Comparative bioavailability study of Ondansetron hydrochloride sustained-release and immediate-release tablets in healthy volunteers under fasting condition

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Abstract

The objective of the study was to compare the rate and extent of absorption of Ondansetron sustained-release and immediate-release in healthy volunteers. This was an open-label, randomized, single dose, three-way cross-over bioequivalence study under fasting conditions. The treatment periods were separated by a one-week washout period. Blood samples were drawn at different time points and the separated plasma was kept frozen at -30°C degrees for subsequent analysis. Plasma samples were analysed by using the validated high performance liquid chromatographic (HPLC) method. Pharmacokinetic (PK) parameters Cmax, Tmax, t1/2, AUC0-t, AUC 0-∞, and kel, were determined for the Ondansetron Sustained Release (SR) Tablets and Marketed Immediate Release (IR) Tablets. Pharmacokinetic parameters calculated obtained by using software (Winnonlin® 5.1) by non-compartmental method. The developed SR tablets confirmed a lasting long time to reach a peak concentration than the marketed tablets and appeared to be more consistent overall performance. This was no significant difference in extent of absorption as assessed by measurement AUC0-t. However AUC 0-∞ values for the SR tablets was higher than the marketed IR tablets indicating more efficient and controlled drug delivery, which would maintain plasma Ondansetron levels well. This also was evident by the lower elimination rate constant and higher t1/2 values. The study results indicate that Ondansetron SR formulation was similar to IR formulation in terms of pharmacokinetics and were well tolerated, with no serious adverse events reported. Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of adverse events.

Keywords: Comparative bioavailability, Ondansetron sustained-release, Human studies.
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Introduction

Ondansetron is a potent highly selective 5HT3 receptor antagonist indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of post-operative nausea and vomiting [1]. Ondansetron is completely and rapidly absorbed following oral administration and reaches maximum plasma concentrations after 1-2 hours. The absolute bioavailability of Ondansetron is 50-70% due mainly to hepatic first pass metabolism. Bioavailability is only slightly increased when administered after a standard meal but unaffected by antacids. Ondansetron is widely distributed and binds moderately (70 to 76%) to plasma proteins. Clearance occurs by hepatic metabolism (95%) rather than renal excretion[2]. The elimination half-life of Ondansetron ranges from 3 to 6 hours depending on the route of administration.

Literature survey has been conducted and found several pharmacokinetic studies were reported for Ondansetron[3-16]. Objective of the study was to evaluate the bioavailability of developed Ondansetron sustained-release in comparison to marketed conventional formulations.

Materials and Methods

Study design

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (Seoul, 2008) and in compliance with ICH GCP, GLP and the local guidelines of ICMR. Subjects were recruited from the database of potential healthy volunteers and referrals. The study was initiated after approval by Institutional Review Board. Subjects were asked to read the informed consent document followed by question answer session and queries were resolved before obtaining their consent. No subject was enrolled in the study without obtaining written informed consent and subjects were under medical supervision throughout their stay in the clinical facility to ensure safety and wellbeing of the subjects.

The study was an open label, balanced, randomized, three-treatment, three-period, six-sequence, single-dose, crossover, bioavailability study in healthy, adult human male subjects under fasting conditions comparing equal doses of the test and reference products. Blood samples were collected at pre-dose and at pre-defined intervals over 24.00 hours after dosing in each period. Subjects were confined at the clinical facility from at least 11 hours prior to dosing to at least 24.00 hours post dose. The interval between treatments or washout period was 7 days.

The test or reference product was orally administered as a single dose with 240 ml of water at ambient temperature after an overnight fast of at least 10 hours in each period as per the randomization schedule generated through Microsoft® Excel software. Drinking water was not
allowed from 1 hour before dosing until 2 hours post-dose. Subjects were seated for two hours after dosing. They were not allowed to lie down or walk for 2 hours post-dose except for procedural reasons such as attending the phlebotomy room for blood sampling. Subjects were only allowed to engage in normal activities avoiding severe physical exertion. Standardized meals served at 4 hours after dosing followed by snacks and dinner was served as per the scheduled time. Respective meals were identical for all periods.

**Study Population**

All subjects underwent a screening procedure (performed within 21 days prior to first period check-in). Medical history and detailed demographic data were recorded. Each subject underwent a complete general physical examination and laboratory tests of hematopoietic, hepatic and renal functions, urine analysis, serology and urine scan for drugs of abuse. Only medically healthy subjects with clinically acceptable laboratory profiles, ECG (performed within 21 days prior to study start) and chest X-ray (performed within 6 months prior to study start) were enrolled into the study. No medication, whether over-the-counter or prescribed allowed before admission into the study. All subjects was instructed to abstain from any citrus or xanthine-containing products or beverages (chocolate, tea, coffee or cola drink), orange or their juices, or alcoholic products for 24 hours and grapefruit or their juices for atleast 48 hours prior to dosing until after the last sample collection. All subjects were instructed to abstain from the use of cigarettes and tobacco products 24 hours before dosing until after the last sample collection.

**Inclusion Criteria**

The subjects were included based on the following criteria:

a. Subjects were healthy males within 18-45 years of age (both inclusive).

b. Having a Body Mass Index (BMI) between 18-23 (both inclusive), calculated as weight in kg / height in m².

c. Have no abnormal findings during screening within 21 days prior to administration of first dose of study drug, medical history and examination, laboratory evaluations, 12-lead ECG and X-ray chest (Postero-anterior view) recordings.

d. Able to comply with the study procedures in the opinion of the Clinical Investigator.

e. Able to give written consent for participation in the study.

**Exclusion Criteria**

The subjects were excluded based on the following criteria:

a. Subjects who had history of hypersensitivity to Ondansetron.

b. Subjects who had a history of allergic responses to the heparin or with a known food allergy.

c. Subjects who had vital sign abnormalities (systolic blood pressure < 90 or > 140 mmHg or diastolic blood pressure < 60 or > 90 mmHg or heart rate less than 50 bpm) at pre-study screening.
d. Subjects who had a history of serious cardiovascular, gastrointestinal, renal, pulmonary, haematological, liver and neurological or psychiatric disease.

e. Subjects who had suffered any clinically significant illness within a week of starting the study or who had been hospitalised within the 3 months preceding the start of the study.

f. Subjects who had taken prescription medication or over-the-counter products (including natural products and vitamins) within 7 days prior to administration of Investigational Product, except for topical product without systemic absorption.

g. Subjects who had a depot injection or an implant of any drug 3 months prior to administration of Investigational Products.

h. Subjects who had a history of chronic alcohol consumption or drug addiction or any indication of regular use of more than two units of alcohol per week (1 unit = 150 ml of wine or 360 ml of beer or 45 ml of 40% alcohol).

i. Subjects who were heavy smokers (more than 6 units per day of cigarettes, bidis or any other form) or were in uncontrollable habit of chewing or inhaling nicotine containing products.

j. Subjects who had taken any Investigational Product within 30 days prior to dosing.

k. Subjects who had donated blood (1 unit or 350 ml) or had participated in clinical investigation requiring blood donation within 90 days prior to receiving the first dose of Investigational products or during the study period.

The eligible subjects, who fulfilled the inclusion and exclusion criteria, were enrolled in the study.

Investigational Products

The test product was new Ondansetron hydrochloride slow sustained-release tablet formulation (single dose containing 8 mg), Ondansetron hydrochloride fast sustained-release tablet formulation (single dose containing 8 mg) and the reference product was EMSETRON tablets from Sun Pharma, Mumbai, India (single dose containing 8 mg immediate release Ondansetron hydrochloride). The treatments were administered with 240 ml of water.

Blood Collection and Sample Processing

Blood samples (4 ml) were collected using disposable syringes in pre-heparinised centrifugal tubes at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 h post dosing. Intravenous indwelling cannula was kept patent by injecting 1 ml of heparinised normal saline from the pre-dose sample to the 16.00 hrs post dose sample. Blood samples were collected after discarding the first 1 ml of blood from cannula on each occasion using a separate syringe. The actual time of collection of each blood sample was recorded accurately to the nearest minute on the CRF. If the samples were not collected within two minutes of the scheduled time, the reason for delay was recorded. Blood samples were centrifuged at 8°C and 3000 rpm for 10 minutes. Plasma was separated and placed in two suitable stopper labelled tubes mentioning short study title, protocol no., subject no., period and time point. All plasma samples were stored upright below -30°C until pending assay.

Result and Discussion
Estimation of drugs in plasma samples

Calibration standards for control plasma were prepared by spiking this stock to obtain the concentration levels of 0.50, 1.00, 2.00, 4.00, 10.00, 20.00, 40.00, 50.00 ng/ml in human plasma. Quality control samples were prepared at three different concentration of 0.50 ng/ml (LLOQ QC), 1.00 ng/ml (LQC), 10.00 ng/ml (MQC), and 40.00 ng/ml (HQC). Quality control samples were interspersed with in the method validation and subject samples during the analysis to check the performance. The calibration curves were linear in the range between 0.5-50.0 ng/ml. The validated lower limit of quantification was 0.5 ng/ml. Correlation coefficient \( r^2 \) was greater than 0.9982. The absence of any matrix effects was observed. Both intra-day and inter-day accuracy and precision showed good reproducibility. Average analytical recovery of analyte was 87.36 % and for IS was 95.34%. The analyte found to be stable in human plasma at least for 4 days when stored below -50°C and for 4 hours and 22 minutes when stored on bench top at room temperature. The analyte was stable in human plasma after being subjected to four freeze-thaw cycles. The results were reproducible after re-injection. The analyte and internal standard in stock dilution and stock solution were stable. The analyte and internal standard were stable after sample processing in the auto sampler. The validation results showed that the method was suitable for analysis of Ondansetron. Plasma samples were analysed by using a validated HPLC method. Sample preparation accomplished by solid phase extraction method. Etrocoxib was used as internal standards (IS). Ondansetron and IS were extracted using 60:40 acetonitrile-50 mM phosphate buffer (pH 7.0) as mobile phase and analysed on Princeton SPHER C18 (250 x 4.6 mm i.d., 5μ). Compounds were monitored by UV detection at 305 nm.

Pharmacokinetic Analysis

The primary pharmacokinetic parameters i.e. C\(_{\text{max}}\), AUC\(_{0-t}\) and AUC\(_{0-\infty}\) and secondary primary pharmacokinetic parameters i.e. T\(_{\text{max}}\), Kel, T\(_{1/2}\) computed by using non-compartmental model as given in Table 1.

Table 1. Pharmacokinetic Parameters of the Developed Sustained Release (SR) Tablets and Marketed Immediate Release (IR) Tablets of Ondansetron

<table>
<thead>
<tr>
<th>S. No</th>
<th>Pharmacokinetic Parameters</th>
<th>Developed SR tablets Slow Release</th>
<th>Developed SR tablets Fast Release</th>
<th>Marketed IR tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C(_{\text{max}})</td>
<td>44.73 ± 4.26</td>
<td>44.99 ± 2.28</td>
<td>40.43 ± 2.38</td>
</tr>
<tr>
<td>2</td>
<td>T(_{\text{max}})</td>
<td>5.33 ± 1.03</td>
<td>4.67 ± 1.03</td>
<td>2.00 ± 0.32</td>
</tr>
<tr>
<td>3</td>
<td>AUC(_{0-24})</td>
<td>459.62 ± 39.35</td>
<td>445.16 ± 48.58</td>
<td>177.45 ± 29.29</td>
</tr>
<tr>
<td>4</td>
<td>AUC(_{0-\infty})</td>
<td>476.89 ± 47.22</td>
<td>461.75 ± 45.00</td>
<td>183.59 ± 28.63</td>
</tr>
<tr>
<td>5</td>
<td>AUC(_{%\text{Extrap}})</td>
<td>3.50 ± 2.72</td>
<td>3.69 ± 1.61</td>
<td>3.46 ± 1.20</td>
</tr>
<tr>
<td>6</td>
<td>MRT</td>
<td>8.39 ± 0.54</td>
<td>8.02 ± 0.79</td>
<td>6.17 ± 1.48</td>
</tr>
<tr>
<td>7</td>
<td>T(_{1/2})</td>
<td>4.09 ± 0.75</td>
<td>5.08 ± 1.05</td>
<td>4.40 ± 0.82</td>
</tr>
</tbody>
</table>
The short biological half-life (3-5h) and dosing frequency more than one per day make Ondansetron an ideal candidate for sustained release. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of Ondansetron is desirable. Pharmacokinetic (PK) parameters Cmax, Tmax, t1/2, AUC0-t, AUC 0-∞, and kel, were determined for the Ondansetron Sustained Release (SR) Tablets and Marketed Immediate Release (IR) Tablets. The developed SR tablets confirmed a lasting long time to reach a peak concentration than the marketed tablets and appeared to be more consistent as mentioned in the Fig. 1.

![Pharmacokinetic Concentration-time profile of Ondansetron hydrochloride from developed Sustained release tablets (test) and marketed immediate release tablet (Reference)](image)

**Fig. 1: Pharmacokinetic Concentration-time profile of Ondansetron hydrochloride from Developed Sustained Release (SR) Tablets and Marketed Immediate Release (IR)**

Cmax for Developed SR tablets Slow Release, Fast Release and Marketed immediate releaseIR tablets 44.73 ± 4.26, 44.99 ± 2.28 and 40.43 ± 2.38 respectively, For AUC0-24, 459.62 ± 39.35, 445.16 ± 48.58 & 177.45 ± 29.29 respectively, AUC0-∞, 476.89 ± 47.22, 461.75 ± 45.00 and 183.59 ± 28.63. AUC0-24 and AUC0-α value for the sustained release slow and fast release tablets were higher than the marketed immediate release tablet indicating more efficient and controlled drug delivery, which would maintain plasma levels better. However, the sustained release slow and fast release formulation exhibited a longer elimination half-life (t1/2) than the immediate release tablet, thus demonstrating sustained release properties, unlike the reference. The study results indicate that Ondansetron sustained release formulation was similar to immediate release formulation in terms of pharmacokinetics and were well tolerated, with no serious adverse events reported. Once-daily use of an Ondansetron sustained release formulation may progress the
convenience of treatment compare to immediate release formulation taken two times daily and increase patient compliance.

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of adverse events.

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Reference


