Original Article:
Bioequivalence Study of Two Formulations of Tramadol Capsules in Healthy Myanmar Volunteers

Ye Htut Linn[1*] (ID), Myat Myat Soe[2] (ID), K Khine Thu[1] (ID), Thida Tun[1] (ID), Mi Kun Kaw San[1] (ID), Nyein Chan Pyae[1] (ID), Nu Nu Aye[1] (ID)

1. Department of Pharmacology, University of Medicine 1 Yangon, Yangon, Myanmar.
2. Department of Pharmacology, School of Medicine, University of Medicine, Magway, Myanmar.

* **Corresponding Author:**
Ye Htut Linn, PhD.

Address: *Department of Pharmacology, School of Medicine, University of Medicine, Magway, Myanmar.*
E-mail: dryehtutlinn@gmail.com

ABSTRACT

Background: Tramadol is one of the most commonly used analgesics, thanks to its efficacy and safety. It is widely used in Myanmar for postoperative and cancer pain control. The use of generic drugs has been steadily increasing worldwide, mostly in developing countries. Generic drugs should have efficacy and safety comparable to their innovators or other approved generic products.

Objectives: This study aims to compare the bioequivalence of locally producing, Tramadol BPI® capsule (test product) with the Tramazac® capsule (reference product) in healthy Myanmar volunteers.

Methods: The bioequivalence was determined in 16 healthy Myanmar volunteers after a single oral administration of 100 mg tramadol (under fasting condition) in a randomized, open-label, two-period, and two-treatment crossover study with a two-week washout period. Blood samples were collected at specified times, and plasma tramadol concentrations were measured with a validated high-performance liquid chromatography method with a fluorescence detector. Pharmacokinetic parameters were determined using the plasma concentration-time data in a non-compartmental model.

Results: The analysis of variance of the logarithmically transformed parameters (maximum plasma concentration (C_{max}), Area Under the concentration-time Curve from the time of administration to the last measured concentration (AUC_{0-t}), and to infinity ($AUC_{0-\infty}$) revealed no sequence, period, and formulation effects between the test and reference products. Significant differences were found between the subjects within the sequence for both AUC_{0-t}, and $AUC_{0-\infty}$, indicating a substantial inter-subject variation. The geometric mean ratio of test/reference and their 90% confidence intervals were within the ASEAN (Association of Southeast Asian Nations) bioequivalence acceptance interval of 80% to 125%.

Conclusion: Tramadol BPI® and Tramazac® capsules, after a single oral administration of 100 mg, were bioequivalent in respect of their rate and extent of absorption under fasting condition.

Introduction

Tramadol is a centrally-acting opioid analgesic whose effect is dependent on the ability of the parent drug to block serotonin and norepinephrine reuptake. Also, its metabolite, O-desmethyltramadol, acts on the μ-opioid receptor. It has proven efficacy and safety in acute pain conditions such as trauma, renal, or biliary colic. Chronic pain of benign or malignant origin, particularly neuropathic pain, is a common indication for tramadol administration. Tramadol is available in various forms for oral administration, such as tablet, capsule, and sustained release formulation [1, 2].

Tramadol is absorbed more than 90% after oral administration and has 70% bioavailability. Its 100 mg ingestion reaches its peak plasma concentration (0.31 μg/L) after 1 to 2 hours. Tramadol undergoes extensive hepatic metabolism by several pathways, including Cytochrome P450 2D6 and 3A4, and by conjugation with subsequent renal excretion. The elimination half-life is 5 to 6 hours [1, 3, 4].

Tramadol is considered a relatively safe analgesic drug compared with the classical opioid analgesic, i.e. morphine. In healthy subjects, tramadol did not reduce the ventilatory response to hypoxia. Side effects of tramadol include malaise, nausea, vomiting, dizziness, dry mouth, sedation, and constipation. Tramadol can precipitate seizures and may exacerbate seizures in patients with predisposing factors. At therapeutic concentration, tramadol-induced respiratory depression is very rare (0.01-0.1%) both in adults and children [1, 5].

Bioequivalence and bioavailability of drugs are assessed by a single dose in healthy volunteers using relevant pharmacokinetic parameters, such as the peak plasma drug concentration (maximum plasma concentration (C_{max})) and the Area Under the concentration-time Curve (AUC) [6, 7].

Although numerous pharmaceutical products contain the same active ingredients, they follow a different production process and use various accessories. These factors may influence the rate of release and extent of absorption in vivo. Therefore, the primary purpose of bioequivalence testing is to determine whether the two formulations have the same effect on humans. Bioequivalence is defined as follows: "Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailability (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same" [8].

The original patents of generic medicines have expired so they can be produced by manufacturers other than the original innovator (patent holding) company. The use of generic drugs has been steadily increasing worldwide as a result of economic pressure on drug budgets [8]. Generic medicines are generally much cheaper than the innovator ones and are identical or within a bioequivalent acceptable range to the brand name counterpart concerning their pharmacokinetics and pharmacodynamics [9]. In developing countries, generic drugs are widely used because of financial limitations and availability. Most of the countries require bioequivalence data for the registration of generic medicines, which are not included in the World Health Organization (WHO) biowaiver list. Therefore, bioequivalence studies are done to compare generic drugs with the innovator ones or other locally available approved generic drugs.

In Myanmar, tramadol is one of the most widely prescribed opioids for controlling pain. According to an analgesic utilization study done among 24-hour postoperative patients in surgical wards of Yangon General Hospital and Thingangyun Sanpya General Hospital, tramadol was the most prescribed drug (84.5%) for the treatment of postoperative pain [10]. In the Medical Oncology Department of Yangon General Hospital, tramadol was used in 46.7% of the patients with cancer pain [11].

Generic tramadol brands are available in Myanmar, and they are imported from foreign countries. Their availability is limited due to the legal restrictions and low-interest margin for importing such drugs. The locally produced medications from the state-owned enterprise are affordable and readily available all the time to the public, but they should be proved efficacious and safe. As the tramadol is not included in the WHO biowaiver list, it must undergo bioequivalence study. This research aims to compare the bioequivalence of locally producing, Tramadol BPI® capsule with a proven-marketed tramadol preparation Tramazac® capsule. This study can assure the clinicians and patients of the quality and safety of the locally used tramadol for pain control.

Materials and Methods

Product information

Tramadol (BPI)® capsule (Tramadol HCl BP 50 mg [hydrochloride (British Pharmacopoeia)]), manufac-

tured by Burma Pharmaceutical Industry (BPI), Insein, Myanmar was used as the test product, and Tramazac® capsule (Tramadol HCl BP 50 mg), manufactured by Cadila Healthcare limited, India was used as a reference product. Pharmaceutical properties such as weight and content uniformity, disintegration and dissolution of both capsules were tested and compared according to the British Pharmacopoeia, 2013 before this study [12].

Study design and subjects selection

This single-dose, randomized, open-label, two-period, two-treatment crossover study was conducted from August 2018 to January 2019. Healthy volunteers from Lanmadaw and Latha townships, Yangon were selected according to ASEAN (Association of Southeast Asian Nations) ASEAN guidelines for the conduct of bio-equivalence studies (2015) [7]. The selected volunteers were between 18 and 55 years old of either sex. Their body mass index ranged between 18 to 30 kg/m^2. They were non-smoker, non-drinker, and not under any medications two weeks before the randomization. Also, their chest x-rays, blood for complete picture, liver enzymes aspartate transaminase (AST) and alanine transaminase (ALT), Electrocardiograph (ECG), Random Blood Sugar (RBS), and renal function tests (urea, creatinine) were within normal range. Those with a history of allergic reactions to tramadol, history of epilepsy and women of childbearing age with positive urine chorionic gonadotropin test were excluded from the study. Figure 1 shows the study procedure.

Drug administration and sample collection

16 volunteers were randomized to two sequences by random allocation software [13]. In the first period, the volunteers were given either Tramadol (BPI)® (test) or Tramazac® (reference) capsules and the other product in the second period. There was a two weeks washout period between the two periods. For each period, the volunteers received a single oral dose of tramadol (100 mg), either reference or test capsules, with a glass of drinking water (150 mL) after 8-hour overnight-fasting. Food ingestion was not permitted until 4 hours after taking the drugs. The volunteers were allowed to take water 1 hour before and 1 hour after the drug administration. A standard lunch was entitled to every volunteer 4 hours after taking the drug, and standard food was given up to 12 hours after administration. After that, the volunteers can take any meal. A cannula was inserted into a peripheral vein of the volunteer's forearm under aseptic conditions. Blood samples (3 mL) were collected in heparinized tubes before drug-administration and 1, 2, 3, 4, 6, 10, and 24 hours after drug administration. Blood samples were centrifuged (3000 g or 5000 rpm for 10 min), and the collected plasma was stored at -20° C until further analysis.

Sample preparation and analysis

Plasma tramadol concentration was determined by High-performance Liquid Chromatography (HPLC) with fluorescence detector at Common Research Laboratory of the University of Medicine 1, Yangon, according to a method adapted from the Zhou and Liu in 2015 [14]. The HPLC system (Shimadzu Prominence UFLC, LC-20AD, Shimadzu, Kyoto, Japan) was set up with an autosampler (SIL-20AHT), a pump (LC-20AD), a Degassing Unit (DGU-20A3R), a column oven (CTO-20AC), a fluorescence detector (RF-20AXS), and a Communication Bus Module (CBM-20A).

The reference standards were prepared with tramadol standard powder (Tramadol hydrochloride BP2017, Virupaksha Organics Limited, India). A mixture of acetonitrile and 1% potassium dihydrogen orthophosphate (pH 4.0) at 25/75 (V/V) ratio was used as the mobile phase and was filtered with the 0.45-μm membrane filter (Whatman® Cellulose Filter Paper, Sigma-Aldrich, Germany) and degassed with an ultrasonic cleaner (POWER SONIC405, Labtech, Korea). The deionized water was used to prepare the 1% potassium dihydrogen orthophosphate solution. The volunteers' samples stored at -20° C were allowed to thaw at room temperature before processing. The case and reference samples (0.1, 0.25, 0.5, 1, 1.5 μg/mL) were prepared as follows: two fifty microliters of NaOH, ie, 250 microliters of NaOH (0.2 mol/L) were added to a 500 μL aliquot of plasma sample in a clean glass tube and were vortex-mixed for 1 minute, and then 4 mL of ethyl acetate was added. The mixture was again vortex-mixed for 5 minutes. After centrifugation (3000 g or 5000 rpm for 10 min), the upper organic layer was transferred into a clean glass tube and evaporated to dryness at 40° C in the hot water bath under a gentle stream of nitrogen. The residue was reconstituted with 400 μL of the mobile phase. The eluate was filtered with 0.22-μm disposable syringe filter (Shimadzu, Japan) and transferred to an autosampler vial (Shimadzu, Japan). An aliquot of 20 μL was injected into the HPLC system for analysis.

The fluorescence detector was set up at an excitation wavelength of 275 nm and an emission wavelength of 302 nm. The separation was performed through the Shodex Packed column for HPLC (Silica C18M 4D; 150×2.0 mm, 5 μm) (Shodex, Japan) with a guard column (ODP2 HPG-2A, Shodex, Japan) with the mobile

PBR

Linn YH, et al. Study of Tramadol Formulations in Myanmar. PBR. 2019; 5(4):35-44.

37
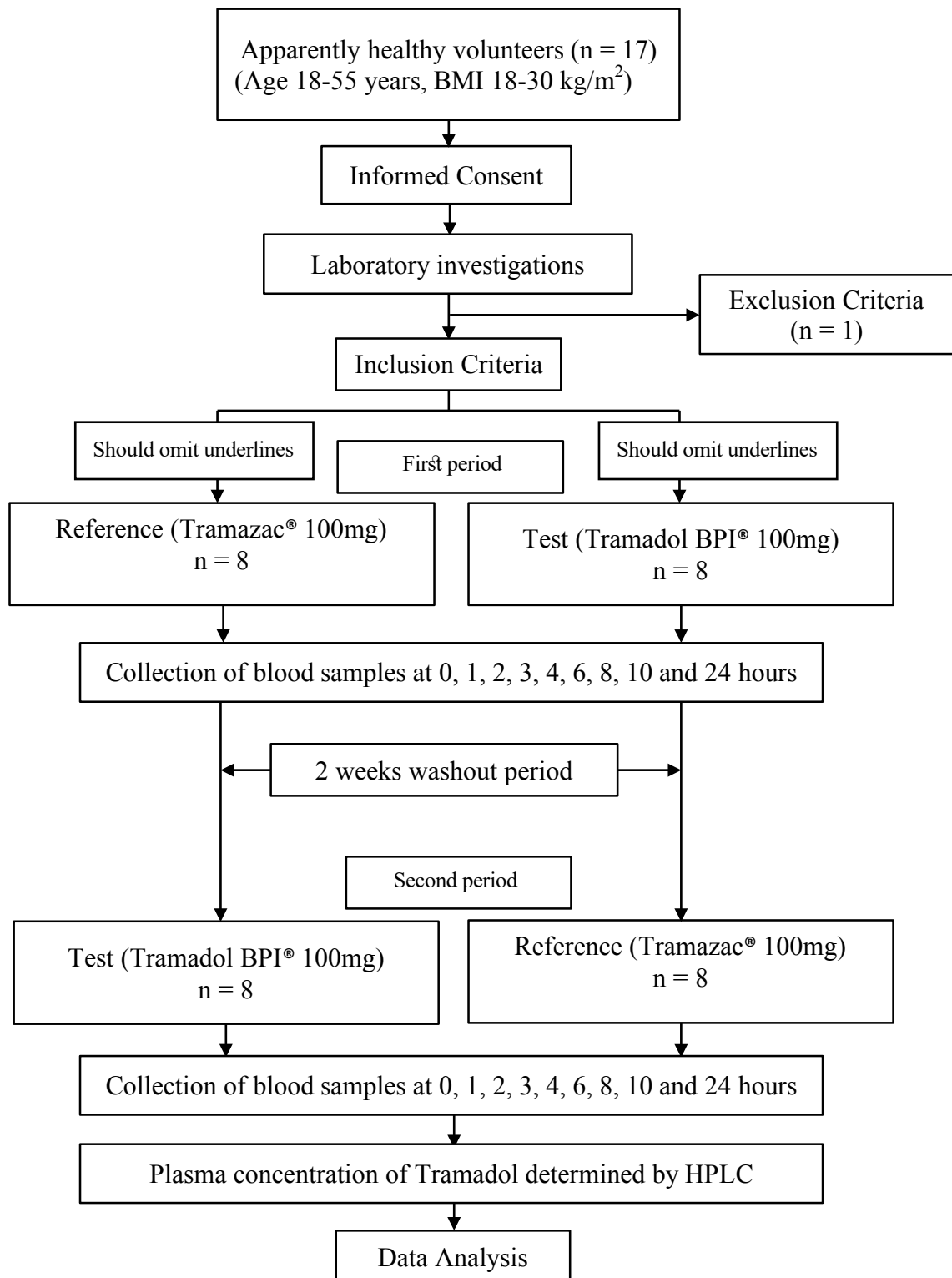
Figure 1. Flow chart of the study procedure

BMI: Body Mass Index HPL; C: High-performance Liquid Chromatography

phase flow rate of 1.0 mL/min. The column oven temperature was maintained at 35°C. The chromatographic running time of each sample was 7 minutes. The HPLC method validation was conducted following the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guideline [15].

Pharmacokinetic and bioequivalence data analysis

The pharmacokinetic parameters were determined by PKSolver 2.0 (China Pharmaceutical University, Nanjing, China) using non-compartmental modeling [16]. The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were obtained from the plasma concentration-time data. The trapezoidal rule was used to calculate the area under the concentration-time curve of tramadol in plasma from the time of administration to the last measurement concentration (AUC_{0-t}). The area under the concentration-time curve from the last measured concentration (C_{last}) to infinity ($AUC_{t-\infty}$) was calculated as C_{last}/λ_z. The total Area Under the Curve ($AUC_{0-\infty}$) was the sum of AUC_{0-t}, and $AUC_{t-\infty}$. The terminal rate constant (λ_z) was determined from the slope of the terminal log-linear portion of the plasma concentration-time curve using least-squares regression analysis, and the terminal half-life ($T_{1/2}$) was calculated as $0.693/\lambda_z$. The apparent total clearance of the drug from plasma after oral administration (Cl/F) and the apparent volume of distribution after non-intravenous administration (Vd/F) were calculated as $dose/AUC_{0-\infty}$ and Cl/λ_z, respectively.

The bioequivalence data analysis was performed by Epi-Tools epidemiological calculators (Ausvet, Canberra, Australia) on logarithmically transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ [17]. The assessment of bioequivalence was based upon a 90% confidence interval for the ratio of geometric means (test/reference) for the parameters above. A confidence interval for the difference between formulations on the log-transformed scale was obtained from the analysis of variance model in which sources of variation were the sequence, subject within sequence, period and formulation. This confidence interval was then back-transformed to obtain the desired confidence interval for the ratio on the original scale. If the ratios were within the acceptance interval of 80% to 125%, the two formulations are bioequivalent [7].

Results

Characteristics of volunteers

A total of 17 volunteers were recruited, and 1 volunteer was excluded from the study due to basal pneumonitis found on chest x-ray and hypochromic microcytic anemia. The age of 16 volunteers ranged from 19 to 54 years (median, 30 years) and have Mean±SD body mass index of 20.84±2.24 kg/m^2. Among them, 13 (81.25%) were males, and 3 (18.75%) were females. Slight drowsiness occurred in all of the participants taking both formulations, and nausea occurred in 2 participants while taking the test product.

Chromatographic analysis

HPLC method validation was done by determination of linearity, quantification, and detection limits, precision,

Table 1. Plasma concentrations of tramadol at various time points after administration of Tramadol BPI® and Tramazac®

Time Point (h)	Plasma Concentrations (µg/mL)			
	Tramadol BPI®		Tramazac®	
	Mean±SD	% CV	Mean±SD	% CV
0	0	-	0	-
1	0.2219±0.1440	64.9015	0.2412±0.1368	56.7341
2	0.3851±0.1046	27.1547	0.3893±0.1569	40.3137
3	0.3582±0.0858	23.9679	0.3336±0.0785	23.5312
4	0.2772±0.0577	20.8156	0.2674±0.0589	22.0078
6	0.2111±0.0522	24.7110	0.2063±0.0498	24.1480
10	0.1496±0.0407	27.2212	0.1383±0.0444	32.0729
24	0.0577±0.0288	49.8817	0.0608±0.0324	53.3114

CV: Coefficient of Variation

PBR

PBR

Linn YH, et al. Study of Tramadol Formulations in Myanmar. PBR. 2019; 5(4):35-44.

39

Table 2. Pharmacokinetic parameters of tramadol after administration of Tramadol BPI® and Tramazac®

Pharmacokinetic Parameters	Tramadol BPI®		Tramazac®	
	Mean±SD	% CV	Mean±SD	% CV
C_{max} (µg/mL)	0.4190±0.0990	23.6393	0.4100±0.1314	32.0330
T_{max} (h)	2.2500±0.5774	25.6600	2.4375±0.6292	25.8114
AUC_{0-t} (µg/mL.h)	3.7642±0.9103	24.1834	3.6540±0.9949	27.2263
$AUC_{0-\infty}$ (µg/mL.h)	4.6817±1.5326	32.7365	4.8825±1.9309	39.5474
$T_{1/2}$ (h)	9.6494±3.2139	33.3064	11.3107±7.5612	66.8501
λ_z (1/h)	0.0792±0.0256	32.3304	0.0770±0.0301	39.1193
Vd/F (L/kg)	5.4387±1.1053	20.3221	5.8780±1.7327	29.4781
Cl/F (L/h/kg)	0.4205±0.1258	29.9182	0.4326±0.1905	44.0409

C_{max}: Maximum plasma concentration; T_{max}: The Time to reach C_{max}; AUC_{0-t}: Area Under the concentration-time Curve from the time of administration to the last measurement concentration; $AUC_{t-\infty}$: Area Under concentration-time Curve from the time of administration to infinity; λ_z: Terminal rate constant; $T_{1/2}$: Terminal half-life; Cl/F: Apparent total clearance of the drug from plasma after oral administration; Vd/F: Apparent volume of distribution after non-intravenous administration; CV: Coefficient of Variation

and accuracy. The retention time of tramadol was around 3.6 minutes. As shown in Figure 2, no significant interferences were seen in the blank plasma chromatogram at the retention time of tramadol. The intra-assay precision and accuracy of the method were evaluated by analyzing on the same day, five replicates of quality control samples against a calibration curve. Inter-assay precision and accuracy were assessed by performing analyses of the same quality control samples, and the procedure was repeated on five different days. Precision was expressed as Coefficient of Variation (CV), and the precision at each concen-

tration level did not exceed 15% CV. The quantification limit and detection limit of tramadol in plasma were 0.152 µg/mL and 0.05 µg/mL, respectively. The calibration curve ranged from 0.1 to 1.5 µg/mL. Figure 3 shows the representative calibration curve.

Pharmacokinetic analysis

Plasma concentrations of tramadol at various time points after administration of Tramadol BPI® and Tramazac® are presented and shown in Table 1 and Figure 4. Pharmacoki-

Table 3. Analysis of variance of logarithmically transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for the assessment of sequence, subject within sequence, period and formulation effects, after administration of Tramadol BPI® and Tramazac®

| Pharmacokinetic Parameters	Analysis of Variance (P)			
	Source of Variation			
	Sequence	Subjects Within Sequence	Period	Formulation
C_{max}	0.86	0.27	0.31	0.65
AUC_{0-t}	0.45	0.02*	0.05	0.56
$AUC_{0-\infty}$	0.87	0.01*	0.17	0.87

* $P<0.05$

C_{max}: Maximum plasma concentration; AUC_{0-t}: Area Under the concentration-time Curve from the time of administration to the last measurement concentration; $AUC_{t-\infty}$: Area Under the concentration-time Curve from the time of administration to infinity

Table 4. Geometric mean ratio (test/reference) and its 90% confidence interval for logarithmic transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ after administration of Tramadol BPI® and Tramazac®

Pharmacokinetic Parameters	Geometric Mean Ratio (Test/Reference) (%)	90% Confidence Intervals (%)	Acceptance Interval [7]
C_{max}	104.43	88.49-123.23	80-125
AUC_{0-t}	104.20	92.34-117.59	80-125
$AUC_{0-\infty}$	98.56	84.28-115.28	80-125

<div align="right">PBR</div>

C_{max}: Maximum plasma concentration; AUC_{0-t}: Area Under the concentration-time Curve from the time of administration to the last measurement concentration; $AUC_{t-\infty}$: Area Under the concentration-time Curve from the time of administration to infinity
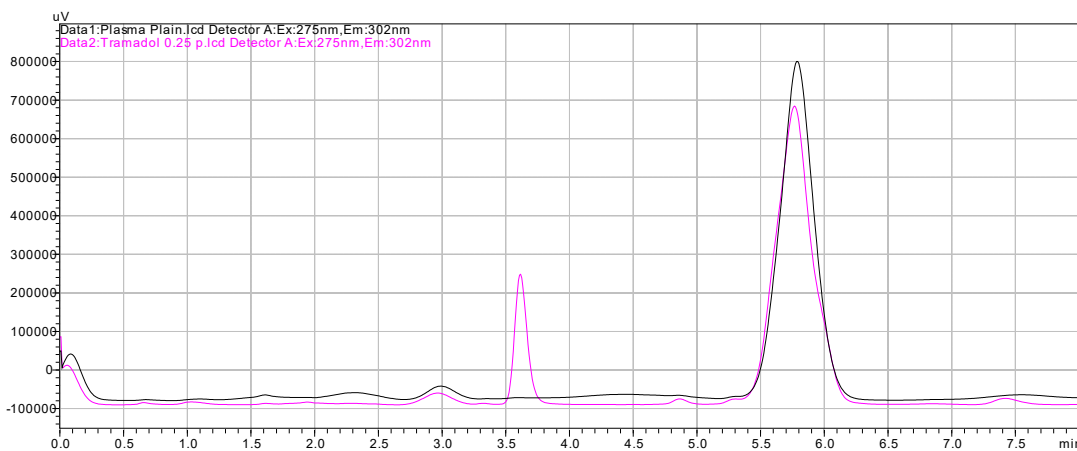

<div align="right">PBR</div>

Figure 2. HPLC chromatograms showing a blank human plasma sample (black) and human plasma spiked with tramadol 0.25 μg/mL (retention time – 3.6 min)

netic parameters (C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $T_{1/2}$, λ_z, Vd/F, and Cl/F) were calculated from individual concentration-time curves and were summarized in Table 2. It was found that the CV of some parameters such as C_{max}, $AUC_{0-\infty}$, $T_{1/2}$, λ_z, and Cl/F were above 30%, indicating that the pharmacokinetics of tramadol was highly variable among volunteers. The

median T_{max} and interquartile range for both Tramadol BPI® and Tramazac® was 2 (2-3) hours.

Bioequivalence evaluation

Table 3 presents the analysis of variance of pharmacokinetic parameters for bioequivalence (C_{max}, AUC_{0-t}, and
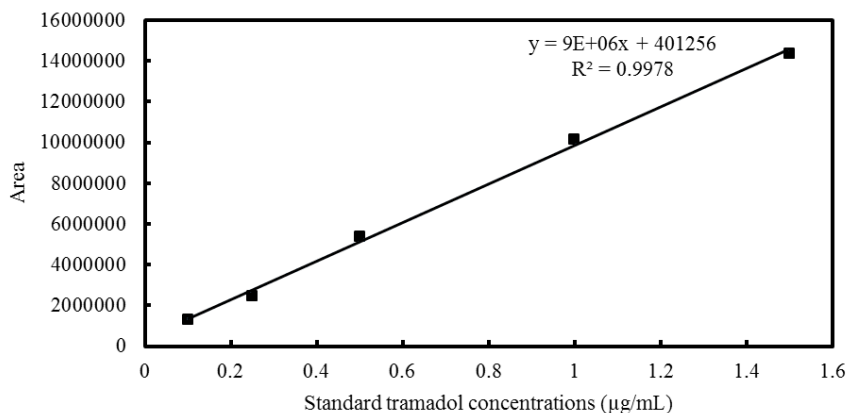
Figure 3. A representative standard calibration curve of tramadol

Linn YH, et al. Study of Tramadol Formulations in Myanmar. PBR. 2019; 5(4):35-44.

41

PBR
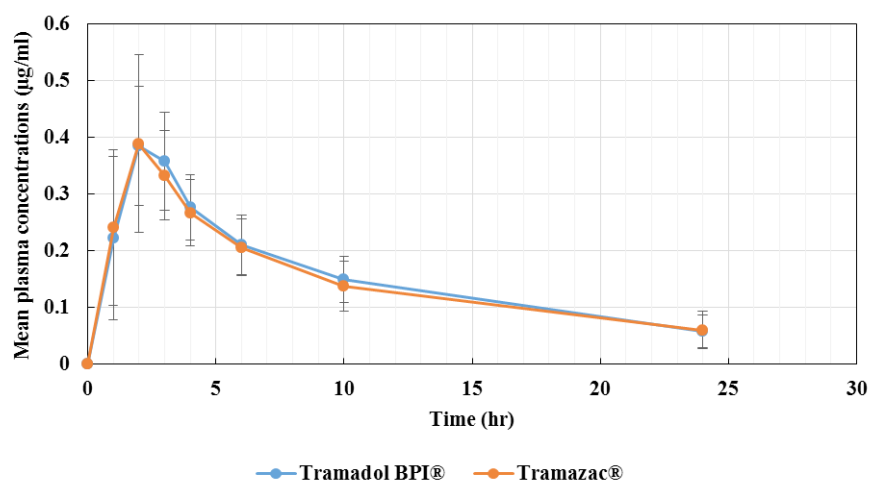
Figure 4. Mean plasma concentration-time curves of tramadol after administration of Tramadol BPI® and Tramazac®

$AUC_{0-\infty}$). There was significant intersubject variability in both AUC_{0-t} and $AUC_{0-\infty}$. Table 4 presents and compares the ratio of the geometric means (test/reference) and its 90% confidence intervals of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ using logarithmically transformed data. The geometric mean ratios (test/reference) of the three parameters and their 90% confidence intervals were well within the acceptance interval of bioequivalence (80% to 125%).

Discussion

We found that the pharmacokinetics of tramadol was highly variable among volunteers because CVs of some of the measured parameters were above 30% [7]. Tramadol is mainly metabolized by O- and N-demethylation, and its metabolites are excreted mostly via the kidneys. The O-demethylation reaction is catalyzed by cytochrome P450 2D6 (CYP2D6), whereas N-demethylation is catalyzed by CYP2B6 and CYP3A4. Therefore, the wide variability in the pharmacokinetic properties of tramadol can partly be due to CYP polymorphisms [4]. The analgesic effect of tramadol is dose-dependent, and serum concentrations of 0.1-0.3 mg/L are considered effective [1]. According to the concentration-time data of the current study, the test product may provide an analgesic effect for approximately 2 to 17.5 hours. Although the analgesic action of tramadol is attributed to the parent compound and its O-desmethyl metabolite, we only measured the parent compound because the ASEAN guideline clearly stated that "evaluation of bioequivalence should be based upon measured concentrations of the parent compound," because C_{max} of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite [7].

The analysis of variance of logarithmically transformed parameters revealed the absence of sequence, period, and formulation effects in C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ between the Tramadol BPI® and Tramazac® capsules. Significant differences were found between the subjects within the sequence for both AUC_{0-t}, and $AUC_{0-\infty}$, indicating a substantial intersubject variation. The geometric mean ratio of test/reference and their 90% confidence intervals were within the ASEAN bioequivalence acceptance interval of 80% to 125% [7].

Although the statistical evaluation of T_{max} is not required for bioequivalence, the rapid release is clinically relevant to the onset of analgesic action of tramadol, and we found no apparent difference in median T_{max} (2 hours) between the two products. This result is consistent with the findings reported in the literature [1, 3, 4, 14].

One of the limitations of the study was the lack of blinding/masking during the randomization because researchers who gave the tramadol capsules to the volunteers and those who measured the plasma concentrations were the same. In our study, we could not compare the test product with the innovator product because the tramadol innovator (Ultram® or Tramal®) had not been registered in Myanmar. Therefore, we chose the generic Tramazac®, and it has been undertaken bioequivalence study with the innovator product [18]. This kind of condition is allowed by the selection criteria of the ASEAN comparator product [7].

Conclusions

Tramadol BPI® and Tramazac® capsules, after a single oral administration of 100 mg, were bioequivalent in respect of their rate and extent of absorption under fasting condition.

PBR

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research and Ethics Committee of the University of Medicine 1, Yangon, and was registered at the Thai Clinical Trial Registry with the trial registration number TCTR20190107001. All procedures performed in this study were following the ethical standards of the institutional and or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The written informed consent was taken from the participants after a thorough explanation of objectives, procedures, benefits, and possible risks of the research.

Funding

Authors' contributions

Conceptualization: Nu Nu Aye; Methodology: Ye Htut Linn, Myat Myat Soe, and K Khine Thu; Investigation: Ye Htut Linn, Mi Kun Kaw San, Nyein Chan Pyae; Data analysis: Ye Htut Linn; Writing-original draft and editing: Ye Htut Linn, Nu Nu Aye; Funding acquisition: Myat Myat Soe, K Khine Thu; Resources: Myat Myat Soe, K Khine Thu, Thida Tun, Nu Nu Aye; Supervision: Thida Tun, Nu Nu Aye; Project administration: Myat Myat Soe, K Khine Thu, Thida Tun, Ye Htut Linn.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

References

[1] Expert Committee on Drug Dependence. Tramadol: Update review report. Paper presented at: Thirty-sixth Meeting of the Expert Committee on Drug Dependence (36th ECDD). 16-20 June 2014; Geneva, Switzerland; 2014.

[2] Schumacher MA, Basbaum AI, Naidu RK. Opioid agonists & antagonists. In: Katzung BG, editor. Basic and Clinical Pharmacology. 14th ed. New York: McGraw-Hill Education; 2018.

[3] Drug Bank. Tramadol [Internet]. 2019 [Updated 2019 January 27]. Available from: https://www.drugbank.ca/drugs/DB00193

[4] Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet. 2004; 43(13):879-923. [DOI:10.2165/00003088-200443130-00004] [PMID]

[5] Joint Formulary Committee, editor. BNF 73 (British National Formulary) March 2017. London: Pharmaceutical Press; 2017.

[6] Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacol Toxicol. 2013; 14:1. [DOI:10.1186/2050-6511-14-1] [PMID] [PMCID]

[7] ASEAN. ASEAN guideline for the conduct of bioequivalence studies [Internet]. 2015 [Updated 2015 March 27]. Available from: https://asean.org/wp-content/uploads/2012/10/BE_Guideline_FinalMarch2015_endorsed_22PPWG.pdf

[8] Birkett DJ. Generics - equal or not? Aust Prescr. 2003; 26(4):85-7. [DOI:10.18773/austprescr.2003.063]

[9] World Health Organization. Generic drugs: the hidden issues of quality and cost. 2000 [Updated 2019 December 31]. Available from: https://apps.who.int/medicinedocs/en/d/Jh1463e/2.html

[10] Min Y, Tun T, Linn YH, Aye NN, Win NHH. Utilization, availability of analgesics and quality of pain control for post-operative pain in surgical patients. Drugs Ther Perspect. 2019; 35(2):93-9. [DOI:10.1007/s40267-018-0582-3]

[11] Thandar-Htar-Lwin. Drug utilization pattern and efficacy of opioid and other analgesics in hospitalized cancer patients with pain [MMedSc thesis]. Yangon: University of Medicine; 2015.

[12] British Pharmacopoeia Commission. British pharmacopoeia. 2013; London: UK Stationery Office; 2012.

[13] Saghaei M. Random allocation software version 1.0.0. 2017.

[14] Zhou X, Liu J. Fluorescence detection of tramadol in healthy Chinese volunteers by high-performance liquid chromatography and bioequivalence assessment. Drug Des Devel Ther. 2015; 9:1225-31. [DOI:10.2147/DDDT.S73723] [PMID] [PMCID]

[15] ICH Expert Working Group. Validation of analytical procedures: Text and methodology Q2(R1). Paper presented at: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 6 November 2005; Geneva, Switzerland.

[16] Zhang Y, Huo M, Zhou J, Xie Sh. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Computer Methods and Programs in Biomedicine. 2010; 99(3):306-14. [DOI:10.1016/j.cmpb.2010.01.007] [PMID]

PBR

Linn YH, et al. Study of Tramadol Formulations in Myanmar. PBR. 2019; 5(4):35-44.

43

PBR
Pharmaceutical & Biomedical Research

[17] EpiTools epidemiological calculators. Bioequivalence analysis - two-period, two-treatment crossover trial [Internet]. 2018 [Updated 2019 January 10]. Available from: http://epitools.ausvet.com.au/content.php?page=bioequivalence

[18] Tramadol: comparative bioavailability and bioequivalence study report. Cadila Healthcare Ltd; 2014.

44

Linn YH, et al. Study of Tramadol Formulations in Myanmar. PBR. 2019; 5(4):35-44.

PBR