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Effects of *Paullinia cupana* extract on lamotrigine pharmacokinetics in rats: A herb-drug interaction on the gastrointestinal tract with potential clinical impact

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ABSTRACT

Paullinia cupana-containing preparations are being consumed worldwide for weight reduction. As obesity and epilepsy are common comorbidities and lamotrigine (LTG) is a broad-spectrum antiepileptic drug, it is likely to find epilepsy patients taking *P. cupana* and LTG simultaneously. Thus, this work aimed to investigate the potential interaction between *P. cupana* extract and LTG in rats. In a study, rats were orally co-administered with a single-dose of *P. cupana* extract (821 mg/kg) and LTG (10 mg/kg). In another study, rats were orally pre-treated for 14 days with *P. cupana* extract (821 mg/kg/day) receiving LTG (10 mg/kg, p.o.) on the 15th day. Rats of the respective control groups received the corresponding volume of the extract vehicle. LTG concentrations were determined at several post-dose time-points and submitted to a non-compartmental pharmacokinetic analysis. The co-administration of *P. cupana* and LTG induced a significant reduction of LTG C_{max} and $AUC_{0\text{-}24}$ and prolonged the mean residence time. However, no significant effects were observed on LTG pharmacokinetics following a 14-day pre-treatment period with the extract. In this study changes in the body weight of rats and in some biochemical parameters were also evaluated. Overall, the results revealed a pharmacokinetic-based herb-drug interaction between *P. cupana* extract and LTG, mainly after their co-administration.

1. Introduction

Paullinia cupana, also known as Guarana, is a species that belongs to the *Sapindaceae* family and it is being consumed worldwide in herbal supplements and stimulating drinks (Portella et al., 2013). This native Amazonian plant has been described as having stimulant effects and other medicinal properties (Schimpl et al., 2013), mainly due to the presence of caffeine (2–8%) in the seeds of its fruits. Other methylxanthines, like theophylline and theobromine, are also found in small amounts (< 0.3%) in the seeds, bark, flowers and leaves of *P. cupana* (Ashihara et al., 2008; Schimpl et al., 2013). Among several species of plants that produce caffeine, *P. cupana* has the higher natural content of this compound when compared to coffee (*Coffea arabica*), tea (*Camellia sinensis*) and yerba mate (*Ilex paraguariensis*) (Ashihara and Crozier, 2001; Ashihara et al., 2008). In fact, depending on how the extracts are prepared, *P. cupana* extracts may contain caffeine in an amount four times higher than that found in coffee beans (Moustakas et al., 2015). Other constituents that can be found in *P. cupana* seeds are polysaccharides, polyphenols (e.g. catechins, epicatechins and tannins), lipids, saponins, proteins, choline and pigments (Schimpl et al., 2013).

P. cupana has a well-established medicinal use for symptoms of fatigue and feeling of weakness (EMA, 2013). However, several other pharmacological effects have been related to *P. cupana* consumption, including antiplatelet aggregation, cardioprotective and chemopreventive effects, and also antioxidant, antidepressant, antimicrobial and anti-obesity properties (Hamerski et al., 2013). Some studies have demonstrated that *P. cupana*-containing products improve lipid metabolism, promote weight loss and increase the basal energy expenditure,

Abbreviations: AED, antiepileptic drug; AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, AUC from time zero to 24 h; $AUC_{0\text{-}t}$, AUC from time zero to the last measurable concentration; $AUC_{0\text{-}\infty}$, AUC from time zero to infinite; C_{max}, peak concentration; HPLC-DAD, high-performance liquid chromatography–diode array detection; IS, internal standard; k_{el}, apparent elimination rate constant; LTG, lamotrigine; MEPS, microextraction by packed sorbent; MRT, mean residence time; p.o., per os; $t_{1/2el}$, apparent terminal elimination half-life; t_{max}, time to reach peak concentration

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acting as thermogenics or metabolic stimulants (Glade, 2010; Hamerski et al., 2013; Portella et al., 2013). Indeed, caffeine increases the excitability of adenosine-sensitive sympathetic nervous system, stimulating fat lipolysis (Glade, 2010).

Overweight and obesity are widely recognized as modifiers of therapeutic response and prognosis of several chronic health conditions. More specifically, obesity has been commonly reported as a comorbid condition of epilepsy, with a high prevalence in children and adults (Arya et al., 2016; Janousek et al., 2013). Recent studies have focused on the association between overweight or obesity and epilepsy. For instance, Ladino et al. (2014) found that 72% of adult patients with epilepsy present overweight, obesity or even morbid obesity, corresponding respectively to 34%, 25% and 13%. Another study referred to that 55.2% of patients with epilepsy were overweight or obese (Janousek et al., 2013). There is also evidence that obesity is more common in patients with refractory epilepsy and in those treated in polytherapy regimens (Baxendale et al., 2015; Chukwu et al., 2014; Janousek et al., 2013). Despite the limited data supporting the role of obesity in seizure severity, obesity may play a central role in the worsening of this neurological disorder (Hafizi et al., 2017).

Taking into account that the use of herbal dietary supplements has increased worldwide at an unprecedented rate, and given the growing prevalence of obesity among patients with epilepsy, it is expected an increasing consumption of herbal weight loss medicines by this patient subpopulation over the coming years. Moreover, bearing in mind that some constituents of plant extracts have been identified as substrates, inducers and/or inhibitors of transporters and/or enzymes responsible for antiepileptic drugs (AEDs) biodisposition (Oga et al., 2015; Roe et al., 2016; Tarirai et al., 2010; Wu et al., 2015), it is important not to neglect the potential risks associated with the combined use of herbal medicinal products and AEDs, which may compromise the control of seizures and even increase the risk of adverse drug reactions.

As lamotrigine (LTG) is an AED extensively used in the clinical practice, particularly due to its broad spectrum of efficacy in several types of epileptic disorders (Patsalos, 2013), and considering its narrow therapeutic range (3–15 μg/mL) (Patsalos et al., 2017) and its pharmacokinetics variability and propensity to interact with other drugs (Patsalos, 2013), it is fully justified to investigate the effects of *P. cupana* extract on the pharmacokinetics of LTG. In fact, up to date, to the best of our knowledge, no study was previously conducted to evaluate the potential of interaction between *P. cupana* and LTG. Therefore, this work was planned to investigate whether a commercial standardized *P. cupana* extract may influence the absorption and biodisposition of LTG in rats after their oral co-administration and following a 14-day *P. cupana* pre-treatment period. In addition, the impact of the repeated treatment with *P. cupana* extract on the body weight of rats and in some relevant biochemical parameters was also evaluated.

2. Materials and methods

2.1. Herbal extract, drugs and materials

P. cupana extract from seeds, containing 12% of caffeine, was purchased from Bio Serae Laboratories (Bram, France) and the corresponding certificate of analysis was received and preserved. LTG dispersible tablets (Lamictal® 25 mg, GSK), chloramphenicol (Sigma–Aldrich, St Louis, USA), used as internal standard (IS), pentobarbital (Eutasil®, 200 mg/ml, Ceva Saúde Animal), sodium chloride 0.9% solution (Labesfal, Portugal), heparin sodium 5000 I.U./mL (B. Braun Medical, Portugal), polyurethane cannula (Introcan® Certo IV indwelling cannula 22G; 0.9 × 2.5 mm; B. Braun Melsungen AG, Germany), disposable cholesterol and triglycerides test strips (Accutrend®, Roche, Germany) and disposable blood glucose test strips (Freestyle Lite, Abbott®) were commercially acquired.

2.2. Animals

Thirty-four healthy adult male Wistar rats (247 ± 14 g) were obtained from local certified animal facilities (Faculty of Health Sciences of the University of Beira Interior, Covilhã, Portugal) and housed at 12 h light/dark cycle under controlled environmental conditions (temperature 20 ± 2 °C; relative humidity 55 ± 5%). The animals were allowed free access to a standard rodent diet and water *ad libitum*.

The experimental procedures were approved by the Portuguese National Authority for Animal Health, Phytosanitation and Food Safety (DGAV – Direção Geral de Alimentação e Veterinária) and all the animal experiments were conducted in accordance with the European Directive (2010/63/EU) for animal experiments.

2.3. Preparation of herbal extract and lamotrigine solutions

P. cupana extract solution was daily prepared by dissolving the powdered extract in distilled water. The dose of *P. cupana* administrated to each animal was 821 mg/kg (p.o.), using an administration volume of 10 mL/kg of rat body weight. The selected dose was defined taking into account the human dose recommendation from the extract supplier, which was converted to rat species following a Food and Drug Administration (FDA) Guidance for Industry, which refers to the conversion of animal doses to human equivalent doses based on body surface area (FDA, 2005). Furthermore, a 10-fold potentiating interaction factor was employed to avoid false negative results.

LTG dispersible tablets were dissolved in a proper volume of distilled water to obtain the LTG solution for rat administration. A LTG dose of 10 mg/kg (p.o.) was administrated taking into consideration an administration volume of 4 mL/kg of rat body weight. LTG dose was selected according to the previous in-house group experience in rat studies, and taking also into account that with this dose, saturation phenomena in the processes of drug absorption and/or elimination are not probable to occur (Avula and Veesam, 2014; Ventura et al., 2016; Yamashita et al., 1997).

2.4. Systemic pharmacokinetic studies

Twenty-four rats were randomly distributed in four groups, each one containing six animals ($n = 6$). These studies were designed to investigate the effects of *P. cupana* extract on the bioavailability and plasmatic kinetics of LTG in two independent experimental assays. In the first pharmacokinetic study, rats of the experimental group were concomitantly treated with a single-oral dose of *P. cupana* extract (821 mg/kg, p.o.) and LTG (10 mg/kg, p.o.). In the second study, rats of the experimental group were orally pre-treated during 14 days with *P. cupana extract* (821 mg/kg/day, p.o.) followed by a single dose of LTG (10 mg/kg, p.o.) administrated on the 15th day. A 14-day period of time was considered for the repeated administration of the *P. cupana* extract based on available scientific literature (ICH, 2009; Ma and Ma, 2016), in which it is described that repeated administration studies should be conducted during at least 14 days. Rats of the control groups received the corresponding volume of the vehicle of the herbal extract (i.e. water) and were similarly treated with LTG.

In each study, on the night before LTG administration, each animal was anaesthetized for insertion of an Introcan® Certo IV indwelling cannula (22G; 0.9 × 2.5 mm) in a lateral tail vein for the subsequent serial blood sampling. Anesthesia was induced with pentobarbital (60 mg/kg) administered intraperitoneally. The rats fully recovered from anesthesia and were fasted before LTG administration, but they were maintained with free access to water. To avoid the food effect on LTG absorption and biodisposition, the fasting period was maintained until 4 h after drug administration.

LTG and *P. cupana extract* (or vehicle, in the control groups) were orally administrated by gavage during the morning in each study. After LTG administration, blood sampling was performed at 0.5, 1, 2, 4, 6, 8,