RESEARCH ARTICLE

Chronopharmacokinetic and Metabolites Investigations of the Cardiovascular Drugs Perindopril

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Received: 07th July, 2023; Revised: 29th September, 2023; Accepted: 19th October, 2023; Available Online: 25th December, 2023

ABSTRACT

The heart and vascular systems are well-coordinated. There is a noticeable uneven distribution of regulatory mechanisms and pathogenic events over the course of a day. In addition, the physiological circadian clock of the cardiovascular system might be disrupted by several disorders. In terms of global mortality and morbidity, heart failure (HF) ranks high. The angiotensin receptor-neprilysin inhibitor perindopril is now a valid option for treating heart failure. There is a lack of comprehensive evaluations of perindopril's safety and effectiveness in HF at the present time. First, we provided an overview of perindopril's pharmacological actions, which include inhibiting the renin-angiotensin system and decreasing natriuretic peptide breakdown in the natriuretic peptide system. After that, we summed up the benefits of perindopril for heart failure patients with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF), such as lowering the risk of death and hospitalization, reversing cardiac remodeling, regulating biomarkers of heart failure, improving quality of life, providing antiarrhythmic effects, enhancing renal dysfunction, and regulating metabolism. Our discussion of perindopril's safety and tolerability in treating HFrEF or HFpEF came to a close. Although there is a considerable risk of hypotension, perindopril demonstrated superior safety and tolerability when compared with placebo. For HFrEF patients, perindopril is a safe and effective therapy option, however, for HFpEF patients, it shows little benefit, according to the majority of studies. Soon, perindopril will likely be one of the most effective drugs available to treat heart failure.

Keywords: Chronopharmacokinetic, Metabolites investigations, Cardiovascular drugs, Perindopril.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.4.43

How to cite this article: Umarkar A, Panda S, Suryavanshi H. Chronopharmacokinetic and Metabolites Investigations of the Cardiovascular Drugs Perindopril. International Journal of Drug Delivery Technology. 2023;13(4):1399-1405.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) performance a major role in the treatment of a variety of medical diseases, with excessive blood pressure, issues with the left ventricle, and heart failure. Although hypertension, heart failure, or difficulties with the left ventricle were not the primary reasons for ACEI medication, new research has revealed that ACEI may minimize the occurrence of cardiovascular events in persons who are at a greater risk for them. Three trials looked at perindopril's effects: ASCOT-BPLA, PROGRESS, and EUROPA. These trials aimed to determine the drug's effectiveness in reducing cardiac events in patients with stable coronary artery disease. Nevertheless, the ASCOT-BPLA does not reveal how perindopril impacts the events that occur in the heart. It is unfortunate that there is no information provided about the impact that perindopril and amlodipine have on cardiac events.[1-3]

In the ASCOT-BPLA trial, the majority of participants who were prescribed amlodipine also required the use of a supplementary medication in order to successfully manage their hypertension. Perindopril was the medication that was used the most often among these options. So, for the great majority of patients who were arbitrarily assigned to the treatment plan based on amlodipine, perindopril was an essential component in the process of bringing down their blood pressure (BP). It has been shown beyond a reasonable doubt that ACEI are an effective treatment for high blood pressure, malfunction of the left ventricle, and heart failure. According to the findings of a number of studies, ACEI may lower the risk of cardiovascular events in groups who are already at an increased risk.[4,5]

This is the case regardless of whether or whether hypertension, malfunction of left ventricle, or heart failure is the major rationale for the use of ACEIs. The number of cardiovascular events was shown to be reduced in individuals

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with stable coronary artery disease who took perindopril alone. Patients who suffered from cerebrovascular illness had a reduction in a number of cardiovascular events as well as cerebrovascular events when they took perindopril and indapamide together. Those diagnosed with hypertension saw a reduction in a number of cardiovascular events when perindopril was combined with amlodipine. When perindopril was supplied, both the incidence of heart problems and the severity of those problems were reduced. Perindopril's ability to lower the risk of cardiovascular events is partially attributable to the medication's effect on blood pressure. The extent to which cardiovascular events were prevented was shown to have a correlation with the size of the drop in blood pressure. It is probable that perindopril must be combined with other medications that reduce blood pressure in order for it to be used effectively in the prevention of cardiovascular events to the greatest extent feasible.[6-9]

MATERIALS AND METHODS

Perindopril was provided by Cipla in the city of Mumbai. Merck India Ltd. in Mumbai, India stocked HPLC-grade acetonitrile, analytical-grade HCl, methanol, NaOH pellets, and sodium dihydrogen phosphate. All of these chemicals were available for purchase. The TKA smart2pure water filtration system in Niederelbert, Germany was able to generate drinkable deionized water.[10] In addition to that, a pH trainer manufactured by Eutech Instruments in Singapore, a Toshiba sonicator imported from New Delhi, and an electronic scale manufactured by Mettler-Toledo were used.

Analytical and Bioanalytical Method Development and Validation of Perindopril

Analytical and bioanalytical method development of racemic perindopril

- *Spectral study of perindopril*

At first, the ultraviolet (UV) spectrum of the candidate drug was made using the right UV spectrophotometer so that the maximum absorbance, or Lambda max (λ_{max}), could be found.[11]

- *Selection of chromatographic method*

The most efficient method will vary depending on the nature of the sample. Reverse phase, ion exchange, and ion pair chromatography are all viable alternatives due to the polar nature of the substance being studied. High performance liquid chromatography (HPLC) technique was selected for first separation because it is user-friendly, adaptable, robust, and useful in many contexts.[12-15]

- *Sample preparation for assay method*

Sample preparation, the first step in chromatography, is very important. So, the best possible care was taken when preparing and processing the samples. The fillers and coating agent used by NDDS, Glenmark Generics Ltd., Mahape, in the tablet dosage form were collected. Many different proportions of Diluent, Buffer, and ACN, like 50:50, 60:40, and 70:30, were shown to be the best. The final ratio, which was found through a lot of testing, is 65:35. So that it would match the standard, a sample with a concentration of about 120 ppm was made.[16-18]

Analytical and bioanalytical method validation of perindopril

When you mix 5 mg of racemic Perindopril with 5 mL of methanol in a volumetric flask, you get a main stock solution of 1-mg/mL racemic perindopril. Through a specific sequence of diluting main stock solutions with mobile phase, perindopril working standard solutions with concentrations of 1, 5, 25, 50, 250, 500, and 750 µg/mL were prepared. Different amounts of perindopril were used to make the plasma standards: 0.02, 0.10, 0.5, 1, 5, 10, and 15 µg/mL. The same procedure was used to create four quality control (QC) standards at different concentration levels on the calibration curve: low (LoQQC = 0.05 µg/mL), medium (MQC = 4 µg/mL), high (HQC = 12 µg/mL), and lower limit of quantification (LoQQC = 0.020 g/mL). In the same way, standards for perindopril in the brain, lungs, liver, kidneys, and heart were set at values between 0.05 and 5 µg/mL. The biosamples were handled according to the instructions in the sample preparation section, and then they were analyzed using the method given.[19-21]

Pharmacokinetics and bio-distribution of perindopril

Like the other chemicals, perindopril came from several sources. We employed a Microson TM ultrasonic cell disruptor and a Sorvall tissue tearer to homogenize tissue. Shears, forceps, glass syringes, and other surgical equipment were used after sterilization.

- *Animals*

Study rats weighed 200 ± 20 g. Animals received a regular laboratory pellet diet and water *ad libitum*. Rats existed in a controlled environment with predictable light and dark cycles, as well as temperature and humidity (12 hours). Overnight, the rats in the study were given water despite fasting. In accordance with the guidelines set out by the CPCSEA, the Institutional Animal Ethics Committee (IAEC/RES/13/07/REV-2/17/14) approved all procedures.[22]

- *Pharmacokinetic and bio-distribution studies*

Single-dose oral and intravenous solutions of the racemic medicines were prepared for the experiment. Drug concentrations in plasma and other tissues were assessed at various periods. The goal of this study was to find out what happened to the chosen medicine after it was administered.[23]

- *IV Dosing and plasma sample collection*

Using a 1-mL syringe, we administered 1.6 mg/kg of perindopril solution into the caudal veins of rats after warming the veins with hot water (25 G x ½ " needle). Three animals were utilised at 0, 4, 8, 16, 30, 42, and 48 minutes, and then again at 0, 1, 2, 4, and 8 hours after the medication was administered. A single blood sample was taken from each animal *via* retroorbital puncture. An overnight blood sample (1-mL) was obtained at each time point. Anticoagulant sodium Ethylenediamine tetra acetate (EDTA) (10% w/v) was added

to 100 µL of blood collected in tubes EDTA. During the next half an hour, the tubes were chilled to a chilly -4°C while being spun at 12,000 rpm. Before being analysed, the plasma samples were frozen to a temperature of -20°C.[24]

- *Oral dosing and plasma sample collection*

Perindopril solution (3.2 mg/kg) was orally infused into the rats. A blood sample was obtained from each animal at various intervals following medicine administration: 5, 10, 15, 30, 1, 2, 5, 6, 9, and 12 hours. An overnight blood sample (1-mL) was obtained at each time point. Blood samples that had been treated with an anticoagulant were spun at 12,000 rpm for 30 minutes at -40°C in 100 µL vials that contained 10% w/v sodium EDTA. Before being analyzed, the plasma samples were frozen to a temperature of -20°C.[25]

- *Tissue sample collection*

Heart, kidney, liver, lungs, and brain were surgically removed 15, 30 minutes, and 2, 6 hours after blood samples were obtained as part of oral pharmacokinetic research. Hence, the abdomen was opened under ether anesthesia so that all internal organs could be examined. Blood was drained from the body by pumping saline solution into the various organs and tissues. The organs were placed in a petri plate containing a frozen saline solution. All of the tissues were washed with a saline solution of 2 to 5 mL. Using filter paper, the tissue was dried before being weighed and combined with a salt solution. We collected the supernatant after centrifuging the homogenates in the same way we did the plasma samples. Before analysis could be conducted, the biosamples were frozen and kept at -20°C.

- *Analysis of biological samples*

In 200 µL of mobile phase and 100 µL of formic acid (5% v/v) were added to 500 µL of plasma and tissue samples. The active ingredient was then solid phase extracted using methanol. An N2 gas stream was used to evaporate the eluate at temperatures of around 400°C. In 500 µL of mobile phase were poured in after the leftovers were recombined. Drug concentrations in biological samples were determined using validated bioanalytical techniques.[26]

- *Pharmacokinetic data analysis*

WinNonlinver 2.1 was used for non-compartmental analysis of plasma and tissue medication amounts at different times. Perindopril and its enantiomers have their C_{max}, AUC0-∞, MRT, VD, Ke, t1/2, and Cl determined. Lastly, $p < 0.05$ statistical tests were used to evaluate the *in-vivo* pharmacokinetics of enantiomers at various dosages.[26]

RESULT AND DISCUSSION

Analytical and Bioanalytical Method Development and Validation of Perindopril

Estimation of racemic perindopril

- *Spectral study of perindopril*

At the beginning, an appropriate UV spectrophotometer was used to produce the UV spectrum of the drug candidate (Figure 1). This was done in order to determine the absorbance

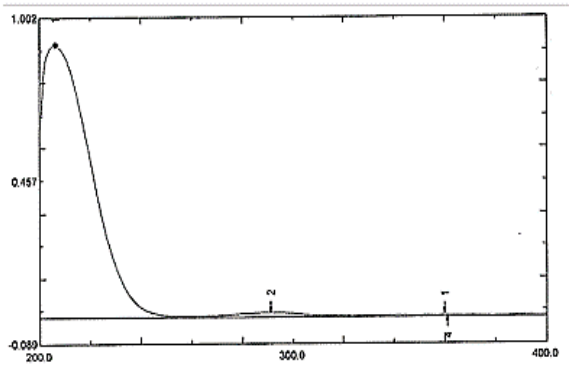

Figure 1: UV Spectrum Obtained from UV Spectrophotometer

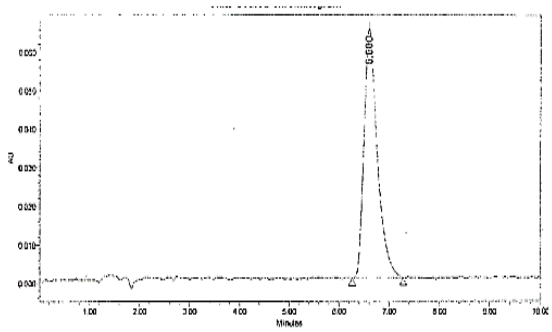

Figure 2: Chromatogram obtained from trial

maximum, also known as the lambda max (λ_{max}). This is very important considering that HPLC detection relies mostly on UV light, and as a result, a 50 ppm solution of perindopril in methanol was used in order to get the following spectra.

- *Selection of chromatographic method*

Samples are given the right treatment after their iconicity, ionizability, molecular weight, and solubility are taken into account. Because the material being looked into is polar, reverse phase, ion exchange, and ion pair chromatography are all viable options. HPLC as chosen for the first separation because it is easy to use, flexible, durable, and can be used in many different situations. We were able to find the best conditions for chromatographic separation, elution, and measurement of perindopril by changing one or two parameters in each test. Then, chromatograms were made with these settings so that the results could be studied.

Observation: The retention time was 6.550 minutes, the area was 1170920, and the tailing factor was 1.00. The chromatogram showed that this parameter was the best one. The drug breaks down at room temperature, so the data on the stability of the solution shows that the solution is unstable. So, during the analysis, the thermostat was set to 100°C (Figure 2).

- *Final method of assay method*

A HPLC method for measuring the perindopril contents has been developed. This process is used to validate if tablets have the correct concentration of the drug (Table 1).

Table 1: Final method of assay

Parameter	*Condition*
Stationary phase	Waters, Spherisorb, C8 (250 x 4.6 mm) 5µm
Mobile phase	Buffer (1.00 g Sodium heptanes sulfonate in 1000 mL water, 1-mL TEA, Ph 2.0+0.05 with Perchloric acid) : Acetonitrile(65:35)
Flow rate	1.5 mL/min
Detection	215 nm
Pump mode	Isocratic
Injection volume	20 µL
Run time	10 minutes
Column temperature	600°C
Thermostat	100°C
Retention time	About 6 to 7 minutes

Analytical and bioanalytical method validation results of perindopril

The selected method was analysed bioanalytically and results obtained are mentioned in Table 2.

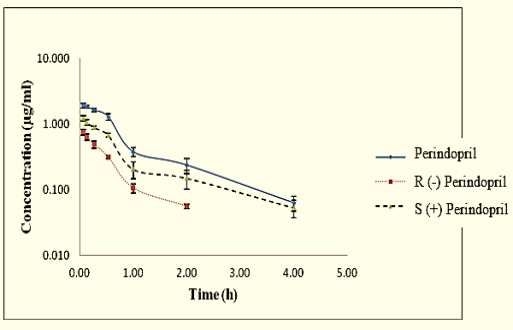

Figure 3: Log plasma concentration - time profiles of perindopril after I.V administration in rat

Table 2: Validation report of a method for assay of perindopril

S. No.	*Validation Parameter*	*Acceptance Criteria*	*Result*
1. Specificity			
1.1	Identification	When it comes to Retention time, the results should be comparable.	Standard solution has an R.T. of 6.350 minutes. R.T. of 6.357 sample solution
1.2	Placebo interference	Perindopril Peak should not show any peak at the same time as Blank and Placebo.	There is no interference. Both the Standard solution and the Sample solution have a pure peak of perindopril.
1.3	Known impurity interference	Assays of spiked and unspiked (control) samples shouldn't differ by more than 1% in terms of their averages. Both the control sample and the sample that has been tampered with should pass the peak purity test.	Complies. Peak purity passes.
1.4	Forced degradation studies	Perindopril's peak should be uniform, and there shouldn't be any other peaks that go with it. The analyte peak purity should pass.	Complies. Peak purity passes.
2	Linearity and range	Correlation coefficient should > 0.999.	Correlation coefficient is 0.99967.
3.	Accuracy (Recovery)	The average rate of recovery should be between 98.0 and 102.0%. RSD shouldn't be higher than 2%.	Mean recovery is 99.0% & RSD is 0.60%
4. Precision			
4.1	System precision	RSD should > 2.0%.	The RSD is 0.25%.
4.2	Method precision	RSD should >2.0%.	The RSD is 0.55%.
5	Ruggedness	Overall RSD for twelve results should >2.0%	Overall RSD is 0.58%
6	Robustness	Each variable condition should meet the test method for system suitability. Overall, the RSD for both control and variable conditions should > 2%.	The testing procedure is reliable under all changeable circumstances.
7	Stability in analytical solution	The difference between the old standard and a freshly made one is between 98.0 and 102.0%. The correlation between the old sample solution and the first test is between 98.0 and 102.0%.	At room temperature, the standard and sample solutions remain stable for a whole day.
8	Filter equivalency	Filters will be considered suitable if the correlation lies between 98.0 & 102.0%	Nylon 0.45 µ & Glass fibres filters are suitable
7	System suitability	The RSD of five injections that were done the same way should not be more than 2%. Perindopril peak tailing factor shouldn't be more than 2.0. There shouldn't be less than 5,000 theoretical plates.	Complies

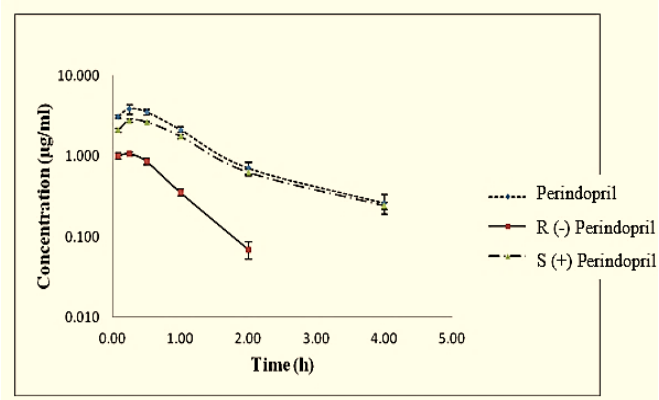

Figure 4: Log plasma concentration - time profiles of perindopril after oral administration of perindopril In rat.

Table 3: Pharmacokinetic parameters of perindopril in plasma after I.V administration in rat

Parameters	*Perindopril*
$AUC_{0-\infty}$ (µg.h/mL)	3.59 ± 0.51
MRT (h)	1.99 ± 0.56
K_e (h^{-1})	0.55 ± 0.15
V_d (L/kg)	20.58 ± 3.20
$t_{1/2}$ (h)	1.48 ± 0.44
Cl (L/h/mL)	11.73 ± 1.60

Pharmacokinetics and bio-distribution of perindopril

- *Administration*

Figure 3 displays the log plasma concentration versus time curve for 40 mg/kg perindopril delivered intravenously. The blood levels of perindopril was higher than normal. The two enantiomers differed significantly from one another in terms of most pharmacokinetic parameters. The area under the curve (AUC0) was much higher for perindopril. Compared to its enantiomer, perindopril has about three times the amount of chloride. Table 3 displays the pharmacokinetic properties of both enantiomers as well as the non-compartmental method paired t-test probability values associated with the differences between them.

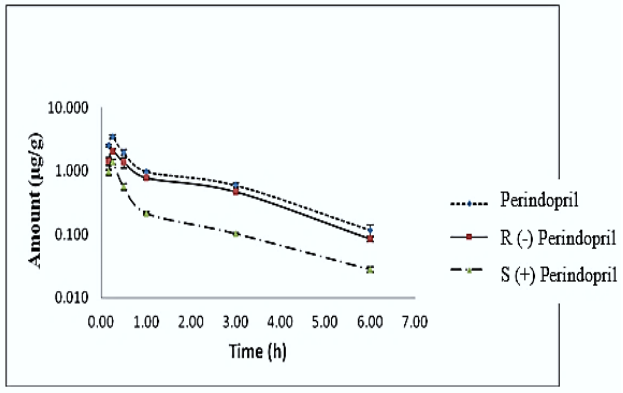

Figure 5: Log amount - time profiles of perindopril in rat brain.

Table 4: Pharmacokinetic parameters of perindopril in plasma after oral administration of perindopril in rat

Parameters	*Perindopril*
T_{max}(h)	0.25
C_{max} (µg/mL)	3.520 ± 0.517
$AUC_{0-\infty}$ (µg.h/mL)	5.768 ± 0.426
MRT (h)	1.216 ± 0.070
K_e (h^{-1})	0.725 ± 0.036
V_d (L/kg)	27.762 ± 1.584
$t_{1/2}$ (h)	0.982 ± 0.006
Cl (L/h/kg)	21.883 ± 1.584
F	0.590 ± 0.055

Table 5: Pharmacokinetic parameters of perindopril in several tissues of rat after oral administration of perindopril

Biological sample	*Parameters*	*Perindopril*
Brain	T_{max} (h)	0.25
	C_{max} (µg/g)	2.469 ± 0.257
	$AUC_{0-\infty}$ (µg.h/g)	3.754 ± 0.111
	MRT (h)	2.003 ± 0.130
	K_e (h^{-1})	0.455 ± 0.061
	$t_{1/2}$ (h)	2.543 ± 0.223
	Cl (L/h/kg)	25.152 ± 0.589
Heart	T_{max} (h)	0.25
	C_{max} (µg/g)	3.498 ± 0.042
	$AUC_{0-\infty}$ (µg.h/g)	3.957 ± 0.142
	MRT (h)	1.886 ± 0.053
	K_e (h^{-1})	0.476 ± 0.014
	$t_{1/2}$ (h)	1.456 ± 0.043
	Cl (L/h/kg)	30.349 ± 1.076
Kidney	T_{max} (h)	0.25
	C_{max} (µg/g)	13.794 ± 0.726
	$AUC_{0-\infty}$ (µg.h/g)	13.017 ± 0.547
	MRT (h)	1.281 ± 0.026
	K_e (h^{-1})	0.553 ± 0.018
	$t_{1/2}$ (h)	1.241 ± 0.040
	Cl (L/h/kg)	9.229 ± 0.0.395
Liver	T_{max} (h)	0.25
	C_{max} (µg/g)	17.129 ± 0.330
	$AUC_{0-\infty}$ (µg.h/g)	14.107 ± 0.242
	MRT (h)	1.073 ± 0.041
	K_e (h^{-1})	0.663 ± 0.045
	$t_{1/2}$ (h)	1.048 ± 0.073
	Cl (L/h/kg)	8.524 ± 0.153
Lungs	T_{max} (h)	0.25
	C_{max} (µg/g)	6.414 ± 0.498
	$AUC_{0-\infty}$ (µg.h/g)	8.171 ± 0.305
	MRT (h)	1.904 ± 0.055
	K_e (h^{-1})	0.456 ± 0.022
	$t_{1/2}$ (h)	1.22 ± 0.075
	Cl (L/h/kg)	14.7 ± 0.540

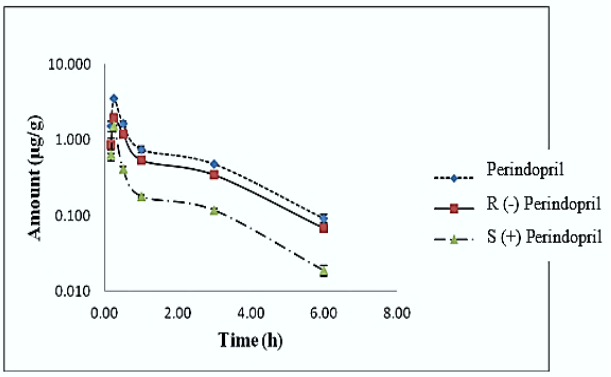

Figure 6: Log amount - time profiles of perindopril in rat heart

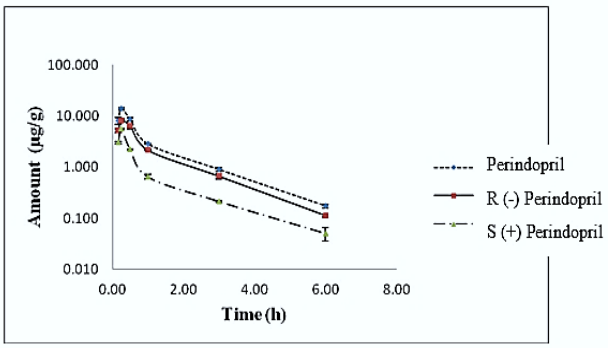

Figure 7: Log amount - time profiles of Perindopril in rat kidney

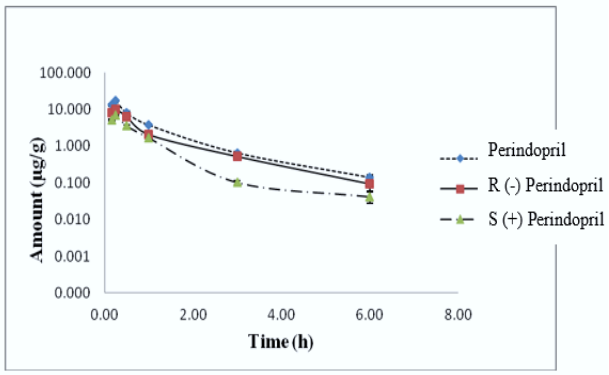

Figure 8: Log amount - time profiles of Perindopril in rat liver

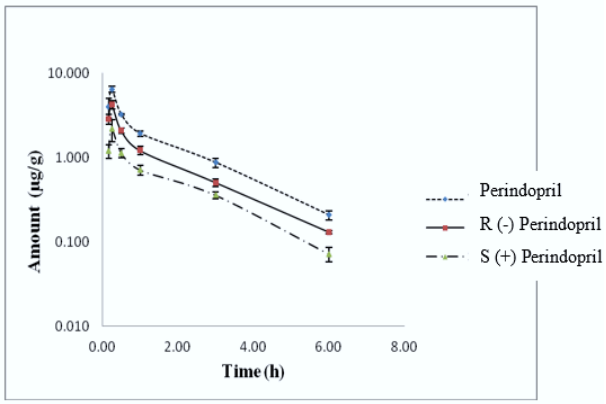

Figure 9: Log amount - time profiles of Perindopril in rat lungs

- *Oralrouteofadministration*

The time-dependent perindopril blood concentration is shown in Figure 4. Perindopril's pharmacokinetic characteristics and the difference in paired t-test probabilities between the two enantiomers are shown in Table 4.

There was a dramatic shift in the majority of pharmacokinetic parameters measured in rat plasma. Most of the pharmacokinetic parameters for Perindopril showed big differences.

- *Bio-distribution studies:oral route of administration*

After a single oral dose of 120 mg/kg, the amount of a racemic drug found in rat tissues was calculated and plotted against time. Table 5 shows some of the pharmacokinetic parameters that have been found for perindopril. Figures 5–9 show how much perindopril is in the brain, heart, kidneys, liver, and lungs and how it changes over time.

SUMMARY AND CONCLUSION

Perindopril has been shown to provide a number of health benefits for the cardiovascular system, and these benefits have been thoroughly established. One of the most significant benefits of perindopril is that it reduces blood pressure, and by extension, reduces the chance of developing cardiovascular issues. One of the numerous advantages that comes along with lowering blood pressure is a decreased likelihood of developing cardiovascular disease. Perindopril could be more successful in dropping risk of cardiovascular events if it is used in combination with other medications that are also used to treat high blood pressure. The use of chronopharmacokinetics by clinical pharmacists has the potential to enhance patient care in a variety of ways, including their capacity to monitor pharmacological effects, prevent adverse responses, and perform a variety of other tasks. Chirality is a feature that may be found in both naturally occurring and synthetically created medications, and it is one that has the potential to be used therapeutically in a broad variety of settings. Because of this concept, there is a possibility that the discipline of chemistry may undergo a significant transformation. A chiral molecule with a single stereogenic center may either be enantiopure or contain both enantiomers in equal amounts. Both of these outcomes are feasible. The chiral environment that surrounds an enantiomer leads it to behave far differently than an achiral isomer would. In certain fields, such as metabolism, toxicity, and pharmacology, the behaviors of the two isomers may be diametrically opposite to one another. This leads one to believe that the two parts of an enantiomeric pair often exhibit pharmacokinetic and pharmacological effects that are extremely diverse from one another.

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