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Research Article

TOTAL BODY CLEARANCE AND MEAN RESIDENCE TIME OF TAMOXIFEN IN FEMALE HEALTHY SUBJECTS

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ABSTRACT

Objective: To investigate total body clearance and mean residence time after single oral dose of tamoxifen in female healthy subjects focusing on two concepts pharmenzymonetics and pharmgeonetics for the first time in Pakistan.

Methodology: Two parameters were investigated in eight healthy female subjects after single oral dose of 20mg tablet Nolvadex brand. Blood samples were collected and plasma concentration was determined by Gradient HPLC method to evaluate the total body clearance and mean resident time. Subjects were kept under observation for 4 weeks detecting any adverse signs or symptoms.

Results: Value of total body clearance mean ±SE was 39.7 ± 0.55 L/Hr/Kg and that of mean residence time MRT is 15.18 ± 0.19 Hours. There were no adverse signs reported during 4 weeks of direct observation of subjects after oral single dose. Blood pressure, temperature, pulse rate and appearant activity of subjects remained normal.

Conclusion: The total body clearance and MRT of tamoxifen is greater as compared to literature value in the healthy females of Pakistan due to pharmgeonetics.

Keywords: Total body clearance, mean residence time, tamoxifen body clearance, total body clearance breast cancer medicine.

INTRODUCTION

Breast cancer is the second highly important cause of mortalities in the world. It does not cover only women but also men and food animals. Metastatic breast cancer is more drastic as the main causative agent is not known. Although, multiple causes have been known to be involved in the metastatic breast cancer, but still chemotherapy is a question to absolutely treat this cancer (Shahbaz et al., 2014). 1.3 million Women suffer from breast cancer in United States. Similarly 1 out of every 8 women had breast cancer reported in 2014 (Breast Cancer, 2013). Not only humans but also animals become victim of breast cancer as shown by the research on cow's breast cancer at Harvard University in 2006.

Total Body clearance and mean residual time are important pharmacokinetics parameters. CLB tells speed of drug eliminated, metabolized or distributed throughout the body (Boomers, 2015). Thus how a drug reacts pharmacologically is widely based on the total body clearance of a drug. Mean residence time is how long tamoxifen molecule stays in the body is a critical parameter for the better breast cancer treatment. As the tamoxifen is highly protein bound its MRT differs widely based on the metabolism of tamoxifen prodrug. Due to geographical changes this metabolism differs widely among the individuals of different countries.

Tamoxifen is an anti breast cancer drug being used in the females of Pakistan for more than 5- 10years after being diagnosed with breast cancer. Therefore total body

clearance and mean residence time was calculated in females. However no enzymatic test is carried out before prescription as metabolism of this medicine depends on the enzyme CYP2D6 variants (Abraham et al., 2010, Kristine et al., 2012). Thus how long tamoxifen will stay in the body is an essential factor not been studied in Pakistan for this drug. Optimal therapeutic usage of imported drug is not achieved due to change of total body clearance and mean residence time.

MATERIAL AND METHODS

CLb and MRT were investigated in the eight healthy female subjects selected from University or nearby residential area of Faisalabad.

Selection Criteria

Volunteers of age group 35-60 years were selected after physical examination and clinical history to be declared as healthy. All volunteers were informed about the objective of study, frequency of sampling and possible side effects of drug and written consent with each volunteer was made.

Drug/ Chemicals

Tamoxifen, 20 mg tablet from ICI Pvt. Ltd., Lahore, Pakistan was taken.

The following chemicals used in the entire study were of HPLC grade:

- Ammonium acetate(Merck, Germany)
- Acetonitrile (Fischer Scientific Limited, UK)
- Methanol (Fischer Scientific Limited, UK)
- Deionized water.

A single dose of Tamoxifen 20 mg tablet of Nolvadex brand was given orally to each volunteer after breakfast. In all experiments, a blood blank sample was collected before drug administration. Blood sample of 5ml each was collected from the cubital vein of each volunteer either directly with the help of a disposable syringe or through I.V cannula of 20 gauge needle at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24 hours after oral dose. The pH of fresh sample of blood was noted in each experiment by a pH meter (Beckman HS, Germany) with a glass electrode at 37^0C. Collected blood was centrifuged and plasma was separated and stored at -2^0C.

Drug Analysis

After determination of Tamoxifen concentration in plasma samples using HPLC (Sykam, S-3210) analytical method using UV/Vis detector (Sykam, S-3210) (Kashtiaray et al. 2011), CLB and MRT calculations were done with the computer programme MW/PHARM version 3.02 by F. Rombout, in cooperation with University Centre for Pharmacy, Department of Pharmacology and Therapeutics, University of Gronigen & Medi/Ware, copy right 1987-1991.

RESULTS

The mean ± SE total body clearance (Clb) determined was 39.7 ± 0.55 L/hr/Kg. The mean ± SE mean residence time (MRT) of tamoxifen after single oral dose was 15.18 ± 0.19 hours. The mean ± SE values of total body clearance (CLb) and mean residence time (MRT) are given in the Table 1. Similarly the figure 1 shows variation of the two parameters among the eight individuals of same environment and health condition. Fig. 1 depicts no significant difference of CL and MRT among the individuals which confirms that the two parameters do not alters under same geographical and health conditions. Figure 2 shows the effect of total body clearance on the mean residence time and hence the bars of volunteer 5 show an inverse relation between the two i.e. as the clearance showed a slight change the MRT also changed. Similarly slight decrease in total body clearance suggests slight increase in the mean residence time. This effect is also clear for volunteer 5 in Fig. 1.

After single oral dose of chemotherapeutic medicine tamoxifen, no notable adverse signs were observed and reported within 4 weeks of intake of tablet. This study also suggests that a single dose study do not apparently affects the human subjects. However clinical tests were not carried out in this study.

Table 1: Mean ± SE total body clearance and mean residual time of Tamoxifen following oral administration of 20mg in 8 adult healthy female subjects by one compartment model.

Subject No.	Cl_B (L/Hr/Kg)	MRT (H)
1	41.26	15.09
2	40.55	15.12
3	40.65	15.22
4	40.12	15.31
5	39.82	15.82
6	41.01	14.93
7	41.03	15.15
8	40.80	14.82
Mean ±SE	39.7±0.554402	15.18±0.150

Table 2: Sign and symptoms measured following oral administration of single dose of tamoxifen 20mg in 8 adult healthy female subjects.

Serial No.	**Signs** *Observed* / **Symptoms** Measured*	**Observed After Single Dose In 4 Weeks**
1	Temperature	Normal*
2	Pulse rate	Normal *
3	Blood pressure	Normal*
4	Nausea	*Nil*
5	Vomiting	*Nil*
6	Headache	*Nil*
7	Dizziness	*Nil*
8	Apparent activity	*Normal*

DISCUSSION

The total body clearance of 39.7 ± 0.55 L/hr/kg is higher than one of the study 11.34 L/Hr/Kg (Lien et al., 1990) which is due to more water intake and health condition of female volunteers and the later study was performed on patients rather than healthy volunteers. As in breast cancer patients more estrogen (negative feedback) leads to more competition for tamoxifen molecule to retain in the body (Martine et al.. 2013) and less total body clearance. In the present study, the higher value of Clβ for Tamoxifen than literature cited may be endorsed higher Vd. Half life of drug is dependent on the Clβ (Total body clearance of that drug).The alteration in total body clearance affects the half life (Prescott and Baggot, 1988).

This is described by term "pharmenzymonetics" and "pharmgeonetics".

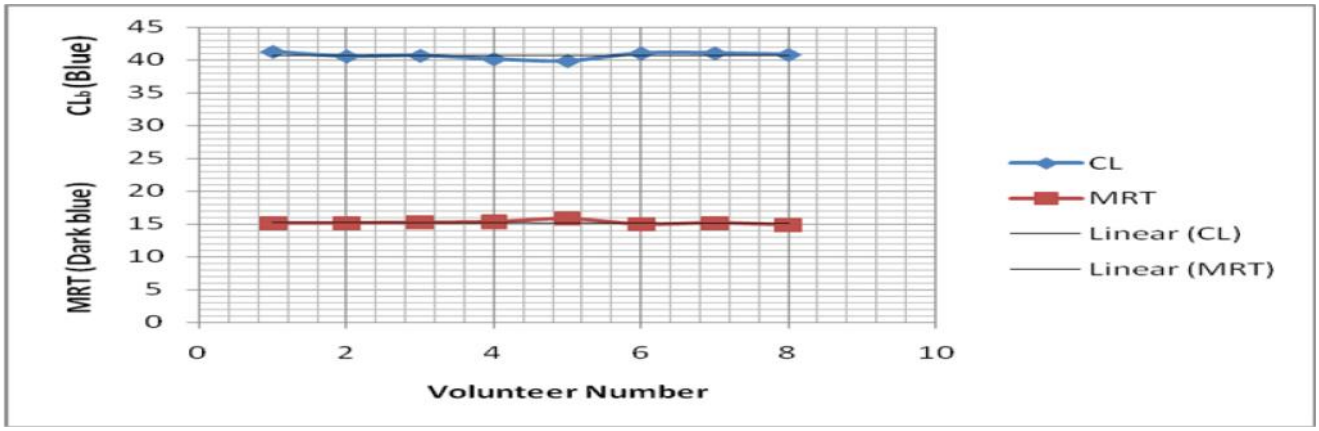

Figure 1: Variation in Total body clearance and Mean Residual Time of Tamoxifen due to environment after single oral administration of 20mg tablet in 8 healthy female volunteers.

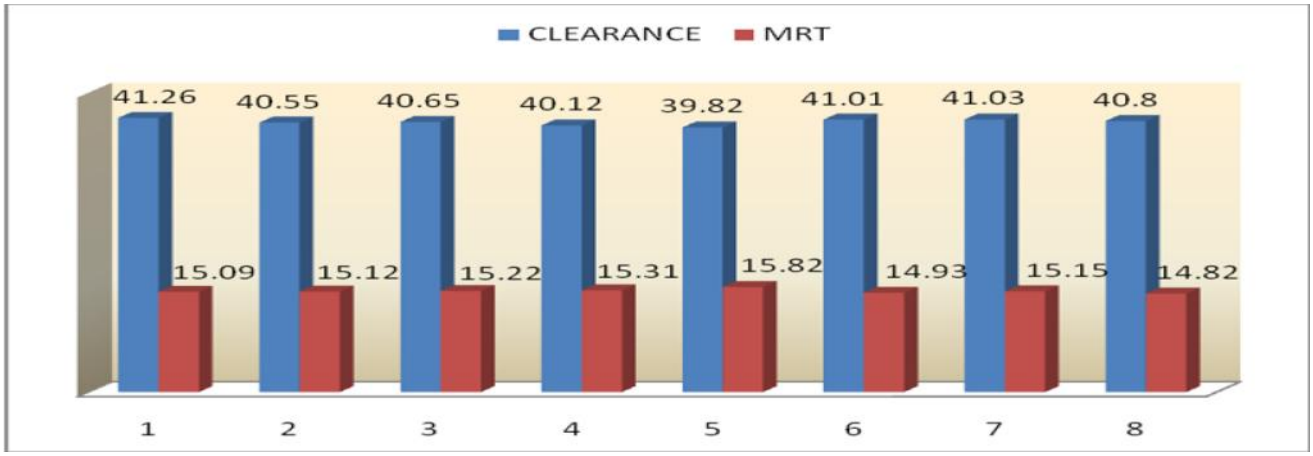

Figure 2: Effect of Total body clearance on Mean Residual Time of Tamoxifen after single oral administration of 20mg tablet in 8 healthy females.

Pharmgeonetics is the study of changed effect of medicine in the living body due to change of environment and genetic makeup. Similarly pharmenzymonetics is the study of changed behavior of medicine in the living body due to enzyme and genetic makeup. Several enzymes are involved in these metabolic pathways of tamoxifen, with CYP2D6 playing a pivotal role (Golander et al., 1980). In subject no. 5, the decrease though very slight in CL showed similar slight increase in the MRT which defines the accuracy of study and natural phenomenon i.e. increase clearance is inversely proportional to residence time.

The clearance of Tamoxifen in the present study is under the range of 41.2-40.8 l/hr/kg.

Total body clearance is altered in body due to various factors include:

1. Fraction of the unbound drug in the body.
2. Maximal ability of the organ to remove the drug.
3. Blood flow to the different organs

Mean residence time is the time required to eliminate the 63% of the drug from the body. Or mean residence time is also defined as the estimate of the persistence time of the drug in the body. The mean residence time of single dose of Tamoxifen 20 mg after oral administration was under the ranged from 15.0-14.2hr of with mean ± S.D was 15.1 ± 0.15hours in the present study. This suggests that health sector is far away from the main therapeutic outcomes and standard treatment guidelines as the research based on geographical region is missing (Shahbaz et al., 2015). No adverse signs after single dose opens way for more clinical trials.

CONCLUSION

The changed values of CL and MRT than literature value suggests that the healthy volunteers of Pakistan behaves in a faster way for clearance of tamoxifen. A comparison of different pharmacokinetics parameter of various drugs in different species of animals verified considerable deviation when compared with the literature values (Nawaz, 1982; Javed et al., 2009).Not only species but we may observe this change in various age groups. As the value obtained of two parameters in current study are different as compared to other species as mice, rat and even dogs. This change is due to pharmaenzymonetics and pharmgeonetics.It may also be concluded in case of Cyp2D6 which varies in different individuals that everybody is a different case for treatment.

REFERENCES

1. Abraham J, M Maranian1, K E Driver1, R Platte, B Kalmyrzaev1, C Baynes, C Luccarini, M Shah1, S Ingle, D Greenberg, HM Earl, AM Dunning1, P Pharoah, C Caldas, (2010). CYP2D6 gene variants: association with breast cancer specific survival in a cohort of breast cancer patients from the United Kingdom treated with adjuvant Tamoxifen. Breast Cancer Research, 12:R64.
2. Adam HK, JS Patterson, JV Kemp (1980). Studies in the metabolism and pharmacokinetics of Tamoxifen in normal volunteers. Cancer Treat Rep 64: 761
3. Baggot JD, (1977). Principles of drug disposition in domestic animals: The basis of veterinary Clinical Pharmacokinetics. W.B. Saunders Co., 199 Ed, Philadelphia,: 72-74.
4. Berliere, M., Duhoux, F. P., Dalenc, F., Baurain, J. F., Dellevigne, L., Galant, C., ... & Machiels, J. P. (2013). Tamoxifen and ovarian function.
5. Dickschen K, Stefan W, Kirstin T, Jörg Lippert, Georg Hempel,and Thomas Eissing. (2012). Physiologically Based Pharmacokinetic Modeling of Tamoxifen and its Metabolites in Women of Different CYP2D6 Phenotypes Provides New Insight into the Tamoxifen Mass Balance. Pharmacol, 3: 92
6. Golander Y, LA Sternson (1980). Paired-ion chromatographic analysis of Tamoxifen and two major metabolites in plasma. J Chromatogr 181: 41.
7. https://www.boomer.org/c/p3/c05/c0510.html. (2015).
8. Javed I, Z Iqbal, Z Rahman, MZ Khan, M Faqir, B Aslam, M A Sandhu and JI Sultan. (2009). Disposition kinetics and optimal dosage of ciprofloxacin healthy domestic ruminant species. Actavet Benro 78: 155-162.
9. Kashtiaray K, H Farahani, Farhadi1, B Rochat and HR Sobhi. (2011). Trace Determination of Tamoxifen in Biological Fluids Using Hollow Fiber Liquid-Phase Microextraction Followed by High-Performance Liquid Chromatography-Ultraviolet Detection. Am J of Anal Chem, 2: 429-436.
10. Li XF, S Carter, NJ Dovichi, JY Zhao, P Kovarik and T Sakuma, (2001). Analysis of Tamoxifen and its metabolites in synthetic gastric fluid digests and urine samples using high-performance liquid chromatography with electrospray mass spectrometry. J Chromatogr A, 914: 5-12.
11. Lien EA, Anker G, Lønning PE, Solheim E, Ueland PM (1990) Decreased serum concentrations of Tamoxifen and its metabolites induced by aminoglutethimide. Cancer Res 50: 5851.
12. Nawaz M, and BH Shah, (1982). Renal clearance of endogenous creatinine and urea in sheep during summer and winter. Res Vet Sci, 36: 220-224.

13. Shahbaz, K., Mehfooz, A., & Khadam, W. (2014). Breast Cancer Vaccination-An Envisioned Future. Indo American Journal of Pharmaceutical Research, 4(3), 1580-1585.
14. Shahbaz, K. (2015). Comparison Between Standard Treatment Guidelines Of Preeclampsia Proposed By Who And Current Practice In Tertiary Care Centers. J. PP. Sci, 4(8), 1566-1593.
15. Zhu YB, Q Zhang, JJ Zou, CX Yu, DW Xiao, (2008), Optimizing high-performance liquid chromatography method with fluorescence detection for quantification of tamoxifen and two metabolites in human plasma: application to a clinical study. J Pharm Biomed Anal.46:349-55.

