On-line haemodiafiltration. Safety and efficacy in long-term clinical practice

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Introduction

At present, on-line haemodiafiltration (HDF) offers the best renal replacement therapy (RRT) option for end-stage renal disease (ESRD) patients [1,2]. By combining diffusive, convective and adsorptive transfer in the same exchange module, HDF provides the highest clearances of both small and large solutes [3–5]. By maintaining the haemodynamic stability of the patient, HDF facilitates RRT based on a relatively short treatment time schedule (9–12 h/week) [6–8]. By combining the use of relatively inert high-flux membranes with ultra-pure dialysate and by preventing backtransport phenomena (back-diffusion, backfiltration), HDF offers a more haemocompatible dialysis system [9–11]. The on-line production of sterile and non-pyrogenic fluid by ultrafiltration [12] has several advantages: technical aspects of HDF are simplified; the overall cost of HDF is reduced [13,14], pharmaceutical-quality fluid production is virtually unlimited [15,16]; and bicarbonate-buffered infusate facilitates the correction of acidosis [17]. Finally, on-line HDF provides a multipurpose treatment option permitting all kinds of treatment modalities [18].

Fifteen years ago, we surmised that on-line HDF was the optimal RRT for ESRD patients [19,20]. Following preliminary clinical studies confirming the high performance, the excellent haemodynamic tolerance of HDF and the safety of cold-sterilization processes, provided good medical practices were respected, on-line HDF was developed and extended to virtually all dialysis patients in our group [21]. The aim of this paper is to report our 13 years of clinical experience on on-line HDF. The study covers two aspects: first, analysis of the population treated, and second evaluation of the microbiological safety and efficacy of high-flux HDF used routinely.

Patients and methods

Patients

On-line HDF, initiated in our institution in 1984, has been steadily developed and extended to become our conventional long-term RRT proposed to virtually all ESRD patients. Several of our patients have been treated by other dialysis modalities, haemodialysis (HD), haemofiltration (HF) or continual ambulatory peritoneal dialysis (CAPD) before being transferred to HDF. Because of our role as a regional referring kidney centre, it must be noted that the ESRD population treated is negatively selected as shown by the comorbidity status and is exposed to a high transfer rate.

Over the period 1984–1997, 242 ESRD patients referred to our institution were treated by on-line HDF for 3 months or more in two separate dialysis units (Lapeyronie Hospital Facility and a satellite unit, USDA) based on the same operational conditions. They consisted of 140 males and 102 females with a mean age of 56.7±17.2 (22–94) years. Treatment duration on RRT prior HDF was 32.2±63 months.

The underlying nephropathies were as follows: chronic glomerulonephritis in 34%, hypertensive and nephroangiosclerosis in 21%, systemic disease with secondary renal involvement in 16% (including myeloma, lupus, Wegener, Goodpasture, active cancer, vasculitis, scleroderma, amyloidosis), chronic interstitial nephritis in 14%, autosomic polycystic kidney disease in 8% and diabetes in 7%. Vascular access was obtained via native AV fistula in 80% and polytetrafluoroethylene (PTFE) graft in 8.3%, permanent double catheters (TwinCath [22]) were inserted in 1.7% and others (Thomas shunt) in 1.8%. AV shunts are usually punctured with two 15-gauge needles. Blood flow rate, prescribed according to vascular access, was between 300 and 400 ml/min. The majority of patients (205) were anurics. The residual glomerular filtration rate (GFR) averaged 0.5±0.4 ml/min in the remaining patients.

On-line HDF, treatment schedule and operational conditions

The treatment schedule was based on three HDF sessions/week for all patients with a session lasting 3–4 h.

On-line HDF was performed using a specifically adapted dialysis machine [23] (Fresenius 2008 C,E and 4008E, Fresenius, Bad Homburg, Germany) producing ultra-pure
bicarbonate dialysate at a rate of 600–700 ml/min, of which 100 ml/min was diverted by an infusate pump for two further steps of filtration before being infused post-filter into the blood of the patient serving as substitution or replacement fluid [24] (Figure 1). Simultaneously, the ultrafiltration pump and fluid-balancing module of the dialysis machine compensated for the diverted fluid by ultrafiltering an equivalent amount of plasma from the patient. The final microfilter placed on the infusate line before the blood venous bubble trap consisted of a removable disk filter (0.45 μm) held in a plastic housing. The infusate pump was controlled by the safety monitors and general alarms of the dialysis machine. Total dialysate flow rate delivered by the dialysis machine was $710 \pm 20$ ml/min. Diverted infusate flow rate was $93.3 \pm 2.1$ ml/min. Ultrafiltration flow rate, including body weight loss, was $110.2 \pm 3.1$ ml/min. Dialysate and infusate electrolyte compositions were similar (in mmol/l): Na, $140 \pm 2$; K, $2 \pm 0.2$; HCO$_3$, $36 \pm 2$; Ca, $1.5 \pm 0.1$; Mg, $0.5 \pm 0.1$; Cl, $105 \pm 2$; glucose, 11; acetate, 4.

HDF operational conditions were as follows: the HDF session duration was 208 ±26 min; the effective blood flow rate, measured by the transit bubble time over a calibrated race track tubing segment, was $359 \pm 3$ ml/min; mean total recirculation rate (urea and creatinine) was $11 \pm 3$% unfractionated heparin was used for anticoagulation as an intravenous bolus dose of 50 ± 15 IU/kg followed by a continuous infusion of 1000 IU/h of dialysis.

Highly permeable haemodiafilters (HF80, polysulfone capillary filter, 1.8 m$^2$, Fresenius) were used for all patients. Automatic reconditioning of HF80 was performed immediately after HDF sessions on specific machines (Renatron, Renal Systems, Minneapolis, MN, USA) using peracetic acid solutions (Dialox, CFPO, Paris, France) as the sole cleaning and disinfecting agent until January 1995 [25,26]. HF80 filters were reused up to 20 times. Single use of HF80 was then maintained after 1995. 

On-line HDF performances, treatment adequacy

Dialysis adequacy was monitored according to standard clinical and biochemical criteria. Sixty-two ESRD patients out of the global population currently being treated by on-line HDF were used to evaluate HDF performance. Quantitative assessment of HDF efficacy was based on the analysis of major solutes [27]; urea, creatinine, phosphorus, β$_2$-microglobulin (β$_2$-M). Urea kinetic modelling (UKM) analysis based on a double pool equivalent model was performed monthly over an entire HDF cycle [28].

UKM analysis was used to determine effective dialysis dose delivered (Kt/Vdp), urea time-averaged concentration (urea TAC), and normalized protein catabolic rate (nPCR, g/kg/24 h) as a reflection of the dietary protein intake. In addition, urea, creatinine, phosphorus and β$_2$-M removal were evaluated according to the solute percentage of reduction per session. β$_2$-M time averaged concentration (β$_2$-M TAC) was also calculated to demonstrate the lower β$_2$-M values obtained in the long-term, with its potential benefits on amyloidosis risk in long-term dialysis patients.

On-line HDF safety, microbiological monitoring and disinfection procedures

The safety of the on-line production of infusion fluid was implemented routinely as follows: (i) feeding the dialysis machine with ultra-pure water produced by reverse osmosis (polyamide, U7000, Gambro, Lund, Sweden or polysulfone, HF80, Fresenius) [32]; (ii) the first stage of cold sterilization of the fresh dialysate was produced by ultrafiltration (polyamide, U7000, Gambro, Lund, Sweden or polysulfone, HF80, Fresenius) [32]; (iii) the second stage of cold sterilization of the infusate was produced by ultrafiltration; (iv) the final bacterial microfiltration of the infusate on a disposable 0.45-μm filter membrane (Millipore, Bedford, TX, USA), which was changed after every session (Figure 1). This 0.45-μm membrane was cultured on a R2A medium to check a posteriori the purity of the infusate [33–35]; (v) detection of endotoxin infusate was carried out using a kinetic chromogenic Limulus amebocyte lysate (LAL) assay with a detection of 0.005 EU/ml (Whittaker); (vi) the dialysis machines and ultrafilters were disinfected after each session and filled during night with a peracetic acid solution. Dialysate ultrafilters were replaced every 2 months. The water production and distribution system was disinfected weekly with a mixture of peroxyhydrogen, acetic acid and peracetic acid solution.

Microbiologic results collected over the last 3 years (1994–1997) in our two units are used to summarize the safety of on-line HDF treatment. Bacterial contamination and the endotoxin content of the treated water and the ultrafiltered dialysate are summarized in Figure 3. Bacterial contamination of the 0.45-μm membrane used as final infusate control is presented in Table 1.

Calculation and statistics

Results were expressed as means ± SD. Significant differences according to time were analysed using the paired t-test, comparison being made with the initial value. Probability for significance was accepted for P < 0.05.

Urea and creatinine kinetic analyses were performed using a double pool, variable volume model programmed on a personal computer. β$_2$-Microglobulin concentrations following HDF were corrected for extracellular space contraction as proposed by Bergstrom et al. [36].

Results

Overall HDF experience

HDF population. Of the 242 ESRD patients who started HDF, 56 are still treated regularly using the same modality, 47 received a cadaveric kidney transplant,
Fig. 2. Water-treatment system and distribution loop ensuring production and distribution of ultra-pure water to HDF machines.

Fig. 3. Bacteriometry and endotoxin content of the different sampling sites from tap water to dialysate flowing through the haemodiafilter over a 3-year period.

67 were transferred to another dialysis facility for commodity reasons, four had a late kidney function recovery and 69 died. Causes of death were as follows: cardiovascular disease in 34 (49.2%), evolution of systemic disease (cancer, myeloma) in 15 (21.7%), cachexia in 10 (14.5%), ischaemic colitis in six (8.8%) and cerebrovascular disease in four (5.8%). It is interesting to note that no one case of death may be imputed to the on-line HDF method per se.

Survival. Technical and patient survival are presented in Figure 4. As shown, median technical survival was short at 36 months reflecting the high turnover rate of
Table 1. Infusate bacteriometry over a 3-year period accounting for 19 200 HDF sessions and a total production of 533 594 l of substitution fluid

<table>
<thead>
<tr>
<th>Membranes cultured</th>
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<tr>
<td>HDF sessions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>18 465</td>
<td>96.2</td>
</tr>
<tr>
<td>Positive</td>
<td>735</td>
<td>3.8</td>
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<tr>
<td>Total</td>
<td>19 200</td>
<td>100.0</td>
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<td>Positive membranes</td>
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<td>n cfu</td>
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<tr>
<td>1–9</td>
<td>663</td>
<td>90.2</td>
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<tr>
<td>10–99</td>
<td>48</td>
<td>6.5</td>
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<tr>
<td>100</td>
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<td>3.3</td>
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<td>Total</td>
<td>735</td>
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Safety of infusate production

The microbiological safety of the on-line production was confirmed on a long-term basis provided that the bacteriological purity of the feeding water was ensured and the disinfection procedures were respected. Microbiologic results collected over the last 3 years (1994–1997) in our two units are used only to evaluate risks and hazards of the on-line HDF treatment. In total, 19 200 HDF sessions were performed during this period and 533 594 liters of infusate were analysed.

Pyrogenic reactions (temperature > 38.5 °C not explained clinically) noted during or following the HDF sessions were six episodes accounting for 3.6 episodes for 10 000 HDF sessions. Apart from these episodes, it is interesting to note that body temperature did not change significantly before and after HDF (36.5 ± 0.3 °C; 36.6 ± 0.3 °C).

An inventory of the bacterial contamination and endotoxin content of the treated water and filtered dialysate are summarized in Figure 3. Bacterial contamination of the infusate was controlled by means of the 0.45-μm membrane. During this period, 533 594 l of infusate, representing 19 200 HDF sessions, were produced and analysed. The results are presented in Table 1. Of the 18 465 membranes cultured, 735 were positive. In 90.2% of cases contamination was less than 10 cfu/membrane, 6.5% were less than 100 cfu/membrane and 3.3% were between 100 and 1000 cfu/membrane. Each 0.45-μm membrane filtered a mean of 30 l. The endotoxin content of the infusate determined with a sensitized LAL assay was found in all cases to be under 0.25 EU/ml and in 99.0% to be lower than 0.005 EU/ml.

Efficacy of high-flux HDF

Dialysis adequacy. Dialysis adequacy was easily achieved in all patients according to standard clinical and biochemical criteria.

Survival, %

<table>
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<th>n pt</th>
<th>242</th>
<th>77</th>
<th>43</th>
<th>23</th>
<th>13</th>
<th>10</th>
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<th>4</th>
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Fig. 4. Technical and patient survival of 242 ESRD patients starting HDF.
Fig. 5. Patient survival of HDF patients according to their nephropathy and comorbidity. CGN, chronic glomerulonephritis; HT, hypertension; CIN, chronic interstitial nephritis; Syst Dis, systemic disease; APKD, autosomic polycystic kidney disease; Diab, diabetes.

Dialysis dose. Effective urea Kt/Vdp averaged 1.50 ± 0.27, while urea TAC and PCR were 16.1 ± 0.9 mmol/l and 1.04 ± 0.30 mmol/l. Per cent reduction of urea, creatinine and phosphorus during HDF session (not taking into account post-HDF rebound) were 75.4 ± 5.3, 68.8 ± 4.8 and 51.8 ± 10.3%, respectively.

Arterial pressure control. Supine systolic and diastolic pre-HDF arterial pressure averaged 139 ± 19 and 76 ± 9 mmHg. Twenty per cent of patients were using one antihypertensive medication. Net ultrafiltration during HDF session was 0.618 ± 0.240 l/h of dialysis. The average dry body weight of our patients was 64.2 ± 13.3 kg.

Nutritional status. Lean body mass estimated from creatinine generation rate averaged 44.19 ± 0.3 kg, which is 70 ± 15% of body weight. Creatinine TAC was 589 ± 2.6 mmol/l. Normalized protein catabolic rate equivalent to diet protein intake in a stable patient was 1.04 ± 0.26, which became 1.17 ± 0.2 when normalized to lean body mass. Albumin and pre-albumin were 38.7 ± 3.4 g/l and 348 ± 85 mg/l respectively.

Acidosis control. Bicarbonate concentrations pre- and post-HDF were 21.1 ± 2.1 and 25.4 ± 2.1 mmol/l, respectively.

Calcium and phosphorus control. Serum calcium concentrations pre- and post-HDF were 2.37 ± 0.18 and 2.61 ± 0.24 mmol/l, while serum phosphate concentrations varied between 1.62 ± 0.41 and 0.76 ± 0.19 mmol/l, respectively. Calcium carbonate was used as a phosphate binder in all patients with a mean daily prescribed dose of 4.0 ± 4.4 g/day. Calcidiol and calcitriol (oral 95%, i.v. 5%) were used in virtually all patients with a mean weekly dose of 1.9 ± 1.7 µg. Three subtotal parathyroidectomies were performed during this period for secondary hyperparathyroidy refractory to medical treatment.

Anaemia and rHu-EPO. Mean haematocrit was 32.6 ± 4.1% before the HDF session. Fifty per cent of patients received r-HuEPO (96.7% subcutaneous, 3.3% intravenously) at a mean weekly dose of 6853 ± 5500 IU. Iron supplementation was performed mainly intravenously either as a 1000 mg cure over 10 weeks or as regular dialysis 100 mg supplement per week.

β2-M and β2-M-related amyloidosis

Blood β2-M concentrations were 30.6 ± 11.8 and 8.5 ± 4.8 mg/l in the pre- and post-HDF periods. Post-HDF β2-M concentration was corrected for the extracellular volume contraction, β2-M time averaged concentration was estimated at 17.2 ± 7.5 mg/l.

In this population, 21 ESRD patients were treated by HDF for 5 years or more. In 10 patients on-line HDF was the first and only RRT modality used. None of them developed any symptoms of β2-M-related amyloidosis detectable either clinically or by imaging. In nine patients, in whom β2-M-related amyloidosis
was present before the start of HDF, symptomatology was not improved. However, it is interesting to note that HDF was able to relieve pain during the first 3–6 months of treatment.

**Discussion**

HDF with the on-line production of substitution fluid, as shown in this 13-year study, offers a safe, highly efficient and economical method adapted to treat chronic uraemia with a relatively short treatment time (9–12 h/week).

Infusate production by direct filtration of dialysate requires a clear understanding of the risks and careful monitoring of procedures to ensure the long-term viability of the method. Cold-sterilization of dialysate by ultrafiltration was confirmed as an effective [37] and safe procedure when good practice of production, distribution, handling and microbiological monitoring was satisfied [38,39]. The incidence of pyrogenic reactions (3.6/10,000 sessions) observed during the study period remains low compared with what was reported in high-flux haemodialysis [40]. The ultrapurity of the dialysate delivered was confirmed in all cases, with quite a low level of contamination (<10 cfu/l). Sterility and non-pyrogenicity of the substitution fluid was proved by routine bacteriometric monitoring of the infusate. The limitation of the LAL assay in detecting small fragments of native endotoxins or exotoxins is well known [41]. However, the lack of body temperature changes in our patients through the HDF session, is consistent with the sterility of the dialysate and infusate, and tends to confirm the very low haemocompatibility of the on-line HDF system.

Because of its good vascular stability, high-flux HDF permitted dialysis adequacy to be achieved easily in all patients in a relatively short treatment time (9–12 h/week) [42,43]. At present, the well-preserved intradialytic haemodynamic stability during HDF is not clearly understood. Peripheral vasoconstriction induced by caloric losses via the extracorporeal circuit may be one reason [44]. Removal of vasoactive substances associated with the convective transport phenomenon may be another [45]. Blood pressure was maintained within the normal range in the majority of patients on a long-term basis. Twenty per cent of patients required low-dose antihypertensive drugs (a single drug in all cases) to achieve this primary and essential goal of dialysis adequacy. Correction of acidosis, a major catabolic factor, was also quite satisfactory. Predialysis bicarbonate concentration averaged 21.1 ± 2.1 mmol/l. This correction is clearly facilitated by the use of bicarbonate-buffered infusate. The high efficiency of HDF was confirmed in this study both for small (urea, creatinine, phosphate) and large solutes ($\beta_2$-M) [46]. Body urea Kt/Vdp averaged 1.5. This value is associated with the least morbidity and mortality in dialysis patients and has been proposed as a gold standard [47–49]. The nutritional status of the HDF patients was preserved in the majority of cases as confirmed by the normality of protein markers (albumin and pre-albumin). When dietary protein and/or caloric intake are reduced, it is interesting to note that on-line HDF offers a convenient route for intradialytic parenteral nutrition. In this case, the volume of the nutritional mixture, easily administered post-filter via the infusate line, is automatically compensated for, as the infusate volume is reduced proportionately by the HDF machine.

Is on-line HDF capable of preventing $\beta_2$-M-related amyloidosis? This is probably the more crucial concern for the nephrologist. Clinical experience with HDF is too short to provide any definite answer. On-line HDF in its present form provides the most haemocompatible system reducing the bioreactivity of dialysis by acting on both the membrane and dialysate. Blood–membrane interaction is reduced in the haemodialyzer by the formation of a second protein layer ‘passivating’ the membrane [50,51]. HDF prevents back-transport phenomena from occurring: back-filtration is prevented by the high ultrafiltration rate, back-diffusion is reduced by the protein-coating effect of the membrane [52]. HDF also offers the most efficient RRT modality for removing large-molecular-mass substances [53–57]. As illustrated by this study, removal of $\beta_2$-M by HDF averaged 70% of the circulating pool, ensuring a serum $\beta_2$-M TAC averaging 18 mg/l. Such reduced $\beta_2$-M concentrations may prevent or delay the occurrence of $\beta_2$-M amyloidosis deposits in long-term dialysis patients, but this is purely speculative. It is also worth noting that of the patients treated exclusively with HDF for 5 years or more, none presented any symptoms of $\beta_2$-M-amyloidosis. HDF may also provide the only RRT option able to remove AGEs, a new class of uraemic toxin, which appears implicated in the genesis of long-term dialysis-related complications ($\beta_2$-M-amyloidosis, atherosclerosis, ageing) [58–60]. The on-line production of sterile pyrogenic solution for i.v. infusion by cold sterilization is a major technical advance in RRT, which will permit the implementation of new technical developments such as volumetric biofeedback loop or total automation of dialysis machine for daily home treatment.

In conclusion, on-line HDF offers a safe and highly efficient RRT modality for ESRD patients which has been routinely performed for more than 10 years in our institution. It is now time to define good medical practice in this field to facilitate on-line HDF implementation in standard dialysis facilities.

**References**

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