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Taste acceptance of Captopril and Furosemide Extemporaneous Oral Pediatric Formulations among Hospitalized Children

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Abstract

Many pediatric patients require medications that are not available in age appropriate formulations, especially those with cardiovascular diseases. The use of a suitable vehicle is critical for the preparation of extemporaneous formulations with the expected effect. Considering that palatability is essential to treatment adherence in children, we analyzed the acceptance of extemporaneous formulations of Captopril and Furosemide prepared using a developed vehicle in three flavors: neutral, strawberry and mint. Formulations were administered to hospitalized pediatric patients as prescribed. Acceptance was evaluated through the guardians using the hedonic scale and compared with the researcher's observation. Formulations in neutral and strawberry flavors were considered acceptable for both drugs. Correlation between results from both methods was moderate for Captopril and absent for Furosemide. Neutral taste results showed that the addition of flavoring agents did not improve acceptance. Since it is recommended to avoid components in formulations for infants and newborns, unless strictly necessary, it is important to identify excipients that are dispensable.

Keywords: Cardiovascular drugs; Extemporaneous preparations; Pharmaceutical vehicles; Sensory analysis; Taste assessment; Pediatric formulations; Oral vehicle; Palatability; Children; Taste acceptability; Taste acceptance

Introduction

The lack of drug formulations suitable for children is a worldwide concern, taken into consideration by some developed countries, as well as by organizations such as the World Health Organization [1]. Aside from drugs designed to treat diseases that largely affect infants and children, most drugs are not labeled for use within this group [2], and therefore, are produced only as capsules and tablets for adults [3]. Due to these limitations, it is common, in different pediatric contexts, the use of unlicensed and off-label drugs as well as extemporaneous formulations [4-6]. The lack of appropriate products for use in children is an important risk factor for adverse reactions and drug intoxication. Also children may be not receiving drugs in effective doses, or may be subject to unnecessary risks as compounding and medication error [2,7,8]. In most cases, the stability of the extemporaneous formulations is not determined and only a few clinical studies have been published on the pharmacokinetics and bioequivalence of such preparations [2,9].

In Brazil, as in other countries, there is a remarkable deficiency in pediatric formulations of essential drugs for children, mainly cardiovascular drugs, as showed by Costa [10] and Coelho [1]. Cardiovascular drugs are used in children to treat potentially life-threatening diseases, such as heart failure, arrhythmias and thrombosis [11]. Currently, many cardiovascular drugs have no authorized available forms for children, reason why there is a high off-label use of these drugs in pediatric patients [12-14].

Captopril, an inhibitor of angiotensin converting enzyme, and Furosemide, a loop diuretic, are commonly used cardiovascular drugs for which no suitable licensed oral liquid dosage forms are available [15]. In Brazil, Captopril can only be found as tablets in strengths of 12.5, 25 and 50 mg, and Furosemide as 40 mg tablets or 10 mg/mL solution for injection.

They can only be acquired as oral liquids through pharmaceutical compounding, and still are usually administered as extemporaneous formulation made with crushed tablets dispersed in water. Water is generally used as the vehicle, regardless the formulation's chemical and microbiological stability, viscosity and palatability [8]. Captopril is freely soluble, but unstable in water, undergoing degradation into captopril disulphide [16]. Furosemide is practically insoluble in water and the suspension suffers from physical instability due to particle sedimentation [17]. Besides, it is known that Captopril has a strong sulfur odor and flavor and Furosemide has an unpleasant bitter taste, which requires knowing the acceptability of these formulations among pediatric patients [18-20].

The use of commercially available vehicles helps to simplify the process of preparing extemporaneous oral formulations, making the administration of medicines safer to children in hospitals or at home [21,22].

In the Department of Pharmacy of the Federal University of Ceará, Brazil, a low cost vehicle called "Gute" was developed with few components - glycerol or mannitol, xanthan gum, sucralose, methyl and propylparabens (replaceable by sorbic acid, potassium sorbate or benzoic acid) and disodium edetate - with or without flavoring. The vehicle presents physical, chemical and microbiological stabilities, showed in previous studies [23]. It is appropriate for incorporation of active principles with pKa in the range 3-10 (such as captopril, hydrochlorothiazide and furosemide), and has no equivalent product marketed elsewhere in the country.

Palatability studies are a key element in formulation design, given its important role in compliance [24,25]. Although adherence to treatment has multivariate complex causes, an acceptable taste has a special importance for pediatric patients, especially to treat chronic diseases, since these patients take medicines every day for a long term [24-26]. As children have a low tolerance for unpleasant taste, the use of tasteless or palatable medication can reduce medication waste from spillage and/or spitting [27].

Published palatability studies conducted in developing countries are few, especially about medications for children. Taste preferences vary significantly between cultures, so it's necessary to invest in local studies to develop pleasant pediatric formulations for different populations [28]. Evaluation of the most appropriate flavors for different age groups and drugs must be performed carefully so that the arbitrary choice of flavoring does not limit the acceptance of the medication. Taste preferences may differ between ages, so taste assessment should involve children early in the drug formulation development [27]. Sensory analysis is a stage of product development that analyzes and interprets the reactions produced by its features. Ideally should be performed whenever a new formulation is introduced in a given context [28-30].

Therefore, the primary purpose of this study was to assess the acceptability of Captopril and Furosemide extemporaneous formulations prepared with the vehicle in three different flavors, prescribed and administered to hospitalized pediatric patients. We also assessed the correlation between the results from children's reactions observed by the researcher and the taste scores (hedonic scale) given by the caregiver (parent or responsible).

Material and Methods

The administered formulations were Captopril Oral Suspension 1.25 mg/mL and Furosemide Oral Suspension 4.0 mg/mL in flavors strawberry, mint and neutral (not flavored). All three formulations had the same colour and same appearance. The neutral flavour was incorporated in this study to verify the real need of flavoring agents to mask the active's taste, in order to increase the acceptability of the formulations.

A pharmacist prepared the suspensions by grounding 12.5 mg tablets (always from the same laboratory and lot) to a fine and uniform powder with pestle and mortar. A small amount of the vehicle was added for levigation. Further portions of the vehicle were added to wash out the pestle and mortar and transfer to an amber medicine bottle, before completing the suspension volume, followed by homogenization.

Cautions regarding chemical, physical and microbiological stabilities of the formulations were taken by systematic laboratory analyzes. In addition, a study evaluating the clinical effect and safety of these formulations was performed in parallel [30].

Study Design

This was a single-blind taste-testing study with children, conducted after approval by the Research Ethics Committee of the Hospital de Messejana Dr. Carlos Alberto Gomes Studart and by the Research Ethics Committee of the Federal University of Ceará, and with written informed consent obtained from children's parents or legal guardians of the child before enrolment.

Setting and Subject Selection

Male and female patients aged below 6 years, who had prescription for at least one of the formulations studied, were recruited from a pediatric cardiology unit. This upper limit of the age range was chosen because most children over 6 years of age were able to swallow tablets intact. Subjects were excluded if they were using feeding tubes. Patient data on medical conditions and age was extracted from hospital records.

Bed side taste testing was performed once a day for each patient, and the three tested flavors (mint, strawberry or neutral) were presented one per day in a balanced order. Study formulations were administered by the nursing staff into the mouth cavity using oral plastic syringes and the schedule of administration and doses were maintained according to the prescription. The study was conducted from August to September 2013 for Captopril formulations and from October to November 2013 for Furosemide formulations.

Acceptance test

Immediately after the first test dose, without knowing the flavor, caregiver was asked to rate the child overall liking of the formulation [31,32] by pointing on a gender-specific facial-verbal hedonic scale with seven degrees of liking, ranging from 1, "hate it", to 7, "love it" (Figure 1) (Method 1). Over the next two days, the remaining flavors were tested at the same time of administration, if there was prescription of the formulation. Subjects were also observed by the researcher for spontaneous reactions, through facial or body expressions and comments on likes and dislikes [33-35] (Method 2) and data was recorded and classified into Positive, Negative or No reaction, as shown in (Table 1).

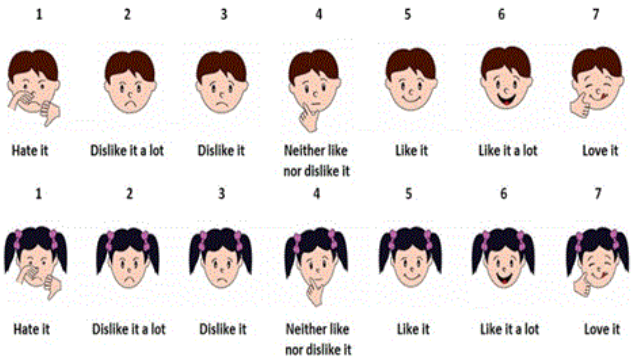

Figure 1: Gender-specific facial-verbal hedonic scales.

Positive reaction	Easy administration, sucking motions, licking lips, smile, stop crying, opening the mouth asking for more, nod positively, say "good," "I want", "liked", "tasty", "very good "or "better than the last one" .
No reaction	Had no reaction, does not woke up, woke up without crying.
Negative reaction	Retching, nod negatively, cover mouth with hands, facial grimacing, crying, spitting, kicking, turning the head, refusing to swallow, cough, complain and say "bad".
Patients' spontaneous reactions observed by the researcher in the taste evaluations of Captopril or Furosemide formulation in three flavors.	

Table 1: Classification of patients' spontaneous reactions in taste evaluation.

Statistical Analysis

The scores from the hedonic scale were analyzed by analysis of variance (ANOVA), General Linear Models (GLM) and Ryan–Einot–Gabriel–Welsch multiple range (REGWq) test for means comparison, using Statistical Analytical Systems (SAS®). Gender and age effects and the interaction between them were examined. Data from Captopril and Furosemide were analyzed independently, but we also compared both drugs in each flavor. Data were presented as mean hedonic scores and frequency distributions plotted as histograms. The results were also subjected to Principal Component Analysis (PCA) using XLSTAT software.

Results from both acceptance methods (Method 1 and Method 2) were correlated by linear Pearson coefficient (r). Absolute frequency of reactions classified into positive, negative or no reaction was correlated with absolute frequency of hedonic responses classified according to the regions of the hedonic scale: acceptance (ranging between the "Like it" and "Love it" categories), indifference ("Neither like nor dislike") and rejection (ranging between the "Hate it" and "Dislike categories).

We also assessed whether the patients subject to surgery differed with respect to acceptance of the formulations, according its situation, pre or postoperative period, by Student's t-tests. All statistical tests employed a level of significance of 0.05.

Results

The most frequent clinical conditions were congenital heart diseases (ventricular septal defect 26.2%, interatrial septal defect 16.9%, complete atrioventricular septal defect 15.4%, patent ductus arteriosus 12.3% and tetralogy of Fallot 12.3%). No adverse effects were noted during or after the sensory tests. A total of 34 children (21 males and 13 females) participated in the tests with Captopril formulations, ranging in age from 2 to 50 months, mean 15.9 (SD ± 14.7); and 36 children (11 males and 25 females) participated in tests with Furosemide formulations, ranging in age from 1 to 66 months, mean 18.0 (SD ± 17.9). Children were divided by age in four groups: A=less than 6 months old; B=6 to 12 months old; C=13 to 24 months old; D=over 24 months old. Of all children, 35.0% were less than 6 months old, 28.6% were over 24 months. From method 1, Captopril and Furosemide ANOVA showed no significant difference in acceptance among flavors or age groups and no significant interactions for Age x Flavor or Gender x Flavor. For Furosemide there was significant difference between genders, but not for Captopril. Within each age or gender group, the flavors did not differ significantly from each other, indicating that boys, girls and all age groups showed consensus on the acceptance of the three samples. In the comparison of the two drugs we found that for neutral and strawberry flavors, Captopril and Furosemide were significantly different (p 0.0002), with Furosemide showing higher hedonic scores (Table 2).

	Neutral	Mint	Strawberry
Captopril	4.81aB	4.28aA	4.69aB
Furosemide	5.10aA	4.34aA	5.03aA
Means with the same lower case letters in lines are not significantly different (p>0.05). Means with the same uppercase letters in columns are not significantly different (p>0.05). Although not significantly different, all three tested flavors for both drugs had hedonic means between 4 and 5, corresponding to "Neither like nor dislike it" and "Like it" categories, respectively.			

Table 2: Mean hedonic scores assigned to Captopril and Furosemide formulations, according to caregivers.

For Captopril (Figure 2), mint showed division of its ratings between the acceptance and the rejection regions, which made its mean be around 4. For Furosemide (Figure 3), all flavors had high frequency of ratings in "Like it" and few ratings in "Dislike it a lot".

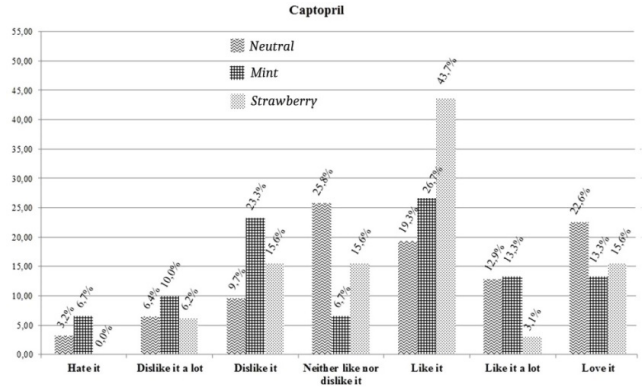

Figure 2: Frequency distributions of children's hedonic values for Captopril formulations.

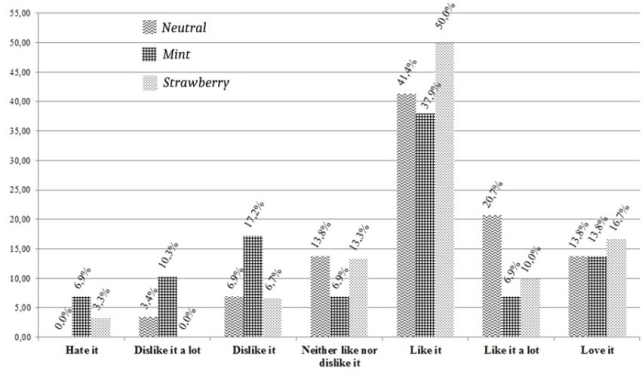

Figure 3: Frequency distributions of children's hedonic values for Furosemide formulations.

From method 2, for Captopril formulations, mint had most reactions classified as Negative, while for Furosemide, Negative reaction was the least frequent reaction for mint. Neutral and strawberry did not significantly differ among Negative reaction, No reaction and Positive reaction for Captopril formulations (Figure 4), and between No reaction and Positive reaction for Furosemide (Figure 4D). The frequency distributions of these two methods presented similar performance for Captopril, illustrating the correlation between them, but did not present similar performance for Furosemide, illustrating the lack of correlation between them for this drug. Pearson correlation results for Captopril showed a significant correlation and Furosemide showed no correlation (Table 3).

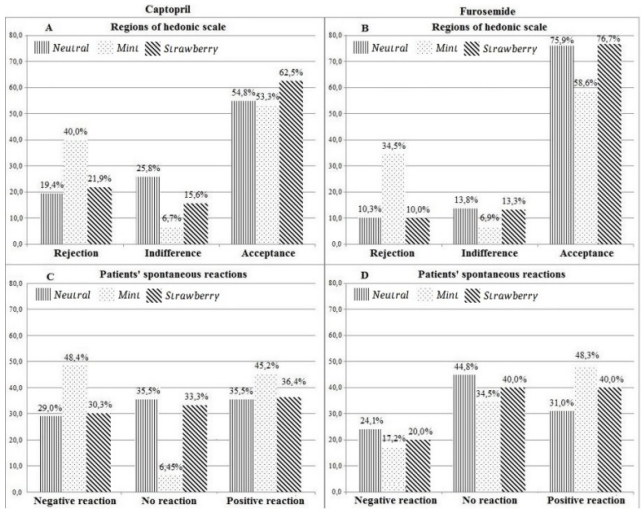

Figure 4: Frequency distributions of regions of hedonic scale and patients' spontaneous reactions for Captopril and Furosemide formulations.

	Hedonic regions x Spontaneous Reactions	
	r	p value
Captopril	0,42	p<0,0001
Furosemide	0,16	P=0,1450

Pearson correlation coefficients (r) and significance (p value) of the hedonic responses by region of the scale and classification of patients' spontaneous reactions for Captopril and Furosemide formulations.

Table 3: Pearson correlation of the hedonic responses and patients' spontaneous reactions.

The Principal Component Analysis (Figure 5) illustrates the individual preferences of each child, according to the caregivers. For both drugs, we can see a concentration of children located in the right quadrants, showing that more children accepted the neutral and strawberry flavors better than mint.

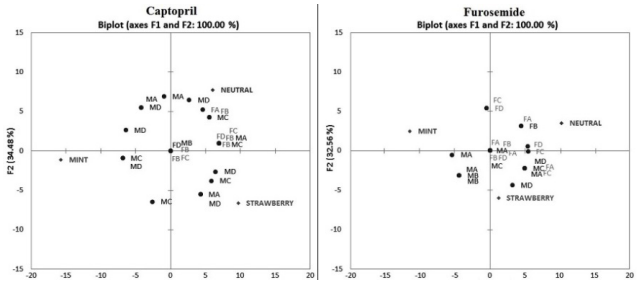

Figure 5: Principal Component Analysis representing the children' acceptance of formulations.

Regarding surgery, for Captopril, the pre-operative group of patients had hedonic mean of 4.4, and the post-operative group had hedonic mean of 5.1, values that differ significantly with p=0.0287. For Furosemide, the pre and post-operative groups of patients had no significantly different hedonic average.

Discussion

Acceptability tests with Captopril and Furosemide formulations showed that all formulations (both drugs in three flavors) had mean hedonic scores corresponding to "Neither like nor dislike it" and "Like it" categories of the scale (Table 3). Although no statistically significant difference among the hedonic scores means has been detected, we could observe some differences in the acceptance, by analyzing the frequency histograms of hedonic values (Figures 2, 3 and 4A and 4B). Among Captopril formulations, strawberry stood out with more than 60.0% of responses in the acceptance region of the scale, and among Furosemide formulations, strawberry and neutral had more than 75.0% of responses in the acceptance region. Mint stood out with the highest percentage of responses in the rejection region (40.0% in Captopril and 34.5% in Furosemide) (Figure 4A and B). For this reason, for both drugs, strawberry and neutral formulations were considered accepted and mint was considered not accepted.

The mean hedonic values were very close to the central region of the scale and very close to each other, so the comparison of means did not allow a great discrimination among flavors. To improve visualization of the results and to identify interesting aspects about different segments of the subjects, acceptance responses of the patients who completed the tests with the three flavors were subjected to Principal Components Analysis [36]. In Figure 5, children represented by letters were plotted far away from the mint flavor for both drugs, showing that these flavors received lower hedonic values a greater number of times in comparison to the others, which means that more children preferred neutral and strawberry in comparison to mint. For Furosemide, more children are close to the strawberry, meaning that this flavor was preferred. Small children prefer sweet and salty flavors, and dislike bitter and peppermint taste [27], which agrees with the fact that the participants of the present study liked mint less than the other flavours.

Regarding the acceptance of Captopril and Furosemide formulations in the neutral flavor, we can observe that formulations were accepted without the addition of a flavoring agent, and in the case of mint, the flavoring agent contributed for less acceptance of the formulation. One less excipients needed is beneficial, especially for new

borns and babies, since for safety issues it is recommended to avoid components in formulations, unless strictly necessary [1,37-39].

Out of the patients who performed acceptance tests with Captopril and Furosemide formulations, 70.6% and 72.2%, respectively, had undergone some surgery earlier, many of them still in post-operative care at the time of testing. Given the conditions under which the tests were conducted, with hospitalized patients, mostly after major surgery, we consider the acceptance results of the suspensions satisfactory, since none of the flavors obtained average values corresponding to the categories of hedonic rejection. Physical and mental health conditions of the participants may affect the mood and therefore dramatically affect their responses in their judgment when tasting samples. Therefore we cannot expect that the results of studies with hospitalized patients to be similar to those with healthy participants or at home, since diseases, psychological and emotional factors may change the sensory evaluation [40-44].

In the comparison of the two drugs, although we know that Furosemide has a bitter flavor, it was more accepted in neutral and strawberry flavors than the formulations with Captopril. It may indicate that the bitter taste of Furosemide is easier to mask than the sulfurous flavor of Captopril.

There are some limitations in our study. The presentation of the samples intended that all patients tasted all formulations, however, due to admissions, transfers, or hospital discharge, as well as the fluctuation of the prescriptions during hospitalization (treatment change), not all patients tasted all flavors, and therefore not all flavors had the same number of tasters. The tests were performed during the medication time according to the hospital ward schedule, which was far from alimentation. Also, the tested formulations were administered before other oral drugs. However patients were not asked to abstain from ingesting food and beverages or other drugs near the time of testing [45,46], what can interfere in the children's taste perceptions. Also it could not be guaranteed that all samples were at the same temperature, or had the same volume, since this varied according to the prescribed dose.

The correlation between the hedonic regions assigned to the flavors and the classification of patients' spontaneous reactions was moderate in tests with Captopril. In tests with Furosemide, there was no correlation (Table 3). In the Figure 4, we can observe that the frequency distribution of the hedonic responses assigned to the three flavors of Captopril and Furosemide suspensions are more concentrated in the acceptance region, while patients' reactions observed by the researcher for these two drugs were divided among "negative Reaction", "No reaction" and "positive Reaction". The reactions classified by "No Reaction" by the researcher may have been interpreted by caregivers as acceptance, which would explain this phenomenon. For children under four years, unable to respond to acceptance tests by themselves, evaluation through the primary caregiver is a good source of information, since the caregiver knows better the child's reactions and can make a comparison with the administration of other drugs, while the researcher observes the child for the first time during the test.

It is a consensus today that the use of extemporaneous formulations should be used only as a last resource and that healthcare professionals should join forces to ensure that appropriate dosage forms are available [8,22]. However, this "ideal" situation is unlikely to be achieved in the short term, especially where resources are limited. Adams et al. [47] noted the frequent need for preparation of drug formulations by crushing the pills made them so bitter to the point of causing vomiting in pediatric patients of rural and urban areas of Tanzania. A similar situation is found in Brazil, where the need to prepare extemporaneous formulations is still a commonplace reality, particularly in pediatrics and even more with respect to cardiovascular drugs [1,10,48,49]. Given the lack of medicines in suitable forms, a vehicle for preparing extemporaneous formulations for pediatric use can greatly make necessary modification in drug easier for professionals and caregivers (both in health services as in households)1,10. In addition, a vehicle provides greater stability of the formulation [50]. Access to safe and palatable pediatric formulations and its rational use must remain a major goal in health development worldwide [47], and may have a substantial effect on child morbidity [28].

More studies should be conducted to demonstrate the palatability of suspensions of other drugs with the vehicle as well as its utility for different age groups and clinical conditions. It is also important assess the palatability after repeated dosing since there are potential changes in taste perception over time.

Conclusion

The Captopril and Furosemide formulations prepared with the vehicle were well accepted in terms of taste among pediatric patients without needing the addition of flavorings, which is a very positive point regarding formulations for use by children.

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