



Assessment of food effect on 12.5 mg Hydrochlorothiazide capsule in healthy Indian subjects

Ashvin M. Patel^{1,2*}, Falguni Majmudar³, Naveen Sharma², Bhavin N. Patel²

1. Research Department, Hemchandracharya North Gujarat University, Patan-384265, Gujarat, India

2. Bio-Analytical Laboratory, Clantha Research Ltd., Bodakdev, Ahmedabad-380054, Gujarat, India.

3. Department of Pharmacology, SMT. N.H.L. Municipal Medical College, Ellis bridge, Ahmedabad 380006, Gujarat, India.

ABSTRACT

For the assessment effect of food on the pharmacokinetic parameters of Hydrochlorothiazide(HCTZ) data of reference product (12.5 mg capsule) from two bio-equivalence studies were combined and evaluated. 36 male healthy subjects participated in the fasting and non fasting study. Subjects received the drug product after 12 hours(h) overnight fast for the fasting study and after 30.0 minutes of high fat breakfast for the non-fasting study. Blood samples were collected from time of dosing to 60 h of the post dosing at predefined time. Blood samples were analyzed for the concentration of the HCTZ by using validated LC/MS/MS technique. Food decrease the C_{max} by about 28% and AUC by about 9%. While T_{max} was delayed about 97%(from 2.185h to 4.320h). food prolonged the mean resident time of HCTZ.

Keywords:Hydrochlorothiazide; food effect; Pharmacokinetics; bioavailability

*Corresponding Author [Email: ashvinpatel1381@yahoo.in](mailto:ashvinpatel1381@yahoo.in)

Received 20 June 2014, Accepted 10 July 2014

INTRODUCTION

Hydrochlorothiazide[HCTZ], a diuretic of the class of benzothiadiazines.¹ Thiazide diuretics are recommended for first-line treatment of hypertension.²⁻³ Hydrochlorothiazide chemically known as (6-Chloro-3,4-dihydro-2H-1,2,4-benzothiazine-7-sulfonamide 1,1-dioxide).⁴ Hydrochlorothiazide has limited solubilities in aqueous media hence poorly absorbed from GI track.³ Hydrochlorothiazide is not metabolized in body and excreted unchanged in urine. The oral bioavailability of the drug was reported to be 60–80% of the administered dose.⁵ Hydrochlorothiazide reduces plasma volume, increases plasma rennin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium.^{1-2,4} Hydrochlorothiazide promotes natriuresis and volume depletion triggering the release of rennin and increasing the dependency of BP control on angiotensin II.⁶ Absorption of hydrochlorothiazide is effected due to presence of anionic exchange resins.² Hydrochlorothiazide is widely used in pharmaceutical formulations to make single or that combined with other antihypertensive drugs, for treating edema hypertension, diabetes insipidus, hypoparathyroidism, etc. The combination of losartan and hydrochlorothiazide is successfully used in the treatment of hypertension.¹ Hydrochlorothiazide is of Class IV agent of BCS classification having poor bioavailability and poorly absorbed over the intestinal mucosa properly.⁶⁻⁷ Absorption is impaired in patients having intestinal shunt surgery and patients with cardiac failure. Plasma half-life averages 10h in subjects with normal renal function. It is prolonged in renal failure as the drug is mainly eliminated via the kidneys in unchanged form.⁸

MATERIAL AND METHODS

Study design

Both the bio-equivalence studies were Single dose, open label, two sequence, two period, randomized, balanced, crossover studies conducted on 36 healthy, adult, male human subjects for fasting and non-fasting phase. In the fasting study Hydrochlorothiazide 12.5 mg capsule (Watson Pharmaceuticals Inc., Corona, CA 92880, USA) was administered after overnight fasting of 12.0 hours, subjects were served food at different time which contained the nutrients as per table-1. In the non-fasting study hydrochlorothiazide 12.5 mg capsule (Watson Pharmaceuticals Inc., Corona, CA 92880, USA) was administered after 30.0 minutes of high fat breakfast, subjects were served food at different time which contained the nutrients as per table-1.

Participants

All the subjects were informed of the aim and risk involved in the study and written consent were obtained. Written consent is the process by which subjects voluntarily confirm their willingness in a particular trial after having been informed of all aspects of the trial which are relevant to decision to participate in trial like purpose, procedures how to conduct, benefits, risks/discomforts of trial in written. The inclusion criteria for subject selection was based on the age (18 years or above), body mass index (between 18.5 and 30.0 kg/height²), general physical examination, electrocardiogram and laboratory tests like hematology, blood chemistry, urine examination and immunological tests, demographics data given in table-2. The exclusion criteria included subject with history of alcoholism, smokers and having a disease which may compromise the haemopoietic, gastrointestinal, renal, hepatic, cardiovascular, respiratory, central nervous system, diabetes, psychosis or any other body system. All the subjects who meet inclusion and exclusion criteria mentioned in protocol and were judged eligible for study, based on medication history, physical examination, vital signs and clinical laboratory tests. Approval for the study was obtained from Independent Ethics Committee. The study was conducted in accordance with internationally accepted standards of good clinical practices (ICH), good laboratory practices (21 CFR 312.61 and local regulatory requirements).⁹

Blood sampling

Blood samples were collected in vacutainers containing K₃ EDTA prior to dosing and at predefined sampling time points as follows, 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 60.0 h Post dosing. Blood samples were centrifuged at 4°C for 15 minutes, plasma was separated, transferred to labeled polypropylene tubes and stored in the freezer set at -20°C ±10°C until analysis.

Bioanalytical Method

Plasma samples of different time point were analyzed for the concentration of Hydrochlorothiazide using validated LC-MS/MS method. Liquid-liquid extraction procedure was used to extract hydrochlorothiazide from plasma samples. Hydrofurothiazide was used as an internal standard. The linear dynamic calibration curves range was kept from 0.2000 ng/mL to 200.0 ng/mL for hydrochlorothiazide and API 4000 tandem mass spectrometer was used for analysis.

Pharmacokinetics Analysis

The analytical data was used to calculate the pharmacokinetic parameters C_{max}, T_{max}, AUC_t (the area under the plasma concentration –time curve from time zero to the time of the last non zero

concentration) and AUC_i (the area under the plasma concentration –time curve from time zero to the infinite time) using a non-compartmental analysis of WinNonlin[®] professional software. The pharmacokinetic parameters and drug plasma concentration were evaluated statistically using SAS[®] for effect of food.

RESULTS AND DISCUSSION

All oral doses were well tolerated by the subjects, and no adverse events were reported. Pharmacokinetic parameters for HCTZ are presented in Table-3. Percentage different on pharmacokinetic parameters (AUC_t , C_{max} and T_{max}) are presented in Table-4 and graphical representation of same done in Figure-1. Mean plasma concentration of HCTZ-Time profile was demonstrated in Figure-2. AUC_t and AUC_i were decreased by about 9% due to presence of food. C_{max} of HCTZ was decreased about 28% in presence of food while as T_{max} was delayed about 97% (2.185h to 4.320h). Fed to fasting ratio for geometric least square mean found 91.41% for AUC_i , 91.21 for AUC_t and 72.53% for T_{max} of HCTZ. 90% confidence interval (CI 90) for AUC_i (83.81-99.68) and AUC_t (83.66-99.54). Statistical result on log transformed data was given in table-5.

Table 1: Nutrition during Study.

| Nutrition | | | | | | | | |
|--------------|--------------------|--------------|---------------|--------------|--------------|--------------|-----------------|---------------|
| Timing | Carbohydrates (gm) | | Proteins (gm) | | Fat (gm) | | Energy (K.Cal.) | |
| | Fasting | NonFasting | Fasting | NonFasting | Fasting | NonFasting | Fasting | NonFasting |
| Dinner* | 163.8 | 117.8 | 31.1 | 22.1 | 26.8 | 21.6 | 1015.5 | 753.2 |
| Breakfast | NA | 62.4 | NA | 33.1 | NA | 62.6 | NA | 944.1 |
| Lunch | 262.14 | 109.7 | 28.4 | 25.5 | 27.2 | 17.9 | 929.5 | 697 |
| | 3.9 | | | | | | | |
| Snacks | 93.2 | 195 | 6.3 | 33.5 | 14 | 2.5 | 523 | 5.8 |
| Dinner | 120.3 | 85.9 | 31.4 | 19.0 | 30.8 | 25.7 | 866 | 649.4 |
| Breakfast | 57.8 | 57.8 | 14.3 | 14.3 | 6.5 | 6.5 | 345 | 345 |
| Total | 579 | 628.6 | 111.5 | 147.5 | 105.3 | 136.8 | 3679 | 3394.5 |

NA=Not Applicable, *=Prior to dosing

Table 2: Demographics table.

| | | Non fasting study | Fasting study |
|-------------------|-----------|-------------------|---------------|
| Subjects enrolled | | 36 | 36 |
| Study completed | | 36 | 36 |
| Gender | | Males | Males |
| Age | Mean(±SD) | 26(±6) | 25(±4) |
| (Years) | Median | 25 | 25 |
| | Min | 18 | 18 |
| | Max | 44 | 37 |
| Weight | Mean(±SD) | 59.7(±7.4) | 58.1(±6.4) |
| (kg) | Median | 59.3 | 58.6 |

| | | | |
|----------------|-----------------|-------------------|-------------------|
| | Min | 47.6 | 45.5 |
| | Max | 72.8 | 69.9 |
| Height (cm) | Mean(\pm SD) | 167.9(\pm 5.0) | 166.8(\pm 5.0) |
| | Median | 168.3 | 167.3 |
| | Min | 157.5 | 155.5 |
| | Max | 178 | 178 |
| Race | | Asian | Asian |

Table 3: Pharmacokinetic parameters of HCTZ.

| Statistical results on pharmacokinetic parameters | | | |
|---|----------------|-------------------|-----------------------|
| Parameters | | Fasting (n=36) | Non fasting (n=36) |
| AUC _t | Mean | 633.5 | 575.5 |
| | Std. Deviation | 141.6 | 118.4 |
| C _{max} | Mean | 85.26 | 60.87 |
| | Std. Deviation | 22.00 | 11.59 |
| T _{max} | Mean | 2.185 | 4.320 |
| | Std. Deviation | 0.758 | 0.844 |

n: Number of subjects enrolled

C_{max}: Maximum plasma concentration

T_{max}: Time to achieve maximum plasma concentration

AUC_t: (the area under the plasma concentration –time curve from time zero to the time of the last non zero concentration)

Table 4: Percentage different on pharmacokinetic parameters

| Parameters | Fasting* | Non fasting | %different of non fasting parameters |
|------------------|----------|-------------|---|
| AUC _t | 633.5 | 575.5 | 90.84 |
| C _{max} | 85.26 | 60.87 | 71.39 |
| T _{max} | 2.185 | 4.32 | 197.7 |

*= considering value of fasting stage as 100%

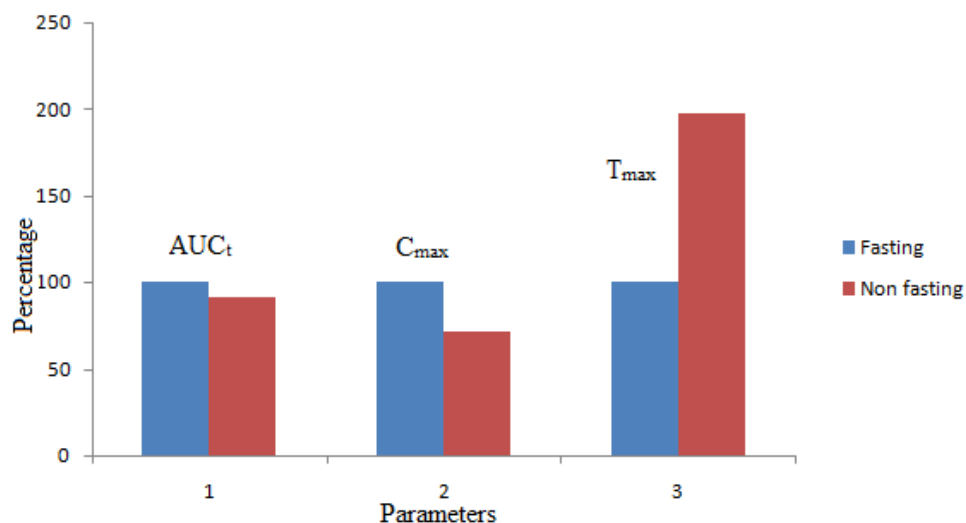
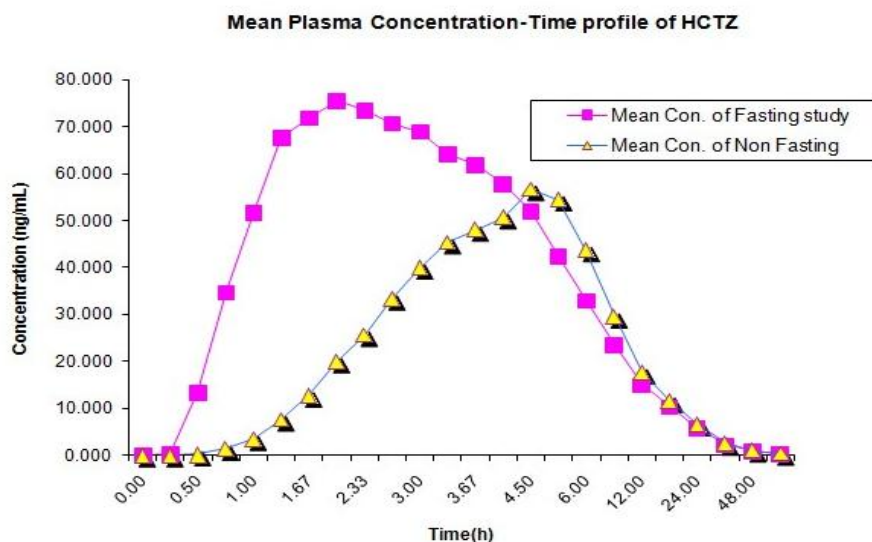


Figure 1: Percentage different on pharmacokinetic parameters**Table 5: Statistical result on log transformed data.**

| Dependent | GeoLSM (Fed) | GeoLSM (Fasting) | (Fed/Fasting) Ration (%) | CI 90 Lower | CI 90 Upper | P- Value | Power |
|-----------------------|--------------|------------------|--------------------------|-------------|-------------|----------|--------|
| Ln(AUC _i) | 569.996 | 623.590 | 91.41 | 83.81 | 99.68 | 0.0884 | 0.9947 |
| Ln(AUC _t) | 563.468 | 617.756 | 91.21 | 83.66 | 99.54 | 0.0806 | 0.9948 |
| Ln(T _{max}) | 59.843 | 82.508 | 72.53 | 66.33 | 79.3 | <0.0001 | 0.9925 |

GeoLSM: Geometric Least Square Means

**Figure 2: Mean plasma concentration –time profile of HCTZ**

CONCLUSION

HCTZ was quantified in biological matrix by mass spectrometry (MS-MS). Use of advance analytical technique gives more accurate results which help to study of pharmacokinetics profile of HCTZ. Food may affect the pharmacokinetics of drugs by different ways, including delayed gastric emptying, solubilization of drug by food and digestive fluids, complexation of drug with food components, alteration in hepatic blood flow and modulation of drug metabolizing enzymes by constituents of food.¹⁰ In addition, food intake has influence on presystemic metabolic clearance of drugs.¹¹ Pharmacokinetics of drug may be altered when co-administered with food.¹² Food intake not only modifies drug transit through the gastrointestinal tract, but may affect the metabolic transformation.¹³⁻¹⁴ Drug-food interactions are classified as those causing reduced, delayed, increased and accelerated absorption, and those in which food has no effect.¹⁵ Food may delayed absorption resulted slower gastric emptying rate and or increased gastric pH.¹⁶ Food decreased C_{max} and AUC of hydrochlorothiazide 21% and 8% respectively. Food also significantly prolonged the median t, 1.5 hours vs 3.5 hours.¹⁷⁻¹⁸ Present research indicates

present of food decreases the AUC of HCTZ about 9% while C_{\max} of HCTZ was decreased about 28%. Due to presence of food T_{\max} was delayed about 97% (2.185h to 4.320h), as HCTZ was excreted unchanged in the urine food only effect on absorption of HCTZ. Food decrease absorption of HCTZ, C_{\max} of HCTZ was decreased significantly as compare to AUC while as T_{\max} was delayed about 97% which indicate food prolonged the mean resident time of HCTZ resulting in decrease AUC 9% only.

ACKNOWLEDGEMENTS

The authors are indebted to Mr. Vijay Patel, Executive Director, Cliantha Research Ltd., Ahmedabad for providing necessary facilities to carry out this work. We gratefully acknowledge Mr. Anshul Dogra, Study Director and Mrs. Arpana Prasad, R & D Supervisor, Cliantha Research Ltd. for their continuous support, motivation and assistance during the course of this project.

REFERENCES

- 1 Sha L, Fan-Long B, Chun-Min W, Gui-Yan Y, Ben-Jie W, Rui-Chen G. Pharmacokinetics of Hydrochlorothiazide, Losartan and E3174 after Oral Doses of Losartan and Losartan/Hydrochlorothiazide in Healthy Chinese Male Volunteers Pharmacology & Pharmacy 2012;3:7-14.
- 2 A.Hilse, M.Zee, S.T. Turner, G.L. Schwartz, A.B. Chapman, O.H. Klungel, and E. Boerwinkle. Demographic, Environmental, and Genetic Predictors of Metabolic Side Effects of Hydrochlorothiazide Treatment in Hypertensive Subjects. Am J Hypertension 2005;18:1077–1083.
- 3 Khaled A, Yousif A, Yousry M. In vivo evaluation of hydrochlorothiazide liquisolid tablets in beagle dogs International Journal of Pharmaceutics 2001;222:1–6.
- 4 W. E. Barrett, R. A. Rutledge, H. Sheppard, and A. J. Plummer. The Pharmacology of Hydrochlorothiazide (Esidrix[™]), A New, Orally Effective Sulfonamide Diuretic. Toxicology And Applied Pharmacology 1959;1:333-349.
- 5 Sietsema, W.K. The absolute oral bioavailability of selected drugs. Int. J. Clin. Pharmacol. Ther. Toxicol. 1989;27:179–211.
- 6 Robert G, David R, Maryanne M, Ravi K, Jean P. Efficacy and Safety of Fosinopril/ Hydrochlorothiazide Combinations on Ambulatory Blood Pressure Profiles in Hypert American Journal of Hypertension APRIL 1996: 9;306-311.
- 7 M. Kataria, A. Bhandari, Biopharmaceutics drug disposition classification system: an extension of bio pharmaceutics classification system, International Research Journal of

- Pharmacy 2012; 3 (3).
- 8 Beermann, Björn; Groschinsky-Grind, Margaretha, Clinical Pharmacokinetics of Diuretics, Clinical Pharmacokinetics, 1980; May/June.
 - 9 Guidance for Industry: ICH E6 Good Clinical Practice, U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Centre for Biologics Evaluation and Research (CBER), (1996).
 - 10 Harris RZ, Jang GR, and Tsunoda S, Dietary effects on drug metabolism and transport. Clin Pharmacokinet 2003; 42 (13): 1071-1088.
 - 11 Melander A and McLean A, Influence of food intake on presystemic clearance of drugs. Clin Pharmacokinet 1983; 8 (4): 286-96.
 - 12 Welling PG. Effects of food on drug absorption. Annu Rev Nutr. 1996; 16: 383-415.
 - 13 Melander, Arne, Influence of Food on the Bioavailability of Drugs. Clinical Pharmacokinetics: 1979 Sep/Oct.
 - 14 Joseph M. Custodio, Chi-Yuan Wu, and Leslie Z. Benet, Predicting drug disposition, absorption elimination transporter interplay and the role of food on drug absorption. Adv Drug Deliv Rev. 2008 March 17; 60(6): 717–733.
 - 15 Singh B. N. Effects of Food on Clinical Pharmacokinetics. Clin Pharmacokinet 1999 Sep; 37 (3) 213-255.
 - 16 Lennernas H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Clin Pharmacokinet 1997 May; 32: 403-25.
 - 17 Vachharajani N.N. Shyu W.C. Greene D.S. Uderman H.D. Effects of Food on the Pharmacokinetics of Irbesartan/Hydrochlorothiazide Combination Tablet Clinical Drug Investigation, 1998; 6, 399-404.
 - 18 Barbhैया, RH, Craig, W. A., Corrick-West, H. P. and Welling, P. G. (1982), Pharmacokinetics of hydrochlorothiazide in fasted and nonfasted subjects: A comparison of plasma level and urinary excretion methods. J. Pharm. Sci., 71: 245–248.



AJPHR is
Peer-reviewed
monthly
Rapid publication
Submit your next manuscript at
editor@ajphr.com / editor.ajphr@gmail.com