Water quality and complications of haemodialysis

Philippe Brunet and Yvon Berland
Service de Néphrologie et Hémodialyse, Hôpital Sainte-Marguerite, Marseille, France

Introduction

Bacterial contamination of dialysate and the potential transfer of bacterial components from the dialysate into the blood compartment have been recognized as factors predisposing to clinical complications during chronic treatment by haemodialysis. This problem, however, has been largely neglected. Concerns regarding the improvement of dialysate quality have been raised further by two modifications in haemodialysis: (i) the increasing use of high-flux dialysers, which enhances backfiltration of dialysate and (ii) the introduction of on-line haemodiafiltration, which requires infusing large quantities of dialysate in the blood compartment as substitution fluid.

The clinical complications associated with bacterial contamination of dialysate are reviewed. The recommendations of Pharmacopoeia are also discussed.

What clinical complications are associated with the transfer of bacterial products from the dialysate into the patient blood?

Short-term complications

Exposure to high levels of bacteria and endotoxin is clearly associated with short-term complications. These complications range from pyrogenic reactions, including chills and fever, to septicemia with severe hypotension and shock. Manifestations attributed to endotoxin exposure also include nausea, myalgia, headache, lassitude and sleepiness [1].

Long-term complications

These complications are considered to result from the stimulation of the organism by long-term endotoxin challenge. They include principally β2-microglobulin amyloidosis (β2m amyloidosis). In addition, exposure to bacteria may also promote two frequent complications in dialysis patients: malnutrition and atherosclerosis. The influence of bacterial contamination of dialysate on the pathogenesis of these complications is difficult to demonstrate because many other factors may intervene. However, there is evidence that the use of contaminated dialysate is linked with β2m amyloidosis [2].

β2m Amyloidosis

The repeated activation of monocytes by bacterial contaminants during haemodialysis sessions could be a determinant factor of β2m amyloidosis. Dialysate contaminated with endotoxin stimulates the release of β2m from monocytes. In addition, β2m amyloid fibrils can be formed in the supernatant of peripheral blood mononuclear cells maintained in culture [3]. Endotoxin also stimulates monocyte production of interleukin-1 (IL-1) and tumour necrosis factor (TNF), which are bone resorbing cytokines.

The study performed in Marseilles in 1991 gave clinical evidence that bacterial contamination of dialysate may increase the incidence of carpal tunnel syndrome [2]. After 10 years of haemodialysis treatment, the proportion of patients with carpal tunnel syndrome was 38% in patients treated with standard water, and it was only 5% in patients treated with ‘ultrapure’ water. Endotoxin concentration in standard water was 0.025 ng/ml or 0.125 endotoxin units (EU)/ml, and it was 0.008 ng/ml or 0.05 EU/ml in ‘ultrapure’ water. In Hanover, Schwalbe et al. reported that β2m amyloidosis prevalence decreased between 1988 and 1996 [4]. The prevalence of carpal tunnel syndrome decreased from 16 to 2% and the prevalence of radiological signs of β2m amyloidosis decreased from 38 to 8%. Such decrease was attributed to higher dialysate purity, after introduction of reverse osmosis water for dialysate preparation in a larger number of

Correspondence and offprint requests to: Prof. Y. Berland, Service de Néphrologie et Hémodialyse, Hôpital Sainte-Marguerite, 270 bd de Sainte-Marguerite, BP 29, F-13274 Marseille Cedex 2, France.
patients in 1996 than in 1988. It is unlikely that differences in haemodialysis membranes account for the results of these two studies. In the first study only cellulosic dialysers were used. In the second the time spent on high-flux dialysers was low in both the 1988 and 1996 time periods.

**Atherosclerosis**

An increasing body of evidence suggests that infections play a role in the development of atherosclerosis. At present chronic low-grade infections like those with Herpesviruses, *Chlamydia pneumoniae*, or *Helicobacter pylori* have been linked with atherosclerosis [5]. The mechanisms that could mediate the effect of bacterial infections on atherogenesis mainly involve lipopolysaccharide (LPS). Thus, it is conceivable that long-term transfer of LPS from dialysate into the patient’s blood may also contribute to atherosclerosis. LPS promotes atherosclerosis and vascular thrombosis by its effects on endothelial cell function [5]. LPS increases the synthesis of proinflammatory cytokines such as IL-1 and TNF in endothelial cells. It induces procoagulant activity in vascular endothelium by increasing the production of tissue factor, plasminogen activator inhibitor, and von Willebrand factor antigen. LPS increases the adherence of granulocytes and monocytes to endothelium. LPS also activates monocytes and stimulates production of acute-phase proteins such as C-reactive protein, which may also control monocyte/macrophage activation. Plasma levels of C-reactive protein are highly predictive of cardiovascular risk [6]. Interestingly, it has been demonstrated that dialysate backfiltration is associated with an increase in C-reactive protein in plasma [7].

Nanobacteria, which are calcification-inducing pathogens, may also be involved. Nanobacteria are micro-organisms that produce carbonate apatite, the solid mineral present in most extraskeletal tissue calcification. Nanobacteria could contribute to calcification of atherosclerosis plaques occurring in haemodialysis patients [8]. Nanobacteria can pass through 0.1-μm filters and possess unusual properties making their detection difficult with standard microbiological methods. They have been detected in human blood and urine, however, it is not known whether they can develop in dialysate.

**Malnutrition**

Bacterial contamination of dialysate may also cause malnutrition in haemodialysis patients through direct effects of LPS, which impairs protein catabolism in skeletal muscle [9] and induces anorexia by stimulating the production of leptin [10]. LPS may also indirectly affect the development of malnutrition by inducing proinflammatory cytokine production by monocytes. These cytokines induce anorexia, enhanced muscle catabolism, and reduced muscle protein synthesis, and protein utilisation.

**Does contamination vary with the type of membrane?**

The transfer of bacterial products from dialysate into blood compartment has been described with all types of haemodialysis membranes. Low-flux membranes do not avoid the risk of contamination because they permit the transfer of bacterial products by backdiffusion [11]. It has been claimed that synthetic membranes reduce the endotoxin transfer from dialysate because they can adsorb these products on their surface. These synthetic membranes, however, have shown large variability in their permeability to endotoxins [12]. This suggests that bacterial contamination of dialysate should be avoided with all types of dialysis membranes.

**Is there a ‘safe’ level of bacterial contamination of dialysate?**

The European Pharmacopoeia currently sets the upper levels of bacteria and endotoxins in dialysis water at 100 micro-organisms and 0.250 EU/ml [13]. It has been shown that pyrogenic reactions are induced by an endotoxin load of 5 EU/kg [14]. This represents a load of 300 EU for a patient weighing 60 kg. A load of 300 EU is attained if 1.2 l of dialysate is backfiltered with an endotoxin concentration of 0.250 EU/ml. Note that much more than 1.2 l is backfiltered during a dialysis session with a high-flux dialyser. This suggests that the standards of the Pharmacopoeia are not sufficiently strict for high-flux haemodialysis.

It is difficult to determine the endotoxin level that guarantees that long-term dialysis complications are avoided. Many long-term complications are linked with increased cytokine production by monocytes. Monocytes produce IL-1 in vitro when incubated with endotoxin concentrations as low as 50 pg/ml (0.250 EU/ml) [15]. This again suggests that endotoxin concentrations in dialysis water should be kept at levels much lower than the standards of the Pharmacopoeia. Maximal benefit could be obtained with the ‘ultrapure’ dialysate; it contains an endotoxin concentration inferior to 0.05 EU/ml and less than 0.1 micro-organisms/ml [2].

The recent development of haemodiafiltration using dialysate as substitution fluid needs special consideration. This technique is achieved by the infusion of large amounts of dialysate, ranging from 15–301 per session. Taking into account the maximal endotoxin load of 5 EU/kg, it is imperative to use sterile dialysate. The definition of sterility used in the pharmaceutical industry cannot be applied to an on-line prepared fluid. However, the maximal quality standards should be achieved for infused dialysate. Micro-organisms should be undetectable and endotoxin concentrations should be inferior to 0.01 EU/ml, the detection limit of the most sensitive Limulus amoeboocyte lysate assays. In addition, the benefit of enhancing clearances of high molecular weight uraemic toxins by haemodiafiltration should be compared for each
patient with the risk of infusing massive amounts of dialysate. Prospective studies are needed to identify which patients will benefit from this technique.

References