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Comparative Bioavailability of Two Oral Oseltamivir Formulations: Commercial Capsules and an Emergency Solution Prepared During the 2009 Influenza a (H1n1) Outbreak in Mexico

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Abstract

This study was designed to evaluate the bioequivalence of two formulations, commercially available capsule of oseltamivir phosphate and an emergency solution prepared to be used under the influenza A (H1N1) outbreak in Mexico. The clinical investigation was designed as a randomized, open-label, two-period, two-treatment, two-period crossover study, in 22 healthy male volunteers. Each formulation was administered with 200 ml of water after 10-hour overnight fast. After dosing, serial blood samples were collected for a period of 24 hours. Plasma concentrations were determined by a validated high-performance liquid chromatographic method with fluorescence detection and pharmacokinetic parameters were obtained by non-compartmental approach. Analysis of variance (ANOVA) was carried out using log-transformed AUC∞, AUC and Cmax and untransformed tmax and 90% confidence intervals for AUC∞, AUC and Cmax were calculated. If the 90% confidence intervals (CI) for AUC∞, AUC and Cmax fell fully within the interval 80 – 125%, the bioequivalence of the two formulations was established. The means (test and reference) for AUC∞ were 3745.386 and 3535.320 ng/ml, for AUC were 3967.991 and 3911.227 ng/ml and for Cmax were 340.335 and 352.737 ng/ml. The geometric mean ratios of the test formulation to reference formulation for AUC∞, AUC, and Cmax (CI) were 101.92% (85.62 – 121.33%), 103.43% (87.29 – 122.56%) and 105.45% (90.86 – 122.39%), respectively. All 90% CI for AUC∞, AUC, and Cmax fell within the Mexican Federal Commission for Prevention of Sanitary Risks (COFEPRIS) accepted bioequivalence range of 80 – 125%. Based on the results, the formulations tested are bioequivalent.

Keywords: Oseltamivir; Bioequivalence; Solution; Capsule

Introduction

In 2009, human infection with the influenza A (H1N1) virus became a health burden throughout the world. Initial cases were seen in the town of La Gloria in the Eastern coastal region of Mexico and thereafter in other parts of the country. Influenza A (H1N1) then expanded globally to reach pandemic levels [1-4]. The greatest initial burden of critical illness and death due to influenza A (H1N1) occurred in Mexico, the largest number of confirmed cases being located in Mexico City [2,4-6]. To cope with this threat to public health, the orally active neuraminidase inhibitor oseltamivir, which has demonstrated to be effective against the H1N1 virus [7,8], was widely used [5,6]. The supply of this antiviral agent, however, presented a serious challenge. Emergency formulations, which did not follow Good Manufacturing Practice Regulations (GMP) were thus prepared. The main formulation studied was an oseltamivir phosphate emergency solution prepared in Mexico during 2009.

Subjects, Material and Methods

Studied formulations were commercial oseltamivir capsules (Tamiflu®), Roche, Basel, Switzerland) and a non-commercial oseltamivir phosphate solution provided by Laboratorios de Biológicos y Reactivos de México S.A. de C.V. (Mexico City, Mexico), as it was prepared during the 2009 influenza A(H1N1) outbreak. Calibration curves were prepared with pure oseltamivir phosphate and OC standards provided by Roche (Mexico City, Mexico).

Twenty-two healthy volunteers of (mean ± SEM) 28.1 ± years of age, 64.3 ± 1.9 kg of weight and 166 ± 2 cm of height participated in this study. All subjects were fit according to medical history, clinical examination and suitable laboratory tests. All volunteers read the informed consent and the study was conducted in accordance with the Helsinki declaration and Mexican Guidelines for Good Clinical Practice (GCP). The study was approved by the Ethics Committee of the National Institute for Respiratory Diseases (Col. Sección XVI. 14080 México, D.F., Mexico, Tel: 5255-54871728; E-mail: miris22@hotmail.com).

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protocol approved by the Institutional Research and Ethics Committee and gave written informed consent for participation. The clinical investigation was carried out as a randomized, open label, two-arm, two-treatment, two-period crossover study, as previously described [12]. Subjects arrived to the hospital the night before the beginning of the study and no food was allowed after 10 pm. After an overnight fast (at least 9 hours) a cannula was placed in a suitable forearm vein and a control blood sample was obtained. Then, volunteers received a single oral dose of 75 mg of oseltamivir, as capsule or as solution, according to the randomized crossover design. Blood samples were drawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24 and 48 h after medication. Plasma was obtained by centrifugation of blood at 3000 rpm for 10 min and stored frozen at -80°C until analyzed for determination of oseltamivir and OC. After a one-week washout period, subjects arrived again to the hospital for the second session, which was carried out in the same way of the first session.

OC, the active metabolite of oseltamivir, was determined by high-performance liquid chromatography by the procedure described by Eisenberg and Cundy [13]. Briefly, plasma samples of 500 μl were subjected to solid-phase extraction on C18 extraction columns. After extraction, OC was derivatized with diphenylcarbazide in the presence of potassium cyanide to produce highly fluorescent cyanol[1] benzoisoindole derivative. Samples were then analyzed by an isocratic reversed-phase high-performance liquid chromatographic method using fluorescence detection at 420 nm excitation and 470 nm emission wavelength.

Individual OC plasma levels-time curves were constructed and pharmacokinetic parameters were obtained according to a non-compartmental approach [12]. The peak concentration (Cmax) and time to reach this maximum (tmax) were obtained directly from these curves. Area under the plasma concentration against time curve until the last concentration observed (AUClast) was calculated by the trapezoidal rule. Extrapolation to infinity was obtained by dividing the last concentration by the elimination constant rate (K). The area under the curve to infinity (AUC∞) was obtained as the sum of AUClast and such extrapolation. K was estimated by linear regression from the points describing the terminal elimination phase in a log-linear plot. Half-life was derived from this rate constant (t(1/2) = ln(2) / K).

In order to establish if the formulations tested were bioequivalent, log-transformed AUC∞ last, AUC∞ and Cmax obtained with the two formulations were compared by analysis of variance for a crossover design. Then, test/reference ratios were calculated and 90% confidence limits. Furthermore, the probability of exceeding these limits was calculated according to the two-one sided t-tests procedure [12,14]. For all calculated ratios, 90% confidence intervals were included in the allowed confidence limits. Additionally, the probability of exceeding these limits was always lower than 0.05. Therefore, both formulations were considered as bioequivalent (Table 2).

### Results

Mean (± SEM) OC plasma levels against time curves after administration of the two formulations tested are shown in Figure 1. It can be observed that, with both formulations, OC appeared gradually in the circulation, reaching its maximal concentration in about 4 h, and decreased thereafter. Pharmacokinetic parameters are shown in Table 1. There was no statistically significant difference between formulations in any of the determined parameters. In order to establish if the formulations are bioequivalent, AUC∞ last, AUC∞ and Cmax test-reference ratios and 90% confidence limits for these ratios were obtained [14].

Discussion

Influenza A(H1N1) outbreak presented in 2009 was faced in Mexico with the use of Oseltamivir, since a vaccine for this virus was not available. It has been reported the potential use of Oseltamivir in the event of an influenza pandemic [15]. Under these circumstances, oseltamivir proved to be an effective agent for both, treatment and prophylaxis [7,8]. However, in many countries, the commercial formulation availability was limited. In the case of Mexico, country that had to cope with the greatest initial burden of critical illness and death due to influenza A(H1N1), oseltamivir availability was critical. Therefore, emergency formulations had to be developed, although
GMP could not be strictly followed [11]. In Mexico, a non-commercial oseltamivir phosphate solution was developed and widely used to treat patients, although no information was available on its bioavailability, and no information about the pharmacokinetics of this drug in Mexicans was available.

In the present study, we compared the bioavailability of OC, the active metabolite of oseltamivir, of this emergency formulation with that of commercial capsules. With both formulations, OC appeared gradually, as expected for a metabolite generated by first-pass biotransformation [8]. Results show that the two studied formulations are bioequivalent. Therefore, the Mexican emergency solution is similar to that of other oral liquid formulation that have been developed elsewhere [9,10]. An important aspect is that concentrations reached with both formulations are in agreement to those reported in other populations [16-18] and considered as effective for other influenza virus strains [19-21]. These data explain the good clinical performance of the Mexican solution when given to patients with influenza A(H1N1). The present results thus justify the preparation of oseltamivir oral liquid formulations during influenza outbreaks [11].

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