Original Communication

Osmolality, pH, and Compatibility of Selected Oral Liquid Medications With an Enteral Nutrition Product

Journal of Parenteral and Enteral Nutrition
Volume 37 Number 5
September 2013 689-694

DOI: 10.1177/0148607112471560
jpen.sagepub.com
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Mark Klang, MS, RPh, BCNSP, PhD[1]; Veronica McLymont, PhD, RD[1]; and Nicole Ng, PharmD[1]

Abstract

When selecting medication for feeding tube administration, the liquid formulation is selected, so as to avoid obstructions that may occur from incompletely crushing a solid dosage form. Liquid medications can present issues of intolerance and compatibility when administered via a feeding tube. A predictor of intolerance is the liquid's osmolarity, and a predicator of compatibility is the liquid's pH value. This study examines 62 liquid formulations for their osmolality, pH, and physical compatibility with enteral nutrition (EN) formulas. These medications were selected as being the most commonly dispensed liquid medications from our outpatient pharmacy department. This study measures osmolality using freezing point depression. Depending on the dose, the osmotic load of a liquid medication may cause cramping and diarrhea. The pH value is predictive of potential interactions with the EN formula. Many drugs are weak bases and require acidic vehicles for optimal stability. The acidic liquids are especially reactive with enteral formulas that contain intact proteins. The result of this interaction can result in an occlusion of the feeding tube as the proteins form a gel-like clog. This study combined the liquid medication directly with the EN formula to determine the potential for feeding tube occlusion. Some drugs formed a solid mass in the test tube immediately, whereas others only presented granules, which may later contribute to obstructing the feeding tube. The prescriber should be aware of the potential impact of their choice in formulation, both in terms of the gastrointestinal tolerance and potential for interaction with coadministered nutrition. (*JPEN J Parenter Enteral Nutr*. 2013;37:689-694)

Keywords

enteral nutrition; drug-nutrient interactions; enteral access

Clinical Relevancy Statement

This study examines 2 physiochemical properties of liquid medications: osmolality and pH. Since liquid medications are often used concurrently in patients requiring nutrition products through enteral feeding tubes, the study also looks at the compatibility of liquid medication with enteral nutrition. Osmolality of oral liquid medications has been linked to causing diarrhea in the feeding tube patient. The clinician can use the data collected here to calculate the appropriate dilution of the medication and improve patient outcome. The acidic pH of liquid medications has been linked to the formation of precipitates, when combined with enteral feeding formulas. The information presented here will alert the clinician to use appropriate flushing before and after drug administration to reduce the risk of obstructing feeding tubes.

Introduction

The patient who receives medications administered through a feeding tube will most likely have nutrition administered by the same route. Medications selected must be compatible with the mechanics of this route. The dosage should be an immediate-release formulation and free of properties that can obstruct the flow through the tube. Solid medication is replaced by a liquid formulation as it is assumed that the liquids would be better tolerated and have less potential obstructing the feeding tube. Some liquid medications are prone to forming obstructions in the feeding tubes when combined with enteral nutrition (EN).[1] It is important to recognize that when selecting a medication, none of the Food and Drug Administration (FDA)–approved liquid medications were designed for feeding tube administration. Liquid medication is designed for those who have difficulty swallowing solid dosage forms orally. Many of these liquids include sugars, flavoring agents, and excipients, which thicken and improve palatability.[2] Sugars such as sorbitol are often added to enhance solubility and palatability. Sorbitol is a more potent cathartic than lactulose and is responsible for osmotic diarrhea in tube-fed patients who receive their doses undiluted.[3] In studies of patients who have contracted diarrhea while receiving EN, many of these cases were found to be caused by the excipients

From the [1]Memorial Sloan-Kettering Cancer Center, New York, NewYork.

Financial disclosure: None declared.

Received for publication April 17, 2012; accepted for publication November 26, 2012.

This article originally published online on January 17, 2013.

Corresponding Author:
Mark Klang, MS, RPh, BCNSP, PhD, Core Manager, Research Pharmacy, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065.
Email: klangm@mskcc.org.

found in the liquid formulations rather than an intolerance to the nutrition.[4,5]

The cause of a feeding tube obstruction is dependent on numerous physical and chemical factors of the nutrient, the medication formulation, and the feeding tube being used.[6] The most validated remedy to unclog a feeding tube is the use of pancreatic enzymes, along with sodium bicarbonate. This combination digests the clabber formed by protein reacting with the acidic gastric fluid.[7] Based on that observation, it is not surprising that liquid medications formulated as acidic syrups would form an obstruction when in contact with a standard polymeric EN formula.[1] Unfortunately, there is a lack of information on compatibility of liquid medications with an EN product that assist in predicting the next feeding tube obstruction. It is necessary to evaluate each liquid medication individually as even generically equivalent products may have different excipients and formulation properties present.[8]

Since liquids are the preferred medication formulation selected for feeding tube administration,[9] we decided to examine the most common liquid being dispensed at Memorial Sloan-Kettering Cancer Center. This study was conducted to evaluate the liquid medications being dispensed for pH and osmolality. We also examined if the combination of these liquid medications with the EN formula would result in a deposit sufficient to obstruct a feeding tube.

Methods

A total of 62 commercially available solutions and suspensions (ie, 58 liquid medications and 4 vehicles) were selected from the outpatient pharmacy formulary based on the high volume dispensed.

Osmolalities were measured in mOsm/kg using an osmometer (Osmette III, Natick, MA). This device calculates osmolality from a determination of freezing point depression.

For those medications in which the osmolality exceeded the osmometer capacity of 2000 mOsm/kg, the medication was diluted with sterile water for irrigation (1:5 dilutions). If the osmolality of the diluted sample was still greater than the osmometer capacity, a 1:10 dilution was made in the same manner. A 10-μL sample was inserted into the device using the device pipette.

The osmometer was calibrated using osmometry reference standards of 100, 500, 1500, and 2000 mOsm/kg (Precision Systems, Natick, MA) at initiation and completion of tests.

The pH value was measured with a pH meter (AB-15, Accumet Basic; Fisher Scientific, Pittsburgh, PA). The pH meter was calibrated using reference buffers of values 4, 7, and 10 (Fisher, Fair Lawn, NJ). Each medication (5 mL in a centrifuge tube) was measured undiluted using the pH meter. The meter probe was rinsed with triple distilled deionized water between measurements.

Five milliliters of each medication, undiluted, was combined with 5 mL of EN formula (Osmolite 1.2; Abbott Nutrition, Abbott Park, IL) in a 10-mL centrifuge tube. This nutrition formula was selected since it is commonly used, is readily available, and consists of intact proteins that have been implicated in several feeding tube obstructions at our institution.

The 2 ingredients were vortexed for 1 minute and then placed for 1 hour inside an incubated shaker at 37°C at 200 rpm. This process was chosen as an attempt to mimic the contact of drug and nutrients if the products were not rinsed appropriately after administration. An attempt was made to pour the contents from the tube through a stem glass funnel (#6180-50, Pyrex; Corning, Corning, NY; 50 mm top diameter, 65 mm stem length, 6 mm internal stem diameter). The obstruction of the glass stem by gravity-flowing contents of the tube was recorded in Table 1 as a clog formation under the "Funnel" column. The stem of the glass funnel is 1.5 times the diameter of a 12 French feeding tube (4 mm). It was assumed that a clog that would obstruct the glass funnels would also obstruct the larger percutaneous endoscopic gastrostomy (PEG) feeding tubes (~20 French). The entire volume (10 mL) that passed through the glass funnel was then poured through a 100-micron nylon screen. Any solid substances found retained on the screen were noted as having a potential for obstructing a fine-bore feeding tube (~8 French) and noted under the "Screen" column.

Results

The osmolalities and pH measurements of the medications are listed in Table 1. Only 1 medication fell below the upper limit osmolar range of 500 mOsm/kg (guaifenesin solution).[10] Seventeen products had osmolalities >5000 and 3 products produced osmolarity >10,000 with a maximum measured osmolality measurement of 16,100. In the products that required additional dilution, it was assumed that the actual osmolality would be related to a linear function of the dilution. This assumption yielded an underestimate of the actual osmolality of the undiluted product.

The pH measurements ranged from 2.39–9.77. Almost all liquid medications are somewhat acidic, with the exception of antacids and potassium iodide (SSKI). Adequate rinsing of the feeding tube is needed to minimize contact with EN formulas as these acidic fluids have a high potential to contribute to an occluded feeding tube.

Several of the acidic suspensions (pH <4.5) formed solid clogs when combined with enteral formula and could not be removed from the test tube, whereas others produced granules that were trapped by the screen. Not all the acidic liquids formed a precipitate in the test tube or in the screen.

Discussion

Generally, when pharmaceutical drug companies design the formulation of oral liquid medications, minimal consideration is

Table 1. pH, Osmolality and Compatibility of Liquid Medications with Enteral Nutrition.

	Product	Concentration	pH	Osmolality	Funnel	Screen	Lot No.	Expiration, Month/Year	Manufacturer
Liquid medications									
1	Acetaminophen solution	325 mg/10.15 mL	4.35	4035[a]	Clog	Clog	0F10	6/12	PAI (Greenville, SC)
2	Acetaminophen suspension	160 mg/5 mL	4.68	6425[a]	Clog	Clog	100863	11/11	Precision Dose (Beloit, IL)
3	Acyclovir oral suspension	200 mg/5 mL	5.8	4205[a]	Passes	Clog	L009104	2/12	Actavis (Morristown, NJ)
4	Aluminum hydroxide gel	320 mg/5 mL	7.21	1501	Clog	Clog	0B44	8/11	PAI
5	$Al(OH)_3$, $Mg(OH)_2$, simethicone	200 mg, 200 mg, 20 mg per 5 mL	7.84	990	Passes	Clog	JAN019	11/12	GeriCare (Brooklyn, NY)
6	Aminocaproic acid (Amicar) solution	0.25 g/mL	6.15	3405[a]	Passes	Passes	H090357A	7/12	Xanodyne (Newport, KY)
7	Atovaquone (Mepron) suspension	750 mg/5 mL	5.87	135	Passes	Clog	0D002	10/11	GSK (Philadelphia, PA)
8	Azithromycin suspension	200 mg/5 mL	9.48	3950[a]	Passes	Passes	MTYG1261	3/13	Greenstone (North Peapack, NJ)
9	Calcitriol solution	1 mcg/mL	7.83	—[b]	Clog	Clog	958360A	10/11	Boehringer (Ridgefield, CT)
10	Calcium carbonate suspension	1250 mg/5 mL	9.16	2490[a]	Passes	Passes	059663A	4/12	Boehringer
11	Carbamazepine suspension	100 mg/5 mL	3.68	4225[a]	Clog	Clog	093677	2/11	Taro (Hawthorne, NY)
12	Dexamethasone intensol	1 mg/mL	3.9	10,600[c]	Clog	Clog	060548A	8/12	Boehringer
13	Digoxin solution	0.125 mg/2.5 mL	6.46	5950[a]	Passes	Passes	956536C7	4/11	Boehringer
14	Diphenhydramine HCl	12.5 mg/5 mL	3.94	3975[a]	Passes	Passes	L063E10C	5/12	Qualitest (Huntsville, AL)
15	Docusate sodium liquid	10 mg/10 mL	6.51	6385[a]	Passes	Passes	0H21	8/12	PAI
16	Ergocalciferol (Calciferol) solution	400 IU/0.05 mL	5.08	16,100[c]	Passes	Passes	00102	1/13	Schwarz (Mequon, WI)
17	Escitalopram (Lexapro) solution	5 mg/5 mL	4.54	6030[a]	Clog	Clog	1076260	4/13	Forest (St. Louis, MO)
18	Ferrous sulfate elixir	220 mg/5 mL	2.39	3445[a]	Clog	Clog	601645	6/12	Hi-Tech (Norcross, GA)
19	Fluconazole suspension	40 mg/mL	4.29	2185[a]	Clog	Clog	0760902	5/13	Greenstone
20	Furosemide solution	40 mg/5 mL	9.77	8975[a]	Passes	Passes	957332A	6/12	Boehringer
21	Gabapentin (Neurontin) solution	250 mg/5 mL	6.31	8275[a]	Passes	Passes	OA9XR	4/12	Pfizer (New York, NY)
22	Guaifenesin solution	200 mg/10 mL	2.78	278	Clog	Clog	OF39	12/11	PAI
23	Guaifenesin DM (dextromethorphan/ guaifenesin) syrup	20 mg/10 mL	2.78	4270[a]	Clog	Clog	0083	4/12	PAI
24	Hydroxyzine HCl syrup	10 mg/5 mL	3.16	3540[a]	Passes	Clog	30460A	6/12	Morton Grove Pharmaceuticals (Morton Grove, IL)
25	Ibuprofen suspension	100 mg/5 mL	3.9	2350[a]	Clog	Clog	L912050	12/11	Actavis
26	Isoniazid solution	50 mg/5 mL	5.86	8850[a]	Passes	Passes	610152	6/12	Carolina (Savannah, GA)
27	Lactulose solution	10 g/15 mL	4.85	4180[a]	Passes	Passes	610152	9/12	Morton Grove Pharmaceuticals
28	Lamivudine (Epivir) solution	10 mg/mL	6	1460	Passed	Passes	0C002	3/12	GSK
29	Levetiracetam solution	100 mg/mL	6.03	5075[a]	Passes	Passes	0595224	3/12	Boehringer
30	Levofloxacin (Levaquin) solution	25 mg/mL	5.13	2115[a]	Clog	Clog	AEB2V00	4/12	Ortho-McNeil (Raritan, NJ)
31	Loperamide	0.2 mg/mL	4.02	6775[a]	Clog	Clog	M101121-86	5/11	Major (Livonia, MI)
32	Magnesium hydroxide suspension	2400 mg/30 mL	9.44	1258	Passes	Clog	OJ14	9/12	PAI
33	Megestrol acetate	40 mg/mL	4.37	3665[a]	Passes	Clog	22818401	10/13	PAR (Spring Valley, NY)
34	Metoclopramide solution	5 mg/5 mL	2.74	5180[c]	Passes	Clog	0C16	3/12	PAI
35	Metoclopramide solution	5 mg/5 mL	2.83	4660[c]	Clog	Clog	5943A	4/12	SilaRx (Spring Valley, NY)
36	Mineral oil		4.89	—[b]	Passed	Clog	0E20	5/12	PAI
37	Multivitamin (Multi-Delyn) liquid		3.41	3655[a]	Clog	Clog	5802A	12/11	SilaRx
38	Neoral (Neo-Fradin) solution	125 mg/5 mL	5.76	4720[a]	Clog	Clog	801820	5/11	X-GEN (Northport, NY)

(continued)

Table 1. (continued)

	Product	Concentration	pH	Osmolality	Funnel	Screen	Lot No.	Expiration, Month/Year	Manufacturer
39	Ondansetron solution	4 mg/5 mL	3.73	2935[a]	Clog	Clog	0611314	10/12	Boehringer
40	Oxcarbazepine suspension	300 mg/5 mL	3.04	1976	Clog	Clog	H0137	5/13	Sandoz (Princeton, NJ)
41	Phenytoin suspension	125 mg/5 mL	4.49	3095[a]	Passed	Clog	209700	7/12	Actavis
42	Posaconazole (Noxafil) suspension	200 mg/5 mL	4.52	2050[a]	Passes	Passes	I0PSN87	8/13	Schering-Plough (Kenilworth, NJ)
44	Potassium chloride solution	10% SF (sugar free)	3.29	4225[a]	Passes	Passes	L160C10A	4/12	Qualitest
45	Potassium iodide (SSKI) solution	1 g/mL	9.21	11,380[c]	Clog	Clog	281424	6/12	Upsher-Smith (Maple Grove, MN)
46	Prednisolone (Na_3PO_4) solution	5 mg/5 mL	6.86	2395[a]	Passes	Passes	604944	3/12	Hi-Tech
47	Propranolol HCl solution	20 mg/5 mL	3.44	8145[a]	Passes	Passes	958876A	1/12	Boehringer
48	Ranitidine solution	15 mg/mL	6.88	637	Passes	Passes	210700	8/11	Vista-Pharm (Birmingham, AL)
49	Senna concentrate	8.8 mg/5 mL	5.05	3390[a]	Passes	Passes	100905	9/12	Major
50	Senna syrup	8.8 mg/5 mL	5.2	3920[a]	Passes	Passes	100905	9/12	Major
51	Simethicone (Infants' Drops)	20 mg/0.3 mL	4.88	170	Clog	Clog	L108J10A	10/12	Qualitest
52	Sirolimus (Rapamune) solution	1 mg/mL	5.36	—[b]	Clog	Clog	CMM	12/11	Wyeth (Madison, NJ)
53	Sodium citrate, citric acid solution	3 g/2 g per 30 mL	4.45	2565[a]	Passes	Passes	0E76	5/13	PAI
54	Sodium polystyrene sulfonate	15 g/60 mL	7.89	2735[a]	Passes	Passes	1010142	10/12	Carolina
55	Sucralfate (Carafate) suspension	1 g/10 mL	3.54	2145[a]	Passes	Passes	1133627	8/13	Wyeth
56	Sulfamethoxazole-trimethoprim	200 mg/40 mg per 5 mL	5.59	5560[c]	Passes	Clog	602492	8/12	Hi-Tech
57	Valproic acid (Depakene) solution	250 mg/5 mL	2.56	5010[c]	Passes	Passes	84018WJ	1/13	Abbott (Abbott Park, IL)
58	Voriconazole (Vfend) suspension	40 mg/mL	4.19	2010[a]	Passes	Clog	07399	1/11	Pfizer/Roerig (New York, NY)
Vehicles									
59	Cherry syrup	82% w/v	2.75	6165[a]	Clog	Clog	532821	9/12	Humco (Texarcana, TX)
60	Ora Plus		4.31	164	Clog	Clog	9499524	11/11	Paddock (Minneapolis, MN)
61	Ora Sweet		4.27	4200[a]	Passes	Passes	9509614	11/12	Paddock
62	Syr Spend SF		4.24	34	Passes	Clog	0601254	2/07	Gallipot (St Paul, MN)

[a]Results calculated based on 1:5 dilution with sterile water.
[b]Osmolality exceeded capacity of osmometer (2000 mOsm/kg) and product was immiscible with sterile water, thereby preventing further dilution.
[c]Results calculated based on 1:10 dilution with sterile water.

$$\frac{\text{mOsm of Medication}}{\text{Desired mOsm}} \times \text{Volume of dose} = \text{Final diluted Volume}$$

Figure 1. Calculation of final diluted volume.

given to its use through an enteral feeding tube. This is clearly evidenced by the hypertonic values recorded throughout the study; some products (eg, dexamethasone, ergocalciferol, furosemide, gabapentin, isoniazid, and potassium iodide) had values even greater than 25 times the osmolar range of the gastrointestinal (GI) tract (127–357 mOsm/kg).[2] Normally, the osmolality is not a concern because the medication is intended to be taken orally—through which saliva, mucous, and gastric juices act to dilute and buffer the medication to a safe pH and osmolar range when it arrives in the duodenum.[11] This is important because the small intestine is exceptionally sensitive to hypertonic solutions and osmolar loads.[12] As a result, administration of hypertonic substances directly into the duodenum or jejunum may result in significant GI intolerance such as osmotic diarrhea. This intolerance may be mistakenly attributed to the feeding formula.[5]

Pharmacists can adjust the osmolarity of a liquid medication by dilution with purified water, just prior to administration. The attached formula may be used to calculate the volume of water that must be added to bring the solution to the optimal osmolarity.[13] The desired osmolarity for gastric administration should be <700 mOsm, since there is usually adequate residual volume in the stomach to reduce the shift in pressure. However, the goal for jejunal administration should be <300 mOsm as there is less residual volume in the small intestine to reduce the stress of a higher osmolar load (see Figure 1).

Some of the liquid medications with a pH range below 4 (eg, diphenhydramine, sucralfate, and valproic acid) did not produce any precipitate when combined with the EN product. This observation demonstrates that obstruction of a feeding tube due to the interactions of liquid medication and nutrition products is not solely dependent on the pH of the medication. Osmolality and the formulation tested (elixir, solution, or suspension) did not have any relationship to the occurrence of precipitate formation. Nutrition formulas contain ingredients that can contribute to clog formation. The protein component, such as caseinate or whey, will precipitate when exposed to acidic solutions and contribute to an obstruction.[14-16] The higher protein concentration of the Osmolite 1.2 used in this study may yield a higher potential for clog formation than a formula containing a lower concentration of protein. Other causes have been speculated upon for obstruction formation factors, such as soap formation, viscosity of ingredients, and reactions with other excipients. These issues demonstrate the myriad possible causes for a feeding tube to clog. It is important to consider all potential issues when selecting an appropriate agent to prevent clogging the feeding tube.

In some cases, a clog was formed immediately in the test tube and could not be poured through a glass funnel. This reaction occurred with ferrous sulfate elixir, Guaifenesin DM (dextromethorphan/guaifenesin), and loperamide. Based on this, it is anticipated that such a fast reaction would also occur from the direct contact of this drug with nutrition formula within a feeding tube. In other cases, precipitate was noted when particles accumulated on the 100-µm nylon screen. These precipitates may contribute to clog formation if the tube is not adequately rinsed.

When preparing a medication for enteral tube use, the volume of medication should also be considered. For medications that require a small dosage volume, the effects of the hyperosmolality may be less pronounced.

Conclusion

Most of the oral liquid medications studied were hyperosmolar and prone to forming precipitates. The results gathered can help shed light on the need for proper administration of hyperosmotic medications to reduce the incidence of GI adverse effects and feeding tube clogs. This study also demonstrates the need for more EN compatibility studies with medications, as there is little predictability with these combinations.

The reader should review the EN practice recommendations from the American Society for Enteral and Parenteral Nutrition for more information and recommendations on drug administration through feeding tubes.[19]

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