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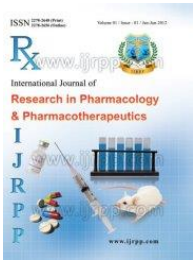

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Clinical outcome of haemodialysis on the pharmacokinetics of levocetirizinedihydrochloride

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ABSTRACT

The Levocetirizinedihydrochloride is a third-generation, non-sedating antihistamine, developed from the second generation antihistamine cetirizine. Chemically, levocetirizine is simply the isolated levorotary enantiomer of cetirizine. Concentrations of Levocetirizinedihydrochloride in serum and dialysate were determined by HPLC. The maximum serum Levocetirizinedihydrochloride concentration and the time to reach that maximum were 204 µg-1 and 0.75 hr, respectively. The terminal disposition half-life of Levocetirizinedihydrochloride in these patients was 8.3 hrs. The haemodialysis clearance of Levocetirizine was 11.0 ml/min^{-1}. Although this is approximately 27% of the apparent total body clearance of Levocetirizinedihydrochloride in subjects with normal renal function, the fraction of the dose removed by dialysis was only 7.2%. Thus, since haemodialysis does not produce a clinically significantly alteration in Levocetirizinedihydrochloride elimination, no supplemental dose should be necessary after dialysis.

Keywords: Levocetirizine, Haemodialysis, Pharmacokinetics, Renal failure.

INTRODUCTION

Levocetirizine, the active enantiomer of cetirizine, is an anti-histamine; its principal effects are mediated via selective inhibition of H1 receptors. The antihistaminic activity of levocetirizine has been documented in a variety of animal and human models. In vitro binding studies revealed that levocetirizine has an affinity for the human H1-receptor 2-fold higher than that of cetirizine (Ki = 3 nmol/L vs. 6 nmol/L, respectively). This increased affinity has unknown clinical relevance. Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet. The accumulation ratio following daily oral administration is 1.12 with steady state achieved after 2 days[1]. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. Food had no effect on the extent of exposure (AUC) of the levocetirizine tablet, but Tmax was delayed by about 1.25 hours and Cmax

was decreased by about 36% after administration with a high fat meal; therefore, levocetirizine can be administered with or without food.

Dose adjustment could also be needed in patients with nephritic impairment. Its has been confirmed that once administration of a 5 mg dose of radiolabeled oral levocetirizine nearly 84.5% as excretory product and and 12.7% in excreta. The result of dialysis on the disposition of levocetirizine but has not been reported [2]. Since the key route of elimination of levocetirizine is nephritic, dialysis may have a serious impact on its elimination. This study was devised to assess the pharmacology and haemodialysis of cetirizine in five patients with end-stage renal failure (ESRD) WHO were receiving chronic dialysis medical therapy.

MATERIALS AND METHODS

The five patients with end-stage renal disease getting chronic haemodialysis therapy has been involved in this current study. All patients were anaemic and hpyertensive and their renal malfunction were secondary to hypertension, nephrosclerosis. Every patient underwent a absolute physical examination and laboratory screening, as well as urinalysis, complete blood count, as well as an electrocardiogram (ECG) previous to participating in this study. Patients with current substantiation of hepatic disease, congestive heart malfunction, endocrine disorders, blood dyscrasias, or cancer were excluded. In due course of time, four weeks beforehand of the study none of the patient had received an investigational drug. For the management of renal failure all the patients were received the drugs.

Drug Administration and Sample Collection

The patients fasted for 8 h prior to drug administration until 2 hours after administration of the oral dose. Four hours beforehand of haemodialysis, each subject given one 10 mg levocetirizine dihydrochloride tablet with 150 ml water. Four hours after given the oral dose and just prior to the start of hemodialysis each patient had standardized food regimen. The characteristics of the dialysis system for each patient are described in Table No 2.

Assay

By high-performance liquid chromatography (HPLC) the concentration of levocetirizine in serum and dialysate has been determined. Amitriptyline has been used as an internal standard. An ethyl ether and n-butanol mixture was used for the extraction of levocetirizine and internal standard. Separation was skilled using a C-8 Sphereisorb, 5µ column. An UV detector set at 230 nm was used. The HPLC method is precise and accurate to 5 ng/ml^{-1} in serum and 3.1 ng. ml ~ in dialysate. The inter assay coefficient of variation ranged from 6.8% to 1.5% at levocetirizine serum concentrations of 5 and 500 ng/ml^{-1}, respectively.

Table No.1 Clinical characteristics of all patients

Clinical Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	39	56	47	68	59
Weight	62.8	72.6	59.3	64.5	68.0
Height	155.4	170.3	154.6	159.1	163.2
Sex	F	M	F	F	F

Around 5 ml of venous blood specimens were collected instantly preceding to and at 0.25, 0.5, 1, 1.5, 2, 3 and 4 hours after ingestion. Dialysis, at standard 4 h time, was begun after the 4 hours sample was obtained. Blood samples (pre filter) were taken at 4, 5, 6, and 7 hours after drug administration (during dialysis).

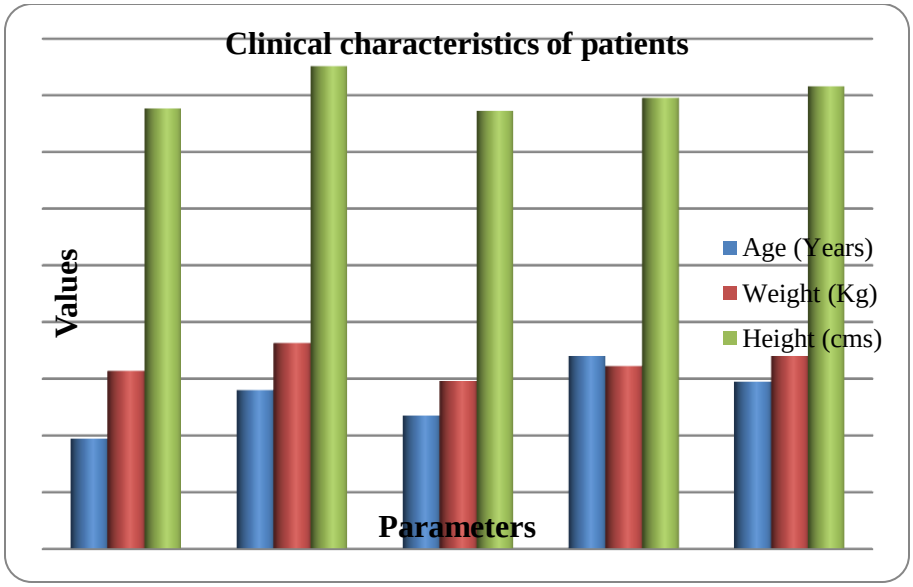

Figure No. 1 Clinical Characteristics of patients

In addition, at the 4 and 6 hours points, 10 ml post filter blood samples were obtained. Venous blood samples were also obtained at 7.25, 7.5, 7.75, 8, 12, 24, 36 and 48 h after drug administration[3-6]. The blood samples were allowed to coagulate at room temperature. After centrifugation, the serum was harvested and stored at - 20 °C until assayed. The total dialysis effluent was collected hourly and a 50 ml aliquot was frozen at - 20 °C until assayed for levocetirizine.

Table No.2 Haemodialysis Characteristics of patients

Clinical Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Average Dialysis Flow rate (ml/min^{-1})	487	495	476	515	513
Average blood pump flow rate (ml/min^{-1})	275	275	275	318	318
Average plasma flow rate (ml/min^{-1})	180	199	197	194	240
Dialyzer creatinine clearance during study (ml/min^{-1})	105	130	127	100	-
Average dialyzer $_{BUN}$ clearance (ml/min^{-1})	135	165	157	137	-

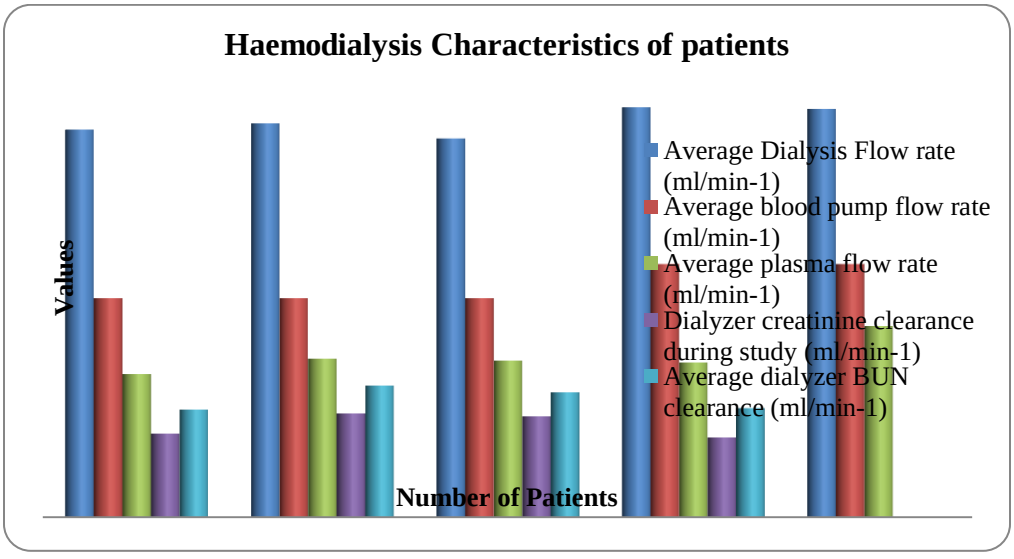

Figure No. 2Haemodialysis Characteristics of patients

SUMMARY

The mean venous serum concentration-time profile of levocetirizine in the 5 subjects has been determined. The C_{max} of levocetirizine (mean and standard deviation) was 40.42 ng/ml and the T_{max} was 0.8 hours. The totality amount of levocetirizine removed by dialysis, demonstrating that the fraction of the dose removed by dialysis significant.

CONCLUSION

In the view point that, the patients with impaired renal malfunction medication dosages are often not justified at clinical front. Especially in patients with stern renal impairment and declining renal impairment required dosage adjustments are often not executed. Therefore, because haemodialysis does not make a clinically significantly alteration in Levocetirizinedihydrochloride elimination, hence no supplemental dose ought to be essential after dialysis procedure.

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