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ORIGINAL ARTICLE

PHARMACOKINETIC OF SINGLE-DOSE ORAL PREGABALIN ADMINISTRATION IN NORMAL CHICKS

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Summary

This study aimed to investigate the concentration of pregabalin in the plasma of chicks to determine its pharmacokinetic parameters. Pregabalin (300 mg/kg) was administered orally to 42 clinically healthy Ross chicks as part of a randomized controlled study. Blood samples were collected from the jugular vein at 0.5, 1, 2, 4, 8, and 24 h after drug administration from six chicks per each time. The concentrations of pregabalin in the plasma samples were determined using a quantitative HPLC assay, and pharmacokinetic parameters were calculated using the PKSolver program. Pharmacokinetic parameters were determined using a noncompartmental model. The concentrations of pregabalin were 133.80 ± 2.35, 183.20 ± 3.91, 295.60 ± 2.82, 248.40 ± 7.60, 219.00 ± 2.72 and 154.00 ± 5.50 µg/ml at the times 0.5, 1, 2, 4, 8, and 24 h respectively. The pharmacokinetics parameters were $t_{1/2\beta}$ 29 h, T_{max} 2 h, C_{max} 295 µg, K_{el} 0.023 h^{-1}, MRT 43h, V_d 1.127 L/h/kg, Cl 0.026 L/h/kg and $AUC_{0-\infty}$ 11420.31 µg.h/ml. This study concluded that pregabalin has a long elimination half-life and poor clearance from the animal body, which is reflected in the prolonged impact of its action.

Key words: Pregabalin; Pharmacokinetic; HPLC; Chicks

Introduction

An innovative therapeutic approach for the management of several pain disorders is provided by a novel family of anticonvulsants known as gabapentinoids. In several clinical studies, the novel anticonvulsant medication pregabalin has been used to relieve pain in patients with fibromyalgia, peripheral neuropathy, and irritable bowel syndrome (1). Pregabalin exhibits anticonvulsant, anxiolytic, and analgesic effects. It works by specifically attaching to the central nervous system's alpha-2-delta-1 for calcium channel voltage-dependent proteins and prevents the release of excitatory neurotransmitters (2). Pregabalin can also open ATP-sensitive potassium channels (KATP), creating anti-nociception and boosting the activity of neuronal glutamate reuptake type 3 transporter (3).

Pregabalin pharmacokinetics have been documented in various species, including humans (4), dogs (5), and cats (6). According to investigations in healthy volunteers and patients with epilepsy, pregabalin is not attached

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to plasma proteins and is not metabolized much, with > 90% of the medication removed unaltered in urine. Pregabalin has a linear pharmacokinetic profile, and its plasma concentrations rise proportionately with dosage increases for single doses of up to 300 mg and repeated doses of up to 900 mg/day. After oral administration, the maximum plasma concentration was attained on average 1.3 hours later, and the half-life of pregabalin elimination was 4.6 to 6.8 hours. Pregabalin has demonstrated little potential for drug interactions (7, 8, 9).

The use of chickens as a research model has become prevalent throughout the history of biology. Research on analgesia, anesthetics, behavior, and toxicity has used chicks as models (10, 11, 12). To our knowledge, the pharmacokinetics of pregabalin has not been investigated in chicks. The goal of this study was to investigate the pharmacokinetic parameters of oral pregabalin in normal chicks after single oral dosing.

Materials and methods

Ethical statement

The chicks were handled in accordance with the recommendations of the Animal Ethics Committee of the College of Veterinary Medicine at the University of Mosul. The animal study was reviewed and approved by the scientific board of Physiology, Biochemistry, and Pharmacology department (Protocol No. 1396).

Animals

Forty-two clinically healthy Ross chicks with age seven days weighing 150 and 200 g were used in this randomized controlled trial. The chicks were maintained in cages designed for breeding poultry at the animal house of the Veterinary Medicine College, which had a sawdust-covered floor, constant illumination, and permitted access to food and water.

Pregabalin Dosing, Sample Collection and Processing

Forty-two healthy chicks were orally administered by gavage needle with a single dose of pregabalin 300 mg/kg body weight (Pioneer Pharmaceutical Company, Iraq) which represents the effective analgesic dose (ED100) for acute pain in chicks, which was found in our previous study (13), physiological saline was used to dilute pregabalin. The volume of adminstration was 5 ml/kg of body weight. Following decapitation, blood samples were collected from the jugular vein at 0.5, 1, 2, 4, 8, and 24 h (six chicks per time). Blood samples were drawn in ethylene-diaminetetraacetic acid tubes, kept chilled and centrifuged at 3000 rpm for 15 min. For analysis, plasma samples were stored frozen at -20°C. Pregabalin concentration was quantitatively determined using a previously reported HPLC procedure (14). Briefly, the HPLC system consisted of a SYKAMN-German. The analytical column was a symmetry C18 ODS (25 cm × 4.6 mm). The mobile phase consisted of 80:10:10 (v/v/v) buffer: acetonitrile: methanol. The flow rate was 1.0 ml/min, and the detection wavelength was 210 nm. The injection volume is 20µL and the retention time of pregabalin is 0.79 minutes (Figure 1).

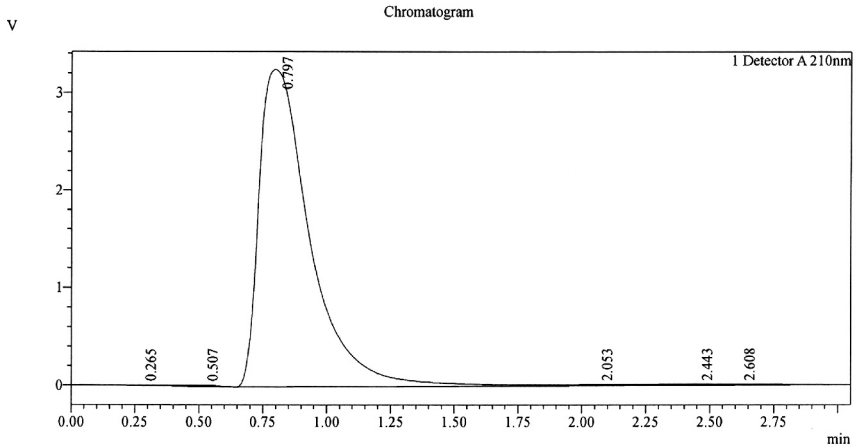

Figure 1. Chromatogram of Standard Preparation of Pregabalin.

Pharmacokinetic Analysis

The non-compartmental method was used to determine pregabalin pharmacokinetics parameters in chicks using a PKSolver program (15) which included elimination half-life ($t_{1/2\beta}$), maximum concentration (T_{max}), time to reach maximum concentration(C_{max}), elimination rate constant (K_{el}), mean residence time (MRT), volume of distribution (V_d), clearance (Cl), and area under the concentration-time curve from time 0 to infinity ($AUC0_{-\infty}$).

Results

Concentration of pregabalin in the plasma of chicks.

The plasma concentration of pregabalin in the chicks treated with oral pregabalin at a dose of 300 mg/kg was as follows (133.80 ± 2.35, 183.20 ± 3.91, 295.60 ± 2.82, 248.40 ± 7.60, 219.00 ± 2.72, 154.00 ± 5.50) µg/ml at the time (0.5, 1, 2, 4, 8 and 24 h) respectively (Table 1). The highest pregabalin concentration was observed at 2 h (Figure 2).

Table 1. Concentration of pregabalin in the plasma of chicks treated with pregabalin (300 mg/kg b.wt, o. p.) at different times.

Time (h)	Concentration (µg/ml)
0.5	133.80 ± 2.35
1	183.20 ± 3.91
2	295.60 ± 2.82
4	248.40 ± 7.60
8	219.00 ± 2.72
24	154.00 ± 5.50

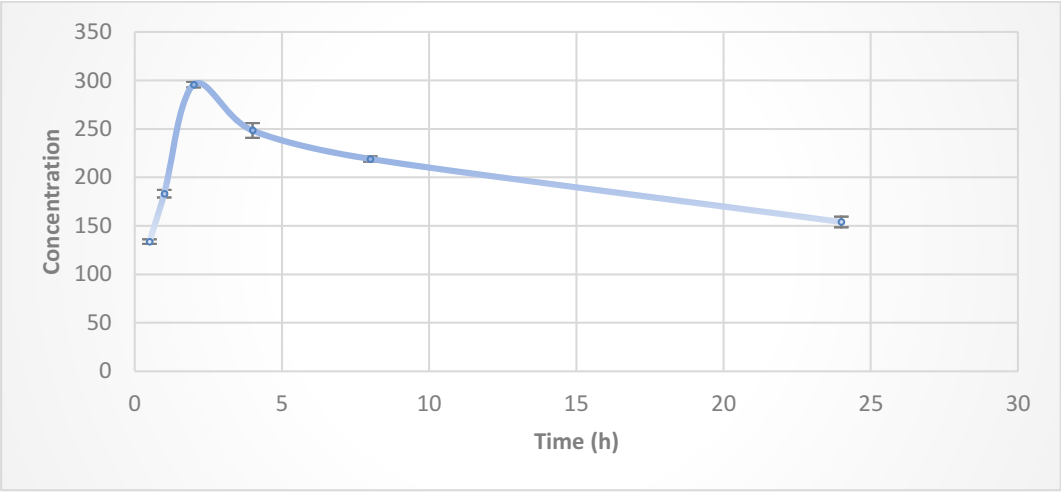

Figure2. Plasma concentration vs. time curve for pregabalin (µg/ml) after oral dosing of 300 mg/kg in chicks (PKSolver program).

Pregabalin pharmacokinetics profiles in the normal chicks.

Pregabalin pharmacokinetics profiles in the normal chickens were as follows $t_{1/2\beta}$ 29 h, T_{max} 2 h, C_{max} 295 µg, K_{el} 0.023 h^{-1}, MRT 43h, V_d 1.127 L/h/kg, Cl 0.026 L/h/kg, and $AUC_{0-\infty}$ 11420.31 µg.h/ml (Table 2).

Table 2. Pharmacokinetic parameters of pregabalin in normal chicks after single (300 mg/kg) oral dosing.

Pharmacokinetics parameters	values	units
$t_{1/2\beta}$	29	h
T_{max}	2	h
C_{max}	295	µg
K_{el}	0.023	h^{-1}
MRT	43	h
V_d	1.127	L/kg
Cl	0.026	L/h/kg
$AUC_{0-\infty}$	11420.31	µg.h/ml

$T_{1/2\,\beta}$ =Terminal Elimination Half-Life, T_{max} = Time to Maximum Plasma Concentration, C_{max} = Maximum plasma concentration, K_{el} = Terminal Phase Elimination Rate Constant, MRT = Mean Residence Time, V_d= volume of distribution, Cl =clearance, $AUC_{0-\infty}$ = Area Under the Curve from time 0 to infinity.

Discussion

The use of a high-performance liquid chromatography device to measure pregabalin concentration in the plasma of chicks confirmed the presence of pregabalin, as it was observed at a high concentration within half an hour of dosing, which indicates the speed of oral absorption. Pregabalin is a hydrophilic substance that cannot passively cross between the intestine and the blood or between the blood and the brain and is actively transported by L-amino acid transporters (LAT), which transport the amino acids phenylalanine, leucine, isoleucine, and valine (16). In humans, pregabalin is easily absorbed after oral administration, with the highest plasma concentration within one hour, and its oral bioavailability is approximately 90% (17). Pregabalin is not metabolized in the liver, does not bind to plasma proteins, and does not inhibit or activate cytochrome P450 enzymes (18). In our study, the highest concentration was reached at the second hour of dosing, which is consistent with oral administration of pregabalin in cats, where the peak concentration was detected after 2.9 hours of oral administration(6). In dogs, the highest concentration was observed 1.5 hours after oral administration (5). In horses, the highest concentration was after an hour of oral administration (19).

Our study provides a clear insight into the speed of absorption of oral pregabalin, and the peak concentration of pregabalin was two hours after treatment and lasted for eight hours, which corresponds to the experience of measuring pain using an electrical stimulator device, as the highest analgesia occurred during the times from two hours to eight hours, which was shown by the analgesia curve over time (13). This provided a clear impression of the compatibility of the pharmacokinetics and pharmacodynamics of pregabalin. Therefore, the study of pharmacokinetics is an important indicator of the availability of a drug in the body, which is reflected in its mechanism of action.

One of the results of our study when pregabalin was given to chicks at the age of seven days at a dose of 300 mg/kg orally, which represents twice the median analgesic dose that was reached through the experiment to determine the median analgesic dose using the electrostimulator device (13). The elimination rate constant was 0.023 h^{-1}, elimination half-life 29 h, mean residence time 43 h, time to maximum plasma concentration 2 h, maximum plasma concentration 295 µg/ml and the area under the time-concentration curve 11420.31 µg.h/ml. In a study conducted on cats that were given pregabalin at a dose of 4 mg/kg orally, the elimination half-life was 10.8 h, time to maximum plasma concentration 2.8 h, maximum plasma concentration 8.3 µg/ml and the area under the time-concentration curve 133.9 µg.h/ml (6). The pharmacokinetic parameters in horses given oral pregabalin at a dose of 4 mg/kg were as follows: elimination half-life 8 h, mean residence time 11 h, time to maximum plasma concentration 1 h, maximum plasma concentration 5 µg/ml and area under the time-concentration curve 47.2 µg.h/ml (19). In dogs given oral pregabalin at a dose of 4 mg/kg, the pharmacokinetic parameters were as follows: elimination half-life 6.9 h, time to maximum plasma concentration 1.5 h, maximum plasma concentration 7.15 µg/ml and area under the time curve - concentration 81.8 µg.h/ml (5). In the fasting and food-consuming human after taking pregabalin

at a dose of 150 mg orally, the kinetic parameters for each of the time to maximum plasma concentration (0.615, 3.17 h), maximum plasma concentration (3.78, 2.59 µg/ml) and the area under the time-concentration curve (26.7, 25.4 µg.h/ml) respectively (4).

The difference in kinetic parameters, which represented long half-life, increased mean residence time, higher concentration and the area under the time-concentration curve in our study compared to the studies mentioned above, may be attributed to the use of a high dose that was identified in the analgesia experiment in our previous study (13).

In conclusion, we also pointed out that the dose used in this study is to relieve acute pain in chicks, which is a very high dose compared to the doses used to relieve neuropathic pain. Therefore, it was necessary to study the pharmacokinetics of pregabalin used for acute pain. This study suggests that oral administration of pregabalin (300 mg/kg) has a rapid absorption through oral route and highest concentration was achieved in 2 h after administration with prolonged half-life of elimination in addition to poor animal body clearance, which is reflected in the prolonged duration of its effects. Further research is warranted to better understand the safety of pregabalin in chicks. Further research is necessary to determine the underlying mechanism of delayed clearance, impact on prescribed withdrawal periods.

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Conflict of Interests

The authors state that they do not have any competing interests.

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