Kardiologia Polska 2017; 75, 1: 48–54; DOI: 10.5603/KP.a2016.0106

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Bioequivalence study of 2.5 mg film-coated bisoprolol tablets in healthy volunteers

Katarzyna Buś-Kwaśnik[1], Piotr J. Rudzki[1], Hanna Ksycińska[1], Andrzej Leś[1, 2], Krystyna Serafin-Byczak[1], Jerzy Raszek[3], Agnieszka Bielak[4], Andrzej Wybraniec[4], Anna E. Płatek[5], Filip M. Szymański[5], Tomasz Łazowski[3,6]

[1]Pharmacology Department, Pharmaceutical Research Institute, Warsaw, Poland
[2]Faculty of Chemistry, Warsaw University, Warsaw, Poland
[3]Clinical Centre CRO Poland Sp. z o.o., Otwock, Poland
[4]ICN Polfa Rzeszow S.A., Rzeszow, Poland
[5]Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
[6]1st Department of Anaesthesiology and Intensive Care, Medical University of Warsaw, Warsaw, Poland

Abstract

Background: Bisoprolol is one of the most widely used beta-blockers characterised by cardioselectivity, and it has no intrinsic sympathomimetic activity. It is commonly used in the treatment of coronary heart disease and heart failure.

Aim: The aim of study was to assess the bioequivalence of the film-coated tablets containing 2.5 mg of bisoprolol (Bisocard® — the medicinal product) to the original medicinal product (Concor Cor 2.5® — the reference).

Methods: A randomised, open-label, two-period, crossover, single-dose, relative bioavailability study was conducted in fasted healthy Caucasian volunteers. A single 10-mg oral dose (four tablets of 2.5 mg) of the test or reference product was followed by a 14-day wash-out period, after which the subjects received the alternative product. Blood was sampled within a period of 60 h post administration in pre-specified time points. Bisoprolol concentrations were determined by a validated LC-MS/MS method. The products were considered bioequivalent if the 90% confidence interval (CI) of the log-transformed geometric mean ratios (test vs. reference) for $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, and C_{max} were within 80–125% limits. Adverse events were monitored during the study based on the subject claims and clinical parameters.

Results: Twenty-six healthy male and female volunteers (mean age ca. 29 years; body mass index 22.7 kg/m^2) were included in the study, and 24 completed the clinical part. The geometric mean ratios (test/reference) for the log-transformed $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, and C_{max} were 95.16% (90% CI 92.52–97.87%), 95.08% (90% CI 92.40–97.83%), and 100.00% (90% CI 94.83–105.45%), respectively. There were no significant differences in the pharmacokinetic parameters between the test and reference formulations. No serious adverse events were reported.

Conclusions: The results of this single-dose study in healthy Caucasian volunteers indicate that Bisocard®; 2.5 mg film-coated tablets are bioequivalent to the reference product — Concor Cor 2.5®; 2.5 mg film-coated tablets. Both products had similar safety profile and have been well tolerated.

Key words: bisoprolol, pharmacokinetics, bioequivalence, relative bioavailability, beta-blocker

Kardiol Pol 2017; 75, 1: 48–54

INTRODUCTION

Bisoprolol is a highly selective β1-receptor antagonist devoid of any partial agonist effect (intrinsic sympathomimetic activity), vasodilatory effect, or membrane stabilising properties. It is well absorbed from the gastrointestinal tract and undergoes minimal first-pass metabolism to achieve oral bioavailability of ca. 90%. Due to its relatively long elimination half-life (10–11 h) it is suitable for a once daily administration [1]. It is cleared in equal parts unchanged by the kidney and by biotransformation in the liver [2].

Address for correspondence:
Piotr J. Rudzki, PhD, Pharmacology Department, Pharmaceutical Research Institute, ul. Rydygiera 8, 01–793 Warszawa, Poland, tel: +48 22 456 38 49, e-mail: p.rudzki@ifarm.eu

Received: 07.04.2016 **Accepted:** 25.04.2016 **Available as AoP:** 08.07.2016

Bisoprolol is marketed worldwide and its indications include hypertension, coronary heart disease, and stable chronic heart failure [2]. It is a β-blocker shown to improve survival in an outcome trial [3]. In hypertension or angina pectoris the usual therapeutic dose is 5–10 mg, and the maximum recommended dose is 20 mg. In heart failure the initial dose of bisoprolol fumarate is 1.25 mg, and it is gradually increased to 10 mg [2]. Beta-blockers are the most commonly used medicines in the therapy of hypertension; they may be used as monotherapy or concomitantly with other drugs. Despite the continuous rise in their prescription rate, bisoprolol and other β-blockers remain underused and underdosed in the treatment of heart failure and other cardiac diseases [4, 5]. It may be partially due to the limited number of available generic formulations.

The aim of this study was to evaluate the relative bioavailability of two oral bisoprolol formulations following a single dosing in healthy subjects in order to investigate the bioequivalence of the test bisoprolol film-coated tablet (Bisocard® by ICN Polfa Rzeszow S.A.) to the reference bisoprolol film-coated tablet (Concor Cor 2.5® by Merck KGaA).

METHODS

Study drugs

The following bisoprolol fumarate film-coated tablets were administered during the study: the test product Bisocard® manufactured by ICN Polfa Rzeszow S.A., Rzeszow, Poland (lot No. 80018173; expiration date: January 2011) and the reference product Concor Cor 2.5® manufactured by Merck KGaA, Beerse, Belgium (lot No. 5787020; expiration date: July 2011).

Study participants

The number of participants was determined assuming a significance level $\alpha = 0.05$, power of test 1 — $\beta = 0.80$, and ratio of the geometric mean of primary pharmacokinetic parameters (test vs. reference product) between 0.95 and 1.05. It was estimated that the intra-subject variability of primary pharmacokinetic parameters would not exceed 21% [6], while the drop-out rate would not exceed 15%. Based on the above assumptions, 26 subjects were included and 22 should complete the study.

There were 54 healthy volunteers invited for the screening — women and men aged between 18 and 55 years, whose body mass index was 18.8–24.9 kg/m^2. After a social interview and medical history, each of the volunteers underwent a medical examination and additional tests: electrocardiography (ECG), chest X-ray examination, urine testing (general and toxicological, pregnancy test in women) and blood — haematology, blood chemistry as well for the serology (human immunodeficiency virus HIV, hepatitis B and C).

The exclusion criteria included: evidence or suspected pathology assessed on the basis of the conducted tests; suspected hypersensitivity to bisoprolol or other ingredients of the medicinal product; second- or third-degree atrioventricular block; systolic blood pressure below 100 mm Hg; bradycardia below 50 bpm; chronic or acute inflammation or infection; allergy symptoms requiring medical treatment; any condition that could affect the pharmacokinetics of the investigational product, as well as any clinically significant abnormality in laboratory test results. It was decided to exclude volunteers who had taken any medications in the period of two weeks prior to the study or a drug with a half-life of over 24 h in the period of four weeks prior to the enrolment. Also excluded were those who had taken part in any other study in the last 60 days prior to the screening, cigarette smokers, alcohol abusers, and those with a special diet (vegetarians) or a specific lifestyle (professional sports). Before admission to the clinical centre qualified volunteers were tested for the presence of prohibited substances in urine, alcohol, and exhaled air.

Study design

The study was designed — in compliance with the applicable guidelines of the European Medicines Agency (EMA) [7, 8] — as a randomised, cross-over, two-way trial following the administration of a single dose of the test and reference product in fasting conditions. Study documents were approved by the Committee on Bioethics at the Regional Medical Chamber (Warsaw, Poland) and the Central Register of Clinical Trials at the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products (Warsaw, Poland). The trial was assigned the EudraCT number 2009-014861-20.

The clinical part of the study was conducted at the Clinical Centre CRO Poland (Otwock, Poland) in accordance with the contents of the Declaration of Helsinki and Good Clinical Practice guidelines [9]. Before the screening all volunteers were informed about the study procedures, risks, insurance, and limitations resulting from their participation in the study. The volunteers were supplied with a clinical trial information form and were allowed to ask questions to obtain additional information. Each volunteer who declared to take part in the study signed an informed consent form.

Drug administration

The volunteers qualified to participate in the study arrived at the test centre the day before the administration (D-0). The next day (D-1) in the morning, after at least a 10-h period of fasting, each volunteer received — under medical supervision, in a sitting position — a single dose of 10 mg (four tablets of 2.5 mg) of the test or reference product with 250 mL water according to the randomisation table. When swallowed, the doctor checked the inside of the mouth to confirm the swallowed dose. The volunteers remained in the clinical centre for the next 4 h resting, sitting, or half-sitting, and could perform normal activities, provided that they stayed within the premises of the clinical centre. Two hours after the ingestion of the test or reference product the subjects were allowed to drink water in order to secure their fluid balance. All participants

stayed at the clinical site for at least 12 h before and 60 h after the administration of the test or reference product, in each of the two study periods. During their stay all study participants ate only standardised meals provided by the clinical centre.

Blood sampling

To determine the concentration of bisoprolol in the plasma, in each of the two study periods 18 blood samples were taken from each volunteer: sample "0" (15 mL) within 60 min before the drug administration, then (9 mL) after 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48, and 60 h. The total volume of blood collected from each participant during the whole study was less than 370 mL. Samples were collected by syringe with an intravenous cannula of "Venflon" placed in the forearm venous vessel, and then the blood was poured into labelled test tubes placed in an ice bath. The blood samples were centrifuged for 10 min at 4°C at 4000 rpm. The plasma separated from each sample was transferred to two labelled polypropylene tubes (primary and backup), and then placed in a freezer at –20°C.

Bioanalysis

The bisoprolol plasma concentrations were determined by high performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The bioanalysis was performed in compliance with the principles of Good Laboratory Practice in the Pharmacology Department of the Pharmaceutical Research Institute, Warsaw. The applied bioanalytical method included slight modifications to the previous reports [6, 10, 11]. Reference standards of bisoprolol fumarate and metoprolol tartrate (the internal standard [IS]), were purchased from USP and Sigma-Aldrich (St. Louis, MO, USA), respectively.

The LC-MS/MS analyses were performed using a Quattro Micro API triple quadrupole mass spectrometer (Waters, Manchester, UK) and an Alliance 2695 series liquid chromatograph with a gradient pump, an autosampler with a cooler, a column oven, and a vacuum degasser (Waters, Milford, MA, USA). The data was processed using MassLynx version 4.1 software (Waters, Manchester, UK). The chromatographic separation from endogenous compounds was performed on a Zorbax SB-C18 column (150 × 3.0 mm, 3.5 μm, Agilent Technologies, CA, USA) preceded by a C18 guard column (4 × 2 mm, Phenomenex, Torrance, CA, USA). Isocratic elution was applied with the mixture of methanol and 0.01 M ammonium acetate containing 0.1% formic acid (62:38 v/v). The flow rate of the mobile phase was set at 0.3 mL/min and the run time was 6 min. The column and the autosampler were maintained at 35 ± 1°C and 20 ± 3°C, respectively. The MS/MS was equipped with an electrospray ionisation source, and multiple reaction monitoring in the positive ion detection mode was used. The transitions of 326.34 → 116.14 m/z and 268.29 → 191.12 m/z were applied for the bisoprolol and IS, respectively. The desolvation temperature was 350°C with the nitrogen flow of 700 L/h. The capillary voltage was 3.5 kV and the source temperature was 80°C. The cone voltage of 32 V for bisoprolol and 30 V for the IS was selected. The cell collision energy was 19 eV for both bisoprolol and the IS. Argon was used as the collision gas.

A frozen human plasma sample was thawed at an ambient temperature, mixed, and centrifuged. A 1.0 mL aliquot of the plasma was mixed with 50 μL of the IS working solution (20 μg/mL). Then the sample was alkalised by the addition of 0.1 M sodium hydroxide. Afterwards, 5 mL of ethyl acetate was added and the mixture was shaken for 5 min on a vortex mixer. After centrifugation, the aqueous phase was frozen, and the organic layer was transferred to a glass tube and evaporated to dryness under a stream of nitrogen. The dry residue was reconstituted in 200 μL of 60% aqueous methanol and mixed. The solution was transferred into an autosampler vial, and 30 μL of this solution was injected into the column.

Pharmacokinetic parameters

$AUC_{(0\text{-}t)}$ (i.e. area under the plasma concentration – time curve from time zero to time t of the last quantifiable concentration), $AUC_{(0\text{-}\infty)}$ (i.e. area under the concentration – time curve from time zero extrapolated to infinity) and C_{max} (i.e. maximum bisoprolol concentration in plasma) were selected as primary parameters. The secondary parameters were: t_{max} (time to reach maximum bisoprolol concentration in plasma), $t_{1/2}$ (elimination half-life), and MRT (mean residence time of bisoprolol in the body).

C_{max} and t_{max} were recorded from plasma concentrations directly. The elimination rate constant (k_{el}) — estimated using three or four last measured concentrations — allowed us to calculate $t_{1/2}$ according to the formula ln $2/k_{el}$. $AUC_{(0\text{-}t)}$ was obtained by the linear trapezoidal method with linear interpolation until the last measured concentration (C_t). The sum of $AUC_{(0\text{-}t)}$ and C_t/k_{el}, was used to calculate $AUC_{(0\text{-}\infty)}$. AUMC (i.e. area under the time course of the statistical first moment curve) was divided by $AUC_{(0\text{-}\infty)}$ to obtain MRT. A non-compartmental pharmacokinetic analysis was performed using the WinNonlin version 5.0.1., (Pharsight Corp.).

Statistical analysis

Shapiro-Wilk, Kolmogorow-Smirnow, Cramer-von Mises and Anderson-Darling tests at the significance level $\alpha = 0.05$ were used to assess the normality of data distribution. Following the ln-transformation of $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, C_{max}, $t_{1/2}$, and MRT, the analysis of variance (ANOVA) was performed using the General Linear Models procedure. It was assumed that bioequivalence is confirmed in cases when 90% confidence interval (CI) calculated for tested vs. reference product geometric means ratio — for each primary pharmacokinetic parameter (i.e. $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, and C_{max}) — is included within acceptance criteria of 80–125% ($p < 0.05$) [7, 8, 12, 13]. For t_{max} non-transformed data was analysed using two one-sided nonparametric Mann-Whitney-Wilcoxon tests. Statistical calculations were performed using SAS for Windows, version 9.1.3. (SAS Institute, N.C., USA).

Safety analysis

The study participants were monitored in order to assess potential side effects. Upon admission to the clinical centre, every 12 h during their stay and at the end of the study their vital signs (pulse rate, blood pressure, body temperature) were measured. Blood samples were drawn to check the morphology and basic biochemical parameters. The investigator evaluated the recorded adverse events (AE) and decided on the need to implement therapeutic actions.

RESULTS

Out of 47 male and female volunteers invited 36 signed up to participate in the study. The volunteers — after signing an informed consent — were screened (medical history, physical examination, ECG, chest X-ray, blood and urine laboratory tests). The blood and urine samples were analysed in a certified clinical laboratory of Mazovian Centre for Lung Diseases and Tuberculosis in Otwock, Poland. After the screening five persons were found to be ineligible and another five persons were eligible but not randomised. Finally, 26 healthy volunteers (demographic data in Table 1) were enrolled, and 24 of them completed the clinical part of the study. One of the volunteers left the study during wash-out, not willing to participate, while another one was withdrawn due to AE during the second period of the study.

Validation of the bioanalytical method

The validation parameters were defined according to the EMA as well as the Food and Drug Administration guidelines [7, 8, 14]. The validation covered all required tests: the carry-over effect, matrix effect, selectivity (analysis of blank human plasma samples derived from six volunteers), extraction recovery, limit of detection and lower limit of quantification, linearity, accuracy and precision, stability and system suitability tests. The stability of bisoprolol was tested in solutions and in biological material under appropriate test conditions and storage time (short-term, long-term, freeze and thaw, and autosampler stability). All parameters met the pre-defined acceptance criteria.

The calibration curve, constructed by plotting the peak area ratios of bisoprolol to the IS against the nominal concentrations of bisoprolol, was linear within the range 0.3––70.0 ng/mL. The accuracy and precision of the method were determined using three concentrations of bisoprolol in plasma (0.9, 30.0, and 60.0 ng/mL). The 90% CI for the intra-run (within one day) and inter-run (within three days) accuracy were within the ranges 93.1–111.1% and 89.8–109.5%, respectively. The intra-run and inter-run precision was within the ranges 1.89–7.03% and 3.04–9.20%, respectively.

Pharmacokinetic evaluation of bioequivalence

No relevant differences between the tested and reference drug in the bisoprolol plasma concentration vs. time profiles (Fig. 1) nor calculated pharmacokinetic parameters (Table 2) were observed. The statistical analysis did not allow us to discard the null hypothesis regarding the ln-normal distribution of $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, $t_{½}$, and MRT. As expected, the distribution of t_{max} differed significantly from the ln-normal one, which confirmed that the choice of a nonparametric test to evaluate this parameter was appropriate. The ANOVA results (Table 3) enabled the construction of 90% CI. The acceptance criteria were met for all primary pharmacokinetic parameters (Table 2). The Mann-Whitney-Wilcoxon test revealed no statistically significant differences between t_{max} of the tested and reference product, and the descriptive statistics for this parameter were comparable for both products.

Table 1. Demographic data of the population included in the study

Variable	Value
Males	16
Females	10
Caucasians	26
Age [years]*	18–43 [29]
Height [cm]*	158–191 [172]
Weight [kg]*	47.5–84.0 [67.9]
BMI [kg/m^2]*	18.8–24.9 [22.7]

*min–max [arithmetic mean]; BMI — body mass index

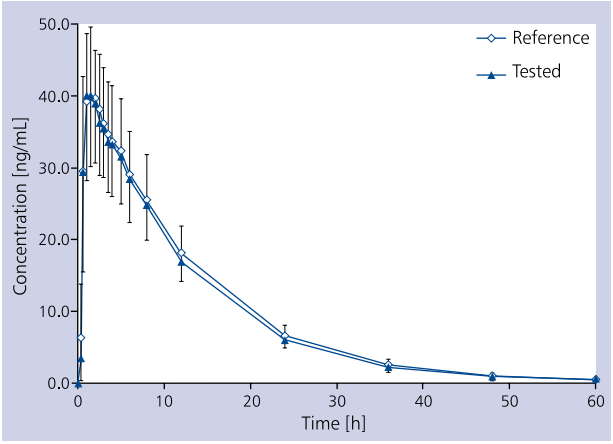

Figure 1. Mean ± standard deviation bisoprolol plasma concentration – time profiles after administration of single 10-mg oral doses (four film-coated tablets of 2.5 mg) of the tested (Bisocard®) and reference (Concor COR 2.5®) products

Safety results

All 26 study participants who received at least one dose of the test/reference product were included in the safety assessment. There were no serious adverse events, six AEs reported in three volunteers were described as moderately severe and

Table 2. Pharmacokinetic parameters of bisoprolol after a single 4 × 2.5-mg dose administration of the test and the reference products (n = 24)

Parameter	Test	Reference	Geometric mean test/reference
	Mean ± SD	Mean ± SD	(90% CI)
$AUC_{(0-t)}$ (ng×h/mL)	541 ± 79	570 ± 98	95.16 (92.52–97.87)
$AUC_{(0-\infty)}$ (ng×h/mL)	548 ± 80	578 ± 99	95.08 (92.40–97.83)
C_{max} (ng/mL)	44.2 ± 9.6	43.9 ± 8.3	100.00 (94.83–105.45)
t_{max} [h]*	1.5 [1.0–3.0]	1.5 [0.7–3.0]	–
$t_{1/2}$ [h]	8.6 ± 1.7	8.9 ± 1.4	–
MRT [h]	12.4 ± 1.9	12.8 ± 1.9	–

*Median and [min–max] for t_{max}; CI — confidence interval; SD — standard deviation; rest abbreviations — see text

Table 3. Results of the ANOVA (performed with the fixed effects model) of ln-transformed pharmacokinetic parameters after a single 4 × 2.5-mg dose administration of test and reference products to healthy volunteers (n = 24). The statistically significant effects are presented in bold

Pharmacokinetic parameter	Source of variation/p value			
	Sequence	Subject within sequence	Formulation	Period
$AUC_{(0-t)}$	**0.006**	**< 0.001**	**0.006**	**0.014**
$AUC_{(0-\infty)}$	**0,012**	**< 0.001**	**0.006**	**0.012**
C_{max}	**0.001**	**< 0.001**	0.999	0.461

Abbreviations — see text

included headache, increased body temperature, nausea, and vomiting. The occurrence of headache and vomiting found in one of the volunteers was classified as probably related to the study medicinal product, other AEs were not associated with the study products. All adverse events resolved during the study. There were no significant changes in blood and urine parameters (blood cell count, liver, and kidney) obtained after the completion of the clinical part of the study.

DISCUSSION

Bisoprolol is a highly selective β1-receptor antagonist. It displays no intrinsic sympathomimetic activity nor membrane stabilising properties. Bisoprolol is well absorbed following oral administration, and its bioavailability reaches 90%. Its pharmacokinetics are linear and age-independent. It seems that fasting or fed conditions do not influence bisoprolol pharmacokinetics. Ca. 30% of the drug is binded by proteins, and its volume of distribution is 3.5 L/kg [3].

The administration of bisoprolol in chronic heart failure and/or coronary artery disease patients is associated with a reduction in heart rate, increase in heart rate variability, and the improvement of left ventricular function [3]. Clinical efficacy of bisoprolol was primarily demonstrated in patients with chronic heart failure — in two large, double-blind, multi-centre randomised clinical trials: CIBIS and CIBIS II [15, 16]. The included patients with chronic heart failure (NYHA class III or IV) were randomly assigned to receive bisoprolol (starting dose of 1.25 mg daily, increased to a maximum of 5 mg [CIBIS] or 10 mg daily [CIBIS II]) or placebo. The patients also received a standard therapy in heart failure (ACE inhibitor and diuretic). It was observed that the addition of a highly selective β1-blocker bisoprolol significantly improved patient survival and reduced the hospitalisation rate. The use of bisoprolol is generally well tolerated in patients. According to the current guidelines β-blockers like bisoprolol constitute basic treatment for patients with chronic heart failure and stable angina, and are also used — among others — in the treatment of hypertension or arrhythmias [17–20].

Bisoprolol generics are used in a large number of patients and in many clinical conditions. It follows that the bioequivalence of these drugs to the reference product should be carefully studied, as was the case here. In our study we evaluated the bioequivalence of Bisocard® 2.5 mg film-coated tablets, manufactured by ICN Polfa Rzeszow S.A., with the reference product. The study was performed in line with the valid EMA guidelines [7, 8]. Since the end of study, some regulatory changes have been introduced, but general bioequivalence rules remain unchanged, so our study is in line with the current EMA requirements [21].

Appropriate selection of volunteers for bioequivalence studies guarantees a minimised variability within the study group and allows the detection of possible differences between the drugs [7]. In order for the measurement of bisoprolol plasma levels to be reliable, high enough concentrations were obtained because the study was conducted after a single dose of 10 mg — administered as four 2.5 mg film-coated tablets.

Based on the half-life of bisoprolol reported 10 to 11 h [1], a 14-day wash-out between the study periods was found to be appropriate. The correct selection of this parameter was confirmed as bisoprolol concentration in all the pre-dose samples below the limit of quantification (0.3 ng/mL).

For each primary parameter, the *a posteriori* power of the study was higher than 0.90, which confirmed the correct number of volunteers. The study results are an interesting example in which the factors determined during ANOVA as statistically significant are not clinically relevant because the acceptance criteria for all primary parameters were met (i.e. 90% CI for the ratio of geometric means were contained entirely within 80–125% limits). In our study very low intra-subject variability was recorded, and as a consequence other factors — i.e. sequence, formulation, and period — became statistically significant contributors to the variability observed in the study.

The sampling schedule allowed proper characterisation of t_{max} and C_{max} because there were no pharmacokinetic profiles (a specific study period for a specific subject) where C_{max} was the first point after the drug administration. In each pharmacokinetic profile $AUC_{(0-t)}$ was greater than 80% of $AUC_{(0-\infty)}$, which confirmed the appropriate selection of the last blood sampling point as well as a suitable bioanalytical method sensitivity. A positive study result is similar to the analogous bioequivalence study of Bisocard® 10 mg film-coated tablets [22]. It is also consistent with the recent meta-analysis that confirmed the efficacy and safety of generic drugs used in the treatment of cardiovascular diseases [23].

CONCLUSIONS

The results of the study conducted in healthy Caucasian volunteers after a single 10-mg administration in fasting conditions indicate that Bisocard® 2.5 mg film-coated tablets manufactured by ICN Polfa Rzeszow S.A. (tested product) are bioequivalent to Concor Cor 2.5®; 2.5 mg film-coated tablets manufactured by Merck KGaA (reference product). Both products were safe and did not cause any clinically relevant adverse events.

Conflict of interest: *The study was sponsored by ICN Polfa Rzeszow S.A.*

References

1. Leopold G. Balanced Pharmacokinetics and Metabolism of Bisoprolol. J Cardiovasc Pharmacol, 1986; 8 (suppl. 11): S16–S20.
2. Martindale. The complete drug reference. 33rd Ed. Sweetman S. London, Pharmaceutical Press, 2002.
3. McGavin JK., Keating GM. Bisoprolol: a review of its use in chronic heart failure. Drugs, 2002; 62: 2677–2696. doi: 10.2165/00003495-200262180-00017
4. Metra M, Nodari S, Bordonali T et al. Bisoprolol in the treatment of chronic heart failure: from pathophysiology to clinical pharmacology and trial results. Ther Clin Risk Manag, 2007; 3: 569–578.
5. Hoffman J, Grimm W, Maisch B. Beta-blockers in therapy of chronic heart failure. Herz, 2002; 27: 150–165.
6. Jovanović D, Cusić S, Rancić D et al. A pharmacokinetic comparison of generic tablets containing bisoprolol with the innovator formulation in healthy volunteers. Clin Pharmacol, 2006; 46: 1217–1222. doi: 10.1177/0091270006291626.
7. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. Committee for Proprietary Medicinal Products (CPMP). London, 26 July 2001.
8. Guideline on the Investigation of Bioequivalence (Draft). European Medicines Agency (EMEA). London, 24 July 2008.
9. OECD Principles of Good Laboratory Practice (as revised in 1997), No. 1, ENV/MC/CHEM(98)17, Environment Directorate, Paris, 1998.
10. Ding L, Zhou X, Guo X et al. LC-ESI-MS method for the determination of bisoprolol in human plasma. J Pharm Biomed Anal, 2007; 44: 520–525. doi: 10.1016/j.jpba.2007.03.001.
11. Bhatt J, Subbaiah G, Kambli S et al. A high throughput and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for the estimation of bisoprolol in human plasma using multiplexing technique. J Chromatogr B Analyt Technol Biomed Life Sci, 2007; 852: 374–381. doi: 10.1016/j.jchromb.2007.01.043.
12. Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. Food and Drug Administration. January 2001.
13. Schuirmann D.J. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharmaceutics, 1987; 15: 657–680.
14. Guidance for Industry. Bioanalytical Method Validation. Food and Drug Administration. May 2001.
15. CIBIS Investigators and Committees. A randomized trial of β-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation, 1994; 90: 1765–1773. doi: 10.1161/01.CIR.90.4.1765.
16. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet, 1999; 353: 9–13. doi: 10.1016/S0140-6736(98)11181-9.
17. McMurray JJ, Adamopoulos S, Anker SD et al.; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J, 2012; 33: 1787–1847. doi: 10.1093/eurheartj/ehs104.
18. Montalescot G, Sechtem U, Achenbach S et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J, 2013; 34: 2949–3003. doi: 10.1093/eurheartj/eht296.
19. Mancia G., Fagard R., Narkiewicz K et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J, 2013; 34: 2159–2219. doi: 10.1093/eurheartj/eht151.
20. Camm AJ, Lip GY, De Caterina R et al.; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J, 2012; 33: 2719–2747. doi: 10.1093/eurheartj/ehs253.
21. Guideline on the Investigation of Bioequivalence. Committee for Medicinal Products for Human Use (CPMP/EWP/QWP/1401/98/Rev. 1 Corr.**). London, 20 January 2010.
22. Buś-Kwaśnik K, Kycińska H, Leś A et al. Bioequivalence and pharmacokinetics of two 10-mg bisoprolol formulations as film-coated tablets in healthy white volunteers: a randomized, crossover, open-label, 2-period, single-dose, fasting study. Int J Clin Pharmacol Ther, 2012; 50: 909–919. doi: 10.5414/CP201726.
23. Manzoli L, Flacco ME, Boccia S et al. Generic versus brand-name drugs used in cardiovascular diseases. Eur J Epidemiol, 2016; 31: 351–368. doi: 10.1007/s10654-015-0104-8.

Cite this article as: Buś-Kwaśnik K, Rudzki PJ, Kycińska H et al. Bioequivalence study of 2.5 mg film-coated bisoprolol tablets in healthy volunteers. Kardiol Pol, 2017; 75: 48–54. doi: 10.5603/KP.a2016.0106.

Ocena równoważności biologicznej tabletek powlekanych bisoprololu 2,5 mg u zdrowych ochotników

Katarzyna Buś-Kwaśnik[1], Piotr J. Rudzki[1], Hanna Ksycińska[1], Andrzej Leś[1, 2], Krystyna Serafin-Byczak[1], Jerzy Raszek[3], Agnieszka Bielak[4], Andrzej Wybraniec[4], Anna E. Płatek[5], Filip M. Szymański[5], Tomasz Łazowski[3,6]

[1]Zakład Farmakologii, Instytut Farmaceutyczny, Warszawa
[2]Wydział Chemii, Uniwersytet Warszawski, Warszawa
[3]Centrum Kliniczne CRO Poland Sp. z o.o., Otwock
[4]ICN Polfa Rzeszów S.A., Rzeszów
[5]Klinika Kardiologii, Warszawski Uniwersytet Medyczny, Warszawa
[6]I Klinika Anestezjologii i Intensywnej Terapii, Warszawski Uniwersytet Medyczny, Warszawa

Streszczenie

Wstęp: Bisoprolol jest jednym z najczęściej stosowanych beta-adrenolityków cechujących się kardioselektywnością i pozbawionym wewnętrznej aktywności sympatykomimetycznej. Jest powszechnie stosowany w leczeniu choroby niedokrwiennej serca czy niewydolności serca.

Cel: Celem pracy była ocena równoważności biologicznej tabletek powlekanych zawierających bisoprolol w dawce 2,5 mg (Bisocard® — lek badany) w odniesieniu do oryginalnego produktu leczniczego (Concor Cor 2.5® — lek referencyjny).

Metody: Przeprowadzono badanie otwarte z randomizacją w schemacie krzyżowym, po pojedynczym podaniu na czczo zdrowym ochotnikom rasy białej bisolprololu w dawce 10 mg (4 tabletki po 2,5 mg). Próbki krwi pobierano do 60. godziny po podaniu leku. Stężenie bisoprololu w osoczu oznaczono zwalidowaną metodą LC-MS/MS. Produkty lecznicze uznano za równoważne biologicznie, gdy 90-procentowe przedziały ufności (CI) stosunków średnich geometrycznych (produkt badany/referencyjny) dla zlogarytmowanych $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$ i C_{max} mieściły się w granicach 80–125%. Działania niepożądane monitorowano na podstawie parametrów klinicznych i zgłoszeń ochotników.

Wyniki: Dwudziestu sześciu zdrowych ochotników obu płci (średnia wieku ok. 29 lat, wskaźnik masy ciała 22,7 kg/m^2) zostało włączonych do badania, a 24 z nich ukończyło część kliniczną badania. Otrzymano następujące stosunki średnich geometrycznych (produkt badany/referencyjny): $AUC_{(0\text{-}t)}$ 95,16% (90% CI 92,52–97,87%), $AUC_{(0\text{-}\infty)}$ 95,08% (90% CI 92,40–97,83%) oraz C_{max} 100,00% (90% CI 94,83–105,45%). Nie zaobserwowano istotnych statystycznie różnic w ocenianych parametrach farmakokinetycznych między produktami badanym i referencyjnym. Nie stwierdzono poważnych zdarzeń niepożądanych w badanej populacji.

Wnioski: W badanej populacji stwierdzono równoważność biologiczną leku generycznego (Bisocard®) z produktem referencyjnym (Concor Cor 2.5®). Oba produkty cechują się porównywalną, dobrą tolerancją i bezpieczeństwem.

Słowa kluczowe: bisoprolol, farmakokinetyka, równoważność biologiczna, względna dostępność biologiczna, beta-adrenolityk

Kardiol Pol 2017; 75, 1: 48–54

Adres do korespondencji:
dr n. farm. Piotr J. Rudzki, Zakład Farmakologii, Instytut Farmaceutyczny, ul. Rydygiera 8, 01–793 Warszawa, tel: +48 22 456 38 49, e-mail: p.rudzki@ifarm.eu
Praca wpłynęła: 07.04.2016 r. **Zaakceptowana do druku:** 25.04.2016 r. **Data publikacji AoP:** 08.07.2016 r.