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In vivo Passive and Iontophoretic Delivery of Lisinopril Using Wistar Rat Model

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ABSTRACT

In-vivo studies using animal model were carried out to investigate the pharmacokinetic profile of passive and iontophoretically delivered lisinopril. Serum concentration versus time profiles from intravenous (IV), oral and iontophoretic routes were analyzed using non-compartmental analysis using TOPFIT ver. 2.0. Pharmacokinetic parameters such as AUC_{0-inf}, terminal elimination rate constant (λ_z), clearance/F and C_{max}, were calculated. To validate the calculations involved in non-compartmental analysis, the serum profiles were fitted using TOPFIT (ver. 2.0) software to the one-compartmental continuous infusion model with zero order absorption. The results of the IV bolus administration of lisinopril showed that the pharmacokinetics could be described by a two-compartment model. The bioavailability of passive and iontophoretically delivered lisinopril was 62.21 and 82.87 %, respectively which is significantly higher as compared to oral route (5.67 %). The corresponding values of C_{max} were found to be 87, 95, 15.33 and 25.6 ng/ml, respectively for oral, IV bolus, passive and iontophoretically delivered lisinopril. The t_{max} for oral and IV route was 10 and 5 min, respectively, while it was 9.0 h both for passive and iontophoretic mediated transport of drug. The simple zero-order input rate and clearance effectively defined the delivery pattern of lisinopril from the iontophoretic patch. Good correlation was observed between the experimental data and data predicted by the model. Clearance estimated by the model is similar to the clearance calculated from intravenous administration, which supports the assumptions in the calculation of dose delivered by non-compartmental analysis.

Keywords: Iontophoresis, Lisinopril, Bioavailability, Transdermal patches, Non-compartmental analysis, TOPFIT, Zero order absorption.

INTRODUCTION

The skin has been identified as a route of drug administration for decades. Several drug delivery systems has been developed for utilizing this route and the ultimate goal is to ensure that compounds are delivered preferably at a specific rate to the systemic circulation. Topical drug delivery system has some limitations, arising mainly from excellent barrier properties of *stratum corneum*. Iontophoresis has potential to overcome many barriers associated with transdermal delivery of drugs and it broadens the spectrum of drugs that can be delivered via skin, increases systemic treatment efficacy, therefore, it is an alternative to invasive routes of drug administration for charged molecules. [1-3] Iontophoresis uses a small electrical current to enhance the transport of both ionic and nonionic molecules across the skin in controlled and programmable manner. [4-5]

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The enhancement of drug due to this method results from a number of possible mechanisms including the ion-electric field interaction (electro repulsion), [5] convective flow (electro-osmosis) [6] and current-induced [7] increase in skin permeability. The main aim of the present study was to evaluate the *in vivo* delivery of lisinopril using fabricated iontophoretic patch to investigate the pharmacokinetic parameters such as rate of delivery and to compare the pharmacokinetic profiles of iontophoretically delivered lisinopril with oral administration, and intravenous injection of lisinopril. Lisinopril was selected as a model drug that can be extensively administered through this route because it is devoid of any pungent skin sensation and burning pain. Furthermore, for clinical implications transdermal formulation of lisinopril delivery is highly desired. [8] Advantages of this route include improved patient compliance, avoidance of first pass hepatic metabolism, controlled delivery and the possibility to modulate the rate of delivery [9-11] which in turn shall lead to patient convenience as well as improved compliance.

MATERIALS AND METHODS

The constant current source (0-4 mA) was designed and fabricated by University Instrumentation Science Centre

(USIC), Guru Nanak Dev University, Amritsar, India, which can be operated at a resistive load of 10KΩ and was assembled by M/S B. S. Electronics, Amritsar, India. Generous gift sample of lisinopril was obtained from Ranbaxy Research Laboratory, Gurgaon, India and analytical grade chemicals were procured from Qualigens fine chemicals, Mumbai. India. Other chemicals and accessories used in the experiments like polyvinyl alcohol, electrode gel (Electrogel®), adhesive tape (Leukoplast®) and drug reservoir receptacles were obtained from Central Drug House, New Delhi, Unichem Laboraties, New Delhi, Beirsdorf (I) Ltd., Ponda, Goa, Newsun Plastics, Faridabad, respectively.

Preparation of lisinopril reservoir gel

It is reported that when the transdermal iontophoretic delivery system is applied *in vivo*, the semisolid dosage formulation may be more appropriate than solution. The gel base provides a fast release of drug substance and a high degree of clarity in the appearance. [12] Moreover, there is always a great volume of water employed in gel formulation, which exhibits a high electrical conductivity. [13] Hence the transdermal iontophoresis from gel base presently developed for *in vivo* investigation.

Gel base [14] (100g) were prepared by adding 8 % HPC to the solvent mixture (ethanol:propylene glycol: water in the ratio of 50:30:20) with constant stirring at 500 rpm for 15 min and then allowed to stand in a water bath at normal temperature of 25°C for 30 min and set aside for 24 h. [14] Since the formulations are to be applied for longer duration of time, therefore, it was fabricated in a reservoir of high-density polyethylene (HDPE) receptacle (Volume = 5.0 ml). It was stuck with an adhesive (Araldite®) on to the stripped adhesive foam tape of the ECG electrode pad. The conductive gel pad of the stripped electrode served as indifferent electrode. The additional conductive gel (Electrogel®) was added to the pad during iontophoresis. Additional polymer polyvinylalcohol (PVA) 20 % w/w was also used for increasing consistency of the formulation in the reservoir. Ingredients of the above prepared gel base plus PVA were dissolved in the citrate buffer (77.5 w/w) by little warming on the water bath with constant stirring. The obtained solution was cooled to a gel of desired consistency. Lisinopril (500 µg/ml) was added to 5.0 ml of the gel and poured into the reservoir (HDPE receptacle with rubber closure) to obtain 2.5 mg of drug. The contents were wrapped in aluminum foil and cooled in a refrigerator at 4°C for 24 h. Before putting it on the rat skin, the smooth paper over the adhesive foam tape was removed and the receptacle placed at the iontophoretic site. It was secured by the foam tape and additional adhesive tapes (Leukoplast®). The rubber closure atop the receptacle served as the entry port for Pt wire electrodes.

Preparations of animals for iontophoresis

Male Wistar rats [15] (10-12 week old) were used in the experiments. Food and water were provided *ad libitum*. The average number of replicates for each study was three. Rats were anesthetized using intra-peritoneal injection of ketamine (75 mg/kg) and xylazine (10 mg/kg). After deep anesthesia was induced, hairs were removed from the abdominal area of the animal by scissors and care was taken to ensure that no abrasion or cuts occur at the selected site. After removal of the hair, the site was wiped with a cotton swab soaked in benzoin tincture. [16] It was then washed, dried, cleaned with an alcohol swab and finally air-dried. Another precaution taken was proper maintenance of hygiene in the animal housing cage. The puncture spot for blood sampling was properly washed with absolute alcohol followed by an antiseptic (Dettol®) and an antibiotic powder (Nitrofurazone®) was sprayed after each sampling. The experiments involving animals were carried out as per the ethical guidelines and housed at appropriate conditions 12 h light and 12 h dark side (CPSCA No 226).

***In vivo* iontophoretic delivery of lisinopril**

The drug reservoir receptacle was placed at the prepared site after removal of the smooth paper covering the foam tape adhesive. It was secured at its place by additional adhesive tapes. The platinum electrode was inserted through the rubber stopper into the reservoir containing lisinopril-PVA gel. The indifferent electrode was placed within conducting distance from the reservoir electrode. Hairs were clipped off at that site and a layer of conductive gel (Electrogel^R) was applied at the site. The Pt-electrode was placed in the gel and covered with the stripped conductive gel pad ECG electrode. It was secured at the place by adhesive tapes. At pH 4.0, lisinopril is ionized upto the extent of 85 % [17-18] and was thus delivered under the positively charged electrode (anode). The ionto-phoretic gel patch was kept at anodal side, while a gel formulation containing 0.9 % sodium chloride was used at cathodal side. The reservoir gels were applied onto the cleaned abdominal area, and the additional batteries and resistor were connected in series.

Presently lisinopril formulation was used at pH 4.0 because the net charge would aid delivery of molecule as iontophoretic flux by the electro osmosis. [19]

Experimental protocol

In iontophoretic studies, the rats were subjected continuously for 24 h to a constant current of density 0.1 mA/cm^2, after which the current treatment was stopped. Current flow was monitored throughout the patch application period. Transdermal administration of drug was accomplished through the application of patch (attached on a 2.5 cm dia leucoplast adhesive) to the abdominal skin area of the rat. Blood samples were collected through either tail or sublingual vein at 3.0, 6.0, 9.0 and 24 h. Blood samples were allowed to clot and centrifuged at 7200 x *g* for 10 min and serum was collected and stored at –20°C until analyzed for serum lisinopril concentrations by HPLC as reported previously. [20]

The current density (0.1 mA/cm^2) used is lower than the current density reported in the literature, [21] so that longer period of iontophoretic treatment would cause no burn or harm the skin. It is also established that at a current density 0.1 mA/cm^2 iontophoresis for longer duration did not produce any irritation and emerged as a valuable substitute for invasive routes such as injections.

Intravenous injection and oral administration of lisinopril

Other routes of administration in rats (n=3) for the purpose of comparison were oral solution and an IV bolus injection with a 5 days washout period in between treatments. Each rat was fasted for 12 h prior to dosing. Male Wistar rats were anesthetized as described before. Lisinopril was dissolved in water for injection (WFI) and 10 µg/kg dose was given intravenously through femoral vein and blood samples were collected at 5, 30, 120, 240 and 180 min and evaluated as described before. The total amount of blood withdrawn in each study was less than 10 % of total blood volume.

The oral dose (10.8 mg drug in 10 ml given as bolus, and 4 ml to flush the tube) was administered as a solution of the drug in distilled water via a gastric tube. Blood samples were withdrawn at 10, 30, 60 and 180 min respectively and analyzed by HPLC method. [20]

Pharmacokinetic data analysis [22]

Serum concentration versus time profiles from IV, oral and iontophoretic routes were analyzed using non-compartmental analysis using TOPFIT ver. 2.0. Pharmacokinetic parameters such as AUC_{0-inf}, terminal elimination rate constant (λ_z), clearance/F and C_{max}, were calculated. Clearance obtained from IV data, was used to calculate the dose delivered during iontophoresis by the following equation assuming that iontophoretic delivery is a zero order infusion:

$$F.\ dose\ delivered = AUC\ iontophoretic \times clearance\ IV \quad (1)$$

Rate of infusion (R_0) at steady state was calculated by the following equation:

$$R_0 = \frac{F \times dose\ delivered}{Duration\ of\ patch\ application} \quad (2)$$

Where, F represents the fraction of dose absorbed into systemic circulation. It measures the drug loss in the skin and subdermal layers. $F \times$ dose delivered is calculated as a single function from eq. 1.

Bioavailability determination

$$Absolute\ availability = \frac{[AUC]_{ev} / dose_{ev}}{[AUC]_{i.v} / dose_{i.v}} \quad (3)$$

AUC was calculated using the trapezoidal rule.

Pharmacokinetic modeling

To validate the calculations involved in non-compartmental analysis, the serum profiles were fitted using TOPFIT (ver. 2.0) software to the one-compartmental continuous infusion model with zero order absorption as follows:

$$C_p = \frac{F \times dose\ delivered}{Cl} \times (1 - e^{-kt}) \quad If\ t \le T_{inf} \quad (4)$$

$$C_p = \frac{F \times dose\ delivered}{Cl} \times (1 - e^{-kt}) \times (e^{-k(t-T\,inf)}) \quad If\ t > T_{inf} \quad (5)$$

Where, C_p is the serum concentration of lisinopril, k the elimination rate constant, Cl the clearance and T_{inf} is the duration of patch application. A number of other pharmacokinetic models were also evaluated and include the one-compartment model with first-order input and two-compartment models with constant and first-order inputs. [23]

Statistical analysis

All data are presented as mean ± S.E. Statistical analysis was performed using analysis of variance (ANOVA); $p < 0.05$ was regarded as significant.

Table 1: Plasma lisinopril levels following different routes of administration (n=3)

S. No.	Time	Mean plasma lisinopril level (ng/ml)			
		Oral	Intaveno us bolus[a]	Trandsermal	
				Passive[a]	Iontophoresis[a]
1	5.0 min	-	95 ± 6.54	-	-
2	10 min	87 ± 5.23	-	-	-
3	30 min	72 ± 4.12	44 ± 5.31	-	-
4	1.0 h	43 ± 3.36	-	-	-
5	2.0 h	-	15 ± 2.33	-	-
6	3.0 h	13 ± 2.15	-	7 ± 1.14	4.3 ± 1.11
7	4.0 h	-	10 ± 1.96	-	-
8	6.0 h	-	-	12 ± 2.11	22 ± 2.78
9	9.0 h	-	-	14.33 ± 2.36	23.60 ± 2.64
10	24 h	-	-	15.33 ± 2.59	25.6 ± 1.99

[a] All values are expressed as mean ± S.D.; n = 3

RESULTS AND DISCUSSION

***In vivo* studies**

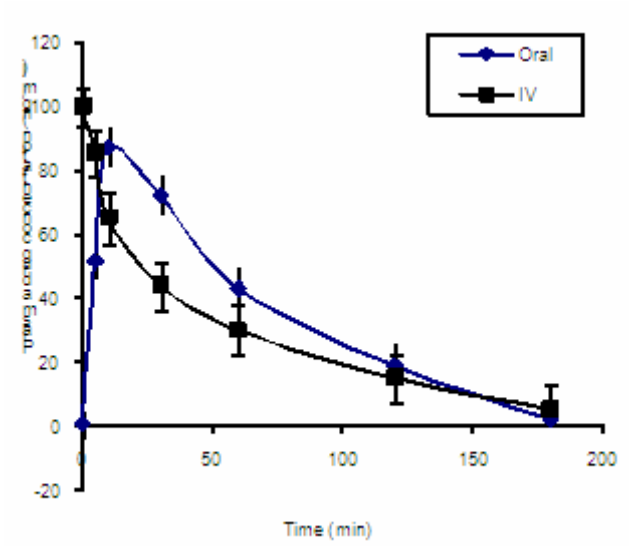

Fig. 1: Plasma drug concentration of lisinopril after IV and oral administration in rats

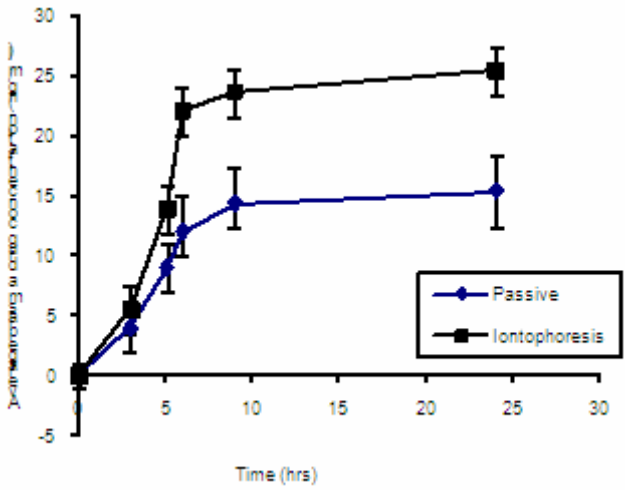

Fig. 2: Plasma drug concentration of lisinopril after passive and iontophoretic applications in rats

Patches **P** (for passive delivery) and **I** (for iontophoretic delivery) were selected for *in vivo* studies. Plasma lisinopril levels were measured by the HPLC method. [20]

The temporal profile of serum lisinopril concentrations after oral administration and intravenous injection is shown in Fig. 1 and pharmacokinetic parameters calculated are given in Table 4. The results indicated that iontophoretic device delivered lisinopril at an average infusion rate of 198.9 ± 51.3 ng/min kg and an average steady state concentration of 23.58 ± 1.24 ng/ml was achieved (Fig. 2).

The bioavailability of transdermal patches **P** and **I** were significantly higher as compared to oral route. Oral bioavailability was determined to be 5.67 %, while **P** and **I** showed bioavailability of 62.21 and 82.87 % respectively (Table 3). The C_{max} was found to be 87 ng/ml for oral, 95 ng/ml for an IV bolus (Table 8.4), 15.33 ng/ml for **P** and 25.6 ng/ml for **I** (Table 5). The t_{max} for oral and IV route was 10 and 5 min, respectively while it was 9.0 h both for **P** and **I** (Table 2). Transdermal patches demonstrated not only better bioavailability but also sustained release property, which can be controlled by proper formulation design.

Table 2: Calculation of the total area using trapezoidal rule.

S. No	Time (min)	Concentration of drug in plasma (ng/ml)	Time interval (min)	Average concentration[a] (ng/ml)	Area[a] (ng. min. ml^{-1})
			Oral (dose: 10.8 mg)		
1	0.0	0.0	-	-	-
2	10	87 ± 5.23	10	43.5 ± 5.33	435 ± 12.21
3	30	72 ± 4.12	20	79.5 ± 6.21	1590 ± 21.21
4	60	43 ± 3.36	30	57.5 ± 4.24	1725 ± 23.2
5	180	13 ± 2.15	120	28.0 ± 3.32	3360 ± 25.8
					Total 7110
			IV bolus (dose: 0.528 mg)		
1	0.0	0.0	-	-	-
2	5.0	95 ± 6.54	5	47.5 ± 6.54	237.5 ± 15.2
3	30	44 ± 5.31	25	69.5 ± 6.98	1737.5 ± 34.33
4	120	15 ± 2.33	90	29.5 ± 3.14	2655.0 ± 36.59
5	240	10 ± 1.96	120	12.5 ± 1.54	1500.0 ± 39.67
					Total 6130
			Passive delivery (dose: 2.5 mg)		
1	0.0	0.0	-	-	-
2	180	7 ± 1.10	180	3.5 ± 0.23	630 ± 16.32
3	360	12 ± 2.30	180	9.5 ± 1.36	1710 ± 23.47
4	540	14.33 ± 2.96	180	13.165 ± 1.24	2369.7 ± 25.45
5	1440	15.33 ± 2.99	900	14.83 ± 2.31	13347 ± 59.84
					Total 18056.7
			Iontophoretic delivery (dose: 2.5 mg)		
1	0.0	0.0	-	-	-
2	180	4.3 ± 0.19	180	2.15 ± 0.24	387 ± 14.61
3	360	22 ± 2.21	180	13.15 ± 1.36	2367 ± 22.36
4	540	23.6 ± 3.01	180	22.8 ± 2.54	4104 ± 25.33
5	1440	20.6 ± 1.99	900	22.1 ± 2.61	19890 ± 62.34
					Total 26748

[a] All values are expressed as mean ± S.D.; n = 3

Table 3: Bioavailability of different formulations

Formulation	Dose	AUC (ng. min. ml^{-1})	% bioavailability
Oral Solution	10.8 mg	7110 ± 36.32	5.67
IV bolus	0.528 mg	6130 ± 32.25	100
Transdermal Route			
Passive delivery	2.5 mg	18056.7 ± 56.65	62.21
Iontophoretic delivery	2.5 mg	26748 ± 65.45	82.87

[a] All values are expressed as mean ± S.D.; n = 3

Table 4: Pharmacokinetic parameters (average ± S.E.) after IV and oral administration of lisinopril in rats.

Parameters	*IV*	Oral
C_{max} (ng/ml)	95 ± 6.54	87 ± 5.23
Cl (ml/min kg)	25.9 ± 0.92	20.21 ± 0.87
λ_z (min^{-1})	0.02	0.03
Half-life (min)	36.5 ± 3.4	58.2 ± 4.4
AUC_{inf} (min ng/ml)	6130 ± 36.89	7110 ± 28.30

Table 5: Pharmacokinetic parameters (average ± S.E) after passive (P) and Iontophoretic transport (I) of lisinopril in rats.

Parameters	Passive delivery (P)	Iontophoretic transport (I)
C_{max} (ng/ml)	15.33 ± 2.59	25.6 ± 1.99
λ_z (min^{-1})	0.03	0.03
Half-life (min)	318 ± 26.54	321 ± 23.45
AUC_{inf} (min ng/ml)	18056.7	26748.0
Dose delivered (μg/Kg)	21.4 ± 2.6	28.4 ± 2.89

The results of the IV bolus administration of drug salt showed that the pharmacokinetics could be described by a two-compartment model (Fig. 1). Results from oral administration of drug indicated that drug is rapidly absorbed from the GIT and that oral bioavailability was about 5.0 %, indicating that extensive loss of drug may be due to enzymatic degradation/hepatic first pass metabolism. On the other hand transdermal administration resulted in bioavailability of over 60 %. Results also indicate that by proper formulation design the bioavailability through transdermal systems could be greatly enhanced (e.g., for **P** = 62.21 % whereas for **I** it was 82.87 %). This substantial increase in bioavailability could be due to the extensive vascular system of the rat skin, forced transport of lisinopril due to iontophoresis as well as circumventing the 'first pass'.

The simple zero-order input rate and clearance effectively defined the delivery pattern of lisinopril from the iontophoretic patch. Good correlation was observed between the experimental data and data predicted by the model. Clearance estimated by the model is similar to the clearance calculated from intravenous administration, which supports the assumptions in the calculation of dose delivered by non-compartmental analysis. Singh *et al.*, [24-25] have shown that for various drugs the zero-order infusion model defines and serves practical purposes of modeling, and less than perfect fit may be due to the contribution of electro osmosis during iontophoresis.

CONCLUSION

The bioavailability of drug can be enhanced nearly 10 folds via the transdermal route and can be further enhanced by proper formulation design. Passive and iontophoretic

transdermal patch gave an effective plasma concentration of 15 and 25 ng/ml, respectively, maintained for about 15 h. The iontophoretic patches delivered therapeutically relevant concentrations of lisinopril in rats and delivery comparable to conventional routes such as intravenous injection was achieved. The result confirm that electronic transdermal delivery can be a potential mode for systemic delivery of therapeutic molecules and present study confirmed the viability of lisinopril delivery from designed and fabricated patch by iontophoresis, using a convenient device configuration.

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