In-vivo evaluation of simultaneous administration of incompatible drugs in a central venous catheter with a decreased port to port distance

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Background: Multilumen catheters are commonly used in critically ill children. Their use, however, is associated with significant morbidity. We studied the simultaneous administration of incompatible drugs using a new triple-lumen catheter with decreased length and port to port distances.

Methods: Ten domestic swine, 10–20 kg in weight, were divided into two groups of five. Total parenteral nutrition was administered through the distal port and phenytoin was administered as a bolus and as an infusion in each group. Samples were taken from two sites during the bolus and at 1, 5, and 15 min during phenytoin infusion. Histograms were generated for particle size and concentration. Samples were also examined under the microscope for particles.

Results: Histograms of particle size did not show any alteration of the histogram that would suggest particle size $>2\,\mu m$ in diameter in the study or control samples. No particles were identified by phase microscope, light microscope, or Wright stain smear.

Conclusions: The use of a triple-lumen catheter with a distance of 0.4 cm between the proximal port and the medial port and 1.3 cm between the medial port and the distal port, for the *in vivo* simultaneous administration of incompatible solutions does not result in precipitates large enough to cause adverse clinical effects.

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Introduction

A multilumen central venous catheter is the preferred vascular access route for critically ill patients requiring multiple drug infusions, parenteral hyperalimentation, and other potentially incompatible drugs [1]. The complexity of delivering these substances becomes more difficult when the size and length of the catheter is limited, as in the pediatric population. A previous study has shown that *in vivo* simultaneous intravenous infusion of physically incompatible substances through a commercially available multiple lumen intravenous catheter, double-lumen peripheral venous catheter (IV-01100, Arrow International, Reading, Pennsylvania, USA) did not cause precipitation in the vascular system or other adverse clinical effects [2].

This study looked at a modified 5.5 F × 5 cm, triple-lumen catheter with a port distance of 0.4 cm between the medial and proximal ports and 1.3 cm between the distal and medial ports (Arrow International), with a total distance of 1.7 cm between the distal port and the proximal port, to assess if decreased port spacing between lumens causes precipitation when incompatible intravenous solutions are administered simultaneously.

Materials and methods

Ten domestic swine weighing 10–20 kg were anesthetized with ketamine 10 mg/kg intramuscularly, atropine 0.01 mg/kg intravenously, and isoflurane for continuous anesthesia. The trachea was intubated with a #5 or #6 uncuffed endotracheal tube and controlled ventilation was instituted to maintain normal blood gases. A lead II electrocardiogram was monitored continuously along with temperature, respiration, and blood pressure. A peripheral vein was isolated and cannulated for fluid and anesthetic administration as necessary during the experiment. The femoral veins in both hind limbs were isolated by the cut-down technique. The experimental triple-lumen catheter, with decreased port to port distances, was inserted into the right femoral vein, and the control catheter was

inserted into the left femoral vein under direct visualization. The control catheter was a 5.5 F × 5 cm, triple-lumen catheter with a standard port distance of 1.6 cm between the proximal and medial ports and 1.6 cm between the medial and distal ports respectively, for a total distance of 3.2 cm between the distal port and the proximal port (Arrow International). The size of the lumens is 20 gauge for the distal lumen, and 22 gauge for the medial and proximal lumens. Placement was confirmed by aspiration of blood from all ports.

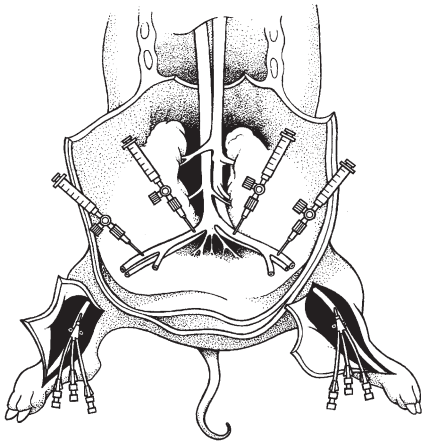
A midline incision was made, the peritoneum was identified, and the incision was extended to isolate and retract peritoneal contents exposing the retroperitoneal vasculature. The iliac vessels and the inferior vena cava were dissected and isolated. Sampling sites were identified immediately distal to the catheter tip and one catheter length distal to the first sampling site. An 18-gauge catheter with a three-way stop-cock was inserted at each sampling site (Fig 1). Hematocrit was between 35% and 45% during the experiment.

Phenytoin and total parenteral nutrition (TPN) were shown to be incompatible *in vitro* in a previous study [3]. A solution of phenytoin with a concentration of 50 mg/ml and pH 12 as evaluated on a pH meter (255 Ph/ISE, CIBA Corning Diagnostics, Oberlin, Ohio, USA) was administered to all animals ($n = 10$) through the distal lumen at the usual maintenance dose of 2.5 mg/kg/dose at a rate of 1 mg/kg/min up to a maximum of 50 mg/min via a syringe infusion pump (1001, Medfusion Systems, Norcross, Georgia, USA). The bolus was followed by a 3 ml normal saline flush. The TPN solution (Table 1), with a pH of 5.8, was administered simultaneously through the medial lumen at the standard clinical maintenance rate calculated in ml/kg/day and divided over a 24-h period using the same syringe infusion pump system. In the second phase of the experiment, the same procedure described above was performed with the phenytoin solution administered through the medial lumen and the TPN administered through the distal lumen. In the final phase, the phenytoin was administered through the proximal lumen and the TPN through the medial lumen. The same methodology was repeated on the opposite limb using the control catheter.

Blood sampling was performed mid-way through the phenytoin bolus administration, and at 1, 5, 10, and 15 min intervals for all ports of both catheters. Sampling was performed simultaneously at both sampling sites; each sample consisted of 1 ml whole blood. Histograms were generated by a coulter counter (Sysmex K-1000, Long Grove, Illinois, USA) for particle size. Quality control on the analyzer is performed on a real-time basis using commercial controls once every 8-h shift on a daily basis (Equinox 16T, Hematronix Inc., Benicia, California, USA). All quality control data are handled according to current College of American Pathologists' standards. Calibration of the analyzer is checked quarterly using a commercial calibrator. Blinded specimens were examined microscopically by phase microscope, light microscope, and Wright stain smears.

The experimental protocol was reviewed and approved by the animal care committee of our institution.

Figure 1



Peripheral multilumen catheter cutdown sites and proximal venous blood sampling sites.

Table 1

The total parenteral nutrition solution

Amino acids	2.5%
Dextrose	10%
Intralipids	1.25%
NaCl	30 mEq
KCl	10 mEq
Ca gluconate	1000 mEq
K_2HPO_4	5 mEq
MVI-12	1 ampule
$MgSO_4$	200 mg
Trace elements	5 ml
Total volume	500 ml

Results

Histograms for particle size, set with apertures for white blood cells (24–300 μm/100 μl), red blood cells (30–250 μm/100 μl) and platelets (2–20 μm/100 μl), did not show any alteration of the histogram suggesting particle size >2 μm in diameter. At no point did any of the

samples, control or study, fail to pass a 2 μm aperture. Upon review of the white blood cells, red blood cells, and platelet histograms generated by the hematology analyzer, we could not identify any foreign particles in the animal blood. We could not rule out the presence of particles in very low concentrations, ie $\leq 3 \times 10^3$ particles/μl, which would be the acceptable background count on this instrument. No particles from various samples could be identified as examined by phase microscope, light microscope and Wright stain smears in both control and study groups.

Mean heart rate, respirations, and temperature were 134 ± 8 beat/min, 22 ± 4 breath/min, and 38 ± 0.7°C, respectively.

Discussion

Central venous catheters in the pediatric population, and especially in the pediatric intensive care setting, are commonly used for the administration of intravenous fluids, drugs, chemotherapeutic agents, inotropic agents, and hyperalimentation. Access to the intravascular space includes the femoral, subclavian, and internal jugular veins. The procedure is not without complications; these include bleeding, venous thrombosis, vessel perforation, sepsis, dysrhythmias, and catheter dislodgment or leakage, among others [4–6]. Complications are relatively common in the pediatric and neonatal population with a reported incidence of 11.6% and 53% in two separate studies [7,8]. Leakage and extravasation of drugs and fluids can have major consequences for the patient. Local edema, inflammation, infection, and necrosis are the most serious complications of fluid extravasation and may lead to tissue loss requiring reconstructive surgery and, in some cases, may cause loss of extremities. Dislodgment of the catheter can also lead to the death of the patient [9].

A plausible reason for this high incidence of fluid extravasation may be the distance between the proximal and distal ports in commercially available multilumen pediatric catheters. While the distal lumen may lie within the intravascular space, the proximal lumen may be close to the site of entry of the vein or even outside the vein. This increases the possibility of extravasation if the catheter is accidentally dislodged or is not sutured properly.

The new triple-lumen catheter, with decreased port to port distances and shorter catheter length compared to commercially available catheters, was developed for use in the smallest possible patients. The shorter port to port distance and catheter length may help to minimize the chance that one of the lumens might be positioned improperly, resulting in the potential for extravascular fluid infusion or catheter dislodgment.

Our findings are consistent with a previous study [2] showing that the simultaneous infusion of phenytoin and TPN solutions did not cause the precipitation of particles large enough to be of clinical significance.

Conclusion

Using previously published methodology for the study of the simultaneous administration of incompatible drugs via a multiple lumen catheter, we conclude that the use of a triple-lumen catheter with a port distance of 0.4 cm between the medial and proximal ports, 1.3 cm between the distal and medial ports, 1.7 cm between the distal and proximal lumens, and overall length of 5 cm, for the *in vivo* administration of incompatible solutions, phenytoin and TPN, using a swine model, did not lead to precipitates large enough to cause adverse clinical effects in our study. This modified catheter was developed to minimize the length of the catheter for use in the smallest possible patients and to decrease the possibility that one of the lumens might be positioned improperly, resulting in the potential for extravasation of fluids or drugs.

References

1. Recker DH, Metzler DJ: Use of the multilumen catheter. *Crit Care Nurse* 1984, **4**:16.
2. Jaimovich DG, Rose WW: *In vivo* evaluation of simultaneous administration of incompatible drugs via a double-lumen peripheral catheter. *Crit Care Med* 1990, **18**:1164–1166.
3. Collins JL, Lutz RJ: *In vitro* study of simultaneous infusion of incompatible drugs in multilumen catheters. *Heart Lung* 1991, **20**:271–277.
4. Strauss RH: Pediatric vascular access. In: *Pediatric Critical Care.* Edited by Fuhrman BP, Zimmerman JJ. St Louis: Mosby Year-Book Inc.; 1992. pp. 129–139.
5. Krasna IH, Krause T: Life-threatening fluid extravasation of central venous catheters. *J Ped Surg* 1991, **26**:1346–1348.
6. Schiff DE, Stonestreet BS: Central venous catheters in low birth weight infants: incidence of related complications. *J Perinatology* 1993, **13**:153–158.
7. Goutail-Flaud MF, Sfez M, Berg A, *et al*: Central venous catheter-related complications in newborns and infants: a 587-case survey. *J Ped Surg* 1991, **26**:645–650.
8. Hruszkewycz V, Holtrop PC, Batton DG, *et al*: Complications associated with central venous catheters inserted in critically ill neonates. *Infect Control Hosp Epidemiol* 1991, **12**:544–548.
9. Lavandosky G, Gomez R, Montes J: Potentially lethal misplacement of femoral central venous catheters. *Crit Care Med* 1996, **24**:893–896.