

SMALL AND MIDDLE MOLECULE REMOVAL IN HYPERTONIC HAEMODIAFILTRATION

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Summary

In seven uraemic patients we assessed the efficiency of standard 270 minute haemodialysis and of a peculiar model of 180 minute hypertonic haemodiafiltration, at a pair-matched blood and dialysate flow rate.

Due to the exceedingly higher clearances observed in hypertonic haemodiafiltration for small (urea, creatinine, uric acid, phosphorus) and middle (netilmicin, inulin) molecular weight solutes under study, hypertonic haemodiafiltration allowed a 33 per cent reduction in dialysis treatment time, achieving a similar small molecule removal (except for a lesser urea elimination), and a larger middle molecule removal, when compared to haemodialysis of 270 minutes.

Introduction

Haemodiafiltration seems to be an effective alternative to haemofiltration and to haemodialysis: the rationale for haemodiafiltration is to achieve a higher removal of small molecules than with haemofiltration and a greater elimination of water and middle molecules than with haemodialysis, due to the combination of convective and diffusive transports [1].

In order to increase the dialysis tolerance and cardiovascular stability of haemodiafiltration, we have developed a particular model of short time (180 minutes) hypertonic haemodiafiltration, with an ultrafiltration rate of 60ml/min and a post-dilution hypertonic reinjection (Na^+ , Cl^- , HCO_3^- : 220, 120 100mEq/L respectively; Bari-Bic, Bieffe, Italy); a standard acetate dialysate is used, containing ~135mEq/L of Na^+ ; the dialyser used has a 1.2m^2 polyacrylonitrile membrane (Biospal 3000S, Hospal, Italy) [2].

The present study compares the efficiency of hypertonic haemodiafiltration sessions of 180 minutes to conventional haemodialysis sessions of 270 minutes with a similar dialysate (Q_D) and blood (Q_B) flow rate.

Materials and methods

Seven uraemic patients on maintenance dialysis underwent one session of hypertonic haemodiafiltration of 180 minutes, as described in the introduction section, and one session of acetate haemodialysis of 270 minutes with a cuprophan 1.0m² dialyser (H 10-10, Hospal, Italy), in a random sequence, always during the midweek dialysis. All hypertonic haemodiafiltration and haemodialysis sessions were performed with the same dialysate delivery module with a volumetric ultrafiltration control (Monitral, Hospal, Italy). In the haemodialysis and hypertonic haemodiafiltration sessions Q_D and Q_B were accurately pair matched, and were ~530 and ~400ml/min respectively.

For the purposes of the study, we selected four endogenous small molecules: urea, creatinine, uric acid and phosphorus and two exogenous solutes whose molecular weights are at the extreme limits of the middle molecule range: inulin, molecular weight ~3000, and netilmicin, an aminoglycoside antibiotic with negligible protein binding [3], molecular weight ~450. Inulin and netilmicin were injected intravenously to the patient 45 minutes before the start of each session, the former as a standard bolus of 5000mg, the latter at the dose of 2mg/kg of body weight.

At the start and at the end of each session blood samples were withdrawn from the arterial line, and at 60 minutes simultaneous arterial and venous blood samples were taken. The plasma concentrations of total protein and of the six above described solutes were measured; haematocrit was determined in the blood collected from the arterial line at 60 minutes. All the outcoming dialysate (D₀) and the ultrafiltrate (V_{UF}) were collected separately, and the concentrations of urea, creatinine, uric acid, phosphorus and inulin were determined (netilmicin concentration could not be reliably measured in these fluids).

Clearances at 60 minutes were calculated by the following formula:

$$K_w = Q_{wi} \frac{C_i - C_o}{C_i} + Q_{UF} \frac{C_o}{C_i},$$

where: K_w=clearance of a given solute, related to plasma water; Q_{wi}=plasma water flow rate at the dialyser inlet, calculated from the inlet blood flow rate (measured by the bubble method) corrected for haematocrit and then for total proteins [4]; C_i and C_o=plasma water concentrations of a given solute at the inlet and at the outlet of the dialyser, calculated correcting the measured plasma concentrations for total proteins [4].

The overall dialysis removal (R) of urea, creatinine, uric acid, phosphorus and inulin was calculated by the formula: R=C_{D₀} · D₀ + C_{UF} · V_{UF}, where C_{D₀} and C_{UF} are the concentrations of a given solute in D₀ and in V_{UF}.

For urea and inulin the extraction index (EI) was calculated:

$$EI = \frac{R}{\text{initial pool}} \times 100;$$

the initial pool of urea was calculated according to Kimura et al [5]. Urea,

creatinine and total proteins were measured by an autoanalyser (Astra 8, Beckman, USA); uric acid was measured by the uricase enzymatic method [6], phosphorus by a Technicon autoanalyser, inulin with the Heyrovsky's method [7], and netilmicin with the large plate, well-agar diffusion method [8] using *Staphylococcus aureus* ATCC 6538P as test organism.

For statistical analysis, paired Student's 't' test was used. All statistical data are expressed as means \pm SEM.

Results

K_w at 60 minutes for each solute under study was significantly greater in hypertonic haemodiafiltration than in haemodialysis (Table I).

TABLE I. Plasma water clearances (ml/min) of small and middle molecules in hypertonic haemodiafiltration (H HDF) and standard haemodialysis (HD)

	urea	creatinine	uric acid	phosphorus	netilmicin	inulin
H HDF (n=7)	154.4 \pm 4.3 *	136.9 \pm 3.8 **	110.7 \pm 3.9 *	115.8 \pm 2.9 *	133.1 \pm 10.1 **	64.5 \pm 4.5 **
HD (n=7)	120.1 \pm 6.5	101.4 \pm 5.2	79.0 \pm 4.3	81.7 \pm 7.3	82.1 \pm 4.2	15.1 \pm 4.7

* $p < 0.01$; ** $p < 0.001$. Paired Student's 't' test. Means \pm SEM

TABLE II. Removal (mg) of small and middle molecules in hypertonic haemodiafiltration (H HDF) and standard haemodialysis (HD)

	urea	creatinine	uric acid	phosphorus	inulin
H HDF (n=7)	40,934 \pm 3,672 *	2,904 \pm 157	995 \pm 51	1,611 \pm 215	2,343 \pm 290 **
HD (n=7)	45,158 \pm 4,120	3,045 \pm 150	1,021 \pm 85	1,685 \pm 153	1,162 \pm 249

* $p < 0.05$; ** $p < 0.01$. Paired Student's 't' test. Means \pm SEM

However, because of the 33.3 per cent difference in the treatment time between haemodialysis (270 minutes) and hypertonic haemodiafiltration (180 minutes), we observed (Table II) a greater removal of urea in haemodialysis, and no significantly different removal of creatinine, uric acid and phosphorus in the two methods; in the case of inulin, the longer treatment time in haemodialysis was not sufficient to compensate for the large difference in K_w : thus, removal of inulin was greater in hypertonic haemodiafiltration.

The behaviour of removal was reflected by the extraction index values: the observed extraction index for urea was 67 per cent in haemodialysis and 61 per cent in hypertonic haemodiafiltration ($p < 0.005$); in the case of inulin, extraction

index was 23 per cent in haemodialysis and 47 per cent in hypertonic haemodiafiltration ($p < 0.001$).

Discussion

The question whether uraemic toxicity is prevalently due to either small or middle molecules is still under debate [9,10]. Thus, at the moment a reasonable goal of dialysis therapy seems to be the simultaneous balanced removal of small and middle molecules. As haemodialysis and haemofiltration selectively remove only one class of molecules (small molecules the former, middle molecules the latter), haemodiafiltration can be an alternative strategy to achieve a satisfactory reduction of both classes of solutes by means of the combination of convective and diffusive forces.

The objection could be raised that our results show higher removal and extraction index of urea in the haemodialysis sessions of 270 minutes, compared to the hypertonic haemodiafiltration sessions of 180 minutes: this is true for our experimental study, in which we wanted to compare both treatments with similar high Q_B . However, the average Q_B for routine haemodialysis in our Centre is not greater than 300ml/min. On the other hand, in our Centre 12 patients are being treated with hypertonic haemodiafiltration (3 x 3hr/week) from 23.7 ± 4.2 months; their routine Q_B is ~ 400 ml/min. In other words, we can reasonably imagine that a routine session of 270 minutes at a $Q_B \leq 300$ ml/min would not provide a larger removal of urea when compared to a routine hypertonic haemodiafiltration session of 180 minutes at a Q_B of ~ 400 ml/min. Indeed, we did not observe any increase in plasma urea and other molecules after the switch of our patients from haemodialysis to hypertonic haemodiafiltration. Furthermore, hypertonic haemodiafiltration is a well tolerated procedure, despite the high Q_B and the high removal rate of fluids, owing to the hypertonic reinjection solution, as described elsewhere [2]; on the other hand, the same high Q_B (~ 400 ml/min), resulted in symptomatic haemodialysis sessions, when used in our experimental study.

In conclusion, hypertonic haemodiafiltration of 180 minutes provides a comparable removal of small molecules and an exceedingly larger removal of middle molecules, when compared to a routine haemodialysis of 270 minutes; thus, hypertonic haemodiafiltration may be a well-tolerated, routine method of long term treatment of uraemia.

References

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