

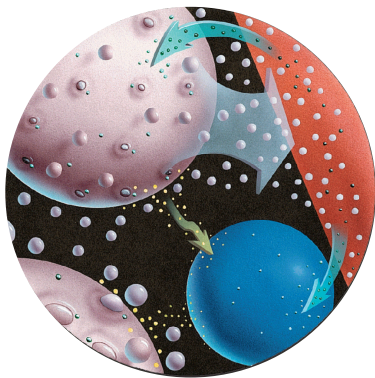
Biocompatibility Assessment of Edwards Vantex Central Venous Catheter with Oligon Material vs. Chlorhexidine and Silver Sulfadiazine (Antiseptic) Coated Central Venous Catheter

Vantex CVC Whitepaper 03 Vantex CVC vs. Antiseptic CVC

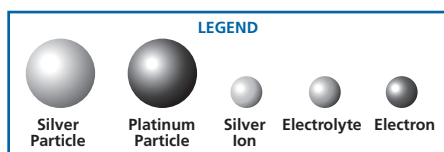
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Body fluids interact with silver and platinum particles in the material, causing a release of silver ions.



Introduction

Central venous catheters (CVC) are integral to the care of critically ill patients. Nosocomial infections associated with CVC's are a serious medical complication. To address this problem, numerous methods have been developed to modify the surface of catheters to reduce bacterial adherence and biofilm formation. Two such products commercially available today are the Vantex Central Venous Catheter with Oligon material (with or without heparin coating*) and a chlorhexidine/silver sulfadiazine coated CVC from Arrow International, Inc. (antiseptic-coated CVC).

The Vantex Central Venous Catheter utilizes an antimicrobial material called Oligon that is extruded from polyurethane combined with natural silver and platinum metals and carbon black. Since the antimicrobial properties are integral to the Oligon material, antimicrobial protection is inherent to both the inner and outer surfaces of the catheter. The antiseptic-coated CVC is comprised of silver sulfadiazine and chlorhexidine, which is only (at the time this test was conducted) applied to the outer surface of the catheter. While both CVC devices have been shown to be efficacious at reducing bacterial growth in limited studies, the potential for allergic or sensitivity response of patients exposed to these catheters has not been thoroughly researched. The aim of this study was to examine the biocompatibility of both of these antimicrobial catheters.

Test Method

The biocompatibility of the Vantex Central Venous Catheter with Oligon material (with or without heparin coating) and the chlorhexidine/silver sulfadiazine coated CVC (antiseptic-coated CVC) were evaluated as suggested in the *International Standards Organization (ISO) 10993-1-1994 Biological Evaluation of Medical Devices – Part 1: Guidance on Selection of Tests and the FDA General Program Memorandum No. G95-1*. The specific test procedures performed were:

In Vivo Tests

- USP Mouse Systemic Injection – Normal Saline and Vegetable Oil Extracts.
- USP Rabbit Intracutaneous Irritation – Normal Saline and Vegetable Oil Extracts.
- Guinea Pig Maximization Test – Normal Saline and Vegetable Oil Extracts.
- USP Rabbit Intramuscular Implantation with Histological Evaluation – Approximately 7- and 30-Day Implant Duration (considered to be Sub-Chronic Evaluation).
- Genotoxicity: Mouse Micronucleus Test – Normal Saline and 5% Ethanol in Normal Saline Extracts.

In Vitro Tests

- Agar Overlay – Solid Sample.
- Medium Eluate Method (MEM).
- Blood Compatibility.
- Genotoxicity: Ames Plate Incorporation Test – Normal Saline and 5% Ethanol in Normal Saline Extracts.
- Genotoxicity: Sister Chromatid Exchange Test – Distilled Water and 1% Ethanol in Normal Saline Extracts.
- Genotoxicity: Mouse Lymphoma Assay – Normal Saline and Ethanol Extracts.

The test articles for this study were treated portions of the representative test samples. This comprised both the internal and external surfaces of the Vantex Central Venous Catheter with Oligon material sample, and only the external treated surface area of the antiseptic-coated CVC. Extracts were prepared at a ratio of 6 cm² of surface area of each test article per milliliter extraction medium (120 cm²/20 mL) as recommended by both the *International Standards Organization (ISO) 10993-12: Sample Preparation and Reference Materials and the United State Pharmacopoeia 23* for material of ≤ 0.5 mm thickness.

Exceptions to the test sample size were the heparin coated Oligon Sister Chromatid Exchange Test samples, which was evaluated at 1.0 cm²/mL as part of a whole device evaluation. Blood Compatibility testing of the non-heparin coated Oligon body tubing was performed at 6 cm²/mL but was reduced to 3 cm²/mL due to slight hemolysis noted at the elevated concentration in the static testing of both the material and extract thereof. The reduction in sample to extract concentrations was considered acceptable based on industry standards for materials evaluation for the Blood Compatibility Test and was required due to the known cytotoxic nature of the test article in the Sister Chromatid Exchange Test.

All extracts were prepared at $70 \pm 2^\circ\text{C}$ for 24 ± 1 hours as acceptable in the same two guidelines (more elevated temperatures were considered inappropriate given the nature of the base materials and the presence of coatings; whereas, reduced temperatures were not selected as the product was exposed to temperatures similar to the 70°C extraction temperature during the sterilization of the product). The exception to the 70°C extraction which uses a $37 \pm 2^\circ\text{C}$ temperature for 24 ± 2 hours per the industry standard test methodology. All studies were conducted in accordance with GLP regulations, in that strict compliance to standard operating procedures was maintained; however, the studies must be considered non-GLP as the protocol, final report, QAU audits and record storage were not in strict compliance to *Federal Register 21 CFR Part 58*.

Test Results and Discussion†

Vantex Central Venous Catheter with Oligon Material Results

The Vantex Central Venous Catheter with Oligon material (non-heparin coated) demonstrated biocompatibility in all test procedures at the maximum concentration evaluated in all procedures except the Blood Compatibility static evaluation of the solid and extract samples. In all other tests, there was no evidence of systemic toxicity, intracutaneous or intramuscular irritation, cytotoxicity, hemolysis (in the dynamic environment more representative of the clinical application), effect on clotting time, or genotoxic potential. The exception to these results was the Blood Compatibility Test on the static samples. Both the solid sample and extracts were all found to be non-hemolytic at levels in excess of the clinical application of the material with the exception of the solid and extract samples in the static environment. When reduced to a sample to extract concentration of 3 cm²/mL, the extract was determined to be non-hemolytic. This solid sample was still determined to be minimally hemolytic (11.6% hemolysis with a non-hemolytic acceptance criteria of $< 5\%$ hemolysis) at the reduced concentration. This minimal hemolysis was not considered significant due to the dynamic environment present in the clinical application and the recognized slightly toxic and antimicrobial properties of this Oligon material.

Similarly, the Vantex Central Venous Catheter with Oligon material (treated with heparin) was determined to show no evidence of systemic toxicity in the Mouse Micronucleus Test, sensitization potential, or genotoxic potential. The heparin-treated catheter did demonstrate cytotoxicity in the Sister Chromatid Exchange (SCE) procedure at the elevated concentrations evaluated, therefore requiring testing at the reduced concentrations. The heparin-treated catheter also demonstrated a host response of mild cytotoxicity intramuscularly at the 7-day duration, with no host response noted at the 30-day explant. These results were anticipated due to the presence of the surfactant used as a binding agent for the heparin, and were evidenced in these procedures due to the sensitivity of the procedures and their static nature, which does not provide a system similar to the clinical application.

Chlorhexidine/Silver Sulfadiazine (Antiseptic) Coated CVC Results

The antiseptic-coated CVC was found to have a heightened response in six of the eight procedures as compared to the Vantex Central Venous Catheter with Oligon material (non-heparin coated) at the maximum concentration evaluated. While there was no evidence of intracutaneous irritation or sensitization potential, there was evidence of the antiseptic-coated CVC being more cytotoxic and systemically toxic than would be expected from a procedural response to a surfactant treatment. The antiseptic-coated CVC, at the elevated concentration, was significantly more cytotoxic in cell culture (100% cytotoxic) and more hemolytic (100% hemolysis). It also produced greater mammalian cellular lysis (complete lysis) in the genotoxicity procedures; a reduction in the test sample size (concentration) was required to demonstrate no genotoxic potential. As mentioned previously, these procedures are sensitive and static in nature, offering a significant challenge to any antimicrobial treatments. However, even in the *in vivo* mouse systemic injection, using both normal saline and 5% ethanol in normal saline extraction mediums, a severely toxic host response was observed in the form of death and convulsions. These extreme *in vivo* toxic responses were observed in a test procedure most closely mimicking the clinical application of the catheter. When retested at the reduced temperature of 37°C, the test article was found to be acceptable; however, the test sample clearly demonstrated cytotoxicity when directly assessed according to ISO and USP guidelines at the same parameters as the Vantex Central Venous Catheter with Oligon material (with or without heparin coating).

Additionally, the host response in an intramuscular implant with a 7-day duration was classified as cytotoxic as compared to the negative control material. In comparing the 7-day findings of the Vantex Central Venous Catheter with Oligon material (non-heparin coated) to the antiseptic-coated CVC, the cytotoxic response to the antiseptic-coated CVC was clearly more intense; the mean severity for myofiber necrosis was approximately 67% greater for the antiseptic-coated CVC (mean necrosis score of 1.5 vs. 2.5

for the antiseptic-coated CVC). Although the differences may not prove to be statistically significant, they do, in the opinion of the pathologist reviewing these results, have biological significance which shows within the scope of these studies: the cytotoxic effect of the antiseptic-coated CVC is substantially more severe than that of the Vantex Central Venous Catheter with Oligon material.

Figure 1 Hemolysis of CVC Extracts Tested

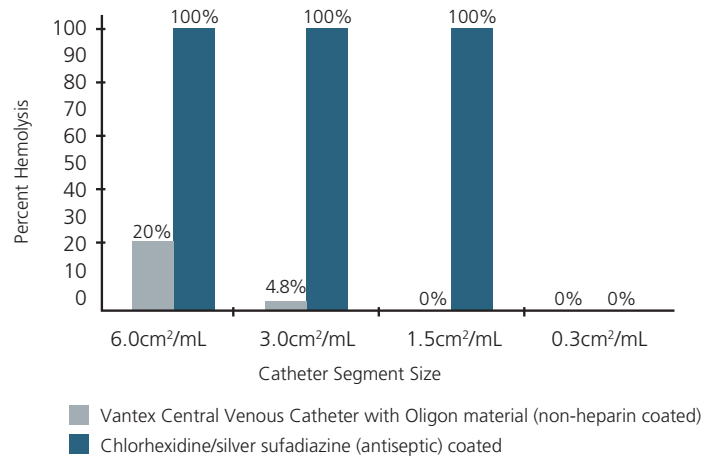
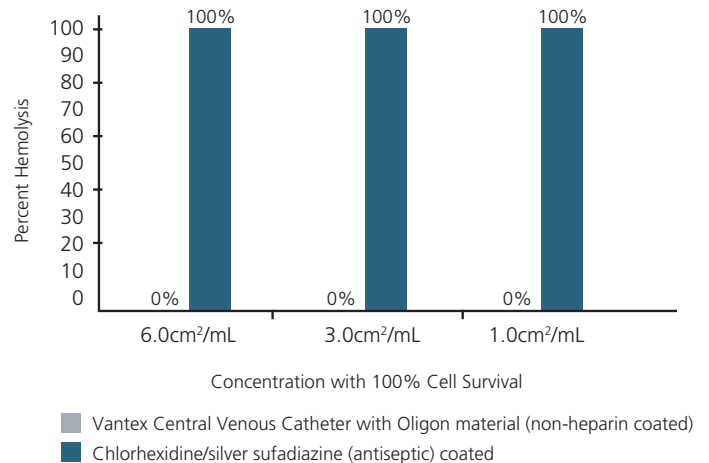
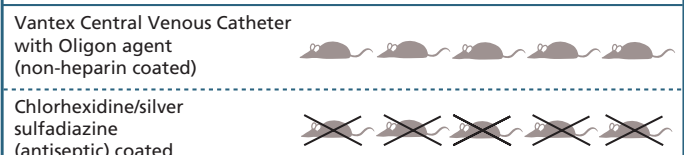


Figure 2 Cytotoxicity of CVC Tested



Survival Rate of Mice Exposed to CVC Extracts during the USP Mouse Systemic Test (extracted 70°C/24 hours)



While the guinea pig maximization assay did not demonstrate potential sensitization, the potential for patient sensitivity to the chlorhexidine component of the antiseptic-coated CVC may be of concern in some countries, due to reports of anaphylactic shock after exposure to chlorhexidine agents. While heparin may also hold the potential for adverse reactions such as heparin-induced thrombocytopenia, the methods of detecting adverse reactions, coupled with the slower onset and the low level of heparin present on the Vantex Central Venous Catheter, make this a minimal risk.

Conclusion

As observed in the testing, the Vantex Central Venous Catheter with Oligon material provides a biocompatible central venous catheter with less potential risk for allergic response than a chlorhexidine/silver sulfadiazine (antiseptic) coated CVC. The potential for improved device compatibility plus the potential to reduce bacterial growth demonstrates that the Vantex Central Venous Catheter with Oligon material is an excellent alternative over an antiseptic-coated CVC.

REFERENCES

- 1 Torricelli R, Wutrich B. Life-threatening anaphylactic shock due to skin application of chlorhexidine. *Clin Exp Allergy*. 1996;26:112
- 2 Gabler WL, Roberts D, Harold W. The effect of chlorhexidine on blood cells. *J Periodontal Res*. 1987;22:150-155.
- 3 Butler WH, Iswarah TJ. Chlorhexidine: Safety Evaluation. Royal Society of Medicine, International Congress and Symposium. Series Number 23.
- 4 Center for Devices and Radiological Health. FDA Public Health Notice, Potential Hypersensitivity Reactions to Chlorhexidine-Impregnated Medical Devices. March 1998.

Antimicrobial activity on the Oligon surface and inner lumens of the catheter during handling and placement has been demonstrated through *in vitro* testing against organisms commonly associated with nosocomial infections. The activity of the antimicrobial agents is localized at the catheter surfaces and is not intended for treatment of systemic infections.

In vitro testing demonstrated that the Oligon material provided broad spectrum effectiveness (≥ 3 log reduction from initial concentration within 48 hours) against the organisms tested: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Candida albicans*, *Escherichia coli*, *Serratia marcescens*, *Acinetobacter calcoaceticus*, *Corynebacterium diptheriae*, *Enterobacter aerogenes*, *GMRSA* and *Pseudomonas aeruginosa*. The impact of Oligon material on infection rates has not been demonstrated.

*Contact inhibition of microbial growth on surface of catheters. Effective against organisms commonly associated with nosocomial infection, e.g., *S. epidermidis*.

Antimicrobial activity associated with AMC THROMBOSHIELD (an Antimicrobial Heparin Coating) has been demonstrated using *in vitro* agar diffusion assays against the following organisms: *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Candida albicans*, *Escherichia coli*, *Serratia marcescens* and *Acinetobacter calcoaceticus*.

†Data on file.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. See instructions for use for full prescribing information.

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