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CLINICAL INVESTIGATION

Palatability of Liquid Anti-Infectives: Clinician and Student Perceptions and Practice Outcomes

Stacy C. Gee, BS, PharmD[1] and Tracy M. Hagemann, PharmD[2]

[1]Innovative Pharmacy Solutions, Edmond, Oklahoma, and [2]Department of Pharmacy: Clinical and Administrative Sciences, University of Oklahoma College of Pharmacy, Oklahoma City, Oklahoma

Oral liquid medications with poor palatability may lead to non-compliance, especially among children. Often, prescribers are not aware of the palatability of the agent that they are prescribing. Eighty-six health-care professionals participated in an open-label taste test of 24 anti-infectives in stock at a pediatric teaching hospital. A sample of the product was placed on a plastic spoon and participants were asked to evaluate their overall impression based on taste, texture, smell, and aftertaste. Participants were then asked to rank the individual products on a visual analog scale. Certain anti-infective formulations were perceived as being much more palatable than others. As a follow-up study, surveys were sent out to assess the impact of the taste test. Participants were asked to evaluate their prescribing and patient counseling habits both before and after the taste test. We found that half of the volunteers had altered their prescribing and/or medication counseling habits as a result of the taste test.

KEYWORDS anti-infectives, oral liquid medications, palatability

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INTRODUCTION

Pediatricians prescribe antibiotics more frequently than any other pharmacotherapy for their patients.[1] Between 2001 and 2004, antibiotics were among the top 100 prescriptions by both retail sales and volume in the United States.[2] Most of these antibiotic preparations are dispensed as a liquid formulation. For children, the smell and taste of the product can be major factors in their acceptance and willingness to comply with the prescribed therapy.[3] Studies have shown that strategies to improve patient adherence such as medication information pamphlets, self-monitoring calendars and telephone reminders do not have as much influence on compliance in children as the child's perception of taste.[3-5] Pediatric health-care providers may not be aware of the ramifications that taste has on a child's compliance, nor of strategies to help improve adherence with a poor-tasting product. The purpose of our study was to educate a variety of practitioners who provide health-care to pediatric patients about the issues associated with taste and compliance in pediatric patients. We report the results of a study of an open-labeled taste-test and follow-up survey comparing 24 commonly prescribed liquid antibiotic preparations.

ABBREVIATIONS TMP-SMX, trimethoprime-sulfamethoxazole

METHODS

Over a period of one year, medical and phar-

Address correspondence to: Tracy Hagemann, PharmD, University of Oklahoma College of Pharmacy Department of Pharmacy: Clinical and Administrative Sciences, P.O. Box 26901, 1110 N. Stonewall Avenue, Oklahoma City, OK 73190, email: Tracy-Hagemann@ouhsc.edu

Table 1. Medications and formulations tested

Medication generic (Trade name)	Sweetener	Flavor
Acyclovir (Zovirax)[a]	Sorbitol	Banana
Amoxicillin (Amoxil 250 mg/5mL)[b]	Sucrose	Bubble gum
Amoxicillin (Trimox)[c]	Sucrose	Strawberry raspberry
Amoxicillin/clavulanic Acid	Saccharin	Orange
Ampicillin 250 mg/5mL (Principen)[d]	Sucrose	Fruit
Augmentin 250 mg/5 mL)[b]		
Azithromycin (Zithromax)[e]	Sucrose	Cherry
Cefixime (Suprax)[f]	Sucrose	Strawberry
Cefpodoxime (Vantin)[g]	Sucrose, lactose	Lemon crème
Cefuroxime axetil (Ceftin)[a]	Sucrose	Tutti-fruiti
Cephalexin 250 mg/5 mL[h]	Sugar	Mixed berry
Clarithromycin (Biaxin)[i]	Sucrose	Fruit punch
Clindamycin (Cleocin Pediatric)[g]	Sucrose	Cherry
Dicloxacillin (Dynapen)[c]	Saccharin, sucrose	
Doxycycline (Vibramycin)[e]	Sucrose	Raspberry
Erythromycin ethylsuccinate (E.E.S., 400)[i]	Sucrose	Orange
Erythromycin Sulfisoxazole (Pediazole)[j]	Sucrose	Strawberry-banana
Fluconazole (Diflucan)[k]	Sucrose	Orange
Furandantin[l]	Saccharin, sorbitol	Banana-Raspberry-Mint
Loracarbef (Lorabid)[m]	Sucrose	Strawberry bubble gum
Metronidazole (Flagyl)[e]	Ora-Sweet	None
Nystatin[n]	Sucrose	Cherry
Oxacillin[h]	Saccharin, Sugar	Cherry
Penicillin VK 250 mg/5 mL[h]	Aspartame, saccharin, sucrose	Fruit
TMP/SMX[o]	Saccharin, sorbitol	Grape

TMP-SMX, trimethoprime-sulfamethoxazole
a = Glaxo Wellcome, Research Triangle Park, North Carolina
b =GSK, Phildelphia , PA
c = Geneva, Princeton, NJ
d = Apothecon, Princeton, NJ
e = Pfizer, Morris Plains, NJ
f = Lederle, Madison, NJ
g = Pharmacia Upjohn, Morris Plains, NJ
h = Teva, North Wales, NJ
l = Abbott, Abbott Park, IL
j = Ross, Columbus, OH
k = Roerig, Morris Plains, NJ
l = First Horizon, Alpharetta, GA
m = Lilly, Indianapolis, IN
n = Alpharma, Baltimore, MD
o = Hi Tech Pharmacal, Amityville, NY

macy students, pediatric medical residents, and attending physicians participated in an open-label taste of 24 anti-infectives that were available and on formulary at a pediatric teaching hospital. All but one of these products, metronidazole, was available commercially; hence, it had to be compounded as an extemporaneous formulation by the pharmacy (Appendix 1).

Volunteers were solicited at the hospital during the pediatric resident noon conferences, at the college of pharmacy during student practicums, and during pediatric teaching rounds at the hospital. Persons who were pregnant or nursing were excluded. Likewise, individuals who had a documented allergy to one of the products or related products were excluded from tasting that anti-infective. Coordinator and participants were aware of the product name before tasting the product. Participants were asked to evaluate their overall impression

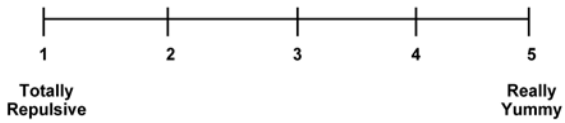

Figure 1. Evaluation rating scale.

based on color, odor, texture, initial taste, and aftertaste of each product.

A total of 24 products were tested (Table 1). With the exception of metronidazole, which was compounded in our inpatient pharmacy from Flagyl (Pfizer) tablets (Appendix 1), all products were commercially available. All products were tasted in the same order during each session, starting with the penicillins, followed by cephalosporins, macrolides, clindamycin, metronidazole, and then other products. A 1 mL sample of the product was placed on a white, plastic spoon and tasted. Participants were permitted to take sips of water and eat an unsalted cracker between tasting of each product sample. After tasting the sample, the participants were asked to immediately document their overall perception of the individual products on a 5-inch Likert derivative scale (Figure 1). The visual analog ranged from one to five with 1 being "totally repulsive" and 5 denoting "really yummy". Products were ranked according to the numerical average (based in inches) from the Likert scale.

Following each session, participants discussed issues related to antibiotic taste and the effects that taste might have on compliance. Discussions included how to increase palatability of products through addition of flavoring agents, by mixing the product with food, and following the dose of medication with a food substance "chaser". In order to increase awareness of the importance of accuracy in dosing these medications in children, the use of oral syringes instead of a regular household spoon was also discussed. At least one month after the taste-test, participants were given a follow-up survey to determine how the taste-test affected their prescribing and/or medication counseling habits.

RESULTS

Eighty-six individuals participated. These included pharmacy students (45%), physicians (30%), medical students (22%), pharmacists

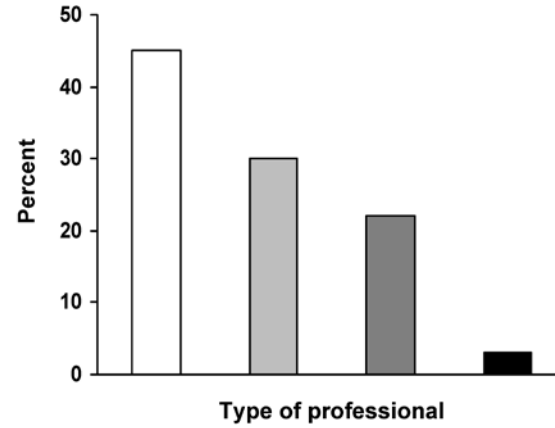

Figure 2. Characteristics of participants.
□ Pharmacy students (n = 38); □ Physicians (n = 26); ■ Medical students (n = 19); ■ Other (pharmacist, n = 2; physician assistant, n = 1)

(2%) and physician associates with prescriptive authority (1%) (Figure 2). Certain anti-infective formulations were perceived as being much more palatable than others (Table 2). The five highest ranked products in our study included loracarbef (Lorabid, Lilly), amoxicillin (Trimox, Geneva), cefixime (Suprax, Lederle), amoxicillin (Amoxil, GSK) and doxycycline (Vibramycin, Pfizer). The five lowest ranked products included clarithromycin (Biaxin, Abbott), dicloxacillin (Geneva), oxacillin (Oxacillin generic, Teva), clindamycin (Cleocin Pediatric, Pharmacia & Upjohn) and metronidazole compounded in our inpatient pharmacy from Flagyl (Pfizer) tablets (Appendix 1). Overall, the higher ranked products included amoxicillin (and it's derivatives), as well as most of the cephalosporins. The lowest ranked products included clindamycin, metronidazole, penicillin VK and the antistaphlococcal penicillins (dicloxacillin, oxacillin). Comments about the lowest ranked products included; lingering aftertaste, bitter initial taste, gritty texture and unpleasant smell. Participating groups were also asked follow-up questions for discussion (Table 3).

It does not appear that there was a particular sweetener or flavor preference among the participants of our study. There was a slight trend toward sucrose containing products ranking more positively. Of the six products tested that contained saccharin, none were in the top performers. Products containing more than one sweetener tended to be ranked lowest in

Table 2. Agent rankings from best overall to least

	Medication*	Rank (mean ± SD)
Best Overall	Loracarbef (Lorabid)	3.8 ± 0.6
	Amoxicillin (Trimox)	3.5 ± 0.1
	Cefixime (Suprax)	3.3 ± 1.0
	Amoxicillin (Amoxil)	3.1 ± 0.9
	Doxycycline (Vibramycin)	3.1 ± 0.7
	Acyclovir (Zovirax)	3.0 ± 1.2
	Azithromycin (Zithromax)	2.8 ± 1.0
	Amoxicillin/clavulanic Acid (Augmentin)	2.7 ± 0.9
	Furandantin	2.6 ± 0.8
	Cefpodoxime (Vantin)	2.5 ± 1.3
	Fluconazole (Diflucan)	2.5 ± 1.2
	Cephalexin	2.5 ± 1.1
	Ampicillin (Principen)	2.3 ± 0.8
	Nystatin	2.1 ± 0.9
	Erythromycin Sulfisoxazole (Pediazole)	1.9 ± 1.1
	Eythromycin ethylsuccinate (E.E.S, 400)	1.7 ± 1.2
	TMP/SMX	1.7 ± 1.0
	Cefuroxime aexitil (Ceftin)	1.6 ± 1.0
	Penicillin VK	1.5 ± 1.1
	Clarithromycin (Biaxin)	1.0 ± 0.9
Worst Overall	Dicloxacillin (Dynapen)	0.8 ± 0.8
	Clindamycin (Cleocin Pediatric)	0.8 ± 0.8
	Oxacillin	0.6 ± 0.9
	Metronidazole (Flagyl)	0.3 ± 0.6

** See Table 1 for product specifications and manufacturer information*
TMP-SMX, trimethoprime-sulfamethoxazole
a = Lilly, Indianapolis, IN
b = Geneva, Princeton, NJ
c = Lederle, Madison, NJ
d = GSK, Philadelphia, PA
e = Pfizer, Morris Plains, NJ
f = Glaxo Wellcome Research Triangle Park, North Carolina
g = First Horizon, Alpharetta, GA
h = Roerig, Morris Plains, NJ
i = Pharmacia Upjohn, Morris Plains, NJ
j = Teva, North Wales, NJ
k = Apothecon, Princeton, NJ
l = Alpharma, Baltimore, MD
m = Ross, Columbus, OH
n = Abbott, Abbott Park, IL
o = Hi Tech Pharmacal, Amityville, NY

our study. Whether this is because of the anti-infective product's taste or the combination of sweeteners is unknown. The least palatable products tended to have more than one sweetener. Flavoring was also not necessarily predictive of preference. Most of the products were fruit-flavored (cherry, strawberry, orange, etc).

At least one month after the taste-test, participants were surveyed to determine if they had altered their prescribing and/or patient counseling habits as a result of their participation in this study (Appendix 2). A total of 86 surveys were distributed and the response rate was 41.8% (n = 36). The majority of survey responses were from physicians (83%, n = 30). Most responders to the survey reported that they had taken the taste test less than six months earlier. Survey response revealed that almost all volunteers remembered their perception of at least one product. The majority

Table 3. Taste test questions

- How do you think taste affects compliance?
- What can you do to improve adherence with liquid anti-infective regimens?
- How will this exercise change the way you prescribe and/or practice?
- How will this exercise change the way you talk to patients and their families about their medications?

remembered the medications with bad taste or aftertaste. Common products in this category included clindamycin and metronidazole. Forty-two percent of the physician responders noticed that their prescribing habits had changed since the initial taste test. Appendix 3 notes the reasons for the changes in habits. The most common reasons included: do not prescribe medications that are known to taste bad realizing the patient won't take them, prescribe crushed pills over syrups because less of a bad taste, and take taste and texture into consideration. After the taste-test, one individual had avoided prescribing a medication that they specifically remembered as tasting bad during the taste test.

The other half of the survey respondents indicated that their prescribing habits had not changed since the initial taste-test because some medications such as clindamycin and metronidazole had no other equivalent choices. Also, some noted their prescribing habits had not changed but, they were more aware of the products that they chose and spoke to the caregivers about compliance with the medication regimen and about strategies to improve compliance.

DISCUSSION

There have been several reports evaluating the taste and acceptability of liquid antimicrobial medications in both adult and pediatric volunteers. The results of our evaluation correlated with previously published information.[3,6-9] In a blind taste test, 30 adult volunteers evaluated 14 commonly prescribed antibiotics for smell, texture, taste and aftertaste on a 1-5 scale in each category.[3] The cephalosporins ranked highest and the penicillins ranked lowest, while trimethoprim/sulfamethoxazole (Septra brand) was ranked as best tasting. Since this study was published in 1991, some

Appendix 1. Metronidazole 50 mg/mL recipe[11]

Ingredients

500 mg metronidazole tablets
Ora-Plus (Paddock Labs)
Ora-Sweet (Paddock Labs)

Pulverize10 × 500 mg metronidazole tablets in mortar and levigate with water (10 mL). Add 20 mL of Ora-Plus and Q.S. to 100 mL with Ora-Sweet.

Label: Shake well, refrigerate. 30 day expiration date

of the newest antibiotic preparations were not marketed yet, and therefore, not evaluated. In another study, 22 antibiotic suspensions were evaluated in five independent categories including appearance, smell, texture, taste and aftertaste.[6] Twenty-six adult health-care professionals ranked each preparation on a 1-10 scale and the investigators found that generally the cephalosporins were ranked high, and that azithromycin was slightly superior to erythromycin and clarithromycin. Some antibiotics were found to be unpalatable to an extent that may jeopardize compliance and these included dicloxacillin, oxacillin, erythromycin/sulfisoxazole and cefpodoxime. Within the penicillin class, amoxicillin and ampicillin were preferred, tastewise, over penicillin VK. This also was evident in our study. In another study, brand and generic suspensions were compared in a pediatric group and demonstrated that brand name liquid antibiotics do not necessarily taste better than their generic counterparts.[7] In our study, a generic version of amoxicillin was ranked as better overall than the brand name version.

Several other studies have specifically examined the child's perception of taste in oral liquid antibiotics. A single-blind taste test of four suspensions (cloxacillin, cephalexin, erythromycin and fusidic acid) in 20 healthy volunteer children using a taste visual analog scale with faces found that cloxacillin was the most unpalatable of those studied.[8] In another study, researchers evaluated another four suspensions (amoxicillin clavulanic acid, azithromycin, clarithromycin, and erythromycin/sulfisoxazole) in 50 healthy children and 20 healthy adults.[9] They used a 10 cm visual analog scale that incorporated a facial hedonic

Appendix 2. Taste test survey: Part II

1. How long has it been since you took the taste test?

☐ < 1 year ☐ > 1 year

2. Which of the following best describes your status at the time of the initial taste test? (Please check one)

☐ Student (pharmacy)
☐ Student (medicine)
☐ Pediatric medical resident
☐ Attending physician

3. Were there any medications that you specifically remember being distinct?

☐ Yes ☐ No

Do you remember what they were? _____

If so, why do you remember them? _____

☐ Good taste ☐ Good texture
☐ Bad taste ☐ Bad texture
☐ Good smell ☐ Bad texture
☐ Bad smell
Other (please specify) _____

4. Have your prescribing or patient counseling habits changed since taking the taste test?

☐ Yes ☐ No

If so, how? _____
_____
_____
_____
_____
_____

Appendix 3. Selected survey comments from insert number physicians

- Less likely to prescribe bad tasting medications
- I think of the taste, smell and texture of medicine as an important component of compliance
- I take means to avoid placing the patient in additional discomfort
- Decreased my prescribing on bad tasting medicines (e.g., Ceftin)
- I use the most concentrated product available if I know it tastes bad
- I encourage older children to swallow the tablet or capsule
- I talk to the parents of ways to help their children take the medication
- I am more attentive to the tastes of the medications that I prescribe
- I spend a little more time thinking of the issues that affect compliance, like taste.
- I try to avoid the terrible tasting medications if possible.

scale to evaluate each product. Azithromycin was rated most highly by the children and adults in the study, but there were some differences between the groups in the other antibiotics tested.

Our study has some obvious limitations: even though the products were consistently tasted in the same order each time, the perception of a "totally repulsive" medication could have potentially altered the perception of the products that followed it. Volunteers were given unlimited sips of water and unsalted crackers as needed after each taste, but lingering taste could have altered subsequent product perception. Additionally, our participants were all adults. While we believe that it is important for health-care providers to be aware of the issues associated with medication adherence and compliance in pediatric patients, of which taste plays a big part, the true test is whether the child will tolerate the medication's palatability. It is well established that taste perception diminishes with age and therefore, products that taste good to an adult may be perceived very differently in a child.[3,4,10] It can be a struggle to administer a medication to a child when the child finds the taste of the product unpalatable. Pharmaceutical manufacturers develop oral liquid products for children and attempt to make them more acceptable by the addition of colors, sweeteners, artificial flavoring agents, and preservatives. A sweet flavoring generally helps cover the initial taste of a product, but the bitter aftertaste of the active ingredient is most difficult to mask. The attitude of the child's caregiver toward the smell or taste of the product may be transferred to the child and result in non-compliance with the product.[3]

After each tasting session, we discussed methods for increasing compliance with prescribed medications, such as mixing unpleasant tasting medications in foods like applesauce, pudding or chocolate syrup as well as the use of flavoring agents. At the time of our study, the FLAVORx liquid medication flavoring system (Bethesda, MD) was not available at

our institution, but this system and others are now more widely available in community pharmacies and may help disguise the unpleasant taste of some medications. These flavorings can also be customized to the child's preference. The use of oral syringes for administration of medication was explained and demonstrated to the participants in our study. Other methods included having a liquid "chaser" such as grape juice or apple juice available for the child to swallow immediately after the medication.

The worst performer in our study was our compounded metronidazole product. This was the only compounded product in our study and it is not surprising that it was a poor performer. The metallic aftertaste of metronidazole is well known and pharmacists should counsel patients on this. Crushing the tablets and using suspending and sweetening agents, does not improve on the palatability of the product. Since our study, there are several area community pharmacies in our area compounding metronidazole into a more palatable formulation. The bitter, pungent aftertaste is still noticeable, but to a slightly lesser extent. Because metronidazole is the preferred antiinfective for treatment of *Clostridium difficile*, especially as an oral outpatient treatment, there is an immediate need for investigation into the use of an artificial flavoring agent on the palatability and stability of compounded metronidazole products.

Taste is only one factor that health-care providers should consider when choosing an antibiotic for a child; cost, antimicrobial coverage and side effects should be a major part of the decision, especially in times of increasing antimicrobial resistance. Pediatric health-care providers should weigh all of these factors when considering antibiotic treatment. We found that the process of tasting and evaluating the antibiotic products available in our institution by the health-care providers and trainees contributed to more cognizant prescribers and providers. A majority of the survey responders indicated that they were more aware and more comfortable talking to the patients and caregivers about their liquid antibiotics and how to improve compliance with the treatment regimen in the pediatric population.

CONCLUSION

Our results demonstrated that health-care professionals who participated in the taste-test had positively altered the way that they prescribe and practice. Participants are more cognizant of factors related to compliance, including palatability of the prescribed product. They are more likely to discuss issues of palatability and compliance with the child and caregivers. This exercise continues to be incorporated into the pediatric pharmacy practicum and the pediatric medical resident training programs at our institution.

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