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Preparation and evaluation of unitary doses of propafenone used in children with supraventricular tachycardia: a pilot study

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Abstract. – PURPOSE: The aim was to prepare and evaluate unitary doses of propafenone (UDP) used in children with supraventricular tachycardia.

METHODS: UDP were prepared from four brands of tablets at doses of propafenone, 11, 25 and 90 mg, used in the Cardiology Service of this Institute. The stability of doses was determined at 20±5°C and 40°C for up to day 30. Besides, a weight variation test was performed. Plasma levels of propafenone were determined at steady state in 3 children diagnosed with supraventricular tachycardia under treatment with UDP. Concentrations of drug in blood were measured using a high pressure liquid chromatography method, previously validated.

RESULTS: The stability of UDP, showed no significant statistical differences ($p > 0.05$) between doses or brands up to day 30, at both temperatures. The coefficient of variation from the weight variation was less than 6%. The plasma levels of propafenone at steady state were: patient 1, 31.57 ng/ml; patient 2, 226.46 ng/ml; and patient 3, 221.29 ng/ml.

CONCLUSIONS: The actual administered dose for the patients could vary up to 6%, and doses prepared from different brands of tablets remain stables for up to day 30 at both temperatures. UDP is a temporal, safe and alternative option when pediatrics formulation of this drug is lacking.

Key Words:
Children, Propafenone, Supraventricular tachycardia, Unitary doses.

Introduction

Errors in medication are frequently caused by lack of presentations that contain a specific dose required by the patients, and this is important in drugs with a narrow therapeutic range, especially when pediatric patients are considered. In order to solve this need, hospital staffs have resorted to the preparation of the formulas, which contain the specific dose level required by each patient.

There are several reports in the literature that mentioned the importance and use of these types of formulations due to *the lack of commercially available pediatric presentations*. Horn et al[1] reported that thyroid function disorders are among the most frequent endocrine problems in the area of pediatrics. The treatment for such disorders includes L-thyroxine, which is commercially produced in 50, 100 and 500 µg presentations, although the initial dose for newborns is 10 µg/kg/day. Therefore, prepared formulations are required since it is not possible to obtain the adequate dose by cutting or compressing tablets. The latter practice has led to errors in a large number of cases. Domínguez-Gil[2] noted that oral formulations of digoxin registered in Spain have been reduced to two presentations, tablets of 250 µg and a pediatric solution containing 50 µg/ml. However, these two presentations do not satisfy medical needs since the recommended dose for patients is 125 µg per day, which means that staffs need to use the 50 µg/ml presentation and adjust the dose.

In special, there are little data evaluating the quality and stability of powder papers and capsules that are prepared from tablets. Taketomo et al[3] carried out a stability study of captopril powder papers under three storage conditions over a 24 week period at room temperature. The powder papers were prepared from tablets and the study concluded that captopril remained stable for at least 12 weeks when the papers are stored in vials, moisture-proof barrier bags and plastic ziplock bags. Colucci et al[4] studied the quality control of captopril capsules prepared from tablets that contained a dose of 1 mg used in the treat-

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ment of patients with congestive heart disease. In 1994, the same group studied the weight variation and uniformity of the capsule content concluding that the weight variations were within acceptable limits, as described in the United States Pharmacopeia (USP), and that the dose that patients received could vary up to 24.5%. Mathaut et al[6] studied the quality control of capsules in a pediatric hospital in France by determining the content of the different product batches. They found that the lower doses had a greater possibility of non-conformity in terms of active ingredient when compared with batches of higher doses. In addition, they suggested that a content test was an important criterion to determine the conformity of each batch. This study allowed the Authors to implement new procedures for ensuring the best quality in capsule preparation. Helin-Tannien et al[7] carried out a comparative, uniformity study of nifedipine in paper envelopes and prepared capsules using two different excipients. The aim was to see if the capsules could be used in place of the paper envelopes as a therapeutic alternative for pediatric patients. They concluded that the preparation of nifedipine capsules is safe whether the excipient is monohydrate lactose or microcrystalline cellulose. Capsules appeared to be a good way to administer medications to pediatric patients given that the loss of nifedipine was found to be greater from paper envelopes.

Over the past few years, there has been an increase in the size of generic medicine in Mexican market, since they have shown to be as efficacious and safe as their patented counterparts with a much lower price tag[8]. Furthermore, these presentations have proved to be a better option for pediatric patients who are treated at the National Institute of Pediatrics (NIP), especially because the population that are attended in this Institute do not have social health insurance and most of them are low income people.

In collaboration with the Cardiology Service at the NIP, a study was started to look at the preparation of unitary doses of propafenone (UDP), which is an anti-arrhythmic drug prescribed for the treatment of chronic supraventricular tachycardia (SVT). The practice of preparing formulations is due to the absence of a pediatric presentation of this drug in Mexico[9].

Besides, there is no reported data related to stability study of a prepared formulation of propafenone from generic tablets for pediatric population. This study is aimed at developing a simple and standardized method for the preparation of unitary doses of propafenone inserted in capsules from four brands of tablets, and to determine the stability of it in these formulations for use in pediatric patients.

Methods

Preparation of the Capsules

The study selected four brands of commercially available propafenone: Norfenon (Abbott Lab., Ludwingshafen, Germany), Nistaken and Medimart (Kendrick Lab., Mexico), and Biopafen (Bioresearch of Mexico, Mexico). Norfenon is the originator and the other three brands are generics. Capsule preparation involved grinding up 150 mg tablets of propafenone in a mortar in order to obtain doses of 11, 25 and 90 mg, which are the doses for three patients attended in the Cardiology Service. The filling of the capsules was made manually. The powder was carefully emptied into 0 and 1 gelatin capsules according to the test dose, and were then stored in amber flasks. Batches of capsules of the four brands of propafenone were prepared. In addition, a batch of 50 capsules was prepared to determine the weight variation in the 11 mg dose capsules prepared using Norfenon tablets.

Determination of Content

A high pressure liquid chromatography (HPLC) method was used for quantifying the propafenone content in capsules, which was based on a recently validated technique reported in our laboratory[9]. The chromatographic system consisted of a 510 model programmable pump, a 717 model injector and a 2475 model multiwavelength fluorescence detector. A Symmetry C18 reverse-phase column 5 µm (150 × 3.9 mm i.d.) was also used. Chromatographic data were analyzed by Millenium software version 32.0. All items were purchased from Waters (Milford, MA, USA).

A standard solution was prepared by emptying the contents of each capsule into a conical flask and dissolving the powder in 500 µl of methanol, to which 1 mg/ml of a 400 µl solution of propanolol (IS) was added and then mixed with 10ml of deionized water. Different dilutions were made in order to obtain propafenone concentrations of 11, 25 and 90 µg/ml. For analysis, 200 µl of each concentration was alkalinized with 100 µl of a 50 mM sodium hydroxide solution and 5 ml of a mixture of di-

ethylether-dichloromethane (50:50 v/v) was added as extraction solvent. The mixture was carefully vortexed for 2 minutes and centrifuged at 800 *g* for 5 minutes. The organic layer was evaporated under a gentle nitrogen stream and warm water bath at 40°C. The dried residue was dissolved with 200 µl of mobile phase, which consisted of 50 mM potassium dihydrogen phosphate adjusted with acetic acid (pH 3.2)-acetonitrile (70:30 v/v). Then 100 µl aliquots were injected into the chromatographic system. Detection was measured by fluorescence at 200 nm (excitation wavelength) and 210 nm (emission wavelength). The linear range of the curve was 10-100 µg/ml, and the concentrations of 30, 50, and 70 µg/ml were used as low, medium and high level controls, respectively.

Determination of Stability

Batches of capsules were stored in amber flasks and samples were analyzed at 0, 7, 15 and 30 days at room temperature (20 ± 5°C) and at 40°C. The relative humidity was 75±5%. A modified HPLC method was used to quantify the propafenone in the capsules[9]. Stability was defined as the retention of at least 90% of the initial concentration[10,11].

Determination of Weight Variation

This test used 50 capsules containing 11 mg of propafenone made from Norfenon tablets and analysis was carried out in duplicate on the same day that the capsules were prepared. The same HPLC method was used to quantify the propafenone in the capsules as was done in the stability study.

Determination of Plasma Levels of of Propafenone

Plasma levels of propafenone were determined at steady state in three pediatric patients diagnosed with supraventricular tachycardia under treatment with unitary doses of propafenone. These patients have been treated in the Cardiology Service of the National Institute of Pediatrics and were included in the study with authorization of their parents. Children received their unitary doses of propafenone every 8 hours, at doses of 11, 25 and 90 mg of prepared propafenone capsules using Norfenon, Nistaken and Medimart tablets, respectively. After reaching the steady state (passing 7 half-lives), two 3 ml blood heparinized samples were taken, the first was predose and the second was 3 hours post-dose. The samples were analyzed to determine the plasma levels of the drug using HPLC method[12].

The work was approved and conducted in compliance with the requirements of the Institutional Human Subjects Research Committee.

Statistical Analysis

Concentration analysis was carried out using the ANOVA test, and when there was no homogeneity in the variances, the Tukey test was used[13]. The PAQUEST statistical computer pack was also used. Statistical significance was considered to be $p < 0.05$.

Results

The coefficient of variation (CV) derived from the weight variation of the 11mg capsules prepared from Norfenon tablets was less than 6% (Table I).

In terms of drug stability, no significant statistical differences ($p < 0.05$) were observed in the different doses or between the four brands of tablets included in the study up to day 30, and at both room temperature and 40°C.

With respect to the level of drug in the plasma of the three patients, the results were as follows: patient 1, 25.93 and 31.57 ng/ml; patient 2, 54.52 and 226.46 ng/ml and patient 3, 55.02 and 221.29 ng/ml, at pre-dose and 3 hours post-dose, respectively. Figures 1 to 3 show the chromatograms of the samples taken from the three patients of pre-dose and 3 hours post-dose.

The plasma levels of patient 1 coincided with the administered dose, and although these levels are subtherapeutic, the clinical response of the patient was favorable at a 2.5 mg/kg/day dose.

Following a 6 and 7.5 mg/kg/day dose, respectively, patients 2 and 3 were both found to have acceptable therapeutic concentrations according to the levels reported in medical literature (330 ± 130 ng/ml)[14]. Clinically, both patients were reported to be in stable condition.

Table I. Weight variation in propafenone capsules made from commercially available tablets.

Parameter	Weight variation (n = 50)
Mean (mg)	11.18
Standard deviation (mg)	0.65
Coefficient of variation	5.81

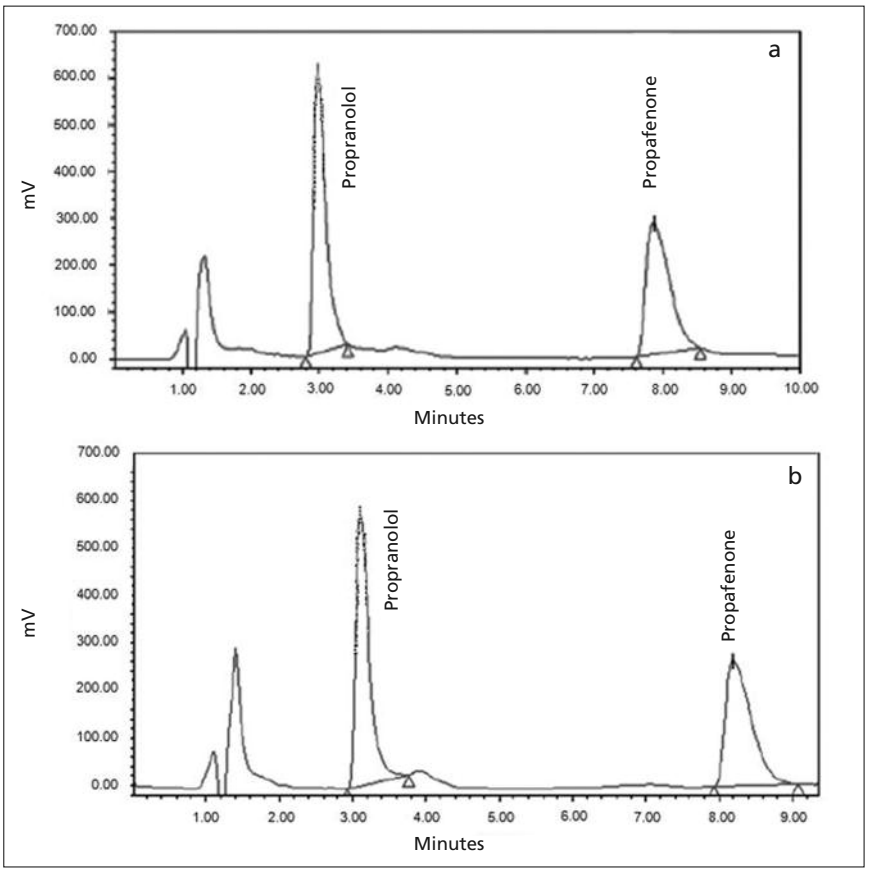

Figure 1. Chromatograms obtained from plasma levels of propafenone in patient 1: pre-dose (*a*) and at 3h post-dose (*b*), taking a 11 mg dose from capsules prepared from Norfenon tablets.

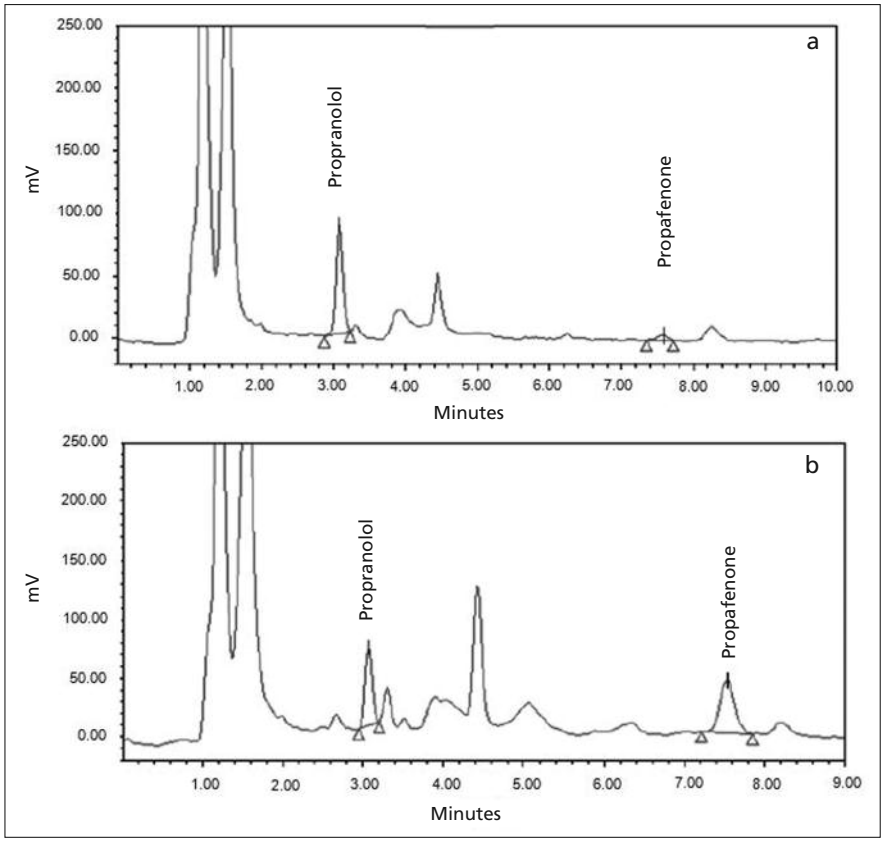

Figure 2. Chromatograms obtained from plasma levels of propafenone in patient 2: pre-dose (*a*) and at 3h post-dose (*b*), taking a 25 mg dose from capsules prepared from Biopafen tablets.

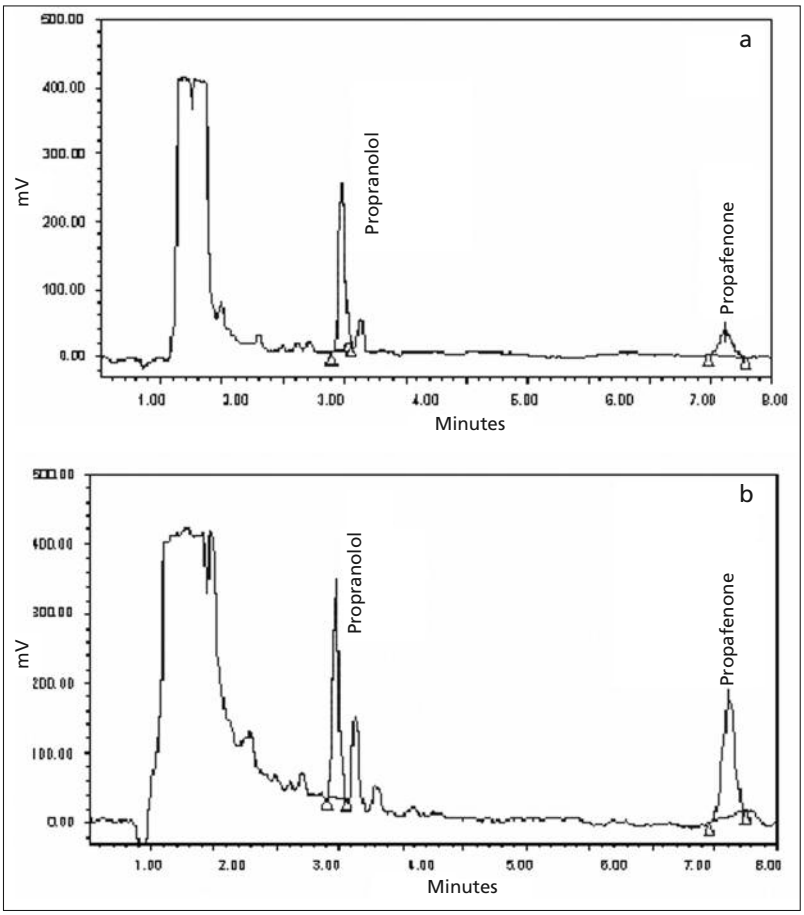

Figure 3. Chromatograms obtained from plasma levels of propafenone in patient 3: pre-dose (*a*) and at 3h post-dose (*b*), taking a 90 mg dose from capsules prepared from Nistaken tablets.

Discussion

In Mexico, there is a lack of pediatrics presentations of important drugs like propafenone, which are very important in clinical applications[15]. The commercial presentations that exist are tablets of 150 and 300 mg. It is worth mentioning that there are countries like Germany where a pediatric formulation in tablets of 10 mg of propafenone is sold. Unfortunately, our hospital attends not only patients with scarce economic resources but also who do not count with social health insurance. For this reason, thinking of importing this pediatric presentation to our country would be highly expensive and inaccessible to the patients.

It is important to mention that the pediatric patients that came to the Cardiology Service of our hospital are sent to our laboratory for the preparation of UDP from the commercial tablets in such a way that the patients receive exact and sure doses for the treatment of their illness. For this, the unitary doses were subjected to quality control test as was established by the Pharmacopeia of the United States of Mexico and the NOM-073-SSA1-1993. Such tests are content uniformity and stability of the samples under different conditions of storage as well as constant clinical evaluation of the patients.

With regard to the weight variation of propafenone capsules, there was no significant difference in the drug fragments. This suggests that the preparation of capsules was standardized and that the actual administered dose could vary up to 6%.

The results show that the originator (Norfenon) and the generics (Nistaken, Medimart and Biopafen) are stable at 30 days with the conservation of 90% of the initial concentration, which complies with stability criteria found in published medical literatures.

It should also be mentioned that the integral health of the patients was monitored by the Cardiology Service using electrocardiographs and a favorable development was seen in each patient.

Conclusions

The actual administered dose for the patients could vary up to 6%, and doses prepared from different brands of tablets remain stables for up to day 30 at both temperatures. The use of UDP inserted in capsules offers a temporal, safe and therapeutic alternative for pediatric patients with supraventricular tachycardia while pediatrics presentation of this drug continues to be in lack.

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