

Review Article

Exploring The Clinical Pharmacokinetics of Eplerenone: A Systematic Review of Published Studies.

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Abstract

Eplerenone is the first selective aldosterone antagonist to manage hypertension and congestive heart failure. This comprehensive review aims to collate all the published pharmacokinetic (PK) data on eplerenone by scavenging the relevant articles following oral route of administration in human subjects (healthy & diseased). Five databases, Science Direct, Cochrane Library, EBSCO, Google Scholar, and PubMed, were used systematically to retrieve the relevant studies containing at least one reported PK parameter of eplerenone. A total of 983 articles were identified, in which 08 studies were included after applying the inclusion/exclusion criteria. Eplerenone shows the linear PK profile as the area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) increase dose-dependently. The C_{max} was found to be increased by 2-fold following the administration of multiple doses in healthy as well as in subjects with renal impairment in comparison with single dose. In dialysis subjects, the peak time (T_{max}) was significantly shorter than that of the healthy population, 1.28 ± 0.47 hr vs. 2.22 ± 0.75 hr. A significant increase in oral clearance (CL/F) was observed in dialysis patients compared to normal subjects after giving multiple doses. Moreover, co-administration of ketoconazole with eplerenone showed a 1.7-fold increase in C_{max} . The current systematic review summarizes all the available PK parameters of eplerenone from the possible accessible studies that can assist clinicians in dosage adjustments in patients with renal failure and avoiding drug-drug interactions.

Keywords: Eplerenone; aldosterone blocker; Pharmacokinetics; PK parameters; Systematic review

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INTRODUCTION

Eplerenone is the first selective mineralocorticoid receptor blocker developed by Pharmacia Corporation and acquired by Pfizer in 2002.¹ Eplerenone was approved by the US Food and Drug Administration (FDA) in 2002 to treat hypertension, congestive heart failure, and chronic central serous chorioretinopathy. It selectively binds to the mineralocorticoid receptor present in the renal, heart, blood vessels, and brain parts that antagonize the effect of aldosterone, a natural substance that helps to regulate sodium and water retention, thus increasing the blood pressure in the body.² Its off-label use is to treat primary aldosteronism, ischemic heart disease, and congestive heart failure subjects with an ejection fraction (EF) value of $\leq 35\%$.³ Eplerenone is administered orally and it is available in 25 mg, 50 mg, and 100 mg tablet dosage forms.

Eplerenone is categorized in Biopharmaceutical Classification System (BCS) Class-II, having low solubility and high permeability properties.⁴ The maximum plasma concentration (C_{max}) is achieved within 1.5 hr with an absolute bioavailability of 69 %, and its absorption remains consistent when administered with food. It is 49 % bound to plasma, primarily alpha 1-acid glycoprotein, and its apparent steady-state distribution volume $V_{d(ss)}$ is 43–90 ml. It is metabolized by the CYP3A4 pathway, but no active drug metabolites have been recognized in humans. Eplerenone is metabolized to 6- β -hydroxy eplerenone via CYP3A4 enzyme and 21-hydroxy eplerenone metabolite via CYP3A4 and CYP3A5 enzymes.⁵ The route of excretion for eplerenone is via feces and urine, i.e. approximately 32 % and 67 % of the dose, respectively.⁵ The apparent normal clearance of eplerenone is about 10 L/hr, and the biological half-life is 3–4 hours.^{6,7}



Eplerenone is an odorless and white to off-white color crystalline solid dry powder substance that is lightly soluble in water (< 1 mg/ml). It is a monoisotopic compound whose molecular mass is 414.5 g/mol, and its chemical formula is $C_{24}H_{30}O_6$. The lipophilicity (Log P) of eplerenone is 1.34, which is in the range of 1–4, indicating its higher permeation of the drug through the skin.² The lipid/water distribution coefficient of eplerenone is about 7.1 at pH 7.⁸

Eplerenone falls in the pregnancy risk category B.² The most commonly side effects of eplerenone are hyperkalemia, dizziness, elevation in creatinine serum level, diarrhea, cough, fatigue, dyslipidemia, abdominal pain, and albuminuria.⁹ The use of eplerenone is contraindicated in patients with serum potassium levels > 5 mmol/L, type-II diabetes patients with microalbuminuria, in patients taking potassium supplement substances, and in the special case of hypersensitivity reactions to any drug product.⁹ The adverse effects worsen in subjects with proteinuria, diabetes, congestive heart failure, and renal failure suggesting a need for dose adjustment based on glomerular filtration rate and serum potassium level in these cases.¹⁰

The rationale of the current study for performing this systematic review is to provide a clear and comprehensive illustration of all available pharmacokinetic (PK) parameters of eplerenone in human subjects. Understanding altered drug PK parameters and desired clinical responses produced in humans is helpful in providing information about dose adjustments of individualized therapy. There are some systematic reviews and meta-analyses of eplerenone that have already been published, such as the pharmacology of eplerenone,² relative safety and efficacy profile,¹¹ cost-effectiveness study,¹² the effect of mineralocorticoid blocker on glucose homeostasis,¹³ the study of efficacy in chronic heart failure patients,¹⁴ assessing the impact of hypertension in adult,⁹ a study of aldosterone blocker in chorioretinopathy patients,¹⁵ and economic evaluation of aldosterone antagonist in post-myocardial infarction,¹⁶ but up to date, there is no review to summarize all the PK variables of eplerenone. The purpose of this current review is to collect, sum up and analyze all the available PK aspects of eplerenone from the included studies in humans for circumventing the adverse drug reactions, drug-drug, and drug disease interactions which may further be used in clinical settings for suggesting optimal dosage regimens in the subjects with renal impairment.

METHODOLOGY

Study Design and search strategy

This systematic search was carried out using Cochrane updated handbook guidelines¹⁷ and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).¹⁸ A systematic analysis was performed to screen the articles related to the PK parameter of eplerenone in human subjects by using different databases such as PubMed, Google Scholar, Cochrane, Science Direct, and EBSCO to retrieve all the relevant articles from 20th May 2023 to 20th August 2023. A standard search was done in PubMed and Cochrane by using Boolean operators and medical subject heading (MeSH) terms while Google Scholar, Science

Direct, and EBSCO databases search was done by utilizing its “advanced search” feature.

Inclusion/Exclusion Criteria

Inclusion criteria consist of peer-reviewed English language articles providing at least one of the reported PK parameters of eplerenone in healthy and diseased human subjects after oral administration. The PK parameters to be evaluated in the current study are the peak concentration of eplerenone in plasma (C_{max}), the maximum time to reach peak plasma concentration (T_{max}), oral drug clearance (CL/F), the area under concentration curve profile (AUC), the elimination half-life ($t_{1/2}$) and apparent volume of distribution (V_d). Exclusion criteria involve abstract articles, editorials, thesis, book chapters, and preceding papers. No restrictions were applied on age, gender, and year of publications.

Study Selection

All articles identified from various databases were transferred into the EndNote program, and duplicates were removed by clicking the word duplicate. After the title, abstract, animals-related, and not accessible screening, 764 articles were excluded. Furthermore, after extensive reading, three articles were ruled out based on the unavailability of PK parameters data, and eight articles were added to the final systematic review.

Quality Assessment

To assess the methodological quality of randomized controlled trials (RCTs) in each of the 08 included studies, the Jadad scoring scale and Critical Appraisal Skill Program (CASP) checklist tools were used in this review. Jadad scoring consists of five items, and “zero” or “one” was recorded in response to each item. Studies with a score of > 4 indicate high quality, scoring in the range of 3–4 shows moderate quality, and a score of < 3 indicates low quality.¹⁹ CASP tool is composed of 11 items that evaluate the validity of the included article, in which scoring criteria > 6 , 4–6, and < 4 indicate high, moderate, and low quality, respectively.²⁰ The Critical Appraisal of the Clinical Pharmacokinetic (CACPK) tool consists of 21 items designed to evaluate PK studies’ quality. It has a ranking score for each item that is yes, I do not know (IDK), no, and not applicable; the study scored > 13 , scoring ranged between 12–13, and scoring numbers < 12 , were high, fair to moderate and poor quality, respectively.²¹ The Cochrane Collaboration tool comprises of 7 questions that are used to determine the risk assessment of bias in relevant randomized trial articles. In this risk of bias assessment, studies which a score < 3 were low quality, studies ranging between 3–4 were moderate, and high-quality studies were > 4 , respectively.²²

Data Extraction

The data regarding the writer’s first name, year, population under study, research method, number of population, age of the participants, route of administration, dose, dosage form, dosage regimen, CL/F, V_d , AUC, C_{max} , and $t_{1/2}$ were then collected from included studies and presented in tabulated form. Two independent reviewers carried out the process of



extraction. Data presented in graph form was extracted using Web plot digitizer and snipping tool.²³ The PK parameters were calculated from the concentration vs. time plasma profile curve of eplerenone by performing a non-compartmental analysis method (NCA). A data-checking step was performed in which the included data of every article was cross-checked with the original article by reviewers to reduce the chance of error and bias. The most commonly used PK parameters, including AUC, C_{max} , T_{max} , CL/F, and $t_{1/2}$ were converted into the same units to maintain the homogeneity of results.

RESULTS

Literature Search Results

After searching from different electronic databases, a total of

983 studies was retrieved, out of which 208 were duplicates. The remaining 775 articles were further screened based on eligibility criteria, and ultimately eight research articles were included in the current systematic review.

Characteristics of included studies

The demographic characteristics of relevant articles comprising of author’s first name, population, number of subjects involved, age, gender, quantity, dosage form, oral dosage regimen, method of administration, primary goal, and intervention are reported in Table 1.

Quality assessment results

For the quality assessment, eight studies were evaluated using the CASP, CACPK, and Jadad scoring scales. Each of the eight

Table 1. Characteristics of included studies										
Reference	N	Gender	Age (years)	Population	Type of Drug	Primary Goal	Primary outcome	Dosage Form	Frequency	Dose (mg)
Chyung S. Cook et al (2003) ²⁸	8	M	20 – 60	Healthy human volunteers	Eplerenone	To investigate the (ADME) of eplerenone in humans	PK Parameters	Tab	OD	100
Ji Y.Zhang et al (2003) ²⁶	80	M/F	N/R	Healthy Volunteers	Eplerenone	Determination of eplerenone and its hydrolyzed metabolite in human plasma	PK Parameters	Tab	OD	100
C.S. Cook et al (2004) ³¹	18	M	N/R	Healthy Subjects	Eplerenone	To predict PK interaction of eplerenone with other drugs	PK Parameters	Tab	QD	100
					Cisapride				BID	20
					Digoxin				QD	200
					Verapamil				QD	240
					Simvastatin(				QD	40
					Sequinavir				TID	40
					Erythromycin				BID	500
William R. RavisphD, et al (2005) ³⁰	64	M/F	18– 79	Healthy and renal impairment subjects	Eplerenone	To examine the effect of renal and hemodialysis on PK	PK Parameters	Tab	OD	100
Yuko Mori et al(2010) ²⁷	100	N/R	19– 62	Healthy Subjects	Eplerenone	To predict nonlinear PK by using a population approach	PK Parameters	Tab	OD	10, 50, 100, 200, 300, 400, 600, 1000
Susana Almeida et al (2011) ²⁵	30	M/F	18–55	Healthy Volunteers	Eplerenone film coated tablet 50mg	To assess the bioequivalence of a new eplerenone vs. reference product.	PK Parameters	Tab	OD	50
J. Chen et al (2015) ²⁴	12	M/F	18–45	Healthy Subjects	Eplerenone	To investigate PK and dose proportionlity	PK Parameters	Tab	OD	25,50,100
Christian W. Thorstensen et al 2022 ²⁹	547	F	≥ 18	Hypertensive patients	Eplerenone	To measure serum concentration and improve the therapy in HTN patients.	PK Parameters	Oral solution	OD	25,50



studies was screened by the CASP tool, demonstrating that 07 studies were of higher quality, scoring > 6, and 01 of moderate quality with a score of < 6. On the Jadad scale, all studies were scored < 3, considered to be of low quality. According to the CACPK tool, four articles were high, three were fair to moderate, and one was of low quality, respectively. In the Cochrane collaboration tool scoring, 1 article was at low risk, five studies were at moderate risk, and the remaining two were at high risk.

Healthy Population

Oral Healthy

A single and multiple-dose study was performed to analyze the PK parameters of eplerenone in which the $t_{1/2}$ and T_{max} ranged from 3.02–3.19 hr and 2.00–3.00 hr, respectively. The C_{max} and AUC_{0-inf} were found to be directly proportional to the dose. The C_{max} was 489 ng/ml, 976 ng/ml, and 1641 ng/ml after administering 25 mg, 50 mg, and 100 mg, respectively. The $AUC_{0-∞}$ was increased from 3030 to 10893 ng/ml after raising the administered dose from 25 to 100 mg.²⁴

A single-dose, two-way crossover study design was conducted to evaluate the bioequivalence of eplerenone formulations (test vs reference product) in which C_{max} for test and reference product were 1173.45 ng/ml and 1106.02 ng/ml, respectively. The T_{max} of 1.00 hr was the same for both products of eplerenone. The $AUC_{0-∞}$ was recorded as 5669.37 ng/ml.hr, and 5682.72 ng/ml.hr respectively after giving a 50 mg dose.²⁵

In another study, the T_{max} and AUC_{0-inf} were 0.9715 hr and 34761.78 ng/ml.hr respectively after the administration of 100 mg of eplerenone. Moreover, the C_{max} and CL/F were reported to be 1569.5 ng/ml and 2.876 L/h.²⁶ One of the studies has reported a mean population CL/F of 12.7 L/h.²⁷ After giving a 100 mg single dose of eplerenone, the T_{max} and C_{max} were found to be 1.3 ± 0.8 hr and 1720 ± 280 ng/ml, respectively. The AUC on following a single oral dose in a healthy population was 9540 ± 3200 ng/ml.hr.²⁸ The remaining parameters can be depicted in Table 2.

Diseased Population

Hypertensive patients

The hypertensive patients were administered a 25–50 mg dose in a study, and the resultant C_{max} was recorded to be 1030.4 ng/ml. In addition, the T_{max} was estimated to be 1.5–2 hr.²⁹

Renal Impairment Patients

Single dose eplerenone

For renal impairment subjects, the AUC was 11005 ± 4922 ng/ml.hr, 12088 ± 6440 ng/ml.hr, 17228 ± 8151 ng/ml.hr, 8120 ± 2565 ng/ml.hr for mild, moderate, severe, and dialysis patients. No significant distinction was found between the $t_{1/2}$ in renal impairment and normal subjects. The T_{max} in dialysis subjects was significantly shorter than that of the normal population, which is 1.28 ± 0.47 hr vs. 2.22 ± 0.75 hr. After giving a 100 mg single dose of eplerenone, the C_{max} for mild, moderate, severe, and dialysis subjects were 1687 ± 265 ng/ml, 1595 ± 467 ng/ml, 2023 ± 511 ng/ml, and 1717 ± 351 ng/ml respectively. The values for CL/F are given in Table 3.³⁰

Multiple dose eplerenone

The T_{max} for mild, moderate, severe, and dialysis patients were reported to be 2.29 ± 0.95 hr, 2.00 ± 0.90 hr, 2.10 ± 1.00 hr, and 1.11 ± 0.65 hr, respectively. The C_{max} for severe renal failure patients was estimated to be 2156 ± 701 ng/ml; for dialysis patients, it was 1709 ± 355 ng/ml. The CL/F in dialysis patients was greater than in normal subjects after administering multiple doses of eplerenone. The values for AUC^a are mentioned in Table 3.³⁰

Drug-drug interaction

A study was held to assess the combined effect of eplerenone with ketoconazole, which showed an increase in the C_{max} of eplerenone from 1550 ng/ml to 2610 ng/ml. On co-administration of eplerenone with erythromycin, the recorded C_{max} and AUC were increased from 1480 ng/ml to 2380 ng/ml and 8330 ng/ml.hr to 23900 ng/ml.hr respectively. When eplerenone was given along with verapamil, the C_{max} and $t_{1/2}$

Table 2. Pharmacokinetic data in healthy population after oral administration						
Reference	Dosage (mg)	t_{max} (hr)	C_{max} (ng/ml)	AUC_{0-inf} (ng · h/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)
Chyung S. Cook et al (2003) ²⁸	100	1.3 ± 0.8	1720 ± 280	9540 ± 3200	N/R	N/R
Ji Y.Zhang et al (2003) ²⁶	100	0.9715	1569.5	34761.78	32.65	34770514.6
Yuko Mori et al (2010) ²⁷	100	N/R	N/R	N/R	N/R	12.7
Susana Almeida et al (2011) ²⁵	50 ^a	1 ^c	1173.45 ^c	5669.37 ^c	3.13 ^c	N/R
		60.3 ^d	19.8 ^d	34.7 ^d	31.8 ^d	N/R
	50 ^b	1 ^c	1106.02 ^c	5682.72 ^c	3.06 ^c	N/R
		58.8 ^d	23.2 ^d	37.2 ^d	35.1 ^d	N/R
J. Chen et al (2015) ²⁴	25	2.00 ^c (0.50, 6.00) ^e	489 ^c (150) ^e	3065 ^c (1 203) ^e	3.15 ^c (0.60) ^e	9.712 ^c (4. 993) ^e
	50	2.00 ^c (0.50, 4.00) ^e	976 ^c (286) ^e	5621 ^c (2 093) ^e	3.02 ^c (0.60) ^e	10.503 ^c (5 394) ^e
	100	3.00 ^c (0.25, 6.00) ^e	1641 ^c (443) ^e	11011 ^c (3 173) ^e	3.19 ^c (0.54) ^e	9.792 ^c (2. 829) ^e
	50 (multiple-dose)	2.50 ^c (0.75, 4.00) ^e	1155 ^c (283) ^e	6470 ^c (2 452) ^e	3.19 ^c (0.63) ^e	8.612 ^c (2. 505) ^e



Table 3. Pharmacokinetic data in disease population after oral administration

Reference	Population	Dosage (mg)	Stages	$t_{\max}$ (hr)	$C_{\max}$ (ng/ml)	AUC ^a (ng·h/mL)	$t_{1/2}$ (hr)	Cl/F (L/hr)
William R. Ravis et al (2005) ³⁰	Healthy and renal impairment subjects	100 eplerenone single dose	Mild	2.21 ± 1.09	1687 ± 265	11005 ± 4922	4.37 ± 2.10	7.60 ± 2.93
			Normal	1.69 ± 0.95	1569 ± 406	11066 ± 2880	3.96 ± 0.82	7.83 ± 3.76
			Moderate	2.48 ± 1.22	1595 ± 467	12088 ± 6440	4.63 ± 1.77	7.44 ± 2.95
			Normal	2.41 ± 1.31	1426 ± 374	10788 ± 5051	4.44 ± 2.63	9.09 ± 4.29
			Severe	2.17 ± 1.06	2023 ± 511	17228 ± 8151	6.81 ± 2.77	6.14 ± 2.02
			Normal	1.97 ± 1.31	1677 ± 329	12123 ± 4583	4.11 ± 1.36	9.08 ± 6.30
			Dialysis	1.28 ± 0.47	1717 ± 351	8120 ± 2565	3.70 ± 2.89	14.71 ± 4.99
			Normal	2.22 ± 0.75	1551 ± 397	8846 ± 2106	3.16 ± 0.85	10.24 ± 3.57
		100 eplerenone multiple doses	Mild	2.29 ± 0.95	1669 ± 493	N/R	N/R	7.21 ± 2.80
			Normal	1.57 ± 0.61	1874 ± 519	N/R	N/R	7.02 ± 2.09
			Moderate	2.00 ± 0.90	1650 ± 526	N/R	N/R	7.40 ± 4.15
			Normal	1.59 ± 0.57	1556 ± 466	N/R	N/R	8.20 ± 3.76
			Severe	2.10 ± 1.00	2156 ± 701	N/R	N/R	6.77 ± 2.31
			Normal	2.26 ± 1.03	1777 ± 500	N/R	N/R	8.28 ± 4.60
			Dialysis	1.11 ± 0.65	1709 ± 355	N/R	N/R	15.80 ± 6.58
			Normal	2.14 ± 0.63	1590 ± 292	N/R	N/R	9.92 ± 3.39
Christian W. Thorstensen et al (2022) ²⁹	Hypertensive patients	25–50 eplerenone		1.5–2	1030.4	N/R	N/R	N/R

were reported to be two-fold higher than normal. A 5.4-fold increase in AUC was found after the co-administration of ketoconazole. The $t_{1/2}$, $C_{\max}$, and AUC of eplerenone were two-fold higher after the administration of saquinavir. Cisapride, digoxin, and simvastatin drug do not change PK parameter of eplerenone. The changes in the PK parameter of eplerenone were seen when given in combination with midazolam, saquinavir, and verapamil and are mentioned in Table 4.³¹

DISCUSSION

The current review aimed to analyze all the PK parameters of eplerenone that were conducted in healthy and diseased subjects. Among the eight studies, five were in the healthy population, two were in diseased patients, and one included drug-drug interaction. The $C_{\max}$ and AUC value was dependent on the dose because it shows a linear relationship, but $T_{\max}$ was not affected by it. Steady-state plasma concentration of the drug was achieved within four days, and no build-up of the drug was observed following the administration of multiple doses. Eplerenone shows a linear PK profile at doses below 100 mg, whereas, above 200 mg dose, it shows a non-linear kinetic profile. The present study suggested that if the dose ratio is less than 2.00, the AUC and $C_{\max}$ are directly proportional to the dose.²⁴ A bioequivalence study was performed to correlate the rate and amount of absorption of test formulations vs. the reference product of eplerenone undergoing fasting. Both products were well tolerated in terms of safety and adverse effects. The value of $t_{1/2}$ for test eplerenone is in line with the reference because the washout period was approximately seven days, which allows the entire removal of the drug from the body and avoids the carry-on effect. Male and female

subjects were included in current studies, but gender did not affect the result. After giving a 50 mg tablet, a bioequivalence study was shown that the ratio of both formulations of PK parameters was within the order of 80–125 %. Eplerenone shows a linear profile up to 100 mg dose and above therapeutic dose, demonstrates a non-linear kinetic profile.²⁵

A study involving hypertensive patients revealed PK variability in eplerenone but this variability was not observed in other drugs such as losartan, valsartan, candesartan, and amlodipine. The $C_{\max}$ of eplerenone was greater than $C_{\min}$ due to the accumulation of the drug in the body, but over time drug concentrations decreased. Studies are needed to determine the plasma drug concentration in hypertensive subjects for monitoring the adverse effects concerning end-organ damage in the heart, renal, and brain. In the future, plasma concentration should be compared in controlled and uncontrolled hypertensive subjects to improve drug adherence, clinical outcome, and pharmacotherapy.²⁹ Following administration of the oral medication, eplerenone was well absorbed throughout the gastrointestinal part of the body. The peak plasma concentration was found to be decreased with a biological half-life, which may be due to the slower absorption than elimination, thus exhibiting the phenomena of flip-flop kinetics. The blood plasma protein binding was limited, demonstrating that it is a concentration-dependent pathway over the therapeutic range. The mean $C_{\max}$ and AUC value of entire radioactivity in blood plasma were greater than those in red blood cells. The result suggested that the binding of the drug to blood plasma is higher than that of whole red blood cells, and entire radioactivity was not diffused into blood cells. The $T_{\max}$ was smaller in the case of saliva than in plasma



Table 4. Drug-drug interactions of eplerenone

Reference	Population	Dosage (mg)	Drug	$t_{\max}$ (hr)	$C_{\max}$ (ng/ml)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)
C. S. Cook et al (2004) ³¹	Healthy subjects	Eplerenone alone	Cisapride	1.67	2170	12800	4.82	N/R
			Cyclosporine	N/R	N/R	N/R	N/R	N/R
			Digoxin	1.75	2040	12200	4.01	N/R
			Erythromycin	1.96	1480	8330	4.4	N/R
			Fluconazole	1.76	1550	9550	3.47	N/R
			Ketoconazole	1.72	1550	9560	3.63	N/R
			Midazolam	N/R	N/R	N/R	N/R	N/R
			Saquinavir	2.6	2140	16200	4.87	N/R
			Simvastatin	2.11	1790	12200	4.19	N/R
			Verapamil	1.69	1890	11600	4.5	N/R
		Eplerenone with test drug	Cisapride	1.42	2210	13300	4.64	N/R
			Cyclosporine	2.18	1850	13400	3.3	N/R
			Digoxin	1.88	1870 ^a	11300	3.83	N/R
			Erythromycin	1.61	2380 ^c	23900 ^c	6.63	N/R
			Fluconazole	1.77	2190 ^c	21400 ^c	5.99	N/R
			Ketoconazole	2.53 ^c	2610 ^c	51500 ^c	9.21	N/R
			Midazolam	2.7	1700	11100	3.46	N/R
			Saquinavir	3.1 ^b	3000 ^c	33700 ^c	6.49	N/R
			Simvastatin	1.78	1890	12600	5.05	N/R
			Verapamil	1.77	2560 ^c	22800 ^c	7.84	N/R

due to the rapid metabolism by CYP3A4 and CYP3A5 enzyme pathways.²⁶

The PK parameters such as $AUC_{0-\infty}$ and $C_{\max}$ were not affected by renal function because eplerenone undergoes less excretion when the dose is < 1 %. In terms of $t_{1/2}$, there was no significant difference observed in the renal dysfunction subject because it was independent of renal clearance and apparent plasma volume of distribution parameters. For hemodialysis patients, the AUC and $T_{\max}$ were decreased which may be attributed to the fluctuations in oral absorption of eplerenone.³⁰ In plasma, the AUC and $C_{\max}$ value of total radioactivity were greater than the red blood cells, possibly due to the total drug binding to plasma being greater than whole blood. In comparison between blood and saliva, the concentration was decreased due to the establishment of steadiness between free drugs and metabolites enzymes.²⁶ In a drug-drug interaction study, the AUC of eplerenone was increased when given with verapamil which may be due to the existence of two possibilities of verapamil. Firstly, it is an asymmetric carbon drug with enantioselective catabolism reaction and plasma binding protein properties; second, it is a substrate for P-glycoprotein (P-gp) that was metabolized in the gastrointestinal tract. When ketoconazole was co-administered with eplerenone, $AUC_{0-\infty}$ was increased because the former is an inhibitor of the CYP3A4 enzyme.³¹

This review provides detailed analysis of PK of eplerenone regarding increase or decrease in $C_{\max}$, AUC, and CL/F thus

providing clinical implications for patients with hypertension, heart failure, and kidney failure due to the requirement of adjustment of doses after multiple drug administration in comorbid patients. The strength of this systematic review is that it includes all healthy and diseased studies of eplerenone from 2003 to 2022. In this review, 08 studies were included from five different databases, so there is less chance of missing data which may further enhance the reliability and validity of the results. Due to expected human error, there is a possible chance of bias. In this current review, the proportion of age, gender, weight, height, and ethnicity of selected studies were not considered. For PK evaluation of eplerenone in diseased populations, only hypertensive and renal failure patients were discussed because PK data are available only for these diseased studies. Moreover, only the oral route of administration was studied. A limited number of studies were available on eplerenone, due to which the results could not be generalized.

CONCLUSION

This review comprises all the previously reported PK studies of eplerenone in healthy subjects, hypertensive and renal failure populations. These studies suggest that PK parameters of eplerenone in the healthy population, such as $AUC_{0-\infty}$ and $C_{\max}$ were directly proportional to dose. Moreover, eplerenone did not alter the PK profile of drugs that belong to CYP450 or P-glycoprotein transporter. The data summarized from the previously published studies can be helpful for the development



of the PK model, as well as for the health practitioners in optimizing doses among hypertensive and kidney failure patients.

CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS:

Conceptualization: MK. RA and AA; methodology: NW, KA software: SA, MA; validation: RJ, HA; formal analysis MK; investigation: SA, HA; resources, SA; data curation: MA, DA; writing-original draft preparation: SY, JA; writing-review and editing: MA; visualization: RA; supervision: MK; project

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