PALL Medical

Scientific Technical Report

Particulate Removal by Infusion Filters

Karen Wilkins, Pall Medical Scientific & Laboratory Services, Portsmouth, UK

Risks of Particulate Contamination in Infusion Therapy

The problems of particulate contamination of infusion solutions and their resultant effects are well known and it is clear that the increasing complexity of intravenous (IV) therapy has only aggravated this situation.[1]

Sources of Particulate Contamination

Particulate contamination can arise from five main sources: drug incompatibility reactions, incomplete reconstitution of drugs, components and systems, lipid macro micelles and entrapped air emboli.

Drug incompatibility reactions

Drug incompatibility reactions occur when two or more solutions are mixed in an infusate and they react either chemically or physically together to form particles (with resultant potential loss of pharmacological activity). It has been reported that 15 - 28% of drugs are administered clinically without knowing their potential for incompatibilities or in spite of known incompatibilities.[2-4] Calcium phosphate precipitates in IV solutions have been reported as causing Adult Respiratory Distress Syndrome (ARDS), granulomatous interstitial pneumonia, pulmonary embolism and death[5,6] and pulmonary arterial occlusion.[7] Finally, precipitation of Ceftriaxone in the presence of calcium salts has been found to cause the death of a neonate.[8,9]

Incomplete drug reconstitution

Incomplete drug reconstitution can lead to the formation of particulate matter. An example of this is shown in a study investigating the reconstitution of Amphotericin B where particle counts originating from un-dissolved drug and the drug vial itself were found to exceed USP guidelines.[10]

Components and systems

There are many reports in the literature of particulates inherent in drug components or associated systems. These range from generic drug formulations being found to be heavily contaminated with particles[11], to demonstration of abrasion of silicone particles during pump-controlled infusion[12] and the discovery of particulate contamination (presumably plastic) isolated from a clot in a catheter.[13]

Lipid macro micelles

Enlarged lipid droplets can arise in admixtures due to inherent instability and the use of plastic bag containers.[14] Infusion of such admixtures has been shown to cause tissue injury and oxidative stress to reticulo-endothelial system organs.[15]

Entrapped air emboli

Air emboli can be caused by the degassing or mixing of solutions, leaks from administration sets or gas residues in syringes and connectors.[16] Air bubbles may transfer into the arterial circulation and cause end arterial obstruction (paradoxical embolism).[17] Similarly, air bubbles as small as 30 - 60 µm may cause an embolism of small arteries followed by tissue ischaemia.[18]

Mechanisms of Particle Toxicity

The following physicochemical characteristics of any particles will determine their level of toxicity: size, size distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge and porosity.[19] There would appear to be a number of main mechanisms by which clinical effects are manifested, namely via thrombogenicity and thrombophlebitis, direct embolism (respiratory distress), inflammation and impairment of micro-circulation and endothelial function.

Thrombogenicity and thrombophlebitis

Post-mortem analysis of lung tissue from ARDS patients revealed foreign bodies as the nucleus for thrombi formation. Analysis of these showed glass from ampoules, rubber from infusion bottle stoppers and plastic from infusion sets.[19] Similarly, micro- and nano-scale inorganic particles were isolated from thrombi on 12 out of 14 explanted vena cava filters and it was considered that the particles were the likely cause for the thrombi.[20] Thrombophlebitis occurs in 5 - 77% of peripherally infused patients.[21] Such episodes may lead to lung embolism in up to 33% of cases and to deep vein thrombosis in 66%.[22]

Direct embolism

There is evidence to show that the presence of particles can lead directly to embolism. For example, glass fragments have been found embedded in post-mortem lung tissue samples from the lungs of neonates.[23] Impairment of micro-circulation

Impairment of micro-circulation

In vitro animal studies investigating the effects of infusions of particles into hamster tissues have concluded that patients with ischaemic tissue damage (due to surgery, trauma, sepsis etc.) are highly vulnerable to particulate contamination.[11]

Effects of Filtration

There are numerous reports in the literature demonstrating the beneficial effects of using filters on infusion lines. A meta analysis of 14 clinical studies showed an increased survival of infusion sites in the filter group compared to controls.[24] Use of the Pall Posidyne® ELD Filter (since rebranded as the Pall NanodyneTM ELD Filter) was found to immediately prevent a reported increase in the rate of deep vein thrombosis most likely caused by particles released from poor quality IV tubing.[25] A study of the use of IV filters in sick newborn infants reported 'The use of this in-line filter leads to a significant decrease in major complications and cost savings'.[26] Finally, a major clinical study recently reported a significant reduction in the incidence of systemic inflammatory response syndrome in critically ill children when using in-line filtration.[27] The European Society for Parenteral and Enteral Nutrition currently recommends 'All PN solutions should be administered through a terminal filter. Lipid emulsion (or all-in-one mixes) should be passed through a membrane of pore size around 1.2 - 1.5 µm. Aqueous only solutions should be passed through a filter of 0.22 µm'.[28]

Nanoparticles and their potential effects

The potential effect of nanoparticles has become an increasingly active area of research. Nanoparticles are defined as being particles with at least one dimension smaller than 100 nm including engineered nanoparticles, ambient ultrafine particles and biological nanoparticles. The toxic effects of such particles will depend on many physicochemical properties such as particle size and size distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge, and porosity.[29] The earliest studies investigating the toxicity of nanoparticles focused on atmospheric exposure to heterogeneous mixtures of environmentally produced ultrafine particulate matter (diameter < 100 nm). Typically the biological activity of nanoparticles has been found to increase as the particle size decreases. Smaller particles occupy less volume and therefore result in a larger number of particles with a greater surface area per unit mass and increased potential for biological interaction.[30] A recent review on the cardiovascular effects

of air pollution reports that global studies have consistently shown that both short- and long-term exposure to particulate matter (PM) are associated with cardiovascular disease, including myocardial ischaemia and infarctions, heart failure, arrythmias, strokes, and increased cardiovascular mortality.[31] (The PM varies in size from a few nm to 10 µm in diameter). Inhaled PM may instigate remote cardiovascular health effects via three general pathways: 1) instigation of systemic inflammation and/or oxidative stress, 2) alterations in autonomic balance, and 3) potentially by direct actions on the vasculature. These responses have in turn been shown to trigger acute arterial vasoconstriction, endothelial disfunction, arrythmias and pro-coagulant/thrombotic actions.

Retention of nanoparticles by filtration

The Pall Nanodyne™ ELD Filter contains 'N_{66}' Posidyne 0.2 µm rated media for fluid filtration. 'N_{66}' Posidyne membrane is Ultipor® 'N66' nylon which has been modified to contain cationic (positively charged) functional groups. This means that it has the characteristic of positive zeta potential and is positively charged for the full pH range over which the zeta potential is effective, (from about pH 3 - 10). A positively charged membrane will remove particles much smaller than its pore size if the zeta potential of the pore walls of the filter media is the opposite sign to that of the challenge particles. Posidyne is therefore extremely useful for filtering negatively charged suspensions and the majority of suspensions, including most particles, bacteria, viruses and bacterial endotoxins are actually negatively charged. The Pall 'N_{66}' Posidyne filter guide highlights the performance characteristics of the filter media.[32] Data obtained for grade NFZ (0.2 µm microbial rating) is summarised in Table 1. It can be seen that this membrane is able to remove 38 nm diameter latex spheres with an efficiency greater than 99.99% (which is the limit of sensitivity of the test method) at a quantity up to 1.98 g/254 mm filter module. Similarly this membrane is shown to remove large amounts of *Escherichia coli* endotoxin (which can be thought of as a 'particle' about 1 nm diameter). More recently similar studies have been performed using a continuous flow challenge of 32 nm polystyrene latex beads.[33] Each filter membrane was challenged at 100 mL/min for 1 hour. Data is shown in Table 2. These data can be contrasted with that obtained for the removal of latex particles by Ultipor 'N_{66}' (negatively charged) as shown in Table 3. Removal efficiency was only found to be < 10%.

Table 1

Contaminant removal by 'N_{66}' Posidyne 0.2 µm rated membrane

Test contaminant	Diameter (nm)	Challenge quantity per 254 mm module (g)	Efficiency (%)
Spherical polystrene	38	1.98	> 99.99
		2.06	99.95
		2.38	98.5
		2.80	85.4
E.coli endotoxin	1	0.016	> 99.997

Table 2

Continous flow challenge of 'N_{66}' Posidyne 0.2 µm rated membrane

Filter media roll number	Upstream challenge (Accumulated Particles/mL)	Downstream challenge (Accumulated Particles/mL)	Efficiency (%)	Log reduction value
5 - 550'	13325.3	2.9	99.98	3.66
4 - 450' #1	13376.0	1.2	99.99	4.05

Table 3

Latex particle removal by 0.2 µm rated Ultipor 'N_{66}' membrane vs 0.2 µm rated 'N_{66}' Posidyne

Test contaminant	Diameter (nm)	Removal efficiency for Ultipor$_{66}$ N	Removal efficiency for N_{66} Posidyne
Latex test particles	38	< 10%	> 99.999%*

**These efficiencies decrease when the quantities of latex incident on the filter exceeds certain levels*

References

1. Jack T *et al. Intensive Care Medicine* Online publication. 18th Feb. 2010.
2. Taxis K and Barber N. *Eur J Clin Pharmacacol.* 2004; 59: 815-817.
3. Vogel Kahmann I *et al*. *Anaesthesist*. 2003; 52: 409-412.
4. Wirtz V *et al*. Pharm World Sci. 2003; 25: 104-111.
5. Shay DK *et al. Infect Control Hosp Epidemiol.* 1997; 18: 814-817.
6. Hill SE. *JPEN*. 1996; 20: 81-87.
7. McNeary T *et al. Digestive Diseases Sciences*. 2003; 48: 1352-1354.
8. Marimbert J, AFSSAPS warning letter, Nov. 30, 2006.
9. Arzneimittelkommission d.dt.Aärzteschaft, (2007) Deutsches Ärzteblat 36: A2445.
10. Sendo T *et al. J Clin Pharmacy and Therapeutics*. 2001; 26: 87-91.
11. Lehr H-A *et al. Am J Respir Crit Care Med*. 2002; 165: 514-520.
12. Dewan PA *et al. Pediatr Surg Int*. 2002; 18: 310-314.
13. Ball PA *et al. Nutrition*. 2001; 17: 933-936.
14. Driscoll DF and Bistrian BR. *Clinical Nutrition*. 2005; 24: 699-700.
15. Driscoll DF *et al*. *Clinical Nutrition*. 2006; 25(5): 842-850.
16. Wald M *et al. Intensive Care Medicine*. 2003; 29: 630-633.
17. Muth CM and Shank ES. *NEJM*. 2000; 342: 476-482.
18. Barak M and Katz Y. *Chest*. 2005; 128: 2918-2932.
19. Walpot H *et al*. *Anästhesist*. 1989; 38: 544-548, 617-621.
20. Gatti A and Montanari S. Appl. *Biomaterial*. 2006; 77B: 307-314.
21. Idval E and Gunningberg LJ. *Adv Nursing*. 2006; 55: 715-722.
22. Noppeney T *et al. Gefässchirurgie*. 2005; 10: 51-54.
23. Puntis JWL *et al. Archives of Disease in Childhood*. 1992; 67: 1475-1477.
24. Hecker JF *Brit. Med. J*. 1992; 304: 619.
25. Danschutter D *et al. Pediatrics*. 2007; 119: 742-775.
26. Van Lingen RA *et al. Acta Paediatrica*. 2004; 93: 658.
27. (http://www.clinicaltrials.gov/ct/show/NCT00209768?order=9) .
28. *J Ped Gastroenterol Nutr*. 2005; 41:S1-S87.
29. Oberdorster G *et al. Particle and Fibre Toxicology*. 2005; 2: 1-35.
30. Warheit DB. *Materials Today*. 2004; 21: 344-353.
31. Brook RD. *Clinical Science*. 2008; 115:175-187.
32. Pall 'N66' Posidyne Filter Guide (1994) USD905g.
33. Pall SLS Laboratory Report Number EU-005274.

PALL Medical

Pall International Sàrl
Avenue de Tivoli 3
1700 Fribourg, Switzerland

+41 (0)26 350 53 00 phone
+41 (0)26 350 53 53 fax
LifeSciences.EU@pall.com email

Filtration. Separation. Solution.SM

Visit us on the Web at www.pall.com/medical

International Offices
Pall Corporation has offices and plants throughout the world in locations such as: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Mexico, the Netherlands, New Zealand, Norway, Poland, Puerto Rico, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, the United Kingdom, the United States and Venezuela. Distributors in all major industrial areas of the world.

The information provided in this literature was reviewed for accuracy at the time of publication. Product data may be subject to change without notice. For current information consult your local Pall distributor or contact Pall directly. This document is not for distribution in the USA.

09/2012, GN11.6154