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Bioavailability of an Extemporaneous Suspension of Propafenone made from Tablets

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ABSTRACT: Propafenone is an effective antiarrhythmic agent used in children, while in Mexico no specific formulation for children is available, which causes errors in adequate dosage. The aim of this study was to determine the bioavailability of a suspension prepared extemporaneously using commercial tablets of propafenone. The bioavailability was determined in two groups of rabbits ($n = 8$): the first group received a single intravenous dose of 2 mg/kg of propafenone; the second was orally administered an extemporaneous suspension of propafenone prepared from commercial tablets. Blood samples were drawn at several times during the next 24 h and analysed by HPLC to determine drug levels. The extemporaneous suspension was tested previously with satisfactory results regarding physicochemical and microbiologic stability. The area under the curve (*AUC*) for the i.v. route was 5600.6 ng/ml.h and for oral administration the *AUC* was 3327.6 ng/ml.h. The bioavailability was calculated at 59.41%. These results are consistent with previous reports for solid dosage forms. The propafenone suspension prepared extemporaneously using commercial tablets is bioavailable using an animal model; nevertheless, it is necessary to carry out human studies either in volunteers or in patients to confirm these results. Copyright © 2006 John Wiley & Sons, Ltd.

Key words: antiarrhythmic agent; bioavailability; children; pharmacokinetics; propafenone

Introduction

Propafenone is an antiarrhythmic agent that acts as a sodium channel blocker, β-adrenergic receptor antagonist and weak calcium antagonist [1,2]. Its principal electrophysiologic effect is to slow down the conduction in tissues that exhibit rapid reply [3]. Orally administered propafenone is largely absorbed and easily metabolized by the liver into active metabolites. Its bioavailability is reduced by approximately 50% due to first-pass metabolism [4]. Propafenone metabolism is mediated by CYP2D6 and it is important to mention that a small increase in the dose (e.g. 10 mg) can produce elevated plasma levels [5]. Ninety percent of the administered dose is eliminated in feces and urine within 60 h [6,7].

Propafenone is completely absorbed after oral administration, with peak plasma concentrations occurring 3.5 h after administration, its elimination half-time ($t_{1/2}$) ranging from 2 to 32 h [5,8]. Propafenone (PPF) is used in the treatment of several tachyarrhythmias in children [9,10]. The recommended oral dose in pediatric patients is

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7–10 mg/kg/day [11]. In Mexico, there are three commercial formulations of PPF: tablets of 150 mg, of 300 mg and ampoules of 70 mg; nevertheless, no suitable oral formulation for pediatric patients is available. The aim of this study was to determine the bioavailability of a propafenone suspension prepared extemporaneously using commercial tablets.

Materials and Methods

Suspension stability analysis

Prior to this study, the stability of the suspension was tested. The suspension was prepared by grinding 1 tablet of 150 mg of hydrochloride propafenone (Norfenon, Abbott Lab, Mexico) in a mortar. The finely ground tablets were then powdered and forced to pass through a mesh (size 100) in order to homogenize the particle size. Then, 100 ml of pomegranate syrup (pomegranate syrup, La Madrileña, Mexico) which was used as diluent, was added to obtain a final concentration of 1.5 mg/ml of propafenone. Six identical samples were prepared of each drug mixture and placed in 2 oz amber plastic flasks with security screw top for children. The preparation and stability of the oral suspension were tested according to previous reports on the preparation of extemporaneous suspensions [12–14]. Three samples of each preparation were stored at room temperature ($15 \pm 5^{\circ}$C) and three were refrigerated (3–5°C). Samples of 1.5 ml were taken from each of the six flasks immediately after being prepared and after 10, 30, 60 and 90 days. The corresponding dilutions were made to obtain concentrations in the range of 2.5–25 μg/ml. Later, triplicate samples were extracted and quantified in a liquid chromatograph. It was always recommended that the suspension be shaken before taking the dose, to resuspend the sediment and thus try to keep the contents and dosage uniform. For analysis, 300 μl of each concentration was alkalinized with 150 μl of a 0.25 M sodium hydroxide solution, and 3.5 ml of a mixture diethylether–dichloromethane (50:50 v/v) was added as extraction solvent. This mixture was carefully vortexed for 2 min and centrifuged at 800*g* for 5 min. The organic layer was evaporated under a gentle nitrogen stream. The dried residue was dissolved with 195 μl of mobile phase and 5 μl of a solution of propranolol (internal standard) at 3 μg/ml was added. Then 100 μl aliquots were injected into the chromatographic system. Samples were visually examined for color and odor changes on each analysis day. Stability was defined as the retention of at least 90% of the initial concentration [15].

Microbiologic analysis

Suspensions were tested on culture media at the same times as the stability evaluation, i.e. immediately after preparation, and after 10, 30, 60 and 90 days for the samples at room temperature ($15 \pm 5^{\circ}$C) and refrigeration (3–5°C). Serial dilutions of the samples in saline solution were prepared and aliquots were cultured in selective and differential media for the growth of mesophile microorganisms, and of objectionable microorganisms such as the coliforms *Escherichia coli* and *Shigella* and microorganisms of the genera *Salmonella abony*, *Pseudomona aeruginosa*, *Staphylococcus aureus*. Cultures were incubated for 48 h.

Microbiological stability was measured by colony forming units (CFU) per milliliter of sample.

Animal studies

The study was carried out in two groups of male rabbits ($n = 8$), average age 1 year and average weight 3.5 kg. The first group received propafenone intravenously from commercial ampoules at a dose of 2 mg/kg. The second group received the suspension orally. The suspension was previously prepared from commercial tablets of propafenone at a dose of 10 mg/kg. Blood samples were drawn after 0, 0.16, 0.33, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12 and 24 h. The samples were frozen at −70°C and then analysed by high performance liquid chromatography (HPLC), which was previously validated for the determination of propafenone in our laboratory as previously reported [16]. The study was approved by The Commission for Animal Protection of the National Institute of Pediatrics.

Extraction method

To 500 µl of blood was added with 25 µl internal standard (propranolol, 500 ng/ml) solution, 150 µl 0.25 M NaOH and 3.5 ml diethylether–dichloromethane (50:50 v/v). The tubes were vortexed for 2 min and centrifuged at 800*g* for 5 min. The organic layer was evaporated to dryness under nitrogen flow, the resultant residue was dissolved in 200 µl mobile phase and 100 µl was injected to the HPLC system.

HPLC system

The chromatographic system consisted of a solvent delivery system Model 510, a 100 µl loop injector (Rheodyne, Cotati CA), and a multi-wavelength flourescence detector (Model 2475). The reverse-phase column was Symmetry C18 5 µm (150 × 3.9 mm i.d.). Chromatographic data were collected with the Millennium software version 32.0 to process control data. All mentioned items were purchased from Waters Co. (Milford, MA, USA).

Chromatographic conditions

The mobile phase consisted of 50 mM potassium dihydrogenphosphate adjusted with acetic acid (pH 3.2)–acetonitrile (70:30 v/v). Following preparation, the mobile phase was filtered through a membrane filter. The flow rate was 1 ml/min at room temperature (15 ± 5°C). Detection was measured by fluorescence at 200 nm (excitation wavelength) and 210 nm (emission wavelength).

Pharmacokinetic analysis

To obtain the pharmacokinetic parameters Winnonlin program version 1.1, with a non-compartmental model was used [17]. The bioavailability of propafenone suspension was determined by comparing the area under the curve (*AUC*) of both formulations obtained in each group of animals. Median values were used due to the large variability of results in the studied group, and the Mann-Whitney *U* test was applied with a value of $p < 0.05$ for significance [18].

Results and Discussion

Table 1 shows the validation parameters of the HPLC method of analysis. As shown, samples used to determine the inter- and intra-day precision and accuracy of the method showed a coefficient of variation (CV) lower than 10%, which is acceptable for pharmacokinetic studies. The pharmacokinetic parameters obtained from both formulations are shown in Table 2. The absolute bioavailability obtained from the *AUC* relation between intravenous and oral administration was 59.4%. The profile of propafenone concentrations obtained for both formulations is shown in Figures 1 and 2. The elimination half-time ($t_{1/2}$) obtained for the two groups was 14.3 h for the i.v. and 17.8 h for the oral suspension. Although they were different ($p < 0.05$, Mann-Whitney *U* test), they are within reported variability range (2–32 h) [5,8]. The volume of distribution (V_d) was also within reported variability values (5.5 l/kg vs 3.6 ± 2.1 l/kg). The time to reach the maximum concentration (T_{max}) was

Table 1. Precision and accuracy of the HPLC method for determination of propafenone in blood

	Inter-assay reproducibility ($n = 9$)		Intra-assay reproducibility ($n = 5$)		
Concentration of added propafenone (ng/ml)	Concentration found after extraction (mean ± SD)[a] (ng/ml)	C.V. (%)	Concentration found after extraction (mean ± SD)[a] (ng/ml)	C.V. (%)	Accuracy (%)[b]
150	152 ± 15	10	160 ± 5	3	+7
250	239 ± 22	9	254 ± 15	6	+2
450	473 ± 44	9	498 ± 10	2	+10

[a] Calculated from linear regression equation.
[b] Accuracy = (measured concentration − theoretical concentration) / theoretical concentration × 100.

Table 2. Pharmacokinetic parameters obtained for two formulations of propafenone in rabbits ($n = 8$ for each group)

Pharmacokinetic parameter	Intravenous administration Median (range)	Oral administration Median (range)
T_{max} (h)		1 (1–1.5)
C_{max} (ng/ml)		148.6 (96.5–193.4)
$T_{1/2}$ (h)	14.3 (10.8–30.2)	17.8 (9.8–28.4)
V_d (l/kg)	5.5 (2.8–7.0)	
Cl (l/kg.h)	0.4 (0.1–0.8)	
AUC_{0-24} (ng/ml.h)	4106.8 (1669.7–13785.7)	1384.8 (905.1–2127.7)
AUC_{0-INF} (ng/ml.h)	5600.6 (2486.1–14589.1)	3327.6 (2426.8–3961.5)
F (%)		59.4 (27.1–97.6)

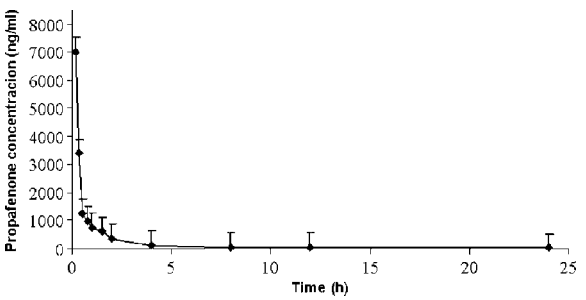

Figure 1. Pharmacokinetic profile of propafenone: Concentration vs time in blood after intravenous administration in rabbits ($n = 8$)

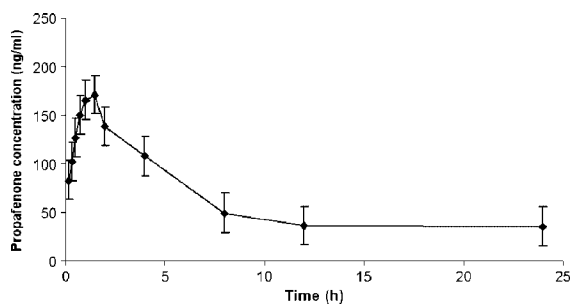

Figure 2. Pharmacokinetic profile of propafenone: Concentration vs time in blood after oral administration in rabbits ($n = 8$)

shorter than reported elsewhere (1 h vs 3.5 h). The bioavailability results for the oral suspension can be due to two factors: first, the drug presented a high level of first-pass effect, which reduced the amount of propafenone in the general circulation, an effect that is not present when it is administered intravenously; and second, with drugs that are orally administered, the excipients can contribute to reduce the total available fraction [19,20]. Our results are consistent with previous reports [6,7] of bioavailability of about 50%, although other authors, e.g. Vozeh *et al*. [21], report a lower bioavailability of 15.5%. Prior to this study, the stability of the propafenone suspension was tested. A 1.5 mg/ml suspension of propafenone was prepared which was stable for at least 90 days when stored at room temperature ($15 \pm 5^{\circ}C$) and when refrigerated (3–5°C), preserving at least 90% of the initial concentration. The prepared medicament showed no ostensible changes in color and odor. Besides, no bacterial growth was found upon analysis. Table 3 presents stability data of propafenone concentrations of the oral suspension under two storage conditions during a period of 90 days. The conservation of the physical, chemical and microbiological stability represents an option for administering the drug to children who have difficulty ingesting commercial tablets. The propafenone suspension prepared extemporaneously using commercial tablets is stable, since it maintained equal concentration values to those reported when the tablet is administered. The administration of an extemporaneous suspension of propafenone represents an option to administer the drug to children when commercial presentations are not available. Although the suspension was tested in an animal model, it is still necessary to carry out human studies either in volunteers or in patients to confirm these results.

Table 3. Stability of oral suspension of propafenone at 1.5 mg/ml prepared from tablets at 3–5°C and 15 ± 5°C

Added concentration (μg/ml)	Storage temperature (°C)	Measured concentration (μg/ml) Day 1	Day 10	Day 30	Day 60	Day 90
6	3–5	6.0 ± 0.2	6.3 ± 0.1	6.4 ± 0.2	6.1 ± 0.1	6.1 ± 0.5
	15 ± 5	6.1 ± 0.2	6.2 ± 0.2	6.1 ± 0.4	6.0 ± 0.5	5.9 ± 0.3
12	3–5	12.1 ± 1.0	12.8 ± 0.3	12.8 ± 0.3	12.5 ± 0.3	12.2 ± 0.9
	15 ± 5	12.3 ± 0.8	12.3 ± 0.5	12.6 ± 0.5	12.9 ± 0.1	12.9 ± 0.2
18	3–5	18.4 ± 0.5	17.8 ± 1.1	17.2 ± 0.2	18.7 ± 2.6	18.4 ± 1.5
	15 ± 5	17.7 ± 0.5	18.0 ± 1.2	18.4 ± 0.4	18.9 ± 0.4	18.7 ± 0.3

The values represent the mean ± standard deviation.

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