PALL Medical

Technical Report

Binding of Monoclonal Antibodies to Pall Supor™ AEF Intravenous Filters

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Introduction

Pall intravenous filters protect patients against particulates, air and inadvertent microbial contamination that may be present in parenteral solutions and the compatibility of these filters with numerous drugs and nutrient admixtures has been demonstrated[1,2,3].

In recent years there has been a significant increase in the use of therapeutic antibodies primarily in the treatment of cancers. Which are delivered intravenously[4].

Biopharmaceuticals are complex, sensitive, and highly developed products which can generally be considered as relatively safe. Even with all the current knowledge available, it is nearly impossible to absolutely exclude the formation of protein aggregates in these optimized formulations. Protein immunogenicity is intensively researched as it can compromise the safety and efficacy of a biopharmaceutical drug. It is impossible to achieve an absolute absence of protein aggregates even for very stable formulations. The application of “bedside filtration,”meaning filtration during the preparation or administration of the drug product immediately before injection, has the potential to increase the safety of every drug container and could prevent the undesired injection of particulate matter into the patient 5-8. The purpose of this study was to evaluate compatibility of Pall Supor AEF Intravenous filters (AEF1E and AEF1NTE) containing a 0.2 µm low protein binding Supor membrane with monoclonal antibody drugs. Binding to a filter with higher known protein binding was also investigated. Two typical monoclonal antibody drug administration scenarios were simulated by infusion of radiolabelled immunoglobulin G (IgG) in saline; one at a relatively high concentration of IgG and one at a lower concentration.

Materials and Methods

IgG was added to 0.9 % sodium chloride solution (Baxter Healthcare, Norfolk UK) to the concentration specified for administration regime. ^{125}I labelled IgG (Perkin Elmer) was added as a tracer to a level of 10^6 cpm/ mL. An administration set (Cardinal Health, Rolle Switzerland) was primed with the radiolabelled IgG in 0.9 % sodium chloride and an AEF1E (Pall Corporation, New York USA) or protein binding reference filter connected. An Ivac 572 volumetric infusion pump (Ivac Corporation, San Diego USA) was set to deliver IgG at the required flow rate. Three filters of each type were tested.

Test 1

Administration regime A (high dose challenge) - infusion of 100 mg/hr IgG increasing by 100 mg/hr at 30 minute intervals to a maximum of 400 mg/hr. IgG concentration was 1.4 mg/mL with the total IgG challenge 747 mg.

Administration regime B (low dosage challenge) - infusion of 30 mg IgG in 100 mL over a 1 hour period

To determine the absolute IgG binding, aliquots of the filtrate were taken and the IgG concentration measured by direct counting using a Wallac Rackbeta 1209 liquid scintillation counter (Wallac, Waltham USA). Following infusion each filter was dissected and the amount of IgG bound to the filter membrane and other filter set components determined by direct counting.

Test 2

The use of a passivation step to prevent binding of IgG to the membrane of the filter using a known protein binding was also investigated. 10 mL of a 1 mg/mL solution of Bovine Serum Albumin (BSA) (Sigma) was passed through the filter as a bolus prior to infusion of 30 mg IgG in 100 mL over a 1 hour period. IgG binding was determined as previously described.

Results

Test 1

Mean IgG bound to the filter medium in each filter type is shown in Table 1. Binding is expressed as an absolute value. Binding to other filter set components was negligible and has not been reported here.

Table 1. Mean Absolute Binding of IgG to Pall Supor AEF Intravenous Filters for Administration regimes A and B

	Administration Regime A IgG Bound	Administration Regime B IgG Bound
Filter	mg	mg
AEF1E	0.08	0.08
Protein Binding Reference	8.76	9.15

Test 2

Mean IgG bound to media in the reference filter following passivation by BSA is shown in Table 2. Binding is expressed as an absolute value. Binding to other filter set components was negligible and has not been reported here.

Table 2. Mean Absolute Binding of IgG to the reference filter following a BSA flush prior to infusion following administration regime B

	Administration Regime B IgG Bound
Filter	mg
Protein Binding Reference	0.07

Discussion

Absolute binding of IgG to the Supor membrane in AEF filters was negligible (0.08 mg) demonstrating that these filters have low protein binding characteristics and can in principle be used with monoclonal antibody based drugs. The results in Table 1 show a finite binding of IgG regardless of administration regime with no statistically significant difference in absolute binding between infusion of 747 mg IgG over a 2½ hour period compared to infusion of 30 mg IgG over 1 hour ($p = 0.4871$).

The potential impact of the absolute binding capacity for immunoglobulins to AEF filters (0.08 mg) has to be evaluated clinically by taking into account the overall dose of the drug applied. For a clinical decision the potential loss of active substance needs to be balanced against the clinical benefits of using the filter. Absolute binding to the media in the reference product was statistically significantly higher at approximately 10 mg ($p < 0.0001$), but could be pacified with a protein flush.

It was shown that by passing 10 mg BSA through the high protein binding reference filter in a 10 mL bolus prior to IgG infusion, it was possible to reduce binding of the IgG to levels similar to those for the low protein binding 0.2 µm Supor membrane.

This study demonstrates that with a full clinical evaluation Pall Supor AEF filters (AEF1E and AEF1NTE) can potentially be used during infusion of monoclonal antibody based drugs.

References

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