral administration, levodopa is completely absorbed in the proximal small bowel but undergoes marked presystemic decarboxylation to dopamine. The plasma elimination half-life of levodopa is about 2 hours. With coadministration of a peripheral decarboxylase inhibitor, degradation to 3-O-methyl-dopa (3-OMD) by catechol-O-methyltransferase (COMT) is the major route of levodopa metabolism [5,6,7,8,9,10,27].

Many pharmacokinetic, pharmacodynamic or pharmacokinetic/pharmacodynamic studies in Parkinson's disease patients have been performed. In particular, nonlinear mixed-effect modelling, a commonly used population-based modelling approach, have been used to identify covariates that could influence the dose-concentration or dose-effect relationship. Population pharmacokinetic/pharmacodynamic approach allowed realizing bayesian dose estimation and adaptation according to population pharmacokinetic parameters and estimated variability in a specific population. Population pharmacokinetic modeling was first introduced in 1972 by Sheiner et al. and thirty years after their introduction, population pharmacokinetic / pharmacodynamic approaches become a reference method for drug evaluation and dose adaptation [28].

Understanding the relationship between pharmacokinetics and pharmacodynamics of levodopa has been at the center of the most discussion of effective management of Parkinson's disease patients experiencing motor fluctuations. The degree of correlation between variations in plasma levodopa concentrations and motor performance has been described by four types of responses to levodopa: the early disease duration of response, late disease duration of response, negative response and dyskinesias. The early disease duration of response assessed by the response to a single dose of levodopa is characterized by: (i) a plasma compartment and central-effect compartment threshold concentration of levodopa required to obtain a clinical response, (ii) a lag-time between peak plasma levodopa concentration and clinical response, (iii) the magnitude of the clinical response follows a dichotomic response after the threshold concentration is reached and (iv) the duration of the clinical response is linearly related to the plasma concentration, there is improvement in motor function that roughly parallels plasma levodopa concentrations [29]. The late disease duration of response is common to most antiparkinsonian agents and is found in mildly and severely affected parkisonian patients. The late disease duration of response is inversely related to disease severity and decays more rapidly in more severely affected patients. It is estimated that the late disease duration of response contributes about 30 to 50 % of the total levodopa response in response fluctuators [30]. The negative response is the deterioration of motor function, which can last from minutes up to an hour and is most frequently observed as the early disease duration of response of levodopa disappears. Dyskinesias are linked to the early disease duration of response, "off" phenomenon occur when plasma levodopa

concentrations are low and the early disease duration of response disappears. Similar to the early disease duration of response, the duration of dyskinesia is proportional to the plasma levodopa concentration and the severity of dyskinesia is an "all or none" response. While much has been achieved in attempts to decipher the pharmacokinetic-pharmacodynamic relationships, the results from several studies still remain equivocal and a clear-cut delineation of the pharmacokinetic-pharmacodynamic relationship of levodopa continues to be a subject of further investigations.

This review presents a synthesis of the population pharmacokinetic, pharmacodynamic or pharmacokinetic/pharmacodynamic analyses performed for levodopa in Parkinson's disease patients. The objective was to describe the different published pharmacokinetic and pharmacodynamic models to determine if there was a consensus on a structural pharmacokinetic (dose-concentration relationship) or pharmacodynamic (dose-effect relationship) model and which motor responses were investigated.

METHODS

PRISMA

We have followed the principles of the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement to guide assessment of quality of this review. The PRISMA statement helps us to improve the reporting of systematic review with checklist [31].

Inclusion criteria

We included all described pharmacokinetic population models of levodopa. The articles were accepted if they met the following inclusion criteria:

- Studied populations: Idiopathic Parkinson's disease.
- Treatment: levodopa.
- Pharmacokinetic analysis: nonlinear mixed effect model by a population approach

Exclusion criteria

The articles were excluded if they are reviews, methodology articles or if the analysis did not used a population pharmacokinetic modelling and population studies not involving a mixed-effects models analysis.

Search strategy

A literature search was conducted from the PubMed database, from their inception through April 2016, using the following terms: (*levodopa* AND *pharmacokinetic*) OR (*levodopa* AND *pharmacokinetic* AND *population*) OR (*levodopa* AND *pharmacokinetic* AND *model(ling)*) OR (*levodopa* AND *pharmacokinetic* AND *nonlinear mixed effect model*) OR (*levodopa* AND *pharmacodynamic*) OR (*levodopa* AND *pharmacodynamic c* AND *population*) OR (*levodopa* AND *pharmacodynamic* AND *model(ling)*) OR (*levodopa* AND *pharmacodynamic* AND *nonlinear mixed effect model*). Moreover, additional studies were identified from the reference list of selected papers. The search was additionally limited to "English language" and "clinical data".

Data extraction

The results of these investigations were closely evaluated and articles were retained if they met the inclusion criteria. Pertinent articles were assessed and the following data were extracted: year of publication, number of patients, number of samples, software, structural model, value and expression of pharmacokinetic parameters, value and expression of pharmacodynamic parameters, included covariates, between-subject and between-occasion variability, residual error and validation method.

Following Brendel et al. [32] and Tod et al. [33], the evaluation methods were divided into three categories according to increasing order of quality: basic internal methods (goodness-of-fit plots), advanced internal methods (bootstrap, cross-validation, Monte Carlo simulations…) and external model evaluation.

Concerning extracted parameters, main pharmacokinetic and pharmacodynamic parameters with clinical link were detailed. Main pharmacokinetic parameters were clearance and volume of distribution to describe the evolution of concentration versus time. Main pharmacodynamic parameters were E_{max} (the amplitude between baseline and maximal effect), EC_{50} (the concentration producing 50% of E_{max}, and the Hill coefficient (the slope of concentration-effect curve) to describe the effect versus concentration and time.

RESULTS

Trial flow

A total of 18 studies were identified through Pubmed database searching. These 18 articles were

screened and a total of 16 articles were first selected to have their full-text versions assessed for eligibility. Among these 4 were excluded regarding to the inclusion and exclusion criteria. A total of 12 articles were finally retained [34,35,36,37,38,39,40,41,42,43,44,45].

Study characteristics

The 12 studies described a pharmacokinetic (n=3) or pharmacodynamic (n=5) or pharmacokinetic/pharmacodynamic (n=4) population model of levodopa and were published between 1996 and 2016 (Table 1). Studied populations consisted of Parkinson's disease patients treated with levodopa since 0 to 24 years. Studied patients were aged 34 - 83 years with Hoehn and Yahr stage between 1 and 4. Levodopa was administered by oral route, duodenal infusion, intestinal infusion and intravenous infusion according to different dosing regimens: once-daily dose or every 6 hours [34,35,36,37,38,39,40,41,42,43,44,45]. The mean values of the doses administered were ranged from 64 to 1409 mg per day.

Data synthesis: Pharmacokinetic

Among the 7 published models, levodopa population pharmacokinetic was described by one-compartment model (n=3) and by two-compartment model (n=4) [34,36,37,39,40,42,43] (Table 2 and Figure 1). Absorption time was modelled by lag time, transit compartment or simple oral absorption. In all the publications, several covariates were tested; five covariates were retained in these final models. The following covariates were selected as interindividual variability factors for clearance (CL or Q): body weight (CL and Q), age (CL), sex (CL), creatinine clearance (CL) and levodopa dose (CL). The following covariates were selected as interindividual variability factors for volume of distribution (V/V_1 or V_2): body weight (V, V_1 and V_2) and sex (V). Age was also selected as covariate on ka. Table 2 summarizes mean values of pharmacokinetic parameters for one- and two-compartment models described in Parkinson's disease patients. The range estimate of mean value of clearance, intercompartmental clearance, central volume of distribution and peripheral volume of distribution were between 17.0 and 36.6 L/h (n=6), 6.8 and 38.7 L/h, 11.0 and 124.0 L, 23.4 and 72.9 L, respectively.

Between-subject variability was modelled using exponential model. The mean values of between-subject variability of clearance, intercompartmental clearance, central volume of distribution and peripheral volume of distribution were ranged from 26 to 62% (n=5), 48 to 53% (n=2), 24 to 80% (n=5), 25 to 39% (n=2), respectively. The mean residual error using proportional or additive were between 19 and 48% (n=3), 0.92 and 1.12 µg/ml (n=2), respectively. The mean residual error using combined model was between 15 and 29 % and 0.30 and 0.59 µg/ml (n=1, with two populations: fluctuators and non fluctuators) for proportional and additive error, respectively.

All models were evaluated with internal or external method (Table 2). Concerning the basic internal evaluation, three authors used this method. This evaluation most frequently used was calculation of indicators of the performance of prediction (bias and precision). Two authors used advanced internal evaluation, with visual predictive check (500 simulations) and bootstrap (1000 simulations). In case of external evaluation, two authors chose to test their model on a prospective group (between 16 and 311 patients).

Data synthesis: Pharmacodynamic

Different pharmacodynamic parameters were used: UPDRS (n=4), Tapping (n=4), Dyskinesia (n=3), treatment response scale (n=1) and CURSΣ (n=1) [34,35,38,40,41,42,43,44,45] (Table 3). The clinical response versus effect site concentration relationship was described with different sigmoidal Emax models (Table 3 and Figure 1). Concerning UPDRS, the mean values of E_0, E_{max} (score), EC_{50} (µg/ml) and γ (Hill coefficient) were ranged from 0 to 54.1, 0.72 to 63.0, 0.812 to 1.41, and 0.503 to 6.2, respectively. The mean values of E_{max} for tapping were between 35 and 146 Taps/min. Concerning dyskinesia, the mean values of E_{max} (score), EC_{50} (µg/ml) and γ were ranged from 1 to 17.9, 0.601 to 6.28, and 2.1 to 30, respectively. The mean values of interindividual variability of E_0, E_{max}, EC_{50} and γ were ranged from 19 to 53% (n=5), 39 to 90% (n=4), 22 to 101% (n=6), 15 to 130% (n=5), respectively.

DISCUSSION

Levodopa remains the single effective agent in the management of Parkinson's disease. There has been continued interest in describing levodopa pharmacokinetics and pharmacodynamics for nearly 20 years and several pharmacokinetic of pharmacokinetic-pharmacodynamic models have been developed in Parkinson's disease patients. Twelve studies were developed by population approach: three pharmacokinetics studies [36,37,39], five pharmacodynamics studies

[34,40,41,42,43] and four pharmacokinetics/pharmacodynamics studies [34,40,42,43].

Levodopa pharmacokinetics was described by a mono-exponential model as much as a bi-exponential model; infusion administrations (duodenal, gel and intravenous infusions) were modelled by two-compartment model whereas oral administration were modelled by one-compartment model. In more, duodenal and gel infusion absorption were modelled with a lag-time or a transit compartment [34,36].

The results expressed by these different models lead only to comparable estimations of clearance. The mean values of clearance were ranged from 17.0 and 36.6 L/h. Average values ranges of intercompartmental clearance, central and peripheral volume of distribution are much wider. Indeed, mean values of intercompartmental clearance, volume of distribution and peripheral volume of distribution are between 6.8 and 38.7 L/h, 11.0 and 124.0 L and 23.4 and 72.9 L, respectively. In this specific population, the pharmacokinetics of levodopa shows strong variability in spite of average values of parameters consistent with aged healthy volunteer. Indeed, Robertson et al. showed that clearance was about 24.4 L/h and volume of distribution was about 43.4 L in aged healthy volunteers (69-76 years) for 50 mg intravenous levodopa associated to carbidopa (50 mg, 6h after intravenous dose of levodopa) [46]. Four of seven models described in this population contain less than 35 patients which could limit the identification of a significant covariate [34,37,42,43]. Nevertheless, the models described in this population were able to identify some covariates having an effect on interindividual pharmacokinetic variability.

The main covariate used was body weight on clearance (and intercompartmental clearance) and central volume of distribution (and peripheral volume of distribution) [34,37,39,42,44]. Clearance and volume of distribution allometrically scaled on 70 kg normalized body weight (or median body weight) with an exponent of 0.75 and 1, respectively. Possibly, prediction could improve after adding more covariates such as state of disease progression, age, sex and others, but it would require a larger patient population. Indeed, two studies with a larger number of patients could include more covariates [36,39]. Othman et al. showed that age almost reached significance for inclusion as a covariate for levodopa clearance (ΔOFV=-7.65, p=0.0057) but was not included in the final model [36]. Jorga et al. included levodopa dose, creatinine clearance and sex as supplementary covariates [39]. None of these covariates had a major influence; the model was optimized only until the concentration data were reasonably well described. The presence of a sex-related effect on levodopa pharmacokinetics has been evaluated in several others studies using non-compartmental approaches and conflicting evidence has been reported [47,48,49,50]. It has been suggested that the apparent sex-related difference in exposure was partly explained by incorrectly normalizing body weight difference between men and women in some analyses [49,50].

The drug concentrations in plasma or blood are correlated with simultaneously measured clinical effects by a suitable pharmacodynamic model which usually assumes a linear or sigmoidal (E_{max}) concentration-effect relationship. The parameters of a sigmoidal model are E_{max} (the amplitude between baseline and maximal effect), EC_{50} (the concentration producing 50% of E_{max}, which might be interpreted as a target concentration necessary to obtain a clinical considerable effect) and the Hill coefficient (above 5 units indicates a very steep concentration-effect curve and suggests a dichotomic response (all-or-nothing) [51]. Despite the heterogeneity of the methodological approaches used (different score systems for the pharmacodynamic response: TRS, UPDRS, CURSΣ, Dyskinesia, Tapping), these studies on levodopa have demonstrated almost ~~consistent~~ comparable findings. All studies ~~prove~~ found the E_{max} model to be suitable for describing the concentration-effect relationship of levodopa [34,35,38,40,41,42,43,44,45]. The steepness of the concentration-effect curves, characterized by the Hill coefficient, was relatively high (between 3 and 5) for one study and very high (>5) for three studies, indicating an almost immediate onset of the pharmacodynamic response to levodopa when the EC_{50} is reached and the appearance of "off" reactions when concentrations falls below this level [34,35,42,45]. Furthermore, the different estimates of EC_{50} indicate that the effect of levodopa is not dependent on the height of the plasma concentrations once the EC_{50} value has been exceeded. Indeed, Kempster et al. showed that the amplitude of the motor response depends on the pretreatment; who describe an increase in the amplitude of the motor response when patients with Parkinson's disease were grouped according to duration of disease [9]. The duration of disease of patients included in these studies is very wide (0.5 and 25 years) and this data was not included as a covariate except in one study.

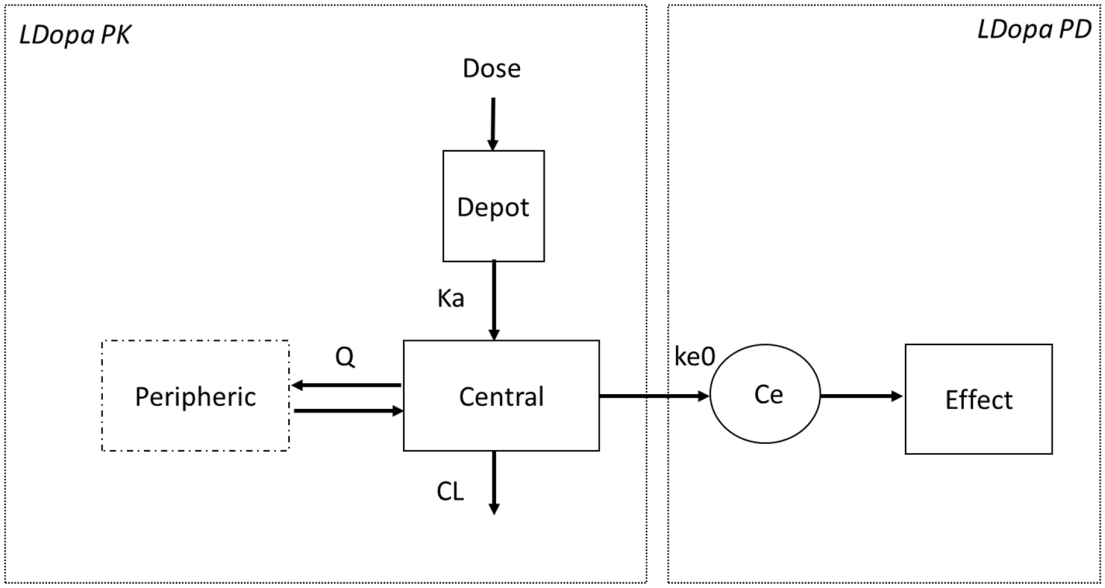

Figure 1. Schematic PK/PD model for levodopa. Ka: absorption rate constant; CL: clearance; Q: intercompartmental clearance; ke0: effect rate constant; Ce: effect compartment concentration

Indeed, Troconiz et al. showed that the relationship between baseline and duration of disease might reflect disease progression [35]. According to their results, the progression of disease was estimated to be an increase of 0.7 points score per year (UPDRS Part III). Indeed, disease progression is characterized by a number of pharmacodynamic modifications. The baseline motor function in the absence of any drug (E_0), which correlates with disease duration, decreases but with no decrease in the maximal therapeutic response (E_{max}), which means that the intrinsic activity remains preserved [40,52]. The levodopa concentration required to obtain 50% of E_{max} (EC_{50}) progressively increases over the years and is at least 2.5 times higher in fluctuating responders compared with stable responders. In addition, it is well known that factors other than levodopa concentration or duration of disease may influence parkinsonian motor symptoms. These factors include stress level, food intake, time of day, physical activity, intake of other pharmaceuticals affecting dopaminergic, or other receptors. None of these factors are included in these studies, and these will therefore seem as unexplained between-subject variability or residual error.

In addition, the role of 3-O-metyldopa (3OMD) in the pharmacokinetic-pharmacodynamic relationship of levodopa has been investigated. This metabolite is a large neutronal amino acid with a long half-life. It crosses the blood-brain barrier but does not bind to the dopamine receptor and has no recognised intrinsic antiparkinsonian activity. Nevertheless, 3OMD can competitively inhibit transport of levodopa [53]. The role of 3OMD in the pharmacokinetic-pharmacodynamic of levodopa has been investigated with concomitant administration of specific catechol-0-methyltransferase (entacapone, tolcapone), and may be helpful in elucidating the relationship between plasma concentrations of levodopa and its effects [35,38,39]. Indeed, Troconiz et al. concluded that entacapone does not alter the concentration-effect curve of levodopa, suggesting that entacapone acts at the level of peripheral pharmacokinetics of levodopa and that plasma levels of 3OMD have a negligible role in the pharmacodynamics of levodopa [35]. Baas et al. showed a gain in clinical improvement with levodopa under tolcapone and could be explained by tolcapone-induced changes of peripheral levodopa pharmacokinetics. They suggested that this interaction study excludes any central effects of tolcapone and any inhibiting effect of 3OMD on levodopa permeation through the blood-brain barrier [38]. And Jorga et al. suggested also clinical benefits when levodopa was coadministered with tolcapone [39]. Others studies have postulated that 3OMD could inhibit the uptake of levodopa across the brain-blood thus suggesting a relationship between the central and peripheral levels of levodopa [54]. The role of 3OMD was still controversial in the pharmacokinetic-pharmacodynamic relationship of levodopa. Nevertheless, the possibility of an antagonistic

effect of 3OMD on levodopa response could be reconsidered.

Evaluation of between-occasion variability was also an important aspect of the care of patients with Parkinson's disease because levodopa is administered as long-term therapy. Ignoring between-occasion variability when it is present can lead to model misspecifications [55]. Between-occasion variability was included in three studies. In the study of Westin et al., the data set was too small to separately distinguish between-subject and between-occasion variability in parameters [34]. Therefore, each occasion was treated as a separate patient, and the resulting parameter variability will approximate the sum of between-subject and between-occasion variability. Chan et al. showed that the most of the overall variability in parameters is due to between-occasion variation [37]. Their results showed that ignoring between-occasion variability inflates both between-subject variability and residual error as demonstrated by Karlsson and Sheiner [56]. In more, their results showed that ignoring between-occasion variability may cause imprecision in parameter estimation and an underestimate of total population parameter variability. Regarding study of Troconiz et al., introducing between-occasion variability in their model did not lead to different covariate models but decreased the objective function value [35]. In more, the important estimated between-occasion variability on k_{e0} (40%) suggests that the events taking place in the biophase are the chief determinants of the unpredictability of the response to levodopa.

Several models were evaluated and confirmed by robust method. Indeed, Othman et al. and Triggs et al. chose to test their model on a prospective group in the same study [36,40]. The model described by Chan et al. was also confirmed by a new publication on twenty *de novo* patients [57]. Chan et al. was also published an external validation of published pharmacokinetic model in 2006 [44, 58]. The aim of this study was to externally validate the model predictions of a DATATOP cohort analysis through application of clinical trial simulation with the study design of the ELLDOPA trial. This model was also used in 2012 by Vu et al. to evaluate the progression of motor and non-motor features of Parkinson's disease [59]. These different evaluation and re-utilization of published models confirmed the appropriateness of the pharmacokinetic-pharmacodynamic model for levodopa.

Sophisticated pharmacokinetic-pharmacodynamic approaches, presented in this study, have been implemented to obtain better interpretations of the relation between blood concentrations and effect [34,35,36,37,38,39,40,41,42]. These models allow to minimize problems due to temporal delay between C_{max} and clinical response and to obtain pharmacokinetic-pharmacodynamic parameters. These different studies allow us to conclude that modifications in stables and fluctuating patients are a reflection of the progression of the disease since the threshold concentrations needed to obtain an appropriate antiparkinsonian effect are increased and the duration of the effect is shortened (EC_{50} and Hill coefficient). These studies allow us to realize interpretation of a patient's clinical picture.

Limitations

Assessing the risk of bias should be part of the conduct and reporting of any systematic review. For systematic reviewers, understanding the risk of bias on the results of studies is often difficult, because the report is only a surrogate of the actual conduct of the study. There are three main ways to assess risk of bias: individual components, checklists, and scales. The new Cochrane risk of bias tool [60.] is one such component approach. According to the Cochrane risk of bias tool, we have highlighted the various biases and limitations of this review (Table 4). This review is only an image, at a given time, in a particular indication and population of the published pk/pd models of levodopa.

CONCLUSION

The importance of individualizing therapy in Parkinson's disease has been well established [61]. The large number of variables which affect final dopamine concentration at receptor sites in the striatum necessitate to move to an individualized dosing approach. The population approach allows the pharmacokinetic and pharmacodynamic characterization of drugs in a target population, the evaluation of the associated within subject and within individual variability, and the identification of covariates affecting such variability. Understanding the variability associated with the pharmacokinetics and pharmacodynamic, and identifying subpopulations with special features can provide clinicians with relevant information regarding dose individualization.

Given the relative low number of studies on population pharmacokinetic and pharmacodynamic modelling of levodopa in Parkinson's disease, news pharmacokinetic and/or pharmacodynamic population modelling studies

could be consider. External evaluation of previous published models should be also continued to evaluate these previous studies. It would be interesting to continue research on pharmacokinetic and pharmacodynamic of levodopa to improve future models and decrease variability, to upgrade the care of patients with Parkinson's disease treated by levodopa.

Knowledge of individual patients' levodopa pharmacokinetics and pharmacodynamics variables, particularly duration of motor effect and matched EC50 values after administration of levodopa oral dose, can help clinicians to objectively assess where Parkinson's disease patients stand in the disease process. This information can also contribute to adapt drug treatment from the early stages and to modify it according disease progression. These knowledges aim to simplify pharmacological treatment schedules as far as possible, to reduce the risks of adverse effects (acute and chronic) and possibly to delay the development of a severe disability.

In a clinical perspective, this review advances relevant information for clinicians and researcher about the pharmacokinetics and pharmacodynamics of levodopa. To optimize levodopa dosage, this review point out the relevant information according to the target population.

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Table 1. Population characteristics of studies included in the review

Auteur	Demographic data			Observations		Disease data		Levodopa treatment			Concomittant administration	Study	Software
	N (M/F)	Age (years)	Weight (kg)	Total	Per patient	Hoehn and Yahr stage	Duration of disease (years)	Formulation	Dose levodopa (mg/day)	Duration of levodopa treatment (years)			
45	86 (54/32)[a]		-	1462	17			oral			bromocriptine, pergolide, ropinirole, amantadine	K/PD	SIPHAR
	23 (15/8) (grade 1)	61 (42-71) (grade 1)				grade 1 (n=23)	2.0 (0.5-5.0) (grade 1)		200 (100-300) (grade 1)	0.5 (0.3-4.5) (grade 1)			
	25 (21/4) (grade 2)	61 (42-72) (grade 2)				grade 2 (n=25)	5.0 (0.5-13.0) (grade 2)		200 (150-500) (grade 2)	2.0 (0.3-11.0) (grade 2)			
	25 (13/12) (grade 3)	62 (35-79) (grade 3)				grade 3 (n=25)	9.0 (1.5-16.0) (grade 3)		400 (200-1200) (grade 3)	6.5 (1.0-16.0) (grade 3)			
	13 (5/8) (grade 4)	66 (38-73) (grade 4)				grade 4 (n=13)	12.0 (6.0-24.0) (grade 4)		600 (500-800) (grade 4)	9.8 (6.0-24.0) (grade 4)			
44	800	-	-	-	19	-	-	oral	300	-	bromocriptine, pergolide	PD	NONMEM 5
43	25 (13/12)[a]	61 (45-75) (De novo)	81 (60-100) (De novo)	275	11	-	-	2 h constant rate IV infusion	160 (64-256)	0 (De novo)	carbidopa	PK/PD	MKMODEL
	De novo 13 (8/5) Chronic 12 (5/7)	60 (37-75) (Chronic)	75 (49-107) (Chronic)							9.7 (4-17) (Chronic)			
34	20 (16/4)	61.2 +/-11.0	66.7 +/- 9.9	*Data of three studies with different blood sampling*		3.8 +/-0.6	16.1 +/- 8.0	duodenal infusion	-	-	-	PK/PD	NONMEM 6
35	19 (11/8)	62.7 (45-75)	68.3 (42-88.5)	-	8-9	grade 2 (n=4) grade 2.5 (n=2) grade 3 (n=12) grade 4 (n=1)	14.1 (6-25)	tablets	100-250	11.2 (6-18)	carbidopa, benserazide, entacapone, dopamine agonists, amantadine, anticholinergics, selegiline	PD	NONMEM 5
36	68 (42/26)[a]	64.4 (8.7)[a]	73.3 (18.1)[a]	-	5-38	-	-	intestinal gel infusion and oral tablets	1164 (LCIG)	-	carbidopa	PK	NONMEM 7.2
	45 (28/17) (LCIG) 23 (14/9)(LC-oral)	64.3 (9.6) LCIG 64.7 (6.9) LC-oral	72.8 (16.7) LCIG 74.5 (21.1) LC-oral						1409 (LC-oral)				
37	20 (12/8)	59.8 +/-10.7 (40-75)	78.7 +/-12.4 (60-100)	-	55	-	-	2 h constant rate IV infusion	427-579	-	carbidopa	PK	NONMEM
38	12 (4/8)	59 (47-72)	-	-	64	grade 2 (n=6) grade 2.5 (n=4) grade 3 (n=2)	8 (3-20)	oral	500 (300-700)	6 (2-16)	benserazide, tolcapone	PD	NONMEM 5
39	412 (262/150)[a]	65 (34-83)[a]	71 (36-153)[a]	-	10-50	On 2 (1-3) (NF) 2 (0-4) (F)	-	oral	-	-	carbidopa, benserazide, tolcapone	PK	NONMEM 4
	97 (NF) 315 (F)	67 (47-83) (NF) 65 (34-82) (F)	72 (44-110) (NF) 71 (36-153) (F)			Off 2.5 (1-3) (NF) 3 (1-5) (F)							
40	46 (31/15)	34-78	-	966	21	grade 1 (n=5) grade 2 (n=14) grade 3 (n=20) grade 4 (n=7)	0.8-24	oral	200-1200	0.3-22	benserazide, carbidopa	PK/PD	NONMEM 4.2
41	27 (21/6)	62.7 (48-81)	-	-	30	grade 2 and 3 (n=23)	-	oral (extended-release and immediate-release formulations)	816.7[b]-2054.4[c]	-	carbidopa, COMT inhibitors, dopamine agonists, MAO-B inhibitors, anticholinergics, amantadine	PD	NONMEM 7.1
43	30 (18/12)	65 (51-78)	63 (40-91)	660	22	grade 3 (n=24) grade 4 (n=6)	12 (6-24)	oral	380 (200-550)	11 (3-23)	*Concomittant mediaction was kept as a minimum during the study day*	PK/PD	NONMEM 7.3

LCIG: levodopa-carbidopa intestinal gel, LC-oral: Levodopa-carbidopa oral, NF: nonfluctuators, F: fluctuators, PK: pharmacokinetic, PD: Pharmacodynamic

[a] *: data on the entire population*

[b] *: immediate-release formulation*

[c] *: extended-release formulation*

Table 2. Pharmacokinetic parameters of studies included in the review

	Modelling properties		Parameters											Between-subject variability (%)					Within-subject variability		Between-occasion variability			
Auteur	Evaluation	Model	Absorption	Formula absorption	Endogenous and exogenous levodopa	Formula CL	CL (L/h)	Formula Q	Q (L/h)	Formula V or V1	V or V1 (L)	Formula V2	V2 (L)	Absorption	CL	Q	V or V_1	V_2	Proportionnal (%)	Additive (µg/ml)	CL	Q	V or V_1	V_2
43	Basic	Two-compartment	-	-	R_{syn}=13.1 µmol/h C_{ess}=3.32 µmol/L (De novo)	-	29.2 (De novo)	-	34.2 (De novo)	-	13.9 (De novo)	-	37.0 (De novo)	-	-	-	-	-	-	-	-	-	-	-
					R_{syn}=22.3 µmol/L/h C_{ess}=1.11 µmol/L (Chronic)		26.3 (Chronic)		33.3 (Chronic)		13.6 (Chronic)		23.4 (Chronic)											
34	Basic	Two-compartment	ALAG=2.9 min	θ_1	-	θ_3x(WT/70)$^{0.75}$	31.2	θ_4x(WT/70)$^{0.75}$	34.8	θ_5x(WT/70)	11	θ_6x(WT/70)	27	NE	27[a]	48[a]	44[a]	25[a]	-	0.92	-	-	-	-
36	External (311 patients)	Two-compartment	Transit compartment K_a= 9.2 h^{-1} (LCIG) K_a=2.4 h^{-1} (LC-oral)	θ1	-	θ_2	24.8	θ_3	6.8	θ_4x(WT/70)$^{0.75}$	61.3	θ_5	72.9	88	32	NE	61	NE	15 (LCIG) 29 (LC-oral)	0.30 (LCIG) 0.59 (LC-oral)	-	-	-	-
37	Advanced	Two-compartment	-	-	R_{syn}=3.1 µmol/h/70kg Css_{pre}=0.075 µmol/L	θ_3x(WT/70)$^{0.75}$	34.7	θ_4x(WT/70)$^{0.75}$	38.7	θ_5x(WT/70)	12.8	θ_6x(WT/70)	30.7	NE	36	53	35	39	19	-	41[b]	58[b]	46[b]	63[b]
39	Basic	One-compartment	(Madopar) t_a=0.48 h^{-1} (NF) t_a=0.77 h^{-1} (F)	θ_3x(Age/median(age))$^{\beta age}$ (NF)	-	θ_4x(CLcr/median(CLcr))$^{\beta Clcr}$x(Levodopa dose/median(Levodopa dose))$^{\beta levodopa\ dose}$ (NF)	(Madopar) 17.0 (NF) 18.1 (F)	-	-	θ_5x(1+θ_{Sex}xI_{sex}) (NF)	124.0 (NF)	-	-	165 (NF)	33 (NF)	-	80 (NF)	-	48 (NF)	-	16 (NF)	-	-	-
			(Sinemet) t_a=1.04 h^{-1} (NF) t_a=0.55 h^{-1} (F)	θ_2 (F)	-	θ_4x(1+θ_{Sex}xI_{sex})x(CLcr/median(CLcr))$^{\beta Clcr}$x(Levodopa dose/median(Levodopa dose))$^{\beta levodopa\ dose}$ (F)	(Sinemet) 24.9 (NF) 28.5 (F)			θ_6x(WT/median(WT))$^{\beta WT}$ (F)	99.2 (F)			84 (F)	26 (F)		42 (F)		38 (F)		29 (NF)			
40	External (16 patients)	One-compartment	k_a=0.0564 min^{-1}	θ_1	-	θ_2	k_{el}=0.0207 min^{-1}	-	-	θ_4	35.4	-	-	103	<0.05[c]	-	24	-	31	-	-	-	-	-
42	Advanced	One-compartment	k_a=1.86 h^{-1}	θ_1	-	θ_2x(WT/70)$^{0.75}$	36.6	-	-	θ_3x(WT/70)	42.9	-	-	110	62	-	NE	-	-	1.12	-	-	-	-

LCIG: levodopa-carbidopa intestinal gel, LC-oral: Levodopa-carbidopa oral, NF: nonfluctuators, F: fluctuators
R_{syn}: Endogenous levodopa synthesis, Css_{pre}: Concentrations arising from exogenous levodopa prior to each trial
[a]: sum of interindividual and interoccasion variability
[b]: between trial variability
[c]: between subject variability on k_{el}
NE: not estimated
Isex: indicator variable sex, 0=male, 1=female

Table 3. Pharmacodynamic parameters of studies included in the review

			Parameters											Between-subject variability (%)					Within-subject variability	Between-occasion variability (%)			
Auteur	Pharmacodynamic parameters	Formula Effect (E)	Endogenous levodopa synthesis	k_{e0} (h^{-1})	$T_{1/2\ effect\ compartment}$ (h)	Formula E_0	E_0 (or BASE)	Formula EC_{50}	EC_{50} (µg/ml)	Formula E_{max}	E_{max}	Formula γ	γ	k_{e0}	E_0	E_{max}	EC_{50}	γ		k_{e0}	EC_{50}	γ	
45	Tapping	E_0+(E_{max}xC^γ)/(C_{50}^γ+C^γ)	-	-	2.22 (grade 1)	-	144	-	0.2	-	45	-	2	-	-	-	-	-	-	-	-	-	-
					1.3 (grade 2)		141		0.29		35		5										
					0.47 (grade 3)		114		0.6		41		7										
					0.33 (grade 4)		117		0.94		55		18										
	Dyskinesia				- (grade 1)		-		-		-		-										
					0.37 (grade 2)		0		0.7		1		14										
					0.32 (grade 3)		0		0.65		3		27										
					0.28 (grade 4)		0		0.98		3		30										
44	UPDRS	(E_{max}xC^γ)/(C_{50}^γ+C^γ)	-	-	-	-	0 (E_{max0})	-	*9.63 mg/d*	E_{max0}+BEML*(1-$e^{-\ln(2)/TEML}$) BEML=-23.3 TEML=0.621	-	-	0.503	-	-	-	44	90	5.59	-	-	-
43	Tapping	(E_{max}xC^γ)/(C_{50}^γ+C^γ)	Rsyn=13.1 µmol/h Cess=3.32 µmol/L (De novo)	-	3.99[a] (De novo)	-	91 (day 1) 86 (day 4) (De novo)	-	1.06 (De novo)	-	137 (De novo)	-	1.30 (De novo)	-	-	-	-	-	-	-	-	-	-
			Rsyn=22.3 µmol/L/h Cess=1.11 µmol/L (Chronic)	-	0.63[a] (Chronic)		95 (day 1) 64 (day 4) (Chronic)		0.907 (Chronic)		146 (chronic)		2.24 (Chronic)										
34	Treatment response scale (TRS)	E_0+((E_{max}xCe^γ)/(Ce^γ+EC_{50}^γ))	0.01 mg/min	-	0.35[b]	θ_6	-1.58	θ_7	1.55	θ_8	2.39	θ_9	11.6	61[a]	44	90	64	15	0.92	-	-	-	
35	UPDRS	E_0x(1-E_{max}x(Ce^γ/(Ce^γ+C_{50}^γ))	-	2.01	0.34	P_{on}x(1+P_{sb}x(DUR-13)) P_{on}=55.2 P_{sb}=0.012	54.1	θ_1	0.951 (carbidopa) 1.238 (benserazide)	0.49*E_0	26.5	θ_2	6.2	51	14	NE	22	130	NE	41	14	-	
38	CURSZ	(E_{max}xC^γ)/(C_{50}^γ+C^γ)	-	1.46	0.47	θ_1	38.4	θ_2	1.35	θ_3	28.2	θ_4	1.62	NE	21	39	NE	NE	NE	-	-	-	
40	Tapping	NA	θ_3*HY	θ_3(min^{-1})=0.004	-	-	NE	θ_4*HY	θ_4(µg/ml)=0.354	θ_5	90 (fixed)	θ_7+θ_8+θ_9*DUR	θ_7=-0.798 θ_8= 0.059 θ_9=0.461 if HY>2 θ_9=0 if HY<2	92	-	-	57	36	58.2	-	-	-	
41	UPDRS (Part III)	$E_{0\ UPDRS}$x(1+($E_{max\ UPDRS}$x$Ce^{\gamma UPDRS}$)/($EC_{50\ UPDRS}^{\gamma UPDRS}$+$Ce^{\gamma UPDRS}$))	-	1.8	0.39	θ_1	31.8	θ2	0.812	θ3	63	θ_4	2.5	90	19	55	101	86	NE	-	-	-	
	Tapping	$E_{0\ Tapping}$+($E_{max\ Tapping}$x$Ce^{\gamma Tapping}$)/($EC_{50\ Tapping}^{\gamma Tapping}$+$Ce^{\gamma Tapping}$)		1.17	0.59		NE		1.59		93.7		1.53	65	-	83	NE	113	NE	-	-	-	
	Dyskinesia	$\Sigma\beta_k$+($E_{max\ Dysk}$x$Ce^{\gamma Dysk}$)/($Ce^{\gamma Dysk}$+$EC_{50\ Dysk}^{\gamma Dysk}$)		1.55	0.45		NE		0.601		7.3		2.1	NE	-	72	NE	NE	NE	-	-	-	
42	UPDRS (Part III)	$E_{0\ UPDRS}$x(1-$E_{max\ UPDRS}$xCe^γ/$EC_{50\ UPDRS}^\gamma$+Ce^γ)	-	1.37	0.51	θ_4	31.4	θ_5	1.41	θ_6	0.72	θ_7	4.26	84	53	56	62	NE	3.15	-	-	-	
	Goets Dyskinesia rating Scale	$E_{max\ Dysk}$xCe/($EC_{50\ Dysk}$+Ce)		NE	-		NE		6.28		17.9			72	-	78	78		2.66	-	-		

CURS 2: Columbia University Rating Scale (measure for all main motor symptoms in Parkinson's disease: gait, dexterity left/right, tremor, rigidity), HY: Hoehn and Yahr status, DUR: duration of disease
[a]: equilibration half-life of the fast compartment (Teqf)
[b]: Effect time constant ($T_{1/2}$)
k(1,2,3,4) Dyskinesia was modeled as an ordered categorical response using a methode described by Mandema and Stanski [ref]
θ_1=1 (fixed), θ_2=-3.91, θ_3=-2.48, θ_4=-3.14, IIVθ_3=98%
NE: Not estimated
NA: Not available
BEML: Levodopa E_{max} change (units)
TEML: levodopa E_{max} half-life (years)

Table 4. Biases of this review according to the Cochrane risk of bias tool

Type of bias	Bias
Selection	Only non linear mixed effects model and parametric approach
Performance	Different populations (Hoehn and Yar stages, concomittant administration…)
Detection	Choice of inclusion and exclusion criteria
Attrition	Missing data in published articles
Reporting	Published articles inPubMed database