A Method for Simulating Clinical Use of Luer Valve Disinfectant Caps for Estimating a Worst-Case-Exposure-Dose of Isopropyl Alcohol (IPA) in Neonatal Intensive Care Unit (NICU) Patients

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Abstract

Isopropyl alcohol (IPA)-filled caps are single-use devices that attach to luer access valves (LAV). The IPA-filled caps are intended to be used to disinfect and provide a physical barrier to contamination of the LAV. Previous studies have simulated clinical use of IPA caps in neonatal intensive care units (NICUs) and reported altered appearance of luer valves, as well as excess IPA quantity in saline infusates. In the present study, a mock central line circuit and drug infusion protocol were developed to simulate worst-case use of IPA-filled disinfectant caps and estimate a maximum blood concentration of IPA and its metabolite acetone (ACT) that might occur in NICU patients. The mock drug infusion protocol was based on a worst-case clinical use scenario, as determined using survey information from NICUs, and included the following steps: (1) incubating LAV with IPA caps at 37°C, (2) hourly drug infusions, and (3) wiping proximal end of the LAV with a commercially available medical IPA impregnated pad after cap removal, as well as before subsequent attachment of a fresh IPA-filled cap. The control and test groups were the LAV + IPA pad only and LAV + IPA disinfectant cap + IPA pad, respectively. The quantity of IPA in collected infusates was determined by head-space gas chromatography with flame ionization detector. IPA concentrations in infusates were used to estimate the blood concentrations of IPA and ACT in NICU using pharmacokinetic modeling and simulations for four hypothetical clinical use scenarios (6, 12, 18, and 24 intravenous (*i.v.*) pushes hourly) that would result in 6, 12, 18, and 24 caps used in a single day. Simulating twenty-four *i.v.* pushes hourly resulted in measured IPA concentration that were up to 20x higher in IPA disinfectant cap infusates compared to the IPA pad alone. Based on the pharmacokinetic model, hourly *i.v.* pushes predicted accumulation of IPA in neonatal blood that were higher with disinfectant cap use compared to IPA pad alone.

Introduction

IPA-filled disinfectant caps are single-use devices that attach to needleless LAVs that permit general intravenous (IV) administration of drugs into patients. The IPA-filled caps are intended to be used to disinfect and provide a physical barrier to contamination of the LAV.

Clinical use of a catheter and LAV to access circulating blood is associated with Central Line Associated Blood Stream Infections (CLABSI), which is a bloodstream infection unrelated to infection at another site. Prevention of CLABSI in hospitalized patients, including NICUs, is considered most effective when a combination of interventions is used and implemented correctly and reliably.

Sauron *et al.* (2015) conducted a laboratory bench simulated-use study to investigate whether NICU patients could be exposed to IPA from the use of disinfectant caps. The investigators simulated the use of the disinfectant and two LAVs (i.e., SmartSite and CARESITE). The investigators reported no detectable IPA when an IPA wipe alone was used; whereas, the concentration of IPA in infused saline of the SmartSite LAV test samples were 6x to 10x higher compared to infused saline of the CARESITE LAV. Sauron et al. (2015) concluded "*Although the use of isopropyl alcohol impregnated disinfection caps has proved to be beneficial in reducing central line associated bloodstream infections rates in the literature, the presence of significant amounts of isopropyl alcohol in the line when the SwabCap was used, in this study, seems unsafe for term and preterm neonates.*"

In this study, we developed and applied a simulated-use approach for predicting worst-case concentration of IPA and ACT in NICU patient blood.

Materials and Methods

Test Circuit: A model circuit was constructed from the following:

(a) 40-mL sample collection vials

(b) Needle-less SmartSite™ or MicroClave™ LAVs

(c) Y-connector set with 2 ports

(d) Crimps to close tubing.

Simulated-Use Protocol: Simulating clinical use of IPA cap included:

(a) Attaching an IPA cap to LAV hub and incubation at 37oC for 1 hour

(b) Swiping LAV hub with an alcohol swab for 20 sec and waiting 20 sec to allow alcohol to evaporate

(c) Connecting pre-filled needless syringe to LAV hub and injecting 0.5mL (pre-flush) saline

(d) Connecting a second and third pre-filled syringe to the LAV hub and injecting 0.3mL saline (*i.v.* push) and 0.5mL saline (post-flush), respectively

(e) Attaching a fresh disinfectant cap to the LAV hub

Worst-Case Clinical Use Scenario: Simulated-use "injections" were performed hourly for a total of 24-hourly injections.

Quantification of IPA: Infusates were collected and analyzed for IPA by gas-chromatography (GC) and flame ionization detector (FID) using a modified USP<467> method.

Exposure Estimation: A 2-compartment pharmacokinetic model to describe IPA and ACT distribution in a 2-month old neonate was developed and calibrated using available pharmacokinetic data (Parker and Lera 1992). The calibrated model was used to predict IPA and ACT blood concentrations for simulated-use scenarios (6, 12, 18, and 24 hourly *i.v.* injections) based on experimentally measured IPA concentration for SmartSite™ and MicroClave™ valves with alcohol wipe + disinfectant caps (Test) versus alcohol wipes alone (Control).

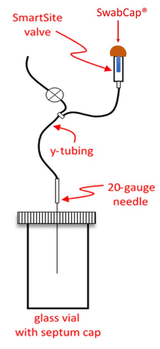

Figure 1. Test Circuit

Results and Discussion

Concentration of IPA in Collected Infusates (Table 1):

Simulating the use of alcohol wipe + disinfection caps for SmartSite™ valves resulted in 20x greater IPA concentration in collected saline infusates compared to use of an alcohol wipe alone. For MicroClave™ valve, IPA concentration in collected saline infusates were 16x greater compared to use of an alcohol wipe alone. Concentration of IPA in saline infusates was relatively greater for SmartSite™ compared to MicroClave™ valves.

Table 1. SmartSite™ or MicroClave™ Luer valves incubated with disinfection caps containing 70% IPA for 1 hour prior to simulated hourly infusions. Saline served as a solvent control when analyzing by HS-GC-FID.

Sample	Sample	Mean (µg/mL)	Standard Deviation
Procedure Day 1	Alcohol Wipe Alone	85 (n=3)	50
	SmartSite™	**1651** (n=10)	154
Procedure Day 2	Alcohol Wipe Alone	29 (n=3)	15
	MicroClave™	**466** (n=10)	44

*Concentration in the vial (not a blood concentration).

Pharmacokinetic (PK) Calibration (Figure 1):

Model predicted serum concentrations of isopropyl alcohol (IPA, triangle) and acetone (ACT, circle) align with real-world reported blood concentrations of a 2-month-old infant (solid line).

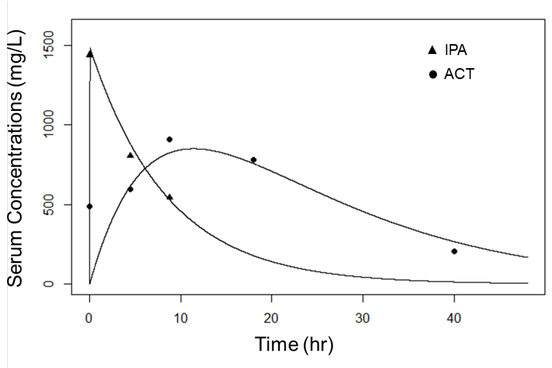

Figure 1. Predicted serum concentrations of IPA and ACT using the calibrated PK model informed by literature-derived input parameters is shown in comparison with pharmacokinetic observations obtained from accidental IPA poisoning data in a 2-month old infant.

PK Model Predicted Exposure Estimates (Figure 2):

The PK model predicts multiple hourly injection could result in a cumulative increase in IPA or ACT concentration in blood.

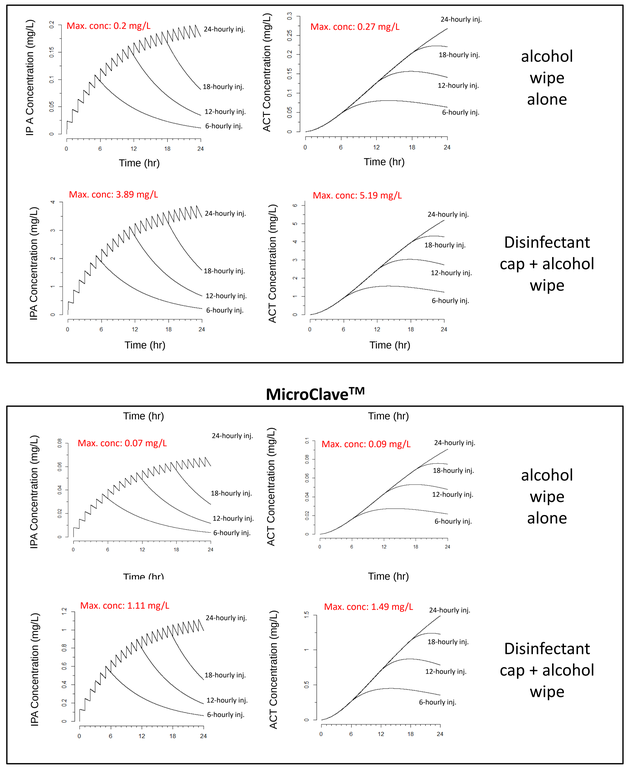

Figure 2. Predicted IPA and ACT blood concentration data in a 2-month old neonate and four use scenarios (i.e., 6, 12, 18 & 24 hourly injections in a day).

Conclusion

Designing a simulated-use study requires detailed knowledge of disinfectant cap clinical use that may not be apparent in the instructions for use.

The PK model predicts use of disinfection caps may result in higher IPA and ACT blood concentrations in NICU patient populations compared to use of alcohol wipes alone.

This exposure estimation approach may be useful for understanding the potential risks associated with disinfectant cap use.