ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Bioequivalence Study of Morphine Hydrochloride Oral Solution versus Immediate Release Tablets

Gildeeva G.N.[1], Belostotsky A.V.[2], Ezhova E.A.[3], Yurkov V.I.[4*]

1. *Organization and Management in the Field of Drugs Circulation Department at the First Moscow State Medical University n.a. Sechenov I.M., Russia.*
2. *Head of the Organization and Management in the Field of Drugs Circulation Department at the First Moscow State Medical University n.a. Sechenov I.M., Russia.*
3. *First Deputy Director General Federal State Unitary Enterprise «Moscow Endocrine Plant», Russia.*
4. *Medical advisor, Clinical Research Department, Medical Development Agency LLC (MDA LLC), Russia.*

***Corresponding Author: Yurkov V.I.**

Abstract

Objective: Comparative study of bioequivalence and safety of Morphine Hydrochloride 2 mg/ml oral solution (T) and Morphine Hydrochloride 10 mg immediate release film-coated tablets (R) after single dose administration (1 ampoule 5 ml, 2 mg/ml / 1 tablet 10 mg) by healthy subjects under fasting conditions. Methods: Open-label, single dose, 2-period crossover, randomized design study in 42 healthy subjects under fasting conditions. Test product: Morphine Hydrochloride 2 mg/ml oral solution (FSUE «Moscow Endocrine Plant», Russia) was compared with the reference product Morphine Hydrochloride 10 mg Immediate Release Tablets (FSUE «Moscow Endocrine Plant», Russia) under fasting conditions. The statistical method is testing for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence study was based upon the 90% confidence interval (90% CI) for the test and reference geometric mean ratio. Bioequivalence was to be assumed if 90% CI fell within the recommended acceptance interval 80%; 125%. Results: Forty-two subjects completed the study. Both Morphine T and Morphine R exhibited peak plasma Morphine concentrations of ~13 ng/ml. 90% CIs of the ln-transformed values of Morphine AUC_{0-t} and C_{max} were within 80% to 125% range for bioequivalence. The most common adverse events were anemia and headache. These data show that, in these subjects, Morphine T was bioequivalent to Morphine R, a treatment for pain with well-established efficacy and safety profiles.

Keywords: *Bioequivalence, Morphine, Solution, Opioids, Pharmacokinetics.*

Introduction

Pain stands for one of the main symptoms that cause suffering in subjects with malignant neoplasms. Despite outstanding progress attained in the field of diagnostics and treatment of tumor diseases, according to the estimates set forth by experts of the World Health Organization (WHO), cancer morbidity and mortality would continue to be on the rise in the nearest future; consistently, the number of patients with pain syndrome induced by neoplastic processes would still be growing [1,2]. Current method implemented by WHO for pain treatment in oncological subjects provides for a three-stage prescription of noninvasive analgesics, ranging from non-opioid agents and less potent opioid drugs to strong narcotic painkillers, depending on pain intensity [3, 4]. Data captured in multiple studies of the efficacy of 'WHO's three-step pain relief ladder' support sharing of common view that 70-90 % cancer patients return adequate painkilling response upon adherence to this method [5,6]. For many years, Morphine used to be the first line remedy in treatment of the pain syndrome with higher intensity. It should be stressed however that recommendations of European Association for Palliative Care also consider other opioid drugs, such as Oxycodone, Fentanyl, Buprenorphine and Hydromorphone. Each of these analgesics stands for the drug of choice

to treat severe pain in oncological patients; still, for selection of daily dose of the opioid agent (dose titration) at the initial phase of therapy, it is recommended to use an oral Morphine preparation with immediate release, which effect is related to the particulars of Morphine pharmacokinetics and broad therapeutic range [7, 9]. With a view to enhance safety of pain relief, various recommendations for pain treatment currently in effect in many countries dictate mandatory performance of titration with lower doses of oral Morphine with immediate release prior to prescription of potent opioid drugs with sustained release, with following calculation of the required dose of the potent opioid agent [10,13].

Morphine with immediate release is the most suitable drug for selection of opioid therapy during titration phase, as this drug is capable to ensure rapid and efficient pain control and is well-tolerated by oncological patients in course of titration stage. Morphine stands for the classic opiate, called by professionals as the 'gold standard' and 'reference remedy' in respect to all opioid analgesics.

Materials and Methods

Study Design

Open label, 1:1 randomized two-period, two-treatment, crossover, single dose evaluation in 42 adult healthy volunteers. In each study period, a single oral dose of either test product (T, Morphine Hydrochloride, 5 ml oral solution 2 mg/ml) or reference product (R, Morphine Hydrochloride, 1 immediate release tablet 10 mg) was administered orally under fasting conditions. Treatments were separated by a wash-out phase of seven days between the periods, according to the (at least) one-week period required in the Study Protocol.

A Naltrexone blockade should be used to remove the risk of any opioid-related adverse events. Naltrexone should be administered well in advance of dosing to achieve adequate blockade of opioid receptors. So, all enrolled subjects were given single oral doses of 50 mg Naltrexone (as Naltrexone Hydrochloride) together with 200 ml of tap water 10 hours pre-Morphine dose, 1 hour pre-Morphine dose and 12 hours post-Morphine dose on Day 0 and Day 1 in two consecutive periods. For single dose pharmacokinetics, blood samples were collected up to 24 hours after drug administration. Safety evaluations were made by adverse event assessments, pulse rate / blood pressure measurements and ECG readings. Subjects were hospitalized for about 35 hours during each period. Alcohol consumption was not allowed from five days prior to drug administration at the clinical center (Eco-Safety LLC, St. Petersburg) until the last blood sampling of each period. Smoking was restricted for the time periods of blood sampling.

Subjects Selection

The study was designed in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and other related national guiding principles. The Study Protocol was reviewed and approved by the Ministry of Healthcare of the Russian Federation and by the Ethics Committee. The subjects were selected according to the inclusion and exclusion criteria. The inclusion criteria were as follows: both males and females aged ≥18 years; body mass index at 18.5 – 30 kg/m^2, including the boundary values.

All subjects signed the informed consent form. The exclusion criteria covered history of or suffering from any serious diseases at present; allergy; surgical operations 12 weeks before the study or planned surgery during the study; medication use 14 days before the study; blood donation and participation in any clinical trials 3 months before the study; excess coffee, tea, caffeinated beverages, or alcohol drinkers per day; smokers with more than 10 cigarettes per day; abnormal alcohol breathing test; drug abusers and subjects with positive drug abuse screening test results; abnormal vital signs (systolic pressure <100 mmHg or > 130 mmHg; diastolic pressure < 70 mmHg or > 90 mmHg); physical examination, electrocardiogram, or laboratory tests results of clinical significance (according to the physician's judgment); subjects unable to use valid means of contraception; subjects unable to complete this study for some other reasons; or those the investigators thought should be excluded. All subjects were fully advised of the nature, purpose, procedures and possible risks of the study by the investigators. All subjects signed the informed consent form before the study.

Diet and Dietary Restrictions

Subjects were asked to fast for at least 10 hours before oral administration. All of them underwent two study periods: taking a single oral dose of 10 mg Morphine Hydrochloride (Test preparation 5 ml oral solution or 1 immediate release tablet 10 mg of reference preparation) with 240 ml of water.

Group 1 was orally given one test preparation, while group 2 was given one reference preparation. The two study periods were separated by a wash-out period of 7 days before they took the other preparation in turn. After administration, the hands and mouths of all subjects were checked. All subjects were required to keep their body upright and were accompanied by the investigator to the toilet 4 hours after administration.

Drinking water was not allowed from 1 hour pre-dose to 2 hours post-dose, except when needed for drug administration. Standardized meals were provided to all subjects 4 and 10 hours after administration. The same food was served to all the subjects during the trial, and the meals were consistent in the two periods of the study. No foods and beverages containing caffeine or other Methylxanthines (coffee, tea, coke, chocolate) and fruit juice were allowed from 72 hours prior to each dosing until the last blood sampling of either period.

No grapefruit and orange products were allowed from 7 days prior to the first dosing until the last blood sampling. Subjects were not allowed to take prescribed systemic or topical medications beginning 30 weeks, and no OTC medications (including herbal remedies) beginning 1 week prior to the start of the study. Subjects were furthermore required not to use either systemic or topical drugs (including herbal remedies) until after completion of the study. In the case of intake or administration of any prescribed systemic or topical medication within 4 weeks before the start of the study because of an insignificant illness, this event should have been recorded in the CRF.

Sample Collections

Pharmacokinetic blood samples were collected at the following study times of Day 1 – Day 2 in each period: 0 h (pre-dose), 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0 and 24 hours post-dose. The blood samples were centrifuged in a vacuum blood vial containing EDTA K_2 to separate the plasma and stored at -70 °C until testing.

Analytical Methods

Concentration of Morphine was quantitatively analyzed by a validated method of high-performance liquid chromatography with mass-spectrometric detection.

Analytical procedures were performed with the aid of Shimadzu Nexera X2 liquid chromatographer (Japan) equipped with Shimadzu LCMS-8060 mass-spectrometer (Japan). The peak due to Morphine was identified according to its characteristic ions, precursor ion and product ion (MRM mode, m/z 285.90 > 152.20).

Lab Solutions, ver. 5.96 software package was used to enable automatic integration of the chromatograms. Calibration curve plotting method was used for the assay purposes. Ratio between the areas of the peak due to the analyte and the peak due to the internal standard (Tolbutamide) was used as the reference parameter.

Reproducibility, precision and accuracy were attained over concentration range of 0.1 – 100 ng/ml. All analytical characteristics of the method complied with the acceptance criteria specified, and therefore, rendered the method suitable for the purpose of Morphine assay in human blood plasma samples.

Safety Assessment

Safety of the preparation was evaluated by close monitoring of the vital signs (blood pressure, pulse and temperature) of the subjects at screening, baseline, 0 hour pre-dose, and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0 and 24 hours after oral administration. Physical examination, laboratory examination and electrocardiogram recording were performed at screening, before the period 2 and at the end of study. Adverse events during the trial were recorded in the source documents. Experienced doctors, nurses and investigators trained by GCP monitored the entire study.

PK Parameters and Statistical Analyses

Mean plasma concentration-time curves for each subject at each sampling time under

each condition were plotted. Area under the concentration time curve (AUC) from time 0 to last measurable concentration (AUC_{0-t}) and AUC from time 0 to infinity ($AUC_{0-\infty}$) were estimated by linear trapezoidal method; maximum serum concentration (C_{max}) over a specified time span and time of maximum serum concentration (T_{max}) were determined by direct observation of the data. Descriptive statistics included calculation of arithmetic means, geometric means, standard deviation, CV, minimum, median and maximum values.

Analysis of variance was performed on ln-transformed pharmacokinetic parameters and included formulation group, sequence, period nested within the group, and subject nested within the group / sequence as a random effect. Analysis of variance included calculation of least square means (LSM), differences between formulation LSM and standard error associated with the differences.

Ratios of ln-transformed LSM values for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were expressed as a percentage relative to the reference formulation; therefore, comparison of interest was treatment A versus treatment B. The primary endpoint was bioequivalence.

Bioequivalence is considered established, if 90% confidence intervals (CIs) for the ln-transformed ratios of AUC and C_{max} fall within 80% – 125% range. For bioequivalence studies involving modified-release products, data from those subjects who experience vomiting during the dosing interval can be removed.

Results and Discussion

Study Subjects, Disposition and Demographics

Of 42 subjects who were enrolled, 42 completed the study per the Protocol. Participants (29 men and 13 women) ranged in the age from 19 to 44 years (mean: 25.5 years), all of them were Caucasians. Mean (standard deviation) height was 175.1 (11.1) cm, and mean weight was 71.1 (14.6) kg. Before being hospitalized, the females were asked to take blood ß-human chorionic gonadotropin test.

All subjects underwent physical examinations, laboratory tests and other necessary tests. All subjects were non-drinkers and non-smokers without abnormalities detected by physical examinations and laboratory tests. All subjects had no history of drug allergy or drug dependence, no chronic diseases, and had not taken any medications before the trial. During the trial, all subjects were provided a bland diet without prescribing drugs other than preparations being studied.

Pharmacokinetic Profile of Morphine

Similar serum Morphine concentration-time profiles were observed for T and R (Fig. 1). Overall, Morphine exposure was similar (Table 1).Although the rate of absorption appeared to be faster for T versus R (median T_{max} 0.55 ± 0.29 versus 0.65 ± 0.3 hours), given the variability of both treatments, the overall difference in T_{max} may not be clinically relevant. Both Morphine T and Morphine R exhibited C_{max} values of ~13 ng/ml at 3 hours post-dose. Total Morphine exposure values (AUC_{0-t}, AUC_{0-1}) were similar between Morphine T and R Morphine.

Table 1: Pharmacokinetic properties of Morphine after single dose administration of Morphine oral solution versus immediate-release tablets Data are given as means (SD)

	T	R
C_{max} (ng/ml) geometric mean	12.8 (5.5)	12.9 (4.9)
T_{max} (h), median	0.55 (0.29)	0.6 (0.3)
T½ (h), arithmetic mean	10.9 (10.8)	9.8 (5.3)
AUC_{0-t} (mmol·h/L), geometric mean	35.5 (12.6)	34.9 (12.0)
$AUC_{0-\infty}$ (mmol·h/L), geometric mean	42.9 (17.9)	42.0 (15.5)

Bioequivalence assessments for Morphine are summarized in Table 2. Ninety percent CI limits for ln-transformed pharmacokinetic parameters for the ratio of MS-sNT to reference ERMS (n = 34) for AUC_{0-t} and C_{max} fell between 80% and 125% range required to establish bioequivalence.

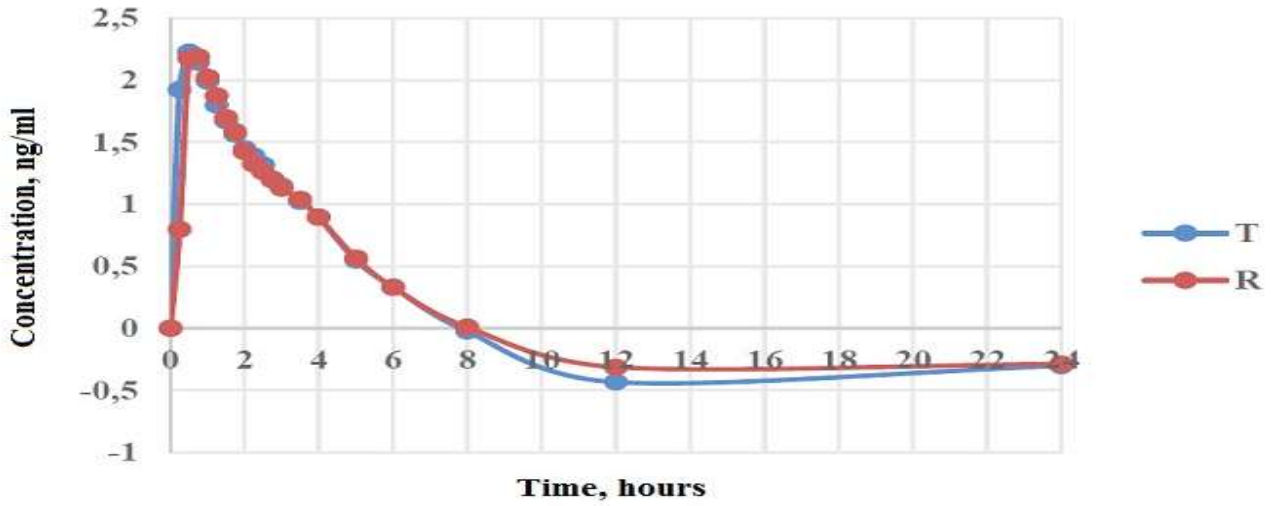

Figure 1: Plasma concentration time profile of Morphine after single dose administration of Morphine oral solution versus immediate-release tablets

Table 2: The 90% confidence intervals for the AUC_{0-t} and C_{max} mean ratios

Parameter	Ratio of the means	Inter-subject variability coefficient	Intra-subject variability coefficient	90 % confidential interval		Bioequivalence criterion	
				Lower limit	Upper limit		
AUC_{0-t}	101.05	36.26	61.04	96.94	105.33	80 – 125 %	MET
C_{max}	97.32	41.91	62.37	89.24	106.14	80 – 125 %	MET

Tolerability

Both drugs showed satisfactory safety profiles. In total, 16 adverse events (AEs) (10 AEs after administration of the study drug and 6 AEs after administration of the reference drug) were reported; none of them necessitated initiation of any therapeutic measures and all adverse events resolved in the recovery without sequelae. Generally, the range of observed AEs fully complies with safety properties of Morphine, according to the data published in literature. Information about adverse events reported is given in the following Table 3.

Table 3: Summary table of AEs incidence rate after administration of every study drug

Adverse event	Morphine, oral solution (T) n = 42		Morphine, immediate-release tablets (R) n = 42		*p* value†
	n	%	n	%	
Laboratory tests and measurement values					
Anemia	2	4.8	2	4.8	1.000
Hyperbilirubinemia	1	2.4	0	0	1.000
Hyperglycemia	1	2.4	0	0	1.000
Thrombocytopenia	1	2.4	0	0	1.000
Cardiovascular system disorders					
Hypotension	1	2.4	1	2.4	1.000
Digestive system disorders					
Abdominal distension	0	0	1	2.4	1.000
Vomiting	1	2.4	0	0	1.000
Nausea	1	2.4	1	2.4	1.000
Nervous system and sensory organs disorders					
Headache	2	4.8	1	2.4	1.000
NOTE: Fischer's exact test was applied; no statistically significant differences were found between the study group Morphine, oral solution (T) and the study group Morphine, film-coated tablets (R)					

Conclusion

In healthy subjects in the present study, Morphine oral solution was found to be bioequivalent to Morphine tablets and can be expected to have efficacy and safety profiles similar to the well-established profiles of immediate release tablets Morphine.

Funding

Sponsorship for this study was funded by the Federal State Unitary Enterprise «Moscow Endocrine Plant», Russia. All authors had full access to all of the data in this study and take full responsibility for the integrity of data and accuracy of data analysis.

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