Optimizing Drug Delivery of Small-Volume Infusions

Kelli Thoele, MSN, RN, ACNS-BC, BMTCN®, OCN® ● Maria Piddoubny, PharmD, BCOP ● Ryan Ednalino, PharmD ● Colin L. Terry, MS

ABSTRACT

When administering intermittent secondary intravenous infusions, commonly referred to as intravenous *piggyback* (IVPB) infusions, residual medication remains in the administration set and bag. No previous studies exist examining the optimal technique to infuse the residual medication. The aims of this study were to identify various IVPB ancillary techniques used to administer medication residing in the secondary administration set and bag following an infusion, evaluate the potential drug loss associated with each technique, and recommend a standard ancillary technique for administration of select small-volume IVPB infusions. Qualitative and quantitative tests were performed, leading to a recommendation for a standard ancillary technique for select small-volume IVPB infusions.

Key words: biotherapy, chemotherapy, infusion, intravenous, piggyback

Intravenous (IV) infusion is the most common route of administration for biologic therapy and chemotherapy. Additionally, intravenous piggyback (IVPB) infusion is the primary route of administration for inpatients receiving antibiotics.[1] Because of the risks associated with medication dosing errors, including reduced efficacy and increased mortality, interprofessional teams must collaborate to optimize drug delivery, minimize risk for error, and support safe practices.[2-5] The increasing use of small-volume infusions has emphasized the potential clinical impact of drug loss during administration, necessitating standardized infusion practice to optimize drug delivery to prevent underdosing as well as prevent inconsistencies in clinical trials. Investigators of this study defined small-volume infusions as those being less than or equal to 50 mL in total volume.

IVPB administration of small-volume infusions carries a risk of significant drug loss in the secondary administration set. At the completion of an IVPB infusion, the secondary administration set may retain as much as 7 mL of drug volume,[6] 14% of a 50-mL IVPB at this institution. When considering minimum inhibitory concentration (MIC)-dependent medications, medications with narrow therapeutic index, and medications given in the curative setting, the potential for clinical impact is concerning, especially in the setting of small-volume infusions.

The Oncology Nursing Society (ONS) recognizes underdosing of chemotherapy as a type of medication error, and the Infusion Nurses Society (INS) states that the standardization of drug administration is a recommended strategy to minimize the risk of errors. Neither the ONS chemotherapy/biotherapy guidelines nor INS' *Infusion Therapy Standards of Practice* address potential drug loss in IVPB administration sets or recommend a standard administration technique.[7,8]

Because of the absence of evidence supporting optimal infusion practice related to small-volume infusions, a large academic health care system in the Midwest had withheld from establishing standard infusion protocols.

Author Affiliations: *Indiana University Health, Indianapolis, Indiana (Ms Thoele, Dr Ednalino, and Mr Terry); and Thomas Jefferson University Hospital, Philadelphia, Pennsylvania (Dr Piddoubny).*

Kelli Thoele, MSN, RN, ACNS-BC, BMTCN®, OCN®, *is a clinical nurse specialist at Indiana University Health in Indianapolis, Indiana. She is interested in evidence-based practice and safe handling of hazardous drugs.* **Maria Piddoubny, PharmD, BCOP,** *is a PGY-2 graduate of Indiana University Health in Indianapolis, Indiana, now working as a hematology/oncology patient care pharmacist at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania. Her interests include chemotherapy medication safety and translational research in oncology genomics.* **Ryan Ednalino, PharmD,** *is a medication safety clinical pharmacist for Indiana University Health. He oversees medication safety initiatives across the multifacility hospital system. He serves on pharmacy and therapeutics and multiple system medication safety committees.* **Colin L. Terry, MS,** *is a biostatistician and serves as program manager for data services at Indiana University Health in Indianapolis, Indiana. He consults and collaborates on a wide variety of research projects and serves on several institutional boards as a lead statistical reviewer.*

The authors of this article have no conflicts of interest to disclose.

Corresponding Author: *Kelli Thoele, MSN, RN, ACNS-BC, BMTCN®, OCN®, Indiana University Health Simon Cancer Center, RM C3226D, 1030 West Michigan Street, Indianapolis, IN 46202 (kthoele@IUHealth.org).*

DOI: 10.1097/NAN.0000000000000268

As a result, technique was found to vary within the health care system. The interprofessional chemotherapy safety committee identified the potential for standardization of practice regarding the infusion of small-volume chemotherapy and biotherapy.

The aim of this study was to determine the amount of drug that remained in the administration set following various ancillary administration techniques used by nursing staff throughout the system to minimize residual drug left in the administration set. Additional aims were to evaluate the implications of each ancillary technique and recommend a standard ancillary technique for the administration of the residual volume of select small-volume infusions. Ancillary administration techniques were defined as the methods used to infuse the residual drug remaining in the secondary administration set at the completion of IVPB infusion.

METHODS

A thorough search of the literature revealed a lack of evidence or published guidelines for the administration of residual drug following an IVPB infusion. An assessment of current practice in the oncology unit, where many critical drugs are administered as small-volume infusions, was performed through direct observations and discussions with staff. It was observed that because of lack of standardization, practice varied throughout the system. Manipulation of the administration set is limited because of the hazardous nature of chemotherapy, but 2 prevalent ancillary techniques were identified: (1) occlude the primary administration set until the majority of the drug in the secondary administration set entered the primary tubing, and (2) lower the secondary bag below the level of the primary bag and allow fluid from the primary bag to flow into the secondary administration set, then infuse the diluted residual medication. For the purposes of this study, these ancillary techniques are referred to as the *pinch technique* and the *backflush technique*, respectively.

After identification of the 2 most prevalent ancillary techniques, 10 oncology nurses were observed using the pinch technique, and 10 different oncology nurses were observed using the backflush technique. Nursing practice was observed to be consistent with the pinch technique, with each nurse occluding the primary tubing until the fluid in the secondary tubing was within 1.5 cm of the needleless connector. The amount of nursing time required to pinch the administration set was timed during the study, with an average of 2 minutes 9 seconds. In contrast, variability was observed among nurses using the backflush technique. The amount of fluid used to backflush ranged from 14 to 52 mL with an average volume of 26.7 mL. The amount of nursing time required to backflush was also recorded. Time ranged from 5.5 to 30.4 seconds, with an average of 12.9 seconds.

A preliminary dye study was performed to visually evaluate efficacy of each ancillary technique. This qualitative study suggested that the pinch technique was more effective than the backflush technique based on visual assessment of improved dilution. A follow-up quantitative analysis using the ancillary techniques identified was performed using vancomycin. Residual vancomycin volumes and concentration levels were assessed to determine the amount and percentage of drug remaining.

Quantitative Analysis

An in vitro quantitative analysis was conducted using 15 IVPB infusions. Each IVPB contained 25 mg of vancomycin in 100 mL of 0.9% NaCl. This allowed each IVPB to start with an equivalent concentration of 250 mcg/mL. This concentration was selected to ensure that the remaining fluid after each method would yield results within the laboratory reportable range of 2 to 50 mcg/mL. Because of the variability of backflush volume noted during preliminary nursing technique observations, 2 separate volumes were assessed for the backflush technique.

Vancomycin IVPB infusion procedure: (1) 0.9% NaCl was used to prime the primary administration set (Alaris REF 2420-0500; Becton Dickinson [BD], San Diego, CA); (2) vancomycin from the secondary bag was used to prime the secondary administration set (Alaris REF 72213N; BD, San Diego, CA); (3) the secondary bag was placed on a hook on the IV pole, and a fully extended hanger from the secondary administration set was used to hang the primary bag; (4) the secondary tubing was connected to a needleless connector on the primary administration set; (5) using an Alaris IV pump (BD, San Diego, CA), the vancomycin was infused until the secondary infusion was complete and the primary fluid started infusing; and (6) after infusion of the vancomycin, either the pinch technique or the backflush technique was used to infuse the residual medication in the secondary administration set (Table 1, Figure 1).

Each ancillary technique was completed 5 times. After each infusion was completed, the remaining fluid in the secondary administration set was drained into an empty medicine cup via gravity. An empty syringe and needle were used to draw up the fluid to measure the volume recorded. This fluid was then injected into a laboratory tube (Vacutainer REF 367878; BD, Franklin Lakes, NJ) and sent to the hospital laboratory to determine the concentration of vancomycin in the remaining volume.

Statistical Methods

The amount of drug remaining in the administration set post IVPB infusion was summarized by a technique using mean and standard deviation. The amount of remaining drug was compared across techniques using analysis of variance. Post hoc testing between individual techniques was performed using Tukey's honest significant difference test with a family error rate $\leq .05$. Additionally, the amount of residual drug was displayed using box-and-whisker plots.

TABLE 1

Ancillary Techniques for Administering Residual Volume Following an Intravenous Piggyback Infusion of Vancomycin

Pinch Technique	Backflush Technique
1. Alaris pump programmed to infuse at 100 mL/h	1. Alaris pump programmed to infuse at 100 mL/h
2. Once the secondary medication bag stopped infusing, a coinvestigator occluded the primary tubing between the primary bag (ie, 0.9% NaCl) and the needleless connecter until the vancomycin volume in the secondary bag was within 1.5 cm of the needleless connector	2. Once the secondary medication bag stopped infusing, a coinvestigator lowered the secondary bag below the level of the primary bag[a]
3. Coinvestigator released the primary administration set and allowed the primary fluid to flow into the secondary administration set filling the volume that would otherwise have been residual drug	3. Allowed gravity[a] to pull about 25-50 mL of base fluid from the primary bag into the secondary administration set and bag, allowing the residual drug to be diluted
	4. Placed the secondary bag back on the hanger and allowed the diluted drug to infuse

[a]For consistency in the vancomycin study, rather than backflush with an uncertain volume of base fluid, the coinvestigator disconnected the secondary administration set at the completion of infusion and injected either 25 or 50 mL into the bottom of the administration set simulating a gravity backflush. The secondary administration set was then reconnected to the primary administration set, and the Alaris pump was restarted at 100 mL/h. The time required to disconnect the secondary tubing and inject fluid was not included in the time measurement for the backflush method.

Abbreviations: cm, centimeters; h, hour; mL, milliliters.

In these plots, the median value for each group is represented by the bold line within the box, while the box is defined by the first and third quartiles (Figure 2).

RESULTS

The results for all measures of remaining volume and drug post IVPB infusion are found in Table 2, and a graphical display of the remaining drug for each technique is presented in Figure 2. The volume of fluid remaining in the administration set was similar for each of the techniques. The amount of remaining drug varied relatively little within each technique; however, there were large differences between techniques. The mean amount of remaining drug was 17.8 mcg for the pinch technique, 44.0 mcg for the 50-mL backflush technique, and 106.0 mcg for the 25-mL backflush technique. These measures were found to be significantly different across techniques ($P < .001$). Post hoc testing detected significant differences between the pinch technique and both of the backflush techniques, and a significant difference was found between the 50-mL backflush technique and the 25-mL backflush technique.

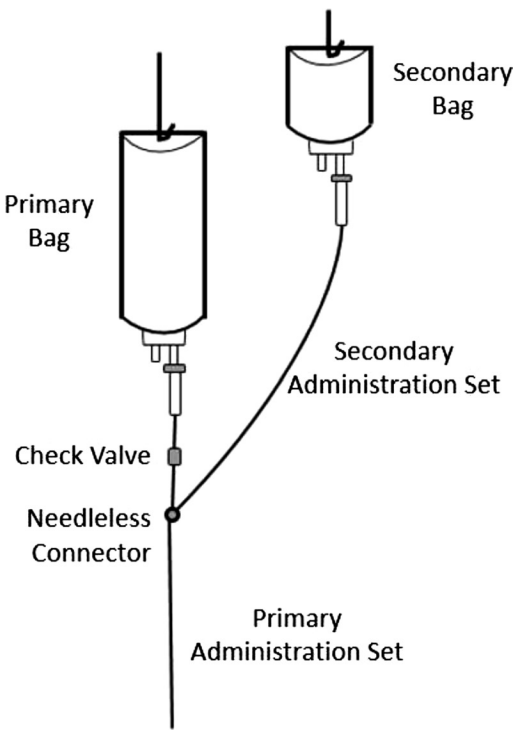

Figure 1 Intravenous pole setup for small-volume infusions. The secondary bag contains a small-volume dose of medication, and the primary bag contains only 0.9% NaCl.

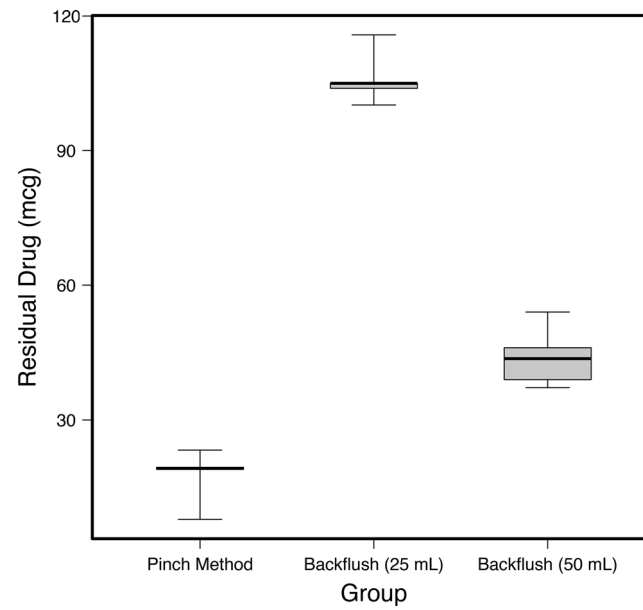

Figure 2 Residual drug measured in the administration set after each IVPB infusion technique. *Abbreviation: IVPB, intravenous piggyback.*

TABLE 2

Quantitative Analysis of Administration Techniques

Sample	Technique	Volume Remaining (mL)	Concentration Remaining (mcg/mL)	Remaining Drug (mcg)	% Remaining of Original Dose[a]
A1	Pinch	2.4	9.7	23.3	0.09%
A2	Pinch	2.6	7.3	19.0	0.08%
A3	Pinch	1.6	4.9	7.8	0.03%
A4	Pinch	2.7	7.2	19.4	0.08%
A5	Pinch	2.0	9.6	19.2	0.08%
Mean (SD)	Pinch	2.3 (0.5)	7.7 (2.0)	17.8 (5.8)	0.07 (0.02)
B1	Backflush (25 mL)	2.8	37.1	103.9	0.42%
B2	Backflush (25 mL)	2.8	37.5	105.0	0.42%
B3	Backflush (25 mL)	3.0	38.6	115.8	0.46%
B4	Backflush (25 mL)	2.7	37.1	100.2	0.40%
B5	Backflush (25 mL)	2.6	40.4	105.0	0.42%
Mean (SD)	Backflush (25 mL)	2.8 (0.1)	38.1 (1.4)	106.0 (5.8)	0.42 (0.02)
C1	Backflush (50 mL)	2.6	16.8	43.7	0.17%
C2	Backflush (50 mL)	2.7	20.0	54.0	0.22%
C3	Backflush (50 mL)	2.4	15.5	37.2	0.15%
C4	Backflush (50 mL)	2.9	15.9	46.1	0.18%
C5	Backflush (50 mL)	2.5	15.6	39.0	0.16%
Mean (SD)	Backflush (50 mL)	2.6 (0.2)	16.8 (1.9)	44.0 (6.6)	0.18 (0.03)

[a]Original dose = 25 mg.
Abbreviations: mcg, microgram; mg, milligram; mL, milliliters; SD, standard deviation.

The percentage of remaining drug in each bag suggested a high level of precision delivery for each ancillary technique (Table 2). However, as predicted, the backflush technique only offered consistent precision if the same volume was used for each flush, with limited variability within each backflush volume group. The pinch method demonstrated precision and consistency, as well as the greatest accuracy in drug delivery.

DISCUSSION

The majority of chemotherapeutic agents, along with select antibiotics, may be classified as having a narrow therapeutic index for which the optimal balance between efficacy and unacceptable toxicity must be meticulously achieved.[9] The use of varying techniques of IVPB residual medication administration for small-volume infusions has the potential to introduce significant variability between the dose ordered and the amount received by the patient.

Pharmacokinetic and pharmacodynamic studies encompassing various antibiotic and chemotherapeutic agents have shown that reduced doses are associated with suboptimal therapeutic outcomes and increased potential for mortality, with much of the supporting literature stemming from trials evaluating dosing in obese patients.[2,3,5] With many oncology clinical trials involving monoclonal antibodies, straight drugs (eg, paclitaxel protein-bound), and other small-volume infusions, there is an unmet need to standardize the administration of these medications for therapeutic efficacy as well as the need for consistent research. Additionally, these concerns may be beneficial to address in other areas such as infectious disease, where there are increasing rates of antibiotic resistance. In such areas, optimizing dosing may improve drug concentrations for bacterial infections displaying elevated MIC.[5]

To minimize residual drug loss during administration, the use of an optimal and consistent ancillary technique is essential. The average volume remaining in the secondary administration set at the completion of the pinch or backflush method was 2.6 mL. If neither ancillary technique were used and 2.6 mL of undiluted drug were lost in the tubing, this would represent 5.2% of a 50-mL infusion. This contrasts with an average of 0.07% to 0.42% drug lost using the pinch and backflush techniques. The pinch technique was found to be associated with the most dilute residual concentration. Based on the concentrations of residual drug with each method, it was estimated that the backflush method could produce similarly diluted residual concentration if a volume of 125 mL was used to backflush.

In addition to the quantitative results of this study, there are other considerations when administering IVPB medication. The pinch technique had less variability among nurses and did not add significant time to the infusion for the patient; however, this method required 2 minutes 9 seconds of direct nursing time to occlude the primary tubing during the study. The backflush technique required less nursing time, at an average of 12.9 seconds, but had great variability among nurses and prolonged the duration of the infusion by as much as 30 to 60 minutes. After evaluating the efficacy of each ancillary technique and the considerations on workflow and time requirements, the interprofessional chemotherapy safety committee recommended the pinch technique as standard practice for flushing small-volume chemotherapy and biotherapy.

With an increasing number of small-volume infusions used in practice and coming to market, the need for precision in administration has become more apparent. The findings of this quantitative study may allow clinical trial investigators to recommend or require a specific administration technique for studies assessing the efficacy of small-volume infusion medications.

Limitations of this study include an unclear clinical impact of standardizing ancillary technique, lack of variability with IV administration setup, and use of a nonvalidated technique to test vancomycin concentration. The clinical significance of these findings is dependent on multiple variables, including but not limited to the disease state, drug, and infusion volume. In clinical practice, IV administration setup including the size of the secondary bag, amount of fluid remaining in the primary bag, and distance between the primary bag and secondary bag may all influence the volume of medication remaining in the secondary tubing. Our study controlled for variation in IV administration setup and may not represent all potential infusion administration setups. Vancomycin is one of the most studied antibiotics and is frequently dose-adjusted on the basis of serum drug levels.[4] Although levels exhibited predicted precision, assessing vancomycin concentrations in 0.9% NaCl is not a validated technique.

CONCLUSION

The residual volume of medication following IVPB infusion accounts for a significant percentage of the prescribed dosage when considering small-volume infusions. Because of a lack of evidence to support a particular technique, this study was performed to evaluate the efficacy of 2 common administration techniques. The pinch technique, despite requiring more direct nursing time, was the recommended ancillary technique for small-volume chemotherapy and biotherapy infusions because of the consistent demonstrated ability to infuse over 99% of the prescribed dosage and the negligible impact on overall infusion time.

REFERENCES

1. Sevinç F, Prins JM, Koopmans RP, et al. Early switch from intravenous to oral antibiotics: guidelines and implementation in a large teaching hospital. *J Antimicrob Chemother*. 1999;43(4):601-606.
2. Tavitian S, Denis A, Vergez F, et al. Impact of obesity in favorable-risk AML patients receiving intensive chemotherapy. *Am J Hematol*. 2016;91(2):193-198.
3. Colleoni M, Li S, Gelber RD, et al. Relation between chemotherapy dose, oestrogen receptor expression, and body-mass index. *Lancet*. 2005;366(9491):1108-1110.
4. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66(1):82-98.
5. Aminzadeh Z, Yadegarynia D, Fatemi A, Tahmasebian DE, Armaki AS. Vancomycin minimum inhibitory concentration for methicillin-resistant Staphylococcus aureus infections; is there difference in mortality between patients? *Jundishapur J Microbiol*. 2014;7(10):e12831.
6. Secondary 77213N. BD Infusion Disposables Catalog. https://catalog.carefusion.com/infusiondisposables/secondary-35487.html. Published May 2016. Accessed May 31, 2016.
7. Polovich M, Olsen M, LeFebvre K. *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*. 4th ed. Philadelphia, PA: Oncology Nursing Society; 2014.
8. Gorski L, Hadaway L, Hagle ME, McGoldrick M, Orr M, Doellman D. Infusion therapy standards of practice. *J Infus Nurs*. 2016;39(suppl 1):S1-S159.
9. Schilsky RL, Schenkein DP, Wilson WH, Jernigan CL, Woodcock J. Re-evaluating criteria for accelerated approval. Conference on Clinical Cancer Research, Washington, DC; November 2012.