Evaluation of the Potential Adverse Effects Associated with Calcium Carbonate Precipitate During Continuous Veno-venous Hemofiltration (CVVH)

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Abstract

Purpose: This study evaluated the potential adverse effects associated with exposure to calcium carbonate precipitate in Accusol 35 Solution (Accusol 35) during CVVH. **Methods:** 14 dogs were anesthetized, instrumented, and received CVVH with the test (6) or negative control article (8) for 6 hr. The test article was Accusol 35 with induced precipitate formation prior to CVVH, containing visible particles and sub-visible particles 36-times higher than the maximum concentration specified in European Pharmacopoeia (EP). The negative control article was Accusol 35 conforming to EP specification. One-half the dogs in the negative control article group received a central venous injection of Sephadex G-50® beads (10 mg/kg) following CVVH as positive control. Select cardiovascular (CV) parameters were measured throughout CVVH. Arterial samples were obtained for blood gas analysis. Samples of the test and negative control articles were obtained hourly during CVVH for determination of pH and subvisible particles. Dogs were euthanized and lung tissue samples were examined histologically. **Results:** All CV parameters remained stable and no differences were observed between the test and negative control articles. Sephadex beads caused an increase ($p<0.01$) in mean pulmonary arterial pressure due solely to a similar increase ($p<0.01$) in pulmonary vascular resistance. No differences in blood gases were observed between the test and negative control articles. Sephadex beads caused a decrease ($p>0.05$) in PO_2 and an increase ($p>0.05$) in PCO_2. No differences in lung histology were observed between the test and negative control articles. The lungs from all dogs given Sephadex beads contained multiple intravascular particles in large caliber blood vessels. **Conclusion:** ***CVVH performed on anesthetized dogs for 6 hr using Accusol 35 containing visible and sub-visible particles 36-times higher than the maximum concentration specified in EP, resulted in no adverse effects on CV parameters, blood gases and electrolytes, and lung histology as compared with Accusol 35 containing no visible particles and sub-visible particles that were within EP specification.***

Background

The clinical use of Accusol 35 Solution has been associated with occasional formation of visible, white, calcium carbonate precipitate in the tubing set during continuous renal replacement therapy (CRRT).

Purpose

To evaluate the potential adverse effects associated with exposure to calcium carbonate precipitate in Accusol 35 Solution during CRRT, more specifically continuous veno-venous hemofiltration (CVVH). Potential adverse effects upon intravenous infusion of calcium carbonate particles include anaphylactoid reactions, physical blockage of and damage to capillaries or larger caliber vessels in the pulmonary circulation leading to pulmonary hyper-tension and/or impaired gas exchange, and worst case death.

Methods

- **Test article**: Accusol 35 Solution (Baxter, lot 08J08G70) pH-adjusted and subjected to a therapy simulation using the AQUARIUS™ system for at least 21 hours prior to connecting to the dogs to maximize exposure to precipitate during CVVH.
- **Negative control article**: Accusol 35 Solution (Baxter, lot 08J08G70) pH-adjusted, but not previously subjected to a therapy simulation.
- **Positive control article:** Sephadex G-50® beads (Sigma-Aldrich, catalog # G50300-50G, dry diameter 100 to 300 mm) suspended in 0.9% Sodium Chloride.

Table 1. Negative Control and Test Articles Befo

Parameter Measured	Negative Control (n = 16)	Test Article (n = 36)
pH	7.44 ± 0.02	7.44 ± 0.02
Subvisible Particles (counts/mL)		
≥10 µm	3 ± 2	900 ± 300
≥25 µm	0.0 ± 0.1	0.5 ± 0.6
Visible Particles	Absent	Present

n = the number of samples.

Test System: Male mongrel dogs (9-14 months of age and 22-29 kg) obtained from Covance Research Products Inc. Dogs were anesthetized to effect with propofol/isoflurane and mechanically ventilated with 1:1 nitrous oxide and oxygen. An 11.5F MAHURKAR™ dual-lumen catheter was placed into the left jugular vein to enable CVVH, a saline-filled catheter was placed in a femoral artery for cardiovascular monitoring and blood sampling, and a 7.5F Swan-Ganz® CCO/VIP catheter was passed through the right jugular vein and into the pulmonary artery for cardiovascular monitoring.

CVVH: The test and negative control articles were administered at a rate of 36 mL/kg/hr before (pre-dilution line at 12 mL/kg/hr) and after (post-dilution line at 24 mL/kg/hr) the hemofilter. The positive control article (10 mg/kg) was administered through the unused hub of the Swan-Ganz® catheter (1 mg/kg every 30 sec over 5 min) after CVVH was completed.

Table

Group	Test Material	N
1	Test Article	6
2	Negative Control Article	4
3	Positive Control Article[1]	4

[1] Administration of the Positive Control Article occurred after CVVH completed with the Negative Control Article.

Test and Negative Control Article Sampling: Samples were obtained from the pre-dilution line hourly during CVVH for determination of pH, subvisible particle counts, and presence of visible particles.

Cardiovascular Measurements: Arterial pressure, pulmonary arterial pressure, central venous pressure, heart rate, and cardiac output were monitored before and during CVVH. Stroke volume, systemic vascular resistance, and pulmonary vascular resistance were calculated.

Clinical Pathology: Arterial blood samples were obtained prior to CVVH and every 30 minutes after the start of CVVH for blood gas and electrolyte analysis.

Necropsy and Histopathology: Necropsy included examination of the thoracic cavity and contents. Tissue samples from the lungs were examined histologically by a veterinary pathologist.

Test and Negative Control Article Sampling: pH and particle analysis during CVVH therapy is summarized in Table 3, where n = the number of samples.

Results

Table 3. Negative Control and Test Articles During CVVH

Parameter Measured	Negative Control (n = 48)	Test Article (n = 36)
pH	7.47 ± 0.06	7.43 ± 0.01
Subvisible Particles (counts/mL)		
≥10 µm	2 ± 2	1,000 ± 300
≥25 µm	0.0 ± 0.1	0.8 ± 1.7
Visible Particles	Absent	Present

Cardiovascular Measurements: All parameters remained stable throughout CVVH. No meaningful toxicological differences were observed between the test and negative control articles. Isolated occurrences of statistical significance were detected for mean arterial pressure, mean central venous pressure, systemic vascular resistance, and pulmonary vascular resistance, and are attributed to biological variability. The administration of Sephadex beads caused an increase ($p<0.01$) in mean pulmonary arterial pressure (Figure 1), which was due solely to a similar increase ($p<0.01$) in pulmonary vascular resistance (Figure 2) as cardiac output (Figure 3) remained unchanged. These changes correlate with the histopathology findings (below).

Clinical Pathology: No meaningful toxicological differences were observed between the test and negative control articles. Although not statistically significant, a decrease in arterial PO_2 (Figure 4) and an increase in arterial PCO_2 (Figure 5) were observed following the administration of the Sephadex beads. These modest changes in blood gases along with the observed changes in pulmonary hemodynamics suggest impaired gas exchange secondary to ventilation-perfusion inequality.

Histopathology: There were no histopathologic observations in the lungs attributed to the administration of the test article as compared with the negative control article (Figures 6 A-B). The lungs from all dogs in the positive control group, given the negative control article followed by Sephadex beads, contained multiple intravascular particles in large caliber blood vessels (>100 µm in diameter), which were interpreted as the beads (Figures 6 C-D).

Measurements for Figures 1-5 at each time point are changes from baseline.

Figure 1. Mean Pulmonary Arterial Pressure

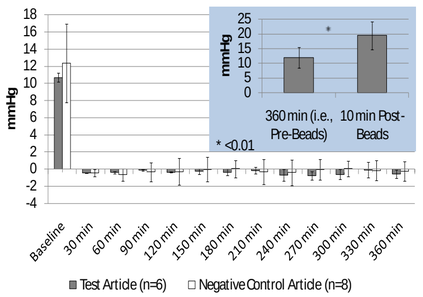


Figure 2. Pulmonary Vascular Resistance

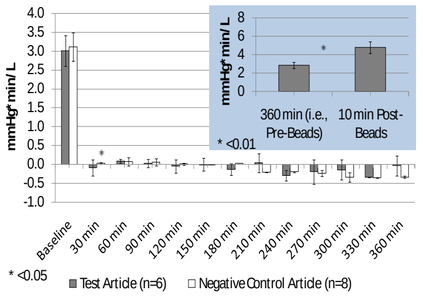


Figure 3. Cardiac Output

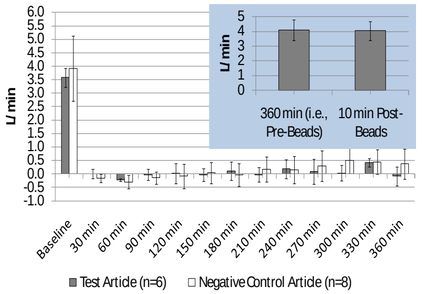


Figure 4. Arterial PO2

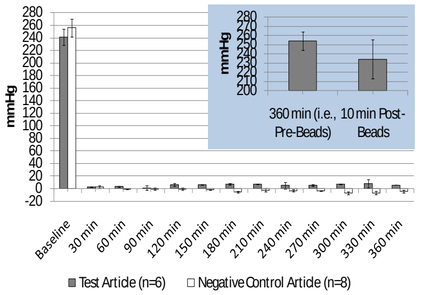
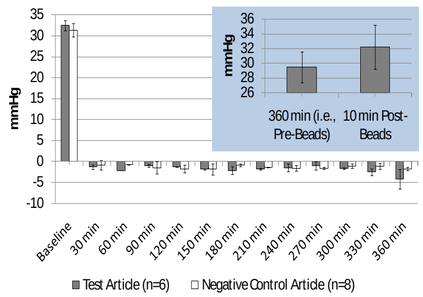
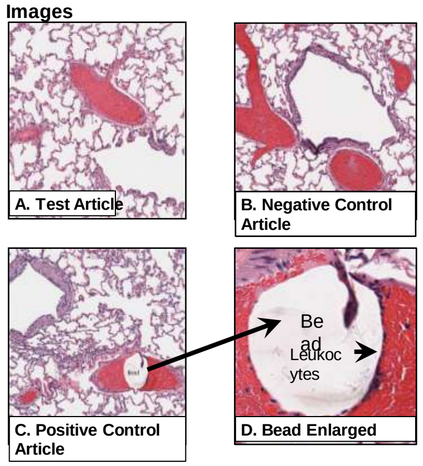


Figure 5. Arterial PCO2



Figures 6A-D. Lung Histology – Representative Images



Conclusions

Under the conditions of this study, continuous veno-venous hemofiltration performed on anesthetized dogs for six hours using Accusol 35 Solution containing visible and sub-visible particles (≥10 µm at approximately 36-times higher than the maximum concentration reported by the governing European Pharmacopoeia monograph titled "Solutions for Haemofiltration and for Haemodiafiltration"), no adverse effects were observed on CV parameters, blood gases and electrolytes, and lung histology as compared with Accusol 35 containing no visible particles and sub-visible particles that were within EP specification.

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