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What can we do to make antihypertensive medications taste better for children?

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ABSTRACT

More and more data indicate the importance of palatability when selecting drugs for children. Since hypertension is uncommon in children, no child-friendly palatable formulations of these agents are currently available. As a consequence, in everyday practice available tablets are crushed and administered mixed with food or a sweet drink.

We started investigating the issue of palatability of drugs among children in 2004 using smile-face scales. In the first trial we compared taste and smell acceptability of pulverized angiotensin receptor antagonists among nephropathic children and found that the score assigned to candesartan was significantly higher than that assigned to irbesartan, losartan, telmisartan and valsartan. In the second trial we compared the taste of pulverized amlodipine and lercanidipine among children and found that the score assigned to lercanidipine was significantly higher. Our third trial was performed using pulverized β-adrenoceptor blockers, angiotensin-converting enzyme inhibitors, calcium-channel antagonists and diuretics among medical officers and pediatricians. The palatability scores assigned to chlorthalidone, hydrochlorothiazide and lisinopril were significantly higher to those assigned to atenolol, bisoprolol, enalapril and ramipril.

In conclusion pulverized amlodipine, atenolol, bisoprolol, enalapril, irbesartan, losartan, ramipril, telmisartan and valsartan are poor tasting. From the child's perspective, lercanidipine, candesartan, chlorthalidone, hydrochlorothiazide and lisinopril are preferable.

1. Antihypertensive medicines that children can take

It has been by tradition assumed that "the worse the taste of the medication, the better is the cure". In everyday practice a dose of a bad tasting medicine experienced by a young patient often precipitates crying, fighting, and vomiting. Parents will hold their child's nose, blow on their face, or use physical immobilization in an attempt to administer the medicine. For antihypertensive treatment regimens, this struggle needs to be repeated daily for years. Often, this experience results in the child spitting out the medicine, which is likely to result in the child receiving only a portion of the therapeutic dose (Baguley et al., 2012; Tuleu, 2012).

More recent research indicates the importance of palatability when selecting drugs, especially with children (Baguley et al., 2012; Tuleu, 2012). Unsurprisingly, it is well recognized that the palatability of certain medicines is so poor that literature suggests these drugs not to be prescribed to children (Baguley et al., 2012). The taste buds of the human tongue distinguish salty, bitter, sour, sweet and humami tastes. Palatability is influenced by a combination of sensory perceptions including taste and smell, and to a lesser extent texture, appearance, and temperature of the products (Baguley et al., 2012; Tuleu, 2012). Companies are aware of the challenges in providing palatable medicines and are working on methods to improve taste in frequently prescribed children's drugs such as common antimicrobials, antihistamines, antipyretics or analgesics (Baguley et al., 2012; Tuleu, 2012; Winzenburg and Desset-Brèthes, 2012; Tuleu and Breitkreutz, 2013).

Over the past decade, the prevalence of childhood arterial hypertension in the pediatric population has increased, likely in correlation with the rise in excess body weight (Lurbe et al., 2009; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Nonetheless, arterial hypertension is relatively uncommon in this age group and few children are prescribed antihypertensive drugs (Lurbe et al., 2009; National High Blood Pressure Education

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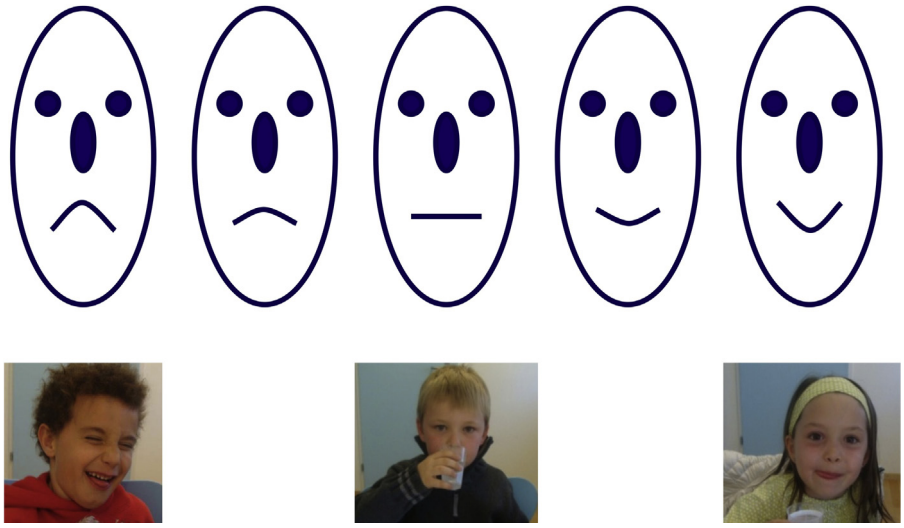

Fig. 1. A 5-point smiley-face scale with 3 different very typical facial reactions.

Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Suspensions or other age-appropriate formulations are mostly unavailable for medications originally designed for use in adults that are uncommonly prescribed in the pediatric population such as antihypertensive drugs. Therefore, available tablets are crushed and administered mixed with food or a sweet drink. Furthermore, parents may give a cold treat immediately before and after the medication to numb the taste buds and minimize the aftertaste of the medication, give a lollipop or other hard candy after taking medication to overpower the aftertaste, or add chocolate syrup or concentrated frozen orange juice to very bitter or salty-tasting drugs (Baguley et al., 2012).

2. The evaluation of drug preferences

Given the critical role of taste in the acceptance of a medication, evaluation of the taste of a formulation is essential in its development. A variety of tools have been used to investigate palatability of drugs, the majority incorporating a line or point scale. Tools for children attempt to be more child-friendly by incorporating a smile-face scale (Davies and Tuleu, 2008). Usually, overall taste is evaluated as it is thought that children are often too young to differentiate aftertaste or texture. There are many advantages with the use of smiley-face scales including reliability, ease of use and simplicity (Davies and Tuleu, 2008). Although a 9- to 10-point scale is often used in the adult population, the most widely used scale length while testing children has been a 3- to 6-point smiley-face scale (Fig. 1). We currently believe that scales should contain an even number (mostly 4) of possible answers and subsequently be balanced, that is, the same number of positive as negative choices, because this strategy requires participants to express a preference. However, having a center point can be advantageous because it does allow the scorer to vote a "neutral" opinion (Davies and Tuleu, 2008). It is crucial to randomize drug preference trials by means of an externally generated randomization list to balance the order of presentation of the preparations. There are several methods for randomizing study participants. We feel that the use of sequentially numbered, opaque sealed envelopes is both inexpensive and successful (Doig and Simpson, 2005).

Since it is intuitive that a study based on a small number of participants has little chance of producing clear-cut conclusions, it is by tradition assumed that a sample of 30 participants (Angelilli et al., 2000) is appropriated for childhood palatability comparison studies (typically no sample size calculation is performed before palatability trials). A palatability trial performed with 30 participants has a high chance (Carlin and Doyle, 2002) of detecting a difference between groups (if one exists) with a power greater than 80% (at $\alpha = 0.05$; two sided test). This means that if the study demonstrates no difference between groups the researcher can be reasonably confident in concluding that none exists in reality.

The taste scores from the visual analog scales are usually analyzed (Davies and Tuleu, 2008) by means of the Friedman test (nonparametric analysis of variance for repeated measures) or the Wilcoxon signed rank test (nonparametric test for two paired samples).

3. The palatability of crushed antihypertensive drugs

Some of us have been evaluating the taste of drug formulations since 2004 (Martínez et al., 2006). Since no studies have evaluated the issue of palatability of antihypertensive agents in children, we started investigating the issue of palatability of crushed angiotensin II type 1 receptor antagonists and calcium-channel antagonists among children and adolescents with secondary arterial hypertension in 2005.

In the first trial we compared taste and smell acceptability of five angiotensin II type 1 receptor antagonists that can be easily administered on a once-a-day basis (1 mg of candesartan cilexetil, 1 mg of irbesartan, 1 mg of losartan, 1 mg of telmisartan and 1 mg of valsartan). All taste tests were done by the same investigator to minimize bias and promote standardization and consistency of the taste procedure (Fig. 2). The score assigned to pulverized commercially available tablets, which contain both the active agent and the excipients, of candesartan cilexetil was significantly higher ($P < 0.001$) than that assigned to pulverized tablets of irbesartan, losartan, telmisartan and valsartan (Meier et al., 2007). The antihypertensive effect of candesartan cilexetil 1.0 mg is roughly identical to telmisartan 2.5 mg, losartan 6.2 mg, irbesartan 9.4 mg and valsartan 10 mg (Conlin, 2000). However, to avoid an excessive dosing potentially leading to significant blood pressure reduction if administered concurrently, 1 mg of each drug was tested instead of assessing the acceptability of angiotensin II type 1 receptor antagonists in a dose-equivalent way.

In the second trial, performed following a roughly similar design, we compared the taste of equivalent test doses of crushed tablets of amlodipine besylate (1 mg) and lercanidipine (2 mg), two calcium-channel antagonists that are usually administered on a once-a-day