Assessing Carrier Fluid Effects on Low Flow Drug Infusions

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Background

Neonates and pediatric patients who are critically ill depend on reliable drug delivery for resuscitation, often requiring multiple low flow medication infusions. The requirements to stabilize this vulnerable population are significantly limited by body mass and limited vascular access secondary to narrow vasculature. These limitations increase the risk of co-morbidities such as cardiopulmonary disease, renal dysfunction, or volume overload, which may already be the underlying etiology of their initial disease process.

Given the limitations on volume, these titratable infusions are often concentrated medications that require low flow infusions concurrent with a maintenance fluid.

Delivery of an intravenous drug with carrier fluid has been shown to be unreliable in extremely low birth weight neonates likely due to poor mixing at the connection, which can cause delays or incomplete delivery of the drug.[3,4] This discrepancy demonstrated that neonates weighing 0.5 kg received only 60% of the intended drug dose at 60 minutes and only 70% at 75 minutes.[3]

We previously demonstrated that syringe size is directly proportional to variability of low flow infusions.[1] We subsequently found greater drug concentrations and total infused drug during 30-90 minutes of infusion with 3- and 10-mL syringes compared to 60-mL syringes.[2] During this previous study, our team noticed significant backward flow which was not anticipated but has been previously reported in the literature, specifically when there are multiple infusions and add-on devices.

Objectives

- Determine whether a higher carrier fluid rate reduces the variability of low flow drug infusion
- Determine whether backward flow of drug into primary infusion tubing contribute to drug administration error

Methods

- Absorption spectrophotometry was used to assess blue food dye concentration curves. Starting drug concentration was empirically set at a dye dilution of 1:16 in yellow dyed normal saline.
- We used our previously described drug infusion model updated with a Bifuse connector per our current NICU standard practice
- Diluted blue food dye was infused as drug from a 10-mL syringe via a smart syringe pump. Carrier fluid was infused via a smart infusion pump.
- Drug concentrations in fold dye dilution were assessed every 5 minutes using two in-line spectrophotometers at the Bifuse carrier fluid tubing and distal T-connector.
- For all trials, drug flow was set at 0.2 mL/hr based on a standard epinephrine concentration of 40 mcg/mL and dose of 0.1 mcg/kg/min for an hypothetical 1.3 kg infant.
- Carrier flows were tested at 1, 3, and 5 mL/hr.
- Single-factor ANOVA, Tukey's honest significant difference (HSD) and Levene's test were performed using QI Macros 2019 software to compare steady-state drug delivery and variance.

Results

- Calibration curves for spectrophotometric dye measurements demonstrated excellent fit with $R^2 = 0.99$ and 0.93.
- All trials reached steady-state flow by 30 minutes or time interval 6.
- Infusions were analyzed from 30 to 60 min.
- **Drug delivery rates per hour mean were 13, 21, and 30** (units of fold dilution multiplied by volume infusion x 1,000) for 1, 3, and 5 mL carrier rates, respectively (single factor ANOVA $p < .001$, Tukey's HSD $p < .001$ for all pairwise comparisons).
- Variances of steady-state drug delivery **were 4.5, 6.4, and 8.4 (Levene's test p = 0.69) for 1, 3, and 5 mL carrier rates**, respectively.
- Analysis of blue absorption in the distal line at interval 0 across trials revealed no significant trend.
- No significant blue absorbance was detected in the Bifuse carrier tubing for any carrier infusion rate.

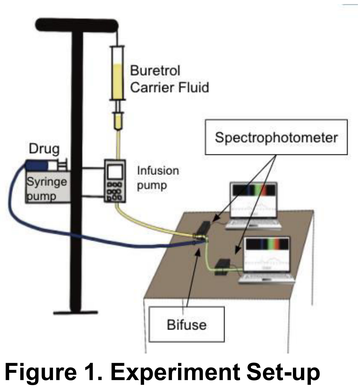

Figure 1. Experiment Set-up

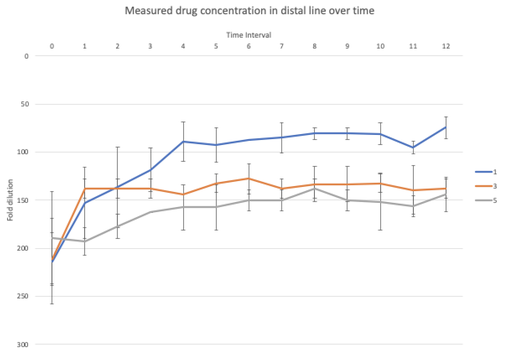

Figure 2. Measured drug concentration and standard deviation over time

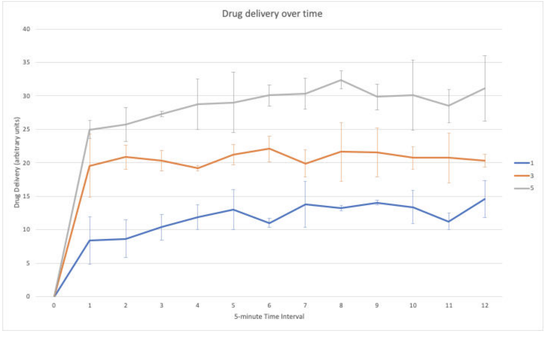

Figure 3. Drug delivery concentration and standard deviation over time

Conclusions

- Our drug model is the first reported novel method of 2 location in-line absorption spectrophotometry.
  - This novel method was validated using calibration curves and found yield consistent results across experiments.
- Total drug delivery was proportional to carrier fluid rate in our low flow drug model.
  - Not accompanied by progressive staining of tubing by blue dye.
  - Higher than expected drug delivery occurred at higher carrier fluid rates.
- Variances and thus, consistency, of drug delivery were similar.
- In contrast to our previous model, use of a Bifuse prevented backward flow of drug into the carrier line.
- When necessary, lower carrier rates may be safely used if drug dosage is empirically adjusted to effect.

Next Steps/Significance

- This encourages considering lower carrier rates which can lower total amount of fluid delivery to hospitalized patients and overall cost.
- Determine whether low flow drug infusions generate a Venturi effect causing higher drug delivery at higher carrier fluid rates.
- Establish similar drug delivery in different set ups including multiple infusions.
- Identify a novel way of directly measuring drug concentration in-line.

Acknowledgements (and/or References)

Thank you to my SOC Members: Audrey Kamzan MD, Kalpashri Kesavan MD, my Program Director: Deepa Kulkarni MD, and additional support: Grace Sund RN, Melanie Lam PharmD, Julie Sasinski RN

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