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Pharmacokinetics of opicapone, a third-generation COMT inhibitor, after single and multiple oral administration: A comparative study in the rat

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ABSTRACT

Opicapone is a novel potent, reversible and purely peripheral catechol-*O*-methyltransferase inhibitor that has been developed to be used as an adjunct to levodopa/aromatic L-amino acid decarboxylase inhibitor therapy for Parkinson's disease. Thus, this study aimed to compare the plasma pharmacokinetics of opicapone and its active metabolite (BIA 9-1079) after the administration of single and multiple oral doses to rats. Wistar rats ($n = 8$ per group) were orally treated with single (30, 60 or 90 mg/kg) or multiple (30 mg/kg once-daily for seven consecutive days) oral doses of opicapone. Blood samples were collected up to 24 h post-dosing through a cannula introduced in the tail vein of rats. After quantifying opicapone and BIA 9-1079 in plasma, a non-compartmental pharmacokinetic analysis was performed. Opicapone was quickly absorbed (time to reach the maximum plasma concentration ≤ 2 h) in both dosage regimens and the extent of systemic exposure to opicapone increased approximately in a dose-proportional manner after single-dosing within the studied dose range (30–90 mg/kg). Opicapone and BIA 9-1079 showed a relatively short plasma elimination half-life (1.58–4.50 h) and a small systemic accumulation after multiple-dosing. Hence, no pharmacokinetic concerns are expected when opicapone is administered with a once-daily dosing regimen.

1. Introduction

Parkinson's disease (PD) is a chronic and progressive degenerative brain condition, recognized as the second most common neurodegenerative disorder worldwide, only surpassed by Alzheimer's disease (Logroscino and Tortelli, 2015). PD is more predominant in the elderly with a prevalence of about 1–2% (Logroscino and Tortelli, 2015; Samii et al., 2004). As the elderly population is increasing, if no cure arises in a near future, the number of individuals with PD is expected to rise very sharply (Dorsey et al., 2007). In fact, several new drugs have emerged over the last decades for the PD treatment (*e.g.*, rasagiline, ropinirole, pramipexole). However, the dopamine replacement therapy with levodopa is still considered the most effective pharmacological treatment for the symptomatic management of the disease (Connolly and Lang, 2014). Nevertheless, as levodopa is extensively metabolized in peripheral tissues, mainly by the aromatic L-amino acid decarboxylase (AADC) and by catechol-*O*-methyltransferase (COMT), the inhibition of this peripheral metabolism is essential to increase the access of levodopa to the brain. Thus, in order to optimize the therapeutic effect of oral levodopa therapy, levodopa is prescribed in combination with an AADC inhibitor and, for patients suffering from motor fluctuations, a COMT inhibitor is also recommended to be associated with the previous combination (Connolly and Lang, 2014; Tarazi et al., 2014).

Up to June of 2016, when opicapone was approved to be use in the European Union by the European Medicines Agency, there were only two COMT inhibitors clinically used (entacapone and tolcapone).

Abbreviations: AADC, aromatic L-amino acid decarboxylase; AUC, area under the drug concentration-time curve; AUC_{extrap}, area under the drug concentration-time curve extrapolated from the time of the last measurable concentration to infinity; AUC_{τ}, area under the drug concentration-time curve within a dosing interval; AUC_{0-inf}, area under the drug concentration-time curve from time zero to infinity; AUC_{0-t}, area under the drug concentration-time curve from time zero to the time of the last measurable concentration; $AUC_{0-24\ h}$, area under the drug concentration-time curve from time zero to 24 h; C_{last}, last measurable concentration; C_{max}, maximum plasma concentration; COMT, catechol-*O*-methyltransferase; HPMC, hydroxypropyl methylcellulose; k_{el}, apparent elimination rate constant; LLOQ, lower limit of quantification; MRT, mean residence time; PD, Parkinson's disease; R_{ac}, observed accumulation ratio; R_0, theoretical accumulation ratio; $t_{1/2el}$, plasma elimination half-life; t_{last}, time of the last measurable concentration; t_{max}, time to reach the maximum plasma concentration; τ, dosing interval.

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However, both exhibit drawbacks related to their pharmacokinetics, pharmacodynamics, clinical efficacy and/or safety which hamper their success (Kaakkola, 2010). After the introduction of tolcapone into the market, severe hepatotoxicity adverse reactions were notified and, consequently, its prescription has been restricted to patients whose therapy with entacapone has failed. In addition, strict monitoring of the liver function is required during the intake of tolcapone. With regard to entacapone, although it is not associated with liver toxicity, its low oral bioavailability (~35%), short duration of action, and low potency (maximum erythrocyte COMT inhibition is around 60% and the enzyme recovers full activity within 8 h post-dosing) at the recommended therapeutic dose of 200 mg limit its clinical efficacy (Kaakkola, 2010). In this context, the reversible and purely peripheral third-generation COMT inhibitor, opicapone arose as an attempt to fulfil the need of a safer, more potent and long-acting COMT inhibitor (Kaakkola, 2010; Kiss et al., 2010).

Non-clinical studies performed in rats demonstrated that opicapone is a longer-acting and more potent peripheral COMT inhibitor than tolcapone and, thereby, also than entacapone (Kiss et al., 2010). Indeed, after the administration of a single oral dose of opicapone (3 mg/kg) to rats, around 50% of the peripheral (liver and kidney) COMT enzyme activity was still inhibited at 24 h post-dose, in opposition to tolcapone, which activity against liver COMT remained only up to 9 h post-dose (Bonifácio et al., 2015b; Kiss et al., 2010). The interaction of opicapone with levodopa has also been evaluated and compared to tolcapone in rats. Two hours after the COMT inhibitor had been administered, levodopa and benserazide, an AADC inhibitor, were administered together and the bioavailability of levodopa increased similarly in the presence of opicapone and tolcapone. However, when the combination levodopa/benserazide was given 24 h after the COMT inhibitor, only opicapone improved the bioavailability of levodopa (Bonifácio et al., 2015b). These findings are favourable to support a once-daily administration regimen of opicapone. Thus, in phase III clinical trials, opicapone was administered once-daily to PD patients with motor fluctuations as an adjunct to levodopa/AADC inhibitor therapy, revealing to be not only safe and well tolerated in short- and long-term use (BIPARK I and II studies) (Ferreira et al., 2015; Lees et al., 2016) but also effective in reducing the OFF-time (BIPARK I study) (Ferreira et al., 2016b) and increasing the ON-time without troublesome dyskinesia (BIPARK I and II studies) (Ferreira et al., 2016a).

As tolcapone was associated with hepatotoxicity in humans, the potential hepatic toxicity induced by opicapone was assessed *in vitro* using primary human hepatocytes and HepaRG cells and revealed a wider safety margin for opicapone than for tolcapone or entacapone (Bonifácio et al., 2015a, 2015b).

In non-clinical studies various metabolites of opicapone were identified, among which BIA 9-1079 stood out as an inhibitor of the COMT enzyme (Almeida et al., 2013); nevertheless, the metabolic profile of opicapone is not extensively documented in rats or other non-human species. Hence, in order to deepen the non-clinical pharmacological knowledge about opicapone and complement the data generated during its clinical development program, the present work was planned to evaluate the systemic pharmacokinetics of opicapone and its active metabolite after oral administration of the parent drug to rats. Thus, firstly, the plasma pharmacokinetics of opicapone and BIA 9-1079 was evaluated following three single oral rising doses and, then, a specific dose was selected to compare the pharmacokinetics of opicapone and BIA 9-1079 after single- and multiple-dose regimens.

2. Materials and methods

2.1. Drugs and reagents

Opicapone (BIA 9-1067) and BIA 9-1079 were kindly supplied by BIAL – Portela & Cª., S.A. (S. Mamede do Coronado, Portugal). Hydroxypropyl methylcellulose (HPMC) for preparation of opicapone oral suspensions was obtained from Santa Cruz Biotechnology (Dallas, Texas, USA). Pentobarbital sodium salt, tamoxifen citrate salt, sodium dihydrogen phosphate dehydrate and hydrochloric acid (37%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Acetonitrile (HPLC gradient grade) and ethyl acetate were acquired from Fisher Scientific (Leicestershire, UK), and the ultra-pure water (HPLC, 18.2 MΩ·cm) was obtained by means of a Milli-Q water apparatus from Millipore (Milford, MA, USA). The *ortho*-phosphoric acid (85%) was purchased from Panreac (Barcelona, Spain). Other used compounds were sodium chloride 0.9% solution for injection and heparin sodium 5000 I.U./mL for injection (B. Braun Medical, Portugal).

2.2. Animals

Healthy adult male Wistar rats (RccHan:WIST), weighting between 300 and 370 g, were supplied by Harlan Laboratories (Barcelona, Spain) and housed under controlled environmental conditions (12 h light/dark cycle; temperature 22 ± 1 °C; relative humidity 50 ± 5%) with free access to a standard maintenance diet (4RF21, Mucedola, Italy) and tap water *ad libitum*. Animals were acclimated for at least one week before use.

Opicapone was daily suspended in a HPMC (0.2%, w/v) solution and it was orally given by gavage using a stainless steel curved feeding needle (4 mL/kg of body weight). In single-dose studies and on the last dosing day of the multiple-dose study, rats were fasted for 12–15 h before the oral administration, and the food was only provided at 4 h post-dose in order to avoid its effect on the oral bioavailability of opicapone. On the remaining days of the multiple-dose study, rats were maintained fasted for at least 12 h before administration and until 2 h post-dosing. Rats had free access to water throughout the experimental period in all the studies.

All the animal procedures were conducted in conformity with the international regulations of the European Directive (2010/63/EU) regarding the protection of laboratory animals used for scientific purposes, the Portuguese law on animal welfare (Decreto-Lei 113/2013) and the employed experimental procedures were reviewed and approved by the Portuguese National Authority for Animal Health, Phytosanitation and Food Safety (DGAV – Direção-Geral de Alimentação e Veterinária).

2.3. Experimental design

The present work comprised two pharmacokinetic studies. The first one consisted in evaluating the plasma pharmacokinetics and dose-proportionality of opicapone after single oral rising doses, and the second one was performed to investigate plasma pharmacokinetics and accumulation of opicapone and BIA 9-1079 after multiple-dose administration of opicapone for seven consecutive days.

2.3.1. Single-dose pharmacokinetic study

In order to study the plasma pharmacokinetics and dose-proportionality of opicapone, twenty-four rats were randomly divided into three groups ($n = 8$ per group). Each group was treated with a single oral dose of opicapone (30, 60 or 90 mg/kg) and blood samples (~0.3 mL) were collected into heparinized tubes at 0.5, 1, 2, 3, 4, 5, 6, 8, 12 and 24 h post-administration.

At the night of the day before opicapone administration, rats were anaesthetized with sodium pentobarbital (60 mg/kg, i.p.), and their lateral tail vein was cannulated by inserting the Introcan® Certo IV indwelling cannula (22G; 0.9 × 2.5 mm; from B. Braun, Melsungen, Germany). This procedure allowed to obtain a complete plasma concentration-time profile from each rat. After full overnight recovery from anaesthesia, rats were dosed and blood was collected through the cannula in conscious rats appropriately restrained only at the moment of the oral administration and blood sampling. The collected blood volume was replaced by the injection of sterile heparinized saline (5 I.U./mL). The blood samples were processed for drug analysis.