Clinical perspectives of on-line haemodiafiltration

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**Introduction**

Compared with haemodialysis, convective blood cleansing seems to improve cardiovascular tolerance to fluid removal [1,2] and to lessen the patient’s burden of $\beta_2$-microglobulin [3,4]. However, the high cost of haemodiafilters and of commercially produced reinfusion fluids is a limiting factor for the widespread use of convective procedures, particularly in this era of limited health care funding. Filter re-utilization is a method extensively employed in the US for cutting costs, but it is associated with some unwanted effects [5].

**On-line production of infusion fluids**

To obtain on-line, low cost, high quality infusion fluids, two approaches have been chosen:

**Regeneration of ultrafiltrate**

Already 20 years have been passed since the pioneering work of Shaldon who introduced regeneration of the ultrafiltrate with the REDY cartridge [6]. Later, some groups followed the same approach with some modifications [7–15]. However, all researchers faced problems of sterility, complexity of the extracorporeal circuit and inadequate composition of the regenerated fluid, such as high concentrations of nitrogen-containing compounds and/or aluminium, low calcium concentrations, etc. Therefore, the interest in this approach has decreased gradually during the last few years.

**Cold filtration of dialysis fluid**

This approach was also first described in 1978 by Henderson [16]. In this pilot investigation, the reinfusion fluid was prepared off-line by dialysis fluid filtration through hollow fibre ultrafilters made of XP-50 membrane and collected in sterile glass carboys before being reinjected into the patient. This approach attracted the interest of nephrologists and suppliers of dialysis equipment and, in 1981, Ramperez et al. published their experience with on-line haemodiafiltration (HDF) with a modified Gambro monitor [17].

**Popularity of on-line techniques**

Since that time, many reports have been published on the feasibility and safety of on-line treatments [18–27]. Moreover, some studies on ionic balance and anticoagulation in on-line HDF have been published [28–32]. This probably means that some researchers, having gained confidence in the safety of on-line prepared fluids, are currently starting to study the potential advantages and peculiarities of on-line treatments. Beyond the published experience, there is a widespread application of on-line treatments nowadays. For instance, $>1000000$ on-line HDF treatments have been performed so far in Europe with Fresenius monitors (G. Orlandini, Fresenius Medical Care, personal communication).

**On-line techniques**

Today, several multipurpose or specifically adapted monitors for on-line techniques are available in the market, e.g. Fresenius 2008E or 4008E, Bellco Multisystem, Gambro AK100 Ultra. On-line HDF, haemofiltration or paired filtration–dialysis are performed in post- and/or pre-dilution mode by re-injecting into the patients part of the dialysis fluid continuously collected by the infusion pump. Dialysis fluid is filtered through two or three filters (polysulfone or polyamide membrane) before being reinjected. The fluid balancing system of the monitors operates in such a way that the ultrafiltration pump draws automatically from the blood a volume of ultrafiltrate...
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exactly corresponding to that reinjected as replacement fluid plus the amount corresponding to the programmed weight loss (Figure 1).

Advantages of on-line techniques

On-line techniques present advantages in terms of clinical benefits as well as considerable organizational advantages. On-line produced replacement fluid contains bicarbonate, a more physiological buffer than the lactate usually employed in commercial bags, and its composition can be modified easily at the bedside merely by adding electrolytes and/or solutes to the acid dialysate concentrate. The replacement fluid temperature can also be modified easily, simply by adjusting the dialysate temperature, thus avoiding replacement fluid heaters. Moreover, the on-line production of replacement fluids results in cost savings for purchase and storage of commercial fluid bags. By this means, the disposal of plastic containers is also solved, thus avoiding an environmental burden. Finally, on-line treatments do not cause an additional workload for the staff. In comparison with standard convective treatments, the slight increase in the sterilization time of the dialysis machine is amply compensated by the easy manageability of the on-line treatment. No connections of infusion bags, known as a source of contamination, are necessary, and the control of weight reduction can be managed independently of interventions by the nursing staff since this is controlled completely by the dialysis machine.

Safety of on-line techniques

All the studies published so far [16–27] have pointed out that on-line prepared fluids can be used safely. The incidence of pyrogenic reactions varied between 0 and 0.2% of the treatments, and none of the authors has reported any severe pyrogenic reaction. Notwithstanding this reassuring evidence, the introduction of techniques with on-line production of replacement fluid still raises concerns among the overwhelming majority of nephrologists regarding exposure of dialysis patients to pyrogenic substances.

Our clinical experience

Our experience with on-line treatments started in January 1991. During the course of 7 years, we have used all commercially available monitors and all types of treatment modalities. Altogether, up to September 1997, we have performed 4750 treatments and reinjected 117 000 l of reinfusion fluid. Thirteen patients

Fig. 1. Schematic diagram of on-line haemodiafiltration performed pre- or post-dilution.
have been treated for $32 \pm 7$ months, with a range of 24–48 months.

We recently have addressed the problem of safety of on-line treatments by very sensitive in vitro and in vivo tests [27]. The results of our experience are summarized here.

(i) The quantitative Limulus amoebocyte lysate (LAL) test of on-line prepared reinfusate always remained below the detection limit of the method (<0.01 EU/ml), while it detected measurable amounts of endotoxins (0.023 ± 0.011 EU/ml, mean ± SD) in commercially available reinfusion fluids.

(ii) We found no difference in the continuous core body temperature recording of patients ('human fever assay') over the course of on-line and standard treatments and the ensuing 24 h.

(iii) The production by normal human monocytes of tumour necrosis factor $\alpha$ (TNF$\alpha$), interleukin 1$\beta$ (IL-1$\beta$) and interleukin-1 receptor antagonist (IL-1RA) [peripheral blood mononuclear cell (PBMC) assay] did not result in significant differences when the monocytes were incubated with either on-line prepared reinfusate or commercially available fluids.

(iv) In patients treated for 26 months, on average, with on-line HDF, the plasma concentrations and the monocyte production of cytokines were comparable with those recorded in a control group of patients treated with traditional convective procedures.

(v) Compared with the previous period on standard haemodialysis, on-line HDF afforded a better cardiovascular tolerance to fluid removal and did not adversely affect patients’ well being, as assessed by indexes of nutritional status, serum acute phase protein and $\beta_2$-microglobulin-associated osteopathy.

These results deserve some comment. The endotoxin concentrations we found with LAL tests in commercial fluids were greater than those found in on-line produced fluids, though still 10 times less than the maximum accepted by the European Pharmacopoeia or AAMI standards (0.25 UE/ml). These limits, established many years ago, are far from reassuring because they do not take into account the large volumes infused with haemofiltration or HDF. It is only thanks to the manufacturers, who stay well under the limits established by law, that we do not administer during standard convective treatments an endotoxin load far greater than the pyrogen threshold for humans, i.e. in the range of 10–20 EU/kg body weight [33]. The exquisite sensitivity of the LAL assay allows measurement of sub-pyrogenic concentrations of endotoxin. However, LAL cannot be considered the ‘gold standard’ for endotoxin or its derivatives because it also reacts with non-pyrogenic substances while it does not respond to pyrogens not derived from endotoxin, such as peptido-
glycans, muramyl-dipeptides, staphylococcal toxic shock toxin, exotoxin A derived from Pseudomonas species and other substances yet to be specified [34,35]. To overcome these limitations, we carried out other tests to investigate the potential hazards of on-line prepared fluids further. The results of the ‘human fever assay’, PBMC assay and of the patients’ cytokine response agree with LAL data. The results of all these tests still do not rule out, however, the possibility that long-term treatment with on-line prepared fluids will not cause hazardous effects. Indeed, it is well known that the plasma half-life of circulating cytokines is very short and, even in septic shock, their presence in plasma can be detected only transiently [36–39]. Moreover, over the last decade, the discovery of newer proinflammatory cytokines and cytokine-specific inhibitory proteins has raised new questions concerning the role of cytokines in dialysis patients [36,40]. Thus, assessment of on-line fluid pyrogenicity in the long-term cannot rely only on sophisticated but sporadically performed cytokine tests, as is the case in chronic diseases [41].

Since the first proposal of the ‘cytokine hypothesis’ [42], many uraemic features have eventually been attributed to chronic cytokine activation: cardiovascular instability, malnutrition, induction of hepatic acute-phase proteins, $\beta_2$-microglobulin osteopathy, etc. [36,40,43–45]. Our observational study shows that none of these symptoms appeared de novo or worsened during a follow-up lasting 2–4 years. Last but not least, we have never observed pyrogenic reactions in the 4750 on-line treatments performed up to now.

Our findings and the literature data on safety of on-line techniques are noteworthy, particularly if compared with those obtained in standard convective treatments. For instance, in the West Germany survey [46] on haemofiltration with commercially produced substitution fluid, 254 febrile reactions in 135 000 treatments were recorded, an incidence of 0.19%, with 24 reactions necessitating admission to the intensive care unit; 12 of the 24 patients died. The authors conclude: ‘using on-line production of infusate, there is no relevant interval between production and use of infusate and therefore the time available for bacterial growth is limited. ... In this case this technique cannot be provided, we advise not to treat patients by haemofiltration’.

Conclusions

There is increasing evidence in the literature to suggest that on-line produced reinfusion fluids are as safe as industrially manufactured fluids with respect to sterility and apyrogenicity. Notwithstanding this evidence, standard convective treatments conform to legal demands while for on-line treatments the legal basis was not defined. In the meantime, the conformity is also given for the latter technique considering the demands by the current legislation which have to be followed by the manufacturer as well as by the user.

Since the available literature is not representative of all existing experience with on-line HDF, prospective multicentre studies are mandatory in order to cut the Gordian knot of safety of on-line treatments and, by doing so, to obtain licences for this technique from the Health Service Authorities in different countries.