Pharmacological Reports 69 (2017) 555–559

Contents lists available at ScienceDirect

Pharmacological Reports

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

The influence of a single and chronic administration of venlafaxine on tramadol pharmacokinetics in a rabbit model

Danuta Szkutnik-Fiedler[a,*], Tomasz Grabowski[b], Monika Balcerkiewicz[a], Michał Michalak[c], Irina Pilipczuk[a], Łukasz Wyrowski[a], Hanna Urjasz[a], Edmund Grześkowiak[a]

[a] Department of Clinical Pharmacy and Biopharmacy, Poznan University of Medical Sciences, Poznań, Poland
[b] Polpharma Biologics, Gdańsk, Poland
[c] Department of Computer Sciences and Statistics, Poznan University of Medical Sciences, Poznań, Poland

ARTICLE INFO

Article history:
Received 25 November 2016
Received in revised form 24 January 2017
Accepted 26 January 2017
Available online 3 February 2017

Keywords:
Tramadol
Venlafaxine
Pharmacokinetic interactions
Rabbits
Serotonin syndrome

ABSTRACT

Background: The combined use of tramadol with selective serotonin and norepinephrine reuptake inhibitors *e.g.* venlafaxine may be associated with serotonin syndrome. No previous studies exist examining the influence of a weak CYP2D6 inhibitor venlafaxine on the pharmacokinetics of tramadol. Therefore, the aim of this study was to determine the effect of a single and chronic administration of venlafaxine on the pharmacokinetics of tramadol using a rabbit model.
Methods: Adult New Zealand white rabbits of both sexes (n = 21) were used. Animals received 100 mg of tramadol *per os* (one slow release tablet) and 75 mg of venlafaxine (one prolonged release capsule), and were divided into four groups: control group – a single dose of tramadol alone, 1 day group – a single dose of tramadol and venlafaxine, 7 and 14 days groups – seven and fourteen days administration of venlafaxine once daily plus a single dose of tramadol on the last day of the study.
Results: Venlafaxine administration over a period of 7 and 14 days resulted in faster elimination of tramadol compared to the control group: significantly higher values of k_{el}, and lower values of $t_{1/2kel}$ and MRT for the 7 and 14 days group were observed. Although no differences in bioavailability of tramadol were obtained.
Conclusion: Using a rabbit model, there is no evidence that the combined administration of tramadol and venlafaxine may increase the plasma exposure of tramadol and therefore increase the risk of serotonin syndrome.

Introduction

The coexistence of pain and depression always requires careful selection of drugs because polypharmacotherapy can lead to dangerous interactions that pose a threat to the health and even the lives of patients. It is estimated that more than half of the patients with depression suffer from pain. Common neurobiological mechanisms of pain and depression can cause that both of these diseases get worse [1]. On the one hand, chronic pain often masks the symptoms of depression, and, on the other hand, it can cause persistent depressed mood and induce depression, which in turn intensifies pain symptoms. Therefore, we are dealing here with a 'closed circle' phenomenon, in which pain can be both a cause and a symptom of depression [1,2]. The simultaneous occurrence of pain and depression requires adequate treatment, both to alleviate aches and pain, and depressive disorders. Therefore, the preferred drugs are primarily about the dual mechanism of action: analgesic and antidepressant. These include tricyclic antidepressants (TCAS) or selective serotonin and norepinephrine reuptake inhibitors (SNRI), including venlafaxine. In terms of chemical structure and the mechanism of action, venlafaxine shows great similarity in relation to the analgesic opioid – tramadol [3]. Being also a serotonin and norepinephrine reuptake inhibitor, tramadol shows antidepressant action as well [4,5]. Both of these drugs are potentially safe and generally well tolerated by patients, but when they must be used together, a risk of serious adverse events may occur [6,7]. We have shown that the combined administration of a low dose of tramadol (5 mg/kg) and venlafaxine (20 mg/kg) in rats may increase antidepressant effect with no severe side effects [4];

* Corresponding author.
E-mail address: d.szkutnik@wp.pl (D. Szkutnik-Fiedler).

http://dx.doi.org/10.1016/j.pharep.2017.01.027
1734-1140/

however, it is known that the combined use of tramadol with serotonergic drugs, especially at high doses and long-term, may be associated with serotonin syndrome, whose symptoms are the result of inter alia transduction severity of serotonin in the central nervous system [8–10].

In the case of serotonin syndrome with concomitant use of tramadol and selective serotonin reuptake inhibitors (SSRIs) or SNRIs, it has been shown that we are dealing with pharmacodynamic, pharmacokinetic and pharmacogenetic interactions as well. Pharmacodynamic interactions have already been widely discussed via neurotransmitter effects of excessive synaptic serotonin. Functional polymorphism associated with CYP2D6, which may have influence on the metabolism of tramadol used in conjunction with drugs of the above-mentioned groups was also described [11].

It is known that tramadol is extensively metabolized to the active metabolite *O*-desmethyltramadol, which is formed by the CYP2D6 isoenzyme [12]. Therefore, concomitant use of CYP2D6 inhibitors may also cause dangerous pharmacokinetic interactions, resulting in increased levels of tramadol in blood, which in turn may increase the risk of serotonin syndrome, as demonstrated for example for paroxetine or fluoxetine [11].

Venlafaxine is generally a weaker inhibitor of CYP2D6 than the above-mentioned drugs [13] and to the best of our knowledge, there is no evidence in the literature regarding the effects of venlafaxine on the pharmacokinetics of tramadol.

Therefore, the aim of this study was to determine the effect of a single and chronic administration of venlafaxine on the pharmacokinetics of tramadol using an animal model.

Materials and methods

Chemicals and reagents

Tramadol hydrochloride, $C_{16}H_{25}O_2N{\cdot}HCl$, CAS: 27203-92-5 and phenacetin, CAS: 62-44-2 were obtained from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Acetonitrile, ethyl acetate, n-hexane, methanol (HPLC grade) were purchased from Merck (Darmstadt, Germany). Sodium hydroxide, monopotassium phosphate, anhydrous potassium hydrogen phosphate (analytical grade, pure for analysis) were supplied by POCH (Gliwice, Poland).

Animals

In this study adult, healthy New Zealand white rabbits of both sexes (n = 21, male = 12, female = 9) were used.

Animals were kept in individual metal cages located in the animal laboratory. All rabbits were maintained under standard conditions of temperature (23 ± 2 °C) and humidity (56–60%) with alternating 12 h light/dark cycles and were provided commercial pelleted diet (Labofeed KB®: 9.8 MJ/kg metabolic energy, 16.00% total protein, 0.65% vitamin P, 15000 IU vitamin A, 1500 JU vitamin D3, and 65 mg vitamin E) and water *ad libitum.* The rabbits were acclimated to local conditions for two weeks prior to the study. Before each experiment, food was withheld for 12 h, but free access to fresh water was provided. The study was performed according to a protocol approved by the Local Ethical Committee (agreement No. 26/2013), respecting the rules and guidelines concerning the care and use of laboratory animals [14].

Experimental design

Animals received orally tramadol (slow release tablets Tramal Retard® 100 mg, Grünenthal, Aachen, Germany) and venlafaxine (Velafax® modified release capsules XL 75 mg, Farmacom Sp. z o.o., Kraków, Poland). To ensure that the capsule or tablet was swallowed, 20 mL of water were given to the rabbits from a syringe. Doses of both drugs used in the study were based on previous studies using our own animal model [4,15].

All the rabbits (n = 21) were divided into four groups:

a) Control group (n = 6) – animals receiving a single oral dose of tramadol (one tablet 100 mg)
b) 1 day group (n = 5) – animals receiving a single oral dose of tramadol (one tablet 100 mg) and a single oral dose of venlafaxine (one capsule 75 mg)
c) 7 days group (n = 5) – animals, which for a period of 7 days received venlafaxine orally at a dose of 75 mg once a day, then on the seventh day of the study, were given a single oral dose of 100 mg of tramadol
d) 14 days group (n = 5) – animals, which for a period of 14 days received venlafaxine orally at a dose of 75 mg once a day, then on the fourteenth day of the study, were given a single oral dose of 100 mg of tramadol.

Drugs were administered between 8 a.m. and 9 a.m. Blood samples (2.0 mL) were obtained from a catheter remaining in the ear vein, prior to drug administration (sample 0) and 5, 15, 30, 45 min and 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0 and 24.0 h after administration. In order to supplement the fluid volume after each blood sample, animals were treated with 2 mL of physiological saline. Blood samples were transferred into collection tubes with lithium heparin, immediately centrifuged at 2880 × *g* for 10 min, then the plasma was frozen at −30 °C until analysis. At the selected time-points (1.0, 1.5; 2.0, 3.0, 4.0, 6.0, 8.0 and 24.0 h), heart rate and oxygen saturation (SpO_2) were measured (3800 Pulse Oximeter, Datex-Ohmeda, Louisville CO, USA).

Analytical method

High-performance liquid chromatography – HPLC (Waters 2695 Separations Module with autosampler) with UV detection (Waters 2487 Dual λ Absorbance Detector) was used to determine the concentrations of tramadol in rabbit plasma [16]. In order to isolate tramadol from blood plasma, a liquid–liquid extraction with a mixture of ethyl acetate-*n*-hexane (1:4, v/v) was used. The UV detection wavelength was set at 218 nm, the column (XTerra® C-8; 4.6 × 150 mm; 3.5 μm, Waters, USA) temperature was maintained at 25 °C. The mobile phase used was acetonitrile and 0.01 M phosphate buffer (30:70, v/v); pH of mobile phase was 3.0, flow rate 1.0 mL/min. Retention times of tramadol and internal standard phenacetin were 2.513 and 4.947 min, respectively, and the total analysis time was 8.00 min.

Data collection and processing were carried out using Empower™ Pro software, v. 1154.

The calibration for tramadol was linear in the range of 50–1000 ng/mL. Intra- and inter-day precision and accuracy were less than 10%. The lower limit of quantification (LLOQ) and limit of detection (LOD) of tramadol were 50 ng/mL and 20 ng/mL, respectively.

Pharmacokinetic and statistical analysis

Pharmacokinetic parameters of tramadol were determined using the non-compartmental methods with validated software Phoenix™ 7.0 WinNonlin® (Certara L.P., Princeton, NJ, USA). The maximum tramadol plasma concentration (C_{max}) and the time at which it was achieved (t_{max}) were determined directly from the concentration *vs.* time curve.

The elimination rate constant (k_{el}), elimination half-life ($t_{1/2kel}$), area under the plasma curve from zero to the last measurable concentration ($AUC_{0\text{-}t}$), area under the plasma curve from zero to infinity ($AUC_{0\text{-}\infty}$), areas under the plasma curves from zero to the