



Available Online through
www.ijptonline.com

BIOEQUIVALENCE STUDY OF LEVOSULPIRIDE FORMULATIONS IN ANIMAL MODEL

S.Shanmugam¹, R.Babu^{2,*}, S.Satheeshkumar², P.Shanmugasundaram²

¹Adhiparasakthi College of Pharmacy, Melmaruvathur, Tamilnadu.

^{2,*}Research Scholar, Vels Institute of Science Technology and Advanced Studies (VISTAS), Vels University, Pallavaram, Chennai, Tamilnadu.

Email: shanmugam.saravanabhavan@yahoo.com

Received on: 11-02-2017

Accepted on: 27-03-2017

Abstract

A single dose complete crossover study of Levosulpiride was carried out in wistar rats. Blood samples were collected after predetermined time intervals. Plasma Levosulpiride concentrations were determined using RP-HPLC method. Plasma Levosulpiride concentrations as well as other pharmacokinetic parameters obtained were subjected to statistical analysis.

Key Words: Levosulpiride, HPLC, Pharmacokinetics.

Introduction

In recent years, sustained release drug delivery systems are gaining more interest as these systems deliver the drug continuously for prolonged period of time to maintain the steady state blood level concentration, therefore providing reduction in the dosing frequency and increasing better patient compliance. These systems are designed mainly for the drugs which are required to be taken frequently.

These sustained release drug delivery systems are prepared by using natural or synthetic or semi synthetic polymers. They offer many advantages like enhanced bioavailability, site specific drug delivery, and sustained release of drug over longer period of time, retention of formulation in entire length of gastrointestinal tract, release of desired concentration of drug at targeted site and improved patient compliance due to reduction in frequent dosing.

Levosulpiride, a sulpiride isomer is a selective D₂ receptor antagonist. It is used as antipsychotic, antidepressant, antiemetic agent, prokinetic and antidyspeptic agent. Plasma half life of 4 to 6 hours, time of peak plasma concentration (T_{max}) 3 hours, pKa 8.9, bioavailability is 25 to 30% and volume of distribution (Vd) is 0.639 L/kg after an oral dose of conventional tablets of levosulpiride. To reduce the frequency of administration and improve patient compliance, the SR formulation of Levosulpiride is desirable. Since Levosulpiride requires frequent dosing to

maintain therapeutic drug concentration, it was chosen as an ideal candidate for SR dosage form. Matrix tablets are prepared either wet granulation/ direct compression method. The study is undertaken to design and evaluate the SR tablets of levosulpiride with polymers like Chitosan, Xanthan gum and Guar gum. Chitosan, Xanthan gum and Guar gum is used because of its non-toxic nature, easy compression, swelling properties and accommodation to high level of drug loading. The aim of this study was evaluate the pharmacokinetics of levosulpiride in wister rats.

Materials and Methods

Materials

Formulated levosulpiride sustained release formulation, marketed levosulpiride sustained release formulation, Wistar rats, HPLC. All other chemicals and solvents were used in analytical grade.

Method

Formulation of levosulpiride sustained release tablets

The levosulpiride sustained release tablets were prepared by wet granulation technique. Levosulpiride was passed through sieve no #40. The release retarding polymers namely chitosan, xanthan gum and guar gum and additive microcrystalline cellulose and magnesium stearate as glidant was passed through sieve #60. Polyvinyl pyrrolidone in isopropyl alcohol was used as granulating agent to get coherent mass. The wet granules were dried at room temperature. The dried granules were passed through sieve no # 14. Mixed with magnesium stearate and compressed into tablets on a 16 station Rotary Cad mach machine.

Study design

The selected matrix tablet (LF3) was compared with marketed sustained release formulation (M1) of levosulpiride to ascertain the bioequivalence of developed product. The experimental protocol has been approved by the institutional animal ethical committee (Registration number is XIX/PCOL/09)

The overnight fasted Wistar rats were divided into 3 groups each containing six animals. Group I animals received pure levosulpiride suspended in 0.5 % carboxy methyl cellulose in distilled water given orally at a dose of 5 mg of the drug/kg body weight of animals. Group II animals received formulated granules of levosulpiride sustained release tablet suspended in 0.5 % carboxy methyl cellulose in distilled water given orally at a dose of 5 mg of the drug/kg body weight of animals and group III animals received crushed granules of marketed levosulpiride sustained release tablet suspended in 0.5 % carboxy methyl cellulose in distilled water given orally at a dose of 5 mg of the drug/kg body weight of animals. Blood samples were collected at intervals of 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 12.0 h after

postdose into heparinized tubes from the orbital sinus of the animals. The plasma was separated immediately by using cold centrifuge at 3000 rpm for 15 min and the plasma was stored at -20 °C until analysis.

The concentration of levosulpiride in plasma was determined by HPLC method. Chromatographic condition-HPLC system consisted of Shimadzu SPD10ATVP pump and rheodyne injector with 20 µL fixed volume loop and shimadzu SPD10A UV detector controlled by the software kinetica. Separation was carried out at room temperature phenomenax C18 (150.0 mm × 4.6 mm with 5 µ particle size) column. The mobile phase was methanol and 0.002 % formic acid, 5mmol/L ammonium acetate in water (80:20). The detector wavelength was set at 292 nm. Total run time was 8 min and the injection volume was 5 µL. Retention time of levosulpiride and IS were 2.79 and 2.93 min.

Result and discussion

Levosulpiride was detectable in plasma within 0.5 h after its oral administration in rats. The absorption was rapid with pure levosulpiride as indicated by low T_{max} value (0.39 h); whereas the sustained release compositions exhibited delayed absorption as demonstrated by high T_{max} (0.82 h) values. This delayed absorption may be due to the extended release effect of the swellable hydrophilic polymer present in the matrix tablets which might have increased the viscosity and hence reduced the absorption rate. The C_{max} of marketed tablet and prepared tablet were lower as compared with pure levosulpiride. However the C_{max} of marketed tablet and prepared tablet were found to be superimposable. The half-life of pure levosulpiride was found to be less which specifies the rapid removal of drug from plasma and the rapid elimination of pure drug was further supported by high elimination rate constant. On the contrary, sustained release compositions exhibited high half-life and low elimination rate constant values indicating that drug remains in the body for longer period of time and exhibits prolonged effect. The low value of area under the curve (AUC) observed with pure levosulpiride may be due to its rapid absorption and elimination from the body. On the contrary, the sustained release compositions showed high AUC values indicating increased bioavailability of drug. All these parameters clearly reveal that the sustained release formulation prepared by us exhibited prolonged effect of levosulpiride in rats.

Table-1: Pharmacokinetic Parameters from the Plasma Concentration- Time Curve in Rats.

Parameters	LS	LF3	M1
C_{max} (µg/mL)	2.10 ± 1.01	1.26 ± 0.56	1.40 ± 0.94
T_{max} (h)	0.39 ± 0.58	0.82 ± 0.34*	0.79 ± 0.42*
$t_{1/2}$ (h)	5.40 ± 0.52	6.10 ± 0.88	6.00 ± 0.26

		<i>R.Babu *et al. /International Journal of Pharmacy & Technology</i>	
AUC _{0-t} (µg-h/mL)	7.65 ±1.40	5.48 ±0.90*	5.70 ±1.25*
K _e (h ⁻¹)	0.201 ± 0.64	0.152 ± 0.48*	0.161 ± 0.80**

All values are expressed as Mean ± SD of six animals each. LS = pure levosulpiride; M1 =composition of marketed tablet; LF3 = composition of F3 tablet; C_{max} = maximum plasma concentration; T_{max}= time for maximum plasma concentration;t_{1/2}= biological half life; AUC =area under the curve; K_e= elimination rate constant. *Significant compared to LS (p < 0.05), **significant compared to M1 (p < 0.05).

References

1. Maryadele J.O' Neil, 4th eds.: The Merck Index: Merck&Co,INC.USA, pp.1542(2006).
2. Chuting Gong, Janvier Engelbert Agbokponto, Pharmacokinetics of levosulpiride after single and multiple intramuscular administration , Acta Pharmaceutica Sinica B, 4,402(2014).
3. Cho HY, Moon JD and Lee YB, Pharmacokinetics and bioequivalence evaluation of 2 levosulpiride preparations after a single oral dose in healthy male Korean volunteers, Int.J.Clin Pharmacol Ther, 42,174(2004).
4. Sparsh Gupta, Levosulpiride: A Review , Delhi Psychiatry Journal, 10,144(2007).
5. www.saingroup.com
6. http://www.mentalhealthamerica.net
7. Ghosh, M.N., Experimental Pharmacology, 3rd edn.,Hilten and company, Kolkatta, 2005, pp. 176-178.
8. Kulkarni, S.K., Handbook of experimental Pharmacology, Ist edn., Vallabha prakashan, New Delhi,1987, pp 67,77.
9. Leon Shargel, Applied Biopharmaceutics and Pharmacokinetics, 5th edn., McGraw Hill, London, 2005,pp. 45,518,525.
10. Tripathy, S.,Sharma, P.K and Banthia, A.K., Preparation , characterization, in vitro and in vivo evaluation of aceclofenac ointment, Indian Drugs, 2005,42, pp. 618.
11. Sandeep Singh Tanwar, Formulation and evaluation of sustained release matrix tablets of levosulpiride, Research Journal of Pharmaceutical and Chemical Sciences, 2013, 4, pp. 1326-1332.
12. Divya G Thakkar, Development and validation of UV- Spectroscopic and RP-HPLC method for simultaneous estimation of levosulpiride tablet dosage form, Journal of Pharmaceutical Sciences and Bio Scientific Research, 2013, 3, pp. 108-114.