Received: 24 July 2019 | Revised: 7 October 2019 | Accepted: 29 October 2019

DOI: 10.1111/jcpt.13079

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Dosing inaccuracy with enteral use of ENFit ® low-dose tip syringes: The risk beyond oral adapters

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Abstract

What is known and objective: As the global adoption of ENFit-compatible syringes becomes more widespread, it is important for syringe users to understand the risk of dosing inaccuracy for both the oral and enteral routes of use. Describing the risk of dosing inaccuracy specifically related to route of use is important to the end users' understanding of the clinical impact of device changes. The objective of this study was to compare the performance of female design ENFit low dose tip (LDT) syringes when used for enteral medication administration to the syringe performance during oral administration conditions.

Methods: This study was a secondary analysis of a prospective study conducted at the University of Florida Health Shands Hospital in conjunction with the University of Florida College of Pharmacy. Dosing variance (DV) up to 10% for low-risk medications and DV up to 5% is the target for high-risk medication administration is considered acceptable. The primary outcome was the frequency of administration volumes exceeding 10% of the expected amount when using the ENFit LDT syringe for both oral and enteral medication administration. Secondarily, the performance of standard ENFit syringes and the frequencies of DV exceeding 5 and 10% were also evaluated in the same conditions.

Results and discussion: A total of 264 tests were evaluated (ENFit LDT, n = 210; ENFit standard tip, n = 54). Using the LDT syringe for the enteral route resulted in statistically significant higher rates of unacceptable dosing variance >10% when compared to the oral application (26.9% vs 12.9%, P = .01). The frequency of LDT syringe DV >5% was significantly greater than >10% variance, regardless of oral or enteral use. Standard ENFit syringes had overall fewer tests with unacceptable dosing variance and showed no difference in performance between applications.

What is new and conclusions: This study raises additional clinical concerns specifically related to the enteral use of ENFit LDT syringes within commonly accepted dosing variance ranges. Enteral and oral application of LDT syringes yield unacceptably high rates of dosing variance for high risk medications with narrow therapeutic index.

KEYWORDS

dosing regimen, medicine use, monitoring, neonates, outpatients, paediatrics, pharmaceutical care, pharmacy practice

1 | WHAT IS KNOWN AND OBJECTIVE

Enteral tubing misconnections are an avoidable and potentially deadly consequence of device misuse.[1] The International Organization for Standardization (ISO) established enteral device criteria (ISO 80369-3) intended to mitigate the risk of misconnection between enteral and intravenous systems. The Global Enteral Device Supplier Association (GEDSA) was created to develop a syringe design compliant with ISO 80369-3. Emerging as the GEDSA-endorsed product, ENFit female syringes are currently the most prevalent option available globally for healthcare systems to convert to an ISO-compliant design. While this design has been shown to prevent tubing misconnections, concerns have been raised regarding its accuracy as a drug delivery device.[2]

As global healthcare consumers transition to ENFit-compatible devices per ISO recommendations, understanding the implications of dosing accuracy on medically fragile patients is increasingly important for appropriate post-marketing surveillance of adverse events.[3] Compromised dosing accuracy with these devices may contribute to unanticipated side effects or treatment failures.[2] When syringe systems compatible with ISO 80369-3 are used correctly, the risk of enteral tubing misconnections to intravenous devices is limited.[4] To preserve this low risk of misconnections, enteral device connectors for both nutrition and medications would ideally be the same. However, in the United States, male slip-tip oral and female ENFit-compatible syringes can be used for both oral and enteral administration.[1] Although the ISO standard (80639-3) is not intended to address oral administration devices, healthcare systems may choose to exclusively use ENFit-compatible syringes to minimize device inventory, potential for waste, and delays in therapy to accommodate need for doses available via both routes.[5]

We have previously described the differences in dosing accuracy between male slip-tip (legacy) syringes compared to a composite use of female low-dose tip (LDT) syringes (both enteral and oral applications).[2] Low-dose tip syringes were found to have a higher incidence of dosing variance exceeding the acceptable threshold (± 10% of intended dose) compared to male slip tips (Figure 1). Oral adapters, low dosing volume and smaller syringes were all associated with increased dosing inaccuracy. The prior analysis did not specifically differentiate between enteral and oral applications of the female syringes. Since the ISO standard only specifically dictates the use of enteral devices for enteral use, this study aims to determine whether there is a difference in dosing accuracy between the ISO 80369-3 intended use (enteral) and the oral application of ENFit LDT syringes.[2]

2 | METHODS

A dosing variance study of ENFit syringes and adapters compared to male slip-tip syringes was conducted at University of Florida Health Shands Hospital in conjunction with the University of Florida College of Pharmacy. This in vitro study evaluated Neomed ® ENFit syringes in four commonly available sizes (0.5 mL, 1 mL, 6 mL and 12 mL). The 12-mL ENFit ® syringe was used as a control for female syringe performance. Each syringe was filled according to the approved instructions for use, and each test condition was repeated three times to ensure consistency and reproducibility. Gravimetric analysis of the final dose delivered was completed by weighing a tared medication boat with the Mettler Toledo ® ME303E electronic scale for every test. Dosing variance was calculated for each test by dividing the difference between the actual volume and intended volume by the intended volume. Dosing variance exceeding 10% of the intended dose was considered unacceptable. Statistical analysis was completed using JMP Pro vs 13.0.0. Chi-square/Fisher's exact test, *t*test, ANOVA and descriptive statistics were used as appropriate. The full laboratory methods and results are available in a previous publication.[2]

In this secondary analysis, the route of administration (enteral versus oral) using the ENFit syringe system was evaluated. Preparation and administration conditions were reviewed and divided into enteral and oral applications (Table 1). Dispensing adapters tested included bottle cap adapters and the pharmacy straw, which is intended for use with medication cups or when an appropriate bottle cap adapter size is not available. All bulk bottle tests used a bottle cap adapter. Enteral conditions included the use of a pharmacy straw or no adapter. Oral adapters included the DoseMate® and DoseMate® DL, which are intended to be used for direct oral administration with ENFit® syringes. The DoseMate® is a rigid nipple-shaped device, and the DoseMate® is a pliable straw shape. Oral conditions included the use of available oral adapters as appropriate.

For low-risk medications, clinically acceptable dosing variance is generally up to 10% of the intended dose. For high-risk medications, this value decreases to variance up to 5% of intended dose, which aligns with the performance standard for intravenous syringes.[6,7] The primary outcome in this analysis was frequency of dosing variance >10% in enteral versus oral application of ENFit LDT syringes. Secondary outcomes included evaluation of standard female ENFit syringes and dosing variance >5% for both syringe types and both route applications.

3 | RESULTS AND DISCUSSION

3.1 | Dosing variance

A total of 264 test conditions were evaluated (enteral, n = 96; oral, n = 168). Of these, 210 specifically evaluated the ENFit LDT (enteral, n = 78; oral, n = 132). As described in Table 1, a total of 5 enteral and 7 oral conditions/combinations were evaluated. Results are presented in Table 2 and expressed as the number (%) of tests that exceed dosing variance (DV) of 10%. Enteral application of ENFit LDT syringes resulted in significantly more tests with DV >10% compared to oral use (26.9% vs 12.9%, $P = .01$). The standard ENFit did not show a difference between enteral and oral applications (0% vs 2.8%, $P = .4$).

When evaluating DV >5%, unacceptable variance increased from 26.9% to 42.3% ($P = .04$) for enteral and from 12.9% to 39.4%

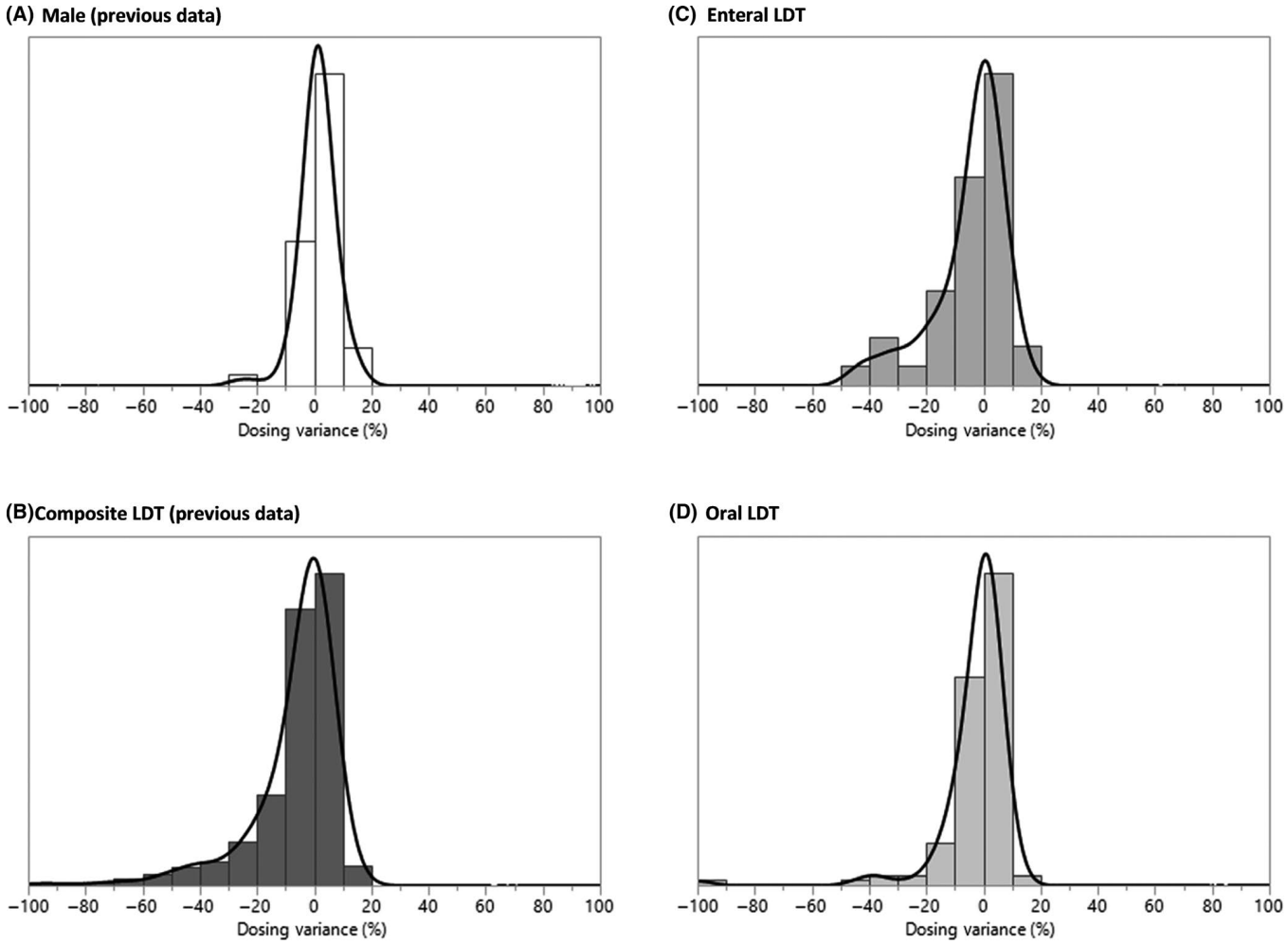

FIGURE 1 The dosing variance by syringe type and by intended route of administration. LDT, low-dose tip

TABLE 1 ENFit testing conditions evaluated

	Enteral		Oral	
	Dispense	**Administer**	**Dispense**	**Administer**
Medication cup	No adapter	No adapter	DM	DM
	Pharmacy straw	No adapter	DM-DL	DM-DL
			Pharmacy straw	No adapter
Bulk bottle	Bottle adapter	No adapter	Bottle adapter	DM
			Bottle adapter	DM-DL
Crushed tablet	No adapter	No adapter	DM	DM
	Pharmacy straw	No adapter	DM-DL	DM-DL

Abbreviations: DM, Dosemate; DM-DL, Dosemate-DL.

($P < .001$) for oral uses. Lowering the dosing variance threshold to 5% eliminated the difference seen with LDT oral use, revealing oral and enteral applications equally performed poorly ($P = .7$).

3.2 | Discussion

Although ENFit syringes were originally intended for enteral use only, many markets now have approval for enteral and oral use.[8] The low-dose tip (LDT) feature was added to the standard female syringe (6 mL and less) because of dosing accuracy concerns from the clinical community.[9,10] Although this feature was intended to enhance the safety of female syringes, peer-reviewed literature evaluating this premise is relatively absent. Our previous study evaluated the composite use of LDT syringes (enteral and oral) and showed that their use was associated with less dosing accuracy compared to male slip-tip syringes (25.9% vs 8.3%, $P < .0001$).[2] This was even more pronounced with the 0.5-mL LDT syringe, where

TABLE 2 Enteral and oral applications of ENFit syringes

Syringe type	DV > 10%, n (%)	*P*-value	DV > 5%, n (%)	*P*-value
Female LDT				
Enteral (n = 78)	21 (26.9)	.01	33 (42.1)	.7
Oral (n = 132)	17 (12.9)		52 (39.4)	
Female standard				
Enteral (n = 18)	0 (0)	.4	0 (0)	.2
Oral (n = 36)	1 (2.8)		2 (5.6)	

Abbreviation: DV, dosing variance.

nearly 40% of doses were outside of the acceptable range. Oral adapter use was also associated with increased risk of inaccurate dosing. Our current analysis demonstrates that the enteral application of LDT syringes results in nearly double the incidence of doses with unacceptable variance compared to specific oral applications. This is particularly concerning since the primary intended usage of these devices is via the enteral route. Based on the results of these two studies, significant dosing inaccuracy with LDT syringes appears to be related to a variety of conditions including enteral use, low dosing volumes, smaller syringe sizes, and use of oral adapters. Provider awareness of potential unsafe drug administration is critical, as device-related fluctuations in drug delivery may cause unexpected variation in patient response to therapy. Pinpointing syringe performance as the cause of inaccurate dosing may be difficult to prove retrospectively and may be missed by the uninformed provider attempting to reconcile an unexpected therapeutic response to a medication. Additionally, patients may experience different applications of the ENFit system across the healthcare continuum, ranging from strictly enteral use, a combination of enteral/oral use, to strictly oral use. Knowing the significant variations in dosing accuracy when switching between routes is critical for monitoring patient response to therapy.

Since there are currently no performance criteria specifically set for oral/enteral syringes, the clinician must discern acceptable variance ranges based on the medications and disease states of their patients. Narrow therapeutic index medications in high-risk populations may require a lower threshold for variance (± 5%) since dosing inaccuracy is more likely to result in significant patient harm.[7] Further complicating the safe and accurate use of ENFit syringes, oral liquid medications administered by caregivers have been shown to carry a high risk of device-dependent dosing inaccuracy.[11,12] Although there are several factors that impact the amount of drug absorbed via the enteral route, many clinically relevant medications have significant oral bioavailability or narrow therapeutic index spectrums, making dosing accuracy a critical component of enteral/oral dosing. Digoxin, cyclosporine, tacrolimus, and antiepileptic drugs are commonly prescribed oral medications with a narrow therapeutic index and high risk of error when administered incorrectly across all patient populations.[13,14] Medically complex patients of any age requiring enteral administration of medications are at risk of dosing inaccuracy when using devices that do not consistently perform as expected. The results of this study show unacceptably high rates of dosing inaccuracy for both oral and enteral applications of ENFit LDT syringes when held to a standard commonly applied to high-risk medications.

Currently in US healthcare systems, a single slip-tip syringe is utilized for preparation, dispensing and administration of oral liquid medications for both oral use and enteral use. In order to streamline the processes, most institutions would prefer to have one syringe type available to prevent waste and delays in medication preparation.[5] Medically complex patients, particularly neonates, may receive their medications enterally or orally depending on developmental stage, wakefulness at the time of administration, and ability to safely swallow liquids. Because of the interchangeability of routes, consistency between them is important. The presented results show variances between the routes lead to further opportunity for suboptimal outcomes due to inconsistent delivery of medication to these patients.

As healthcare providers, we seek safer and more efficacious ways to provide care when patient safety concerns are identified. Tubing misconnections represent a relatively small but significant source of medication errors in current health systems where interchangeability of luer connectors exists.[15] The Global Enteral Device Supplier Association (GEDSA) has recently announced its intention to stop production of legacy tubing and adapters in the United States via a stepwise fashion starting in 2020.[16] Although non-GEDSA manufacturers may choose to continue production of male orientation syringe device lines, this action may ultimately force conversion to ENFit in healthcare settings where the potential risks and incidence of dosing inaccuracy outweigh the frequency of enteral tubing misconnections. As the healthcare community continues to implement device-related processes to prevent tubing misconnections, front-line clinicians must be involved and assured that new potential sources of error not present in traditional systems are not introduced.

CONFLICT OF INTEREST

None declared.

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How to cite this article: O'Mara K, Campbell C. Dosing inaccuracy with enteral use of ENFit ® low-dose tip syringes: The risk beyond oral adapters. *J Clin Pharm Ther*. 2019;00:1–5. https://doi.org/10.1111/jcpt.13079