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Bioavailability Studies and Clinical Pharmacology Studies of Fesoteridne Fumerate Drug on Muscarinic Antagonists

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A B S T R A C T

Pharmaceutically equivalent multi-source pharmaceutical products must be shown to be therapeutically equivalent to one another in order to be considered interchangeable. From the analyses of pharmacokinetic and statistical results it was inferred that, for the ln-transformed data, the 90 % confidence interval about the test to reference ratio of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of drug Fesoteridne Fumerate were falling within the bioequivalence acceptance range of 80.00 % - 125.00 %, which demonstrates the bioequivalence of test formulation 'T' with reference formulation 'R' under fasting conditions. All the study procedures followed were in compliance with the protocol and the ICH-GCP guidelines, Declaration of Helsinki and Schedule Y.

Keywords: Fesoterodine fumarate drug, Bio analytical Process, Pharmacokinetic Analysis, Statistical Analysis.

A R T I C L E I N F O

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1. Introduction

Bioavailability is used to describe the fraction of an administered dose of medication that reaches the systemic circulation, one of the principal properties of the drugs. Bioavailability and bioequivalence of drug products, and

drug product selection have emerged as critical issues in pharmacy and medicine during the last three decades.

Patient Related Factors:

Route of administration:

The resultant bioavailability may differ with respect to the amount absorbed, the rate of absorption or both. The bioavailability fraction f is the fraction of the administered dose that enters systemic circulation.[1]

f = bioavailable dose / administered dose

Bioavailability reflects the extent of the systemic availability of the active therapeutic moiety and is generally assessed by measuring the 'area under the concentration time curve' (AUC), the peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}).

Comparative Bioavailability Universal Approach:

A Universal Approach:

The two primary metrics for such concentration versus time profiles are the area under the curve (AUC) and the maximum observed concentration (C_{max}); the former customarily includes the AUC to the last sampling time in a trial (AUC_t) and the extrapolated total AUC to time infinity (AUC_∞). The time at the maximum concentration (T_{max}) is also of some minor interest. After obtaining the profiles in a comparative trial.

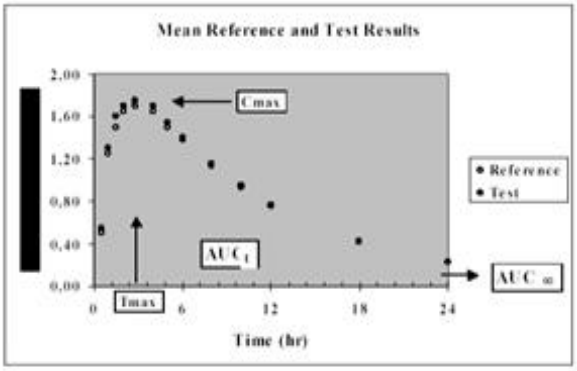


Figure 1: Comparative Bioavailability Trial

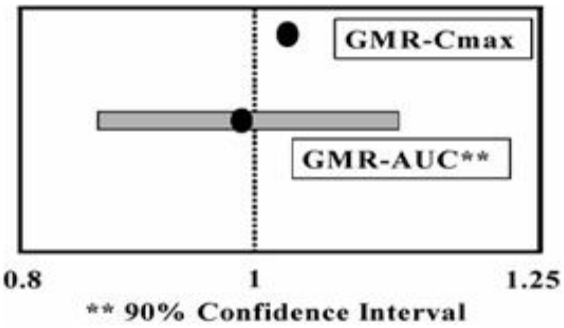


Figure 2: Diagram of urinary bladder and its parts

Pathophysiology: The pathophysiology of OAB is complex [9]. It is primarily caused by *detrusoroveraetivity*, defined as involuntary contractions of the detrusor muscle during thebladder filling phase as a result of continuous and increasing afferent activity from the bladder.[10]

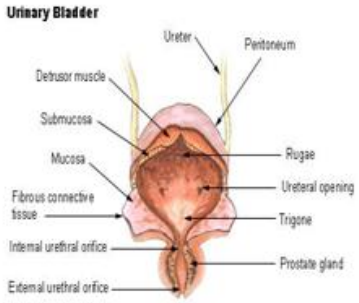
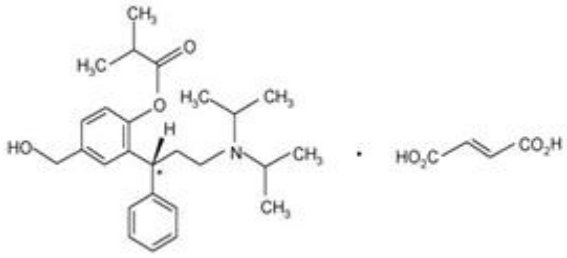


Figure 3: Statistical Assessment.

During normal function, the bladder should be relaxed as urine fills it. OAB is not purely a bladder condition, but may also involve pelvic floor-muscle dysfunction and behavioral issues. No drug can ever correct all facets of this multifactorial disorder.

2. Materials and Methods

Drug Profile: Fesoterodine fumerate



Empiracal Formula : $C_{30}H_{41}NO_7$
Molecular Weight : 527.66.
Category : Treat overactive bladder syndrome

Clinical Pharmacology:

Mechanism of Action

Fesoterodine is a competitive muscarinic receptor antagonist. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by non-specific esterases to its active metabolite 5-hydroxymethyl tolterodine, which is responsible for the antimuscarnic activity and is also one of the active moieties of tolterodine tartrate tablet and tolterodine tartrate extended-release capsules.

Pharmacokinetics:

1. Absorption
2. Effect of Food
3. Distribution
4. Metabolism
5. Excretion
6. Drug Interactions

Bio Analytical Methodology:

Validated LCMS/MS method will be employed for the estimation of Fesoterodinefumaratein plasma. Plasma samples from dropout subjects would not be analyzed, unless such dropouts or withdrawals are due to adverse events related to study drug.

Pharmacokinetic Analysis:

Pharmacokinetic parameters of Aspirin will be calculated using the Win Nonlin4.2 / 5.2 system version 9.1.3:

T_{max}: Time of maximum measured plasma concentration
C_{max}: Maximum measured plasma concentration following each treatment.
AUC_{0-t}: The area under the plasma concentration versus time curve from time zero to the last measurable concentration, as calculated by the linear trapezoidal method.
$AUC_{0-ã}$: The area under the plasma concentration versus time curve, from zero to infinity.
K_{el}: Apparent first order elimination or terminal rate constant calculated from semi log plot of the plasma concentration versus time curve.
$T_{1/2}$: Time required for the plasma drug concentration to decrease to one half.

Treatment of Subjects:

Drug Administration

All subjects were required to fast overnight for at least 10 hours before dosing till 4 hours post dose. In each study period, test -A (fesoterodine fumarate 8mg.) or reference -B (Toviaz® 8 mgextended release tablets) were administered orally with 240mL of water under yellow monochromatic light on the day of dosing as per the randomization schedule under fasting conditions.

General Methods Involved in the Bioanalytical Process:

Mobile Phase (v/v)
Diluent(v/v)
Rinsing Solution (v/v)
Stability buffer (Alpha-toluene sulphonyl fluoride,w/v)

System Suitability Solution: A mixture of analytes and internal standard will be prepared for system suitability test. The concentration of analytes will correspond to middle concentration of calibration range (3.7000ng/ml for both Fesoterodine and 5-HMT) and that of internal standard will correspond to working concentration used for calibration range (25.0000ng/mol of Fesoterodine D14 and 50.0000ng/mol of 5HMTD14). The system suitability test solution will be injected as an aqueous mixture. Aqueous samples will be prepared as per recovery basis. A rear ratio will be considered for system suitability test calculation.

Bioanalytical Conditions:

Column : Kromosii100-5C18, 100*4.6mm, 51Jm (Make: Akzo Nobel)
Mobile phase: HPLC grade methanol 5m Ammonium formate buffer (80:20, v/v)
Rinsing solution : HPLC grade methanol MilliQ/HPLC grade water (50:50, v/v)
Flow rate : 1.000mL/minute (with splitter)
Split ratio : 50:50
Sample Cooler Temperature: 10°C
Column over temperature : N/AP
Injection volume : 15f..IL
Needle Rinsing Volume : 1000f..IL
Rinse Dip Time : 2s
Rinsing Mode : Before and after aspiration
Retention time : Fesotirodine 1.24+/- 0.3 minutes
Fesotirodine D14 1.24 +/- 0.3 minutes
5 HMT1.02±0.3minutes
5HMTD141.03±0.3minutes

Bioanalytical Process:

A high performance liquid chromatography mass spectrometric method for the estimation of Fesoterodine Fumarate, in human plasma, was developed and validated using Amlodipine as an internal standard (IS). Sample preparation was accomplished by Liquid-liquid extraction. The reconstituted samples were chromatographed on Discovery Hs, C18, and 5cm X 4.6mm, 5mu column using a mobile phase consisting of HPLC CAN: 10mM Ammonium acetate (85:15 v/v).
The method was validated over a concentration range of 5,010 ng/mL to 600.839 ng/mL for Fesoterodine Fumarate.

Data Processing: The chromatograms were acquired and processed by peak area ration method using the Analyst 1.4.1 software.

$Y = mx + c$

Where y = peak area ratio of Fesoterodine fumarateto internal standard
m = slope of the calibration curve
x = concentration ratio of Fesoterodine fumarateto internal standard ng/mL
c = y-axis intercept of the calibration curve.

3. Results and discussion

The 90% confidence intervals for the log transformed C_{max},AUC_{o-t} and $AUC_{0\infty}$ of 5-Hydroxymethyltolterodine

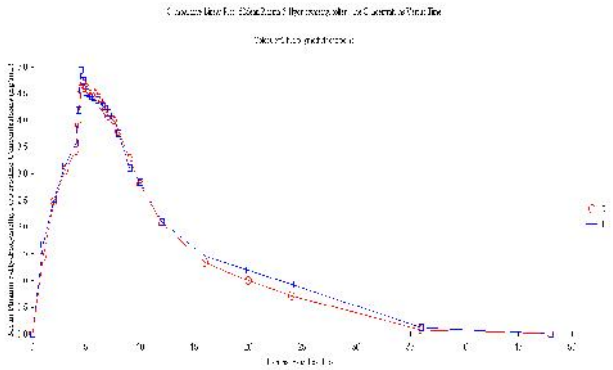


Figure 2: LinearPlots of 5-hydroxymethyl tolterodine mean plasma Concentrations versus Timein Healthy, Adult Human Subjects

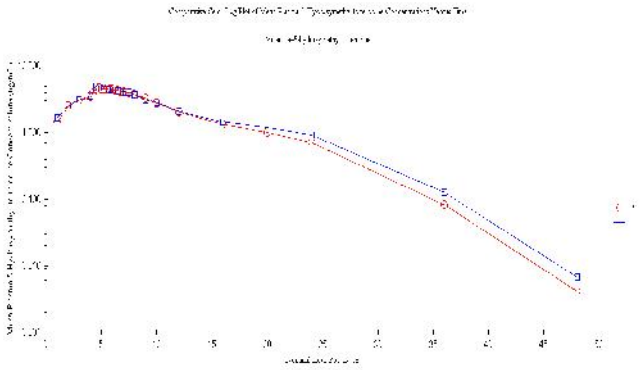


Figure 3: Comparative semi- log Plot of 5-hydroxymethyl tolterodine mean plasma Concentrations versus Time in Healthy, Adult Human Subjects (*N=34*)

Table 1: Pharmacokinetics Results of 5-Hydroxymethyltolterodine

PK Parameters	5-Hydroxymethyl tolterodine Mean (ï S.D.)	
	T	R
T_{max} (hr)	5.103	5.000
	(±0.7860)	(±0.8234)
C_{max}(ng/mL)	5.30025	5.22272
	(±1.829280)	(±1.782846)
AUC_{0-t} (ng.h/mL)	59.29637	54.95113
	(±16.583694)	(±18.378484)
$AUC_{0-\infty}$ (ng.h /mL)	63.30320	58.90338
	(±15.606562)	(±18.276201)
$T_{½}$ (hr)	7.009	6.404
	(±2.3914)	(±1.9484)
K_{el}(1/hr)	0.109	0.117
	(±0.0336)	(±0.0340)
AUC_%Extrap_Obs	6.94098	7.16120
	(±6.222984)	(±5.569438)

Table 2: 90% confidence intervals

Parameters	90% C.I. for log transformed data
	5-Hydroxymethyl tolterodine
C_{max}	93.92 - 110.02
AUC_{0-t}	103.53 - 119.00
$AUC_{0-\infty}$	103.29 - 118.82

Pharmacokinetic Results of 5-hydroxymethyl tolterodine:

Discussion:

Pharmaceutically equivalent multi-source pharmaceutical products must be shown to be therapeutically equivalent to one another in order to be considered interchangeable. From the statistical estimation, pharmacokinetic parameters C_{max}, AUC_{last} and $AUC_{0-\infty}$ between the test and reference products of tablets are within the 80-125% acceptance range. From the analyses of pharmacokinetic and statistical results it was inferred that, for the ln-transformed data, the 90 % confidence interval about the test to reference ratio of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of drug FESOTERIDNE FUMERATE were falling within the bioequivalence acceptance range of 80.00% - 125.00 %, which demonstrates the bioequivalence of test formulation 'T' with reference formulation 'R' under fasting conditions.

Pharmacokinetic Results of Fesoteridinefumerate

The 90% confidence intervals for the log transformed Cmax, AUCo-t and AUC0-∞ of Metoprolol are within the 80.00-125.00 % acceptance criteria

4. Conclusion

Based on clinical, pharmacokinetic and statistical data obtained from 68 healthy, adult, male, human subjects under fasting conditions, it was concluded that a single dose of test formulation'T' containing drug fesoteridine fumerate 8mg was found to be safe and bioequivalent to the reference formulation 'R' Toviaz containing fesoteridine fumerate mg as 90 % confidence interval for the ratios of means of test and reference parameters such as ln-

transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of drug Metoprolol succinate fell within the bioequivalence acceptance range of 80.00% – 125.00 %. The test product, fesoteridine fumerate tablets 8mg (containing 8 mg of fesoteridine fumerate) manufactured by (confidential) is bioequivalent to the Reference product, Toviaz (containing fesoteridine fumerate 8mg) tablets 8 mg manufactured by (confidential) in healthy, adult, human subjects, under fasting conditions.

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