ECONOMIC PREPARATION OF STERILE PYROGEN FREE INFUSATE FOR HAEMOFILTRATION

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Introduction

The high cost of commercial sterile replacement solutions, together with the risk of their contamination during storage, have limited the expansion of haemofiltration as a therapy for end stage renal disease.

Following the initial success of Henderson [1] in producing sterile pyrogen free fluid by ultrafiltration through an Amicon XP 50 polysulphone 1.6 m² hollow fibre ultrafilter, we have developed a system for production of sterile pyrogen free infusate for haemofiltration from treated tap water and haemodialysis concentrate with continuous monitoring of the integrity of the sterilising ultrafilter.

Methods

Tap water is first passed through a cation exchanger (domestic water softener) to remove excess calcium and then through a carbon filter to eliminate chlorine and chloramine and finally through a reverse osmosis system after preheating to 20°C in order to increase the yield (Figure 1). The reverse osmosis (RO) membranes used were either cellulose acetate in sheet form or polyamide in hollow fibre. The 'clean' water obtained from the pretreatment system is delivered at about 2.0L per minute to a modified Gambro haemofiltration monitor HFM 10. The HFM 10 has been modified to handle automatically batch blending of 'clean' water and concentrate, and then to monitor the conductivity, temperature and integrity of the sterilising filter prior to injection of the infusate into the blood stream (Figure 2). The microprocessor programme of the HFM 10 will stop the water input to a container which is being weighed by a load transducer, when the desired weight of fluid added to the container is reached. During filling a volume of concentrate is added to the container, such that at the end a volume of infusate up to 30L has been batch blended. The cutting off of the water input is effected by a solenoid valve controlled by the microprocessor. After completion of the batch, the solution is mixed manually using a plastic fly swatter. The container for the batch is
Figure 1. Batch blended preparation of sterile infusate. Pretreatment of water

Figure 2. Batch blended preparation of sterile infusate. Automatic 'batch' blending and sterilisation of infusate, with continuous monitoring of integrity of sterilising filter. The dots in the loop around the polyamide sterilising filter represent the recirculation of the 2% dextran blue solution in the closed loop (see text)

lined by a sterile disposable 'food quality' polyethylene plastic liner sac to eliminate the need for cleaning the container between uses. The 'batch' is pumped by the infusion roller pump of HFM 10 through a heater and conductivity cell to check on temperature and correct dilution of the concentrate, so that if the
temperature exceeds 41.5°C or the conductivity exceeds the desired level by plus or minus 3% the infusion pump is stopped and an alarm is sounded. The fluid then enters a closed loop with a dead space volume of 200ml, containing a 1.2 m² hollow fibre polyamide haemofilter (Gambro FH 202) (used as a sterilising filter) together with a recirculating circuit around which is pumped, by a recirculating pump, a 2% solution of dextran blue (Sephadex quality - Pharmacia) with a homogenous molecular weight of 2 x 10⁶ daltons. The flow in the recirculating loop is about 400ml per minute (200ml per minute of dextran blue dead space solution, and up to 200ml per minute throughput of the infusate by infusion pump under microprocessor control for balance) during clinical use of the HFM 10 for haemofiltration in a post dilutional mode. The driving pressure required to produce this throughput of ‘batch’ infusate at 200ml per minute is 400mmHg.

The fluid is ultrafiltered out of the closed loop across the polyamide membrane of a FH 202 haemofilter and passes through an UV photo-electric detector cell capable of measuring dextran blue in a concentration of 1 x 10⁶. The cell will activate the alarm system of HFM 10 if the blue is detected and stop the infusion pump. Otherwise, the fluid passes through the detector cell and enters the extra-corpooreal blood circuit after passing through a plastic non return valve. The whole unit including the water pretreatment systems is sterilised in 2% formalin between uses. Before each individual use in the home, and daily in a centre when the system is used for more than one patient, the system is rinsed with water for one hour to reduce the formalin content to less than 1ppm, before the production and monitoring and infusion of sterile infusate.

Initial testing of the polyamide filter FH 202 confirmed its ability to sterilise contaminated solutions and to totally remove bacterial added pyrogen as measured by the limulus lysate assay method. Non bacterial pyrogen was successfully removed by the RO system, as measured by the rabbit assay. All samples down stream of the FH 202 filter have been consistently sterile and non pyrogenic. It appears therefore that polyamide is as effective a bacterial and pyrogen filter as polysulphone, when used to produce sterile non pyrogenic solutions from ‘clean’ pre treated water. It has the additional advantage of being three times more permeable to water and thus necessitating a lower driving force for fluid production, although the membrane resistance is only 10% of the total resistance caused by the recirculation of 2% dextran blue solution.

Results

The system has been used for up to three years with 16 different water sources (13 homes and 3 centres) for production of sterile infusate for haemofiltration. In the last 3000 consecutive treatments (60,000L) no pyrogen reaction has been observed. The average filter life has been 10 months, to produce 2500L of fluid. The dextran blue has remained inert and has not been broken down into smaller molecules by bacterial degradation, probably because of sterilisation between uses and short exposure time to clean water without formalin, on average less than 4 hours.

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Discussion

The ability of the dextran blue monitoring system to detect pin hole leaks in the FH 202 filter is vital to the security of the system. To date it has functioned perfectly and when filters with a pin hole leak have been tested, the detection system has always picked them up. The clinical results confirm the safety of the system. It is to be hoped that further experience with the monitoring system will convince others of the safety of batch blended preparation of sterile infusate for haemofiltration.

On-line preparation using a proportioning system will simplify the procedure. We already have considerable experience of this technique in an on-line situation with haemodialysis [2]. By using dialysate produced from ‘clean’ water and concentrate proportioned in a dialysate proportioning system with minimum dead space and no blind loops, we have eliminated the use of sterile IV fluids for priming and dialyser rinsing as well as restitution of blood at the end of dialysis. The ‘clean’ dialysate is drawn from the machine and passed through a FH 202 filter prior to entering the blood circuit. Thus it seems realistic to anticipate a significant reduction in haemofiltration costs using this technique in the future.

References

1 Henderson LW, Beans E. *Kidney Internat 1978; 14:* 522
2 Ramperez P et al. *Abstract 16th Congress of EDTA. Book of Abstracts 1979:* 77