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Assessing the palatability of medications in children

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Given the potential role of the palatability of medications, particularly liquid preparations, taste should be an important issue in the pharmaceutical development process. Ideally, assessment of the taste of drug formulations that will be used in children should be undertaken in children, although practical and ethical limitations of conducting these studies in this age group may be a challenge. After taking into consideration efficacy and safety, physicians prescribing for young children should take into account factors such as taste that may affect the ease with which parents are able to administer medications to their children.

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Introduction

Taste is defined as "the sensation of flavour perceived in the mouth on contact with a substance"[1]. A food or medication that is palatable is one that is "pleasant to taste"[1]. The primary cells for taste are modified epithelial cells that are grouped in taste buds and are found in the taste papillae of the tongue[2]. There are four basic taste modalities, sweet, salty, sour and bitter. More recently, a fifth modality, umami has been described. Umami is difficult to translate from Japanese but may be "meaty", "substantial" or "delicious"[2].

Taste sensation develops relatively early in life. The human fetus has specialised taste cells by about the seventh or eighth week of gestation with structurally mature taste buds at 13 to 15 weeks[3]. The number of taste buds decreases with age[4]. It is known that newborn infants detect and respond to different tastes[5] based on facial expressions[6]. However, as noted by Darwin in 1877, children are living in different sensory worlds than adults[7]. Children's responses to certain tastes differ from adults[8]. Infants and children have a preference for sweet-tasting substances[3]that decreases to resemble that of adults during late adolescence[7]. On the other hand, aversion to bitterness appears from a very early age and, therefore, bitter flavours are likely to decrease palatability[3]. Indeed, addition of aversive bittering agents has been proposed as a method of preventing toxic ingestions in young children[9].

In addition to developmental changes, there are inherited differences in sensitivity to particular tastes and flavours[5]. Genetically determined sensitivity to certain bitter tastes may be related to variations in genotype of the gene TAS2R38[8]. Cultural influences may also exist[8].

Role of taste in medication adherence

Although adults may think that the worse a medication tastes the better it works, children do not appear to support this belief. Many investigators cite palatability as an important factor in determining medication adherence and completion of drug therapy in children[10-20] although formal studies examining this relationship are lacking. Little direct evidence exists that poor taste decreases

adherence; however, it is not unreasonable to assume that a better tasting drug is easier to administer to infants and young children[14]. After efficacy and safety, taste or palatability was ranked highest among the antibiotic features that were most important to parents[21]. Many have faced the daunting task of forcing a sick struggling child to take an antibiotic that he or she is refusing[22]. The result is often spitting out or vomiting of the medication resulting in the child receiving only a portion of the therapeutic dose[19,23].

Parents of children with HIV have reported difficulty associated with administering anti-retroviral medications due to taste. Changes or omissions in medication regimens were most commonly in response to the foul taste of the medicines[24]. Of ten potential interventions, better tasting medications were rated as "very helpful" by 81% of caregivers of HIV-infected children[25].

Formulations

Availability of an appropriate formulation of a medication is often an obstacle in treating children, especially young ones who are unable to take solid dosage forms. A marketed suspension or extemporaneous liquid formulation prepared by a pharmacist is often the option chosen; however, taste may be an issue as palatability of a liquid formulation may be of greater importance compared with that of a tablet. Use of a non-liquid may not solve the problem as children may reject the taste of crushed tablets, for example refusal to take prednisolone crushed tablets because of the bitter taste[26].

Other characteristics of the formulation such as smell, texture, taste and aftertaste[27] may affect how well it is accepted. However, in adult taste studies, most participants judged taste alone to be the most important category[15,17,28]. The appearance of the medication, for example the potential association between colour and flavour, may also play a role although the effect of colour on taste preference has not been well-studied.

Taste masking

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist[29]. Although various techniques are available for masking the bitter taste of drugs[29], the addition of artificial sweeteners and flavours is commonly used in paediatric liquid and chewable preparations[4]. As noted by the film character Mary Poppins, "a spoonful of sugar helps the medicine go down". However, even high concentrations of intense sweeteners may be unsuccessful in masking the taste of highly bitter drugs and it may be necessary to use other processes (e.g. microencapsulation) in addition to the use of flavours[30]. Taste masking of bitter tasting drugs administered orally to children may be a major formulation hurdle[31].

The chemical properties and flavour of the drug may determine what flavouring agent is chosen as it must effectively mask the unpleasant taste of the drug while not adversely affecting its stability or bioavailability[32]. Children generally prefer sweet preparations with fruity flavours[4]. National favourites are bubble-gum and grape in the United States, citrus and red berries in Europe and liquorice in Scandinavia[27]. However, taste preferences are subjective and it may be difficult to predict what medication a particular child will like better based on knowing its flavouring. Questioning children as to what flavours they do and do not like may not predict what flavoured antibiotic they will prefer[33]. In a study to investigate parents' ability to determine if their child will like or dislike the taste of a particular antibiotic suspension, there was only a fair level of agreement between parents' predictions and children's ratings of taste (kappa 0.395 and 0.385 in 4 to 7 year olds and 8 to 12 year olds)[34].

A flavouring agent, FLAVORx, was added to clindamycin and although it improved the palatability of clindamycin somewhat, the improvement was not enough for it to be considered acceptable[28]. As it may be impossible to completely mask the foul taste of medications, various tips to aid in giving bad tasting preparations have been suggested[35,36]. Hypnosis has also been tried as a way to alter taste perception[37].

Assessment of palatability of medications

Given the potential important role of taste in the acceptance of a medication, evaluation of the taste of a medication formulation is essential in its development. Palatability studies have often been conducted in adult volunteers; however, as sense of taste in children differs from that in adults, the results may not necessarily be applicable to children. Comparison of the taste ratings of various antibiotics by children and adults showed differences between the two age groups[38]. Others have argued that a parent's reaction may influence the child's perception of the medication, and thus adult evaluation may have some value[39].

Panels of adult volunteers have evaluated the taste of medications, generally antibiotics, using a format similar to wine tasting. Adults are asked to rate characteristics such as smell, texture, taste

and aftertaste. In other studies, adult observers have recorded taste acceptance of paediatric patients based on the child's reaction[40]. However, correlation between the scores of parents' judgments of acceptability and the scores of children's taste evaluation were rather weak in a study of two penicillin formulations[10]. Similarly, in a study of antibiotics effective against β-lactamase-producing bacteria, a significant difference was noted between the proportion of children and the proportion of adults who chose each antibiotic as worst tasting[38]. The time a nurse is required to give the medicine to a child has been used as a measure of the effect of different flavours on the acceptance of drugs by infants and children[41].

Child volunteers

Ideally, assessment of the palatability of medications that will be given to paediatric patients should be done in children. Most studies have been undertaken in children with infections[10,13,42,43] or healthy volunteers aged 4 years and older[12,16,33,38,44,45] evaluating the taste of liquid formulations of antibiotics (Table 1). A few studies have involved other medicines[32,46-50] (Table 2). In order to avoid taste fatigue and to prevent confusion of the children, the number of different products to be tested is limited to a maximum of four[27]. The various preparations are presented in a randomised order in an attempt to eliminate an order effect. It has been our experience that children enjoy participating in the taste testing procedure.

Usually only overall taste is evaluated as it is thought that children of this age are too young to differentiate aftertaste and texture. A few different methods have been included in paediatric studies. Spontaneous verbal judgments have been

Table 1 Studies assessing the palatability of antibiotics

Medications	Study participants	Method	Results	Reference
Three bacampicillin suspensions and two penicillin syrups	Children 3–12 years with infection	Child's spontaneous verbal judgment and facial hedonic scale	In children 6 years better discrimination of taste differences using patient's own spontaneous verbal judgments	42
Two pivampicillin mixtures	Children 1–7 years with infection	Child's evaluation of taste or parent's evaluation of administration	Better acceptability and easier administration with banana than cocoa-peppermint taste	43
Two penicillin formulations	Children 3–10 years with otitis media	Child's spontaneous verbal judgment and parent's judgment of acceptability	No differences in taste scores between two suspensions	10
Azithromycin and one of cefprozil, cefpodoxime, loracarbef, cefixime and clarithromycin	Healthy children 4–12 years	Point to version of "smile" face that matched taste and asked medication with preferable taste and colour	Taste rating for azithromycin higher than that of cefprozil, cefpodoxime and clarithromycin	12
Brand and generic antibiotic suspensions	Children 3–14 years with clinical indication	Patient's verbal response and facial hedonic scale to rate taste and aftertaste, and parent's rating of ease of administering medication	Brand name preparations did not necessarily taste better than generic	13
Four antistaphylococcal antibiotics	Healthy children 6–12 years	10-cm VAS with facial hedonic scale, and verbalisation of best and worst tasting	Taste score of cloxacillin suspension lower compared with that of other three antibiotics	33
Four antibiotics effective against β-lactamase-producing bacteria	Healthy children 4–9 years	10-cm VAS with facial hedonic scale, and verbalisation of best and worst tasting	Taste score of azithromycin higher than that of clarithromycin and erythromycin-sulfisoxazole	38
Amoxicillin plus 10 other antimicrobial suspensions used to treat otitis media in children	Adult physicians and children (only three antibiotics)	Appearance, smell, texture, taste and aftertaste rated on scale of 1–10	14/16 children ranked three antibiotics in same relative order as adult group	15
Azithromycin, cefprozil, cefixime and amoxicillin/clavulanate	Healthy children 5–9 years	10-cm VAS with facial hedonic scale, and verbalisation of best and worst tasting	Palatability score for cefixime higher than other three antibiotics	21
Cefdinir plus one of amoxicillin/clavulanate, cefprozil, azithromycin	Healthy children 4–8 years	Taste and smell rated by pointing to visual "smile-face" scale	Taste of cefdinir rated higher than amoxcillin/clavulanate and cefprozil	16
Four antibiotics effective against β-lactamase-producing bacteria	Healthy children 5–8 years	10-cm VAS with facial hedonic scale, and verbalisation of best and worst tasting	More children selected cefixime as best-tasting	44
Pooled analysis of seven trials of cefdinir oral suspension vs. one of four other antibiotic suspensions	Healthy children 4–8 years	Pointing to visual smile-face scale	Taste acceptance score of cefdinir higher that that of comparator agents	45

VAS = visual analogue scale.

Table 2 Studies assessing the palatability of other medications

Medications	Study Participants	Method	Results	Reference
Two flavours of ondansetron syrup	Children 3–12 years undergoing chemotherapy	Panel of five faces and asked preference	Preference for strawberry formulation	46
Activated charcoal with flavouring agents	Healthy children 3–17 years	10-point faces scale (<8 years) or 100-point VAS (≥ 8 years)	Addition of chocolate milk, Coca-Cola or cherry-flavoured syrup improved taste	47
Activated charcoal with four flavouring vehicles	Healthy children 5–9 years	10-cm VAS with facial hedonic scale, and verbalisation of best and worst tasting	Taste score for cola higher compared with other three preparations	48
Lansoprazole delayed release oral suspension vs. ranitidine oral syrup	Healthy children 5–11 years	VAS with a five point facial hedonic scale and asked preference	More children preferred taste of strawberry-flavoured lansoprazole	32
Ranitidine syrup vs. ranitidine effervescent tablets	Healthy children 4–8 years (and parents)	Taste preference	Children preferred taste of ranitidine effervescent tablets	49
Two prednisolone preparations	Children 2–10 years with acute asthma exacerbation	Five point facial hedonic scale (>5 years of age)	Better taste score for Orapred than generic prednisolone	50

VAS = visual analogue scale.

used in children 6 years of age or younger as it has been questioned as to whether children in that age group are able to express differences in taste perception by a preferential method[10,42]. Ranking based on preference or some other characteristic such as bitterness or scoring on a scale is also a possibility[27]. Questioning the child as to which formulation they thought tasted best and which tasted worst has also been done[33,44]. The most liked flavour on a follow-up questionnaire corresponded to the flavour of antibiotic that the child had stated tasted the best at the time of taste testing in only 42% (8/19) of children[33].

Facial hedonic scale

A facial hedonic scale, allowing for indication of preferences by pointing at a pictorial scale of facial expressions[14,27] has been commonly employed. Compared to spontaneous verbal judgment, this method has the advantage of being a more standardised procedure. Studies have shown that children as young as 4 years can understand and use a 7-point hedonic scale to indicate whether a substance is pleasing to their taste[45]. Studies have also been conducted asking the child to rate the taste of medications on a visual analogue scale, a tool widely accepted in paediatrics, modified by the incorporation of a facial hedonic scale[33,38,44] (Figure 1). Correlation between verbal and hedonic assessments has been variable[13,42].

It is important to consider that most taste preference studies involve a single dose of each medication and it is possible that palatability may change with prolonged administration. It is unclear whether the results of these single dose studies are predictive of preference for patient compliance with multiple dose regimens[45].

Since disease may alter taste perception it may be argued that it is more appropriate to evaluate the taste of certain medication formulations in children who actually suffer from the disease for which the drug is indicated. Selection of a good flavour for a paediatric formulation may require consideration of the medical condition of the target population[27]. Altered taste after initiation of chemotherapy has been demonstrated in children with cancer[51]. Taste acuity testing showed that significantly more cancer patients made taste recognition errors, the most common being that they reported a bitter taste[51]. Conducting palatability testing in paediatric patients also avoids some of the ethical concerns that have been raised as an argument for not enrolling healthy volunteer children in these studies, such as the lack of potential benefit to the participant as well as the possible risk of adverse effects from the medication. Ethics review boards may be more likely to approve a study if the children would be receiving the drug to treat a medical illness. Alternatively, an artificial taste sensor may be used to evaluate the bitterness of medications[52] during drug product development.

Summary

The palatability of medications, in particular that of liquid formulations used in young children,

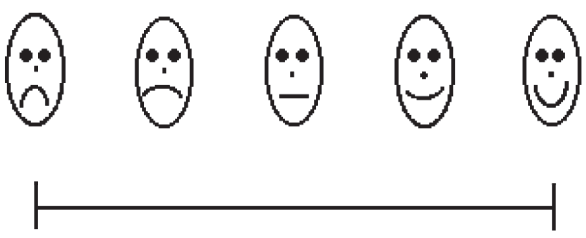

Figure 1 VAS with facial hedonic scale

is an important consideration and probably plays a major role in adherence with drug therapy in paediatrics. Given the developmental changes in taste that occur with age, it is reasonable during the process of drug development to undertake palatability studies in children using one of the methods that have previously been used successfully in this age group. The possibility of differences in taste perception related to the underlying disease process must also be kept in mind, and if possible perhaps taste testing should occur in those children who suffer from the relevant medical condition. Better tasting medications would also make it easier for parents to administer much needed medication. Healthcare workers need to recognise the potentially important role played by palatability when deciding which medication to prescribe to their paediatric patients.

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