Measuring Plasma Conductivity to Detect Sodium Load in Hemodialysis Patients

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Background: Sodium thiosulfate therapy has been proposed for calcific uremic arteriolopathy and nephrogenic systemic fibrosis in hemodialysis patients. The treatment brings 3.7 g (161 mmol) of sodium. How to counterbalance this sodium load was studied.

Design, setting, participants, & measurements: Plasma conductivity (Cp) and mass balance index were compared for 20 sessions without thiosulfate and 20 sessions with thiosulfate infusion. Subsequently, the dialysate conductivity was set to 13.8 mS/cm during the entire session. Next, dialysate conductivity was set to 14 mS/cm for the first 3 h and to 13 mS/cm for the last hour of thiosulfate infusion ($n = 25$).

Results: The Cp variation between beginning and end was equal to +0.005 ± 0.13 mS/cm without thiosulfate, +0.24 ± 0.13 mS/cm with thiosulfate, and 14 mS/cm dialysate conductivity ($P < 0.001$). The decrease in dialysate conductivity at 13.8 mS/cm did not counterbalance the sodium load. The last program adequately compensated the sodium load with a Cp increase of only +0.05 ± 0.14 mS/cm (NS *versus* without thiosulfate). The total of the dialyzed sodium and the sodium load for this last program was equal to 603 mmol compared with 456 mmol for the sessions without thiosulfate, the difference of 147 mmol being close to the known content of 161 mmol in 25 g of infused thiosulfate.

Conclusions: Thiosulfate infusion requires a decrease of dialysate conductivity of −1 mS/cm during the infusion to counterbalance the added 3.7 g (161 mmol) sodium load.

Clin J Am Soc Nephrol 3: 743-746, 2008. doi: 10.2215/CJN.03780907

Sodium thiosulfate treatment has been proposed to treat calcific uremic arteriolopathy in hemodialysis patients (1–4) and recently for nephrogenic systemic fibrosis (5). The dose is 25 g/1.73 m^2 per hemodialysis session during the last 60 min. The formulation of sodium thiosulfate is $Na_2S_2O_3 \cdot (H_2O)_5$ and the infusion of this amount of thiosulfate brings a clinically significant sodium load. The calculated sodium load for 25 g of thiosulfate is 3.7 g (161 mmol), corresponding to the amount of sodium contained in 1 L of isotonic sodium chloride infusion.

The two patients that underwent the thiosulfate treatment had developed severe calcific uremic arteriolopathy of the extremities. We decided to use sodium thiosulfate at a dose of 25 g per dialysis session. As we started the thiosulfate therapy, we rapidly noticed that the infusion induced a notable increase in plasma conductivity (Figure 1). Hence we recorded the plasma conductivity variation during the dialysis sessions under thiosulfate for the two patients and we modified the dialysate treatment to counterbalance the sodium load.

Received September 10, 2007. Accepted January 31, 2008.

Published online ahead of print. Publication date available at www.cjasn.org.

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Materials and Methods

All of the dialysis parameters were recorded on a central server. Integra Hospal Dialysis monitors are equipped with Diascan, a device that automatically measures ionic dialysance and plasma conductivity (6,7) every 15 min, an already validated method (8).

The infusion of thiosulfate was started after 3 h and lasted 1 h. Cp was recorded at the beginning of the dialysis, after 3 h, and at the end of the dialysis for the first ten dialysis sessions on thiosulfate and for the ten previous ones without thiosulfate for the two patients. Forty dialysis sessions were available for analysis, 20 without thiosulfate and 20 with thiosulfate. The per-dialytic variations of Cp and the mass balance index (MBI) with thiosulfate were compared with the ones without thiosulfate (*t* test for nonpaired variables). Dialysate conductivity (Cd) was set to 14 mS/cm. Blood recirculation on both catheters was measured by Transonic and was under 5%. The MBI provided by Diascan was compared with the one derived from the addition of the diffusive and convective flux, as depicted in Appendix 1.

Subsequently, two different dialysate conductivity programs were tested to control the sodium load. First, the dialysate conductivity was kept constant at 13.8 mS/cm during the entire dialysis session. Eleven dialysis sessions were performed with this program. The second program consisted of a 14.0-mS/cm constant dialysate conductivity during the first 3 h and a dialysate conductivity equal to 13.0 mS/cm during the infusion of thiosulfate. Twenty-five dialysis sessions were performed before thiosulfate had to be stopped for clinical reasons (sepsis for one patient; hospital change for the other one).

Results

The ultrafiltration rate was similar for sessions with and without thiosulfate (820 ± 250 ml/h *versus* 860 ± 200 ml/h with

ISSN: 1555-9041/303–0743

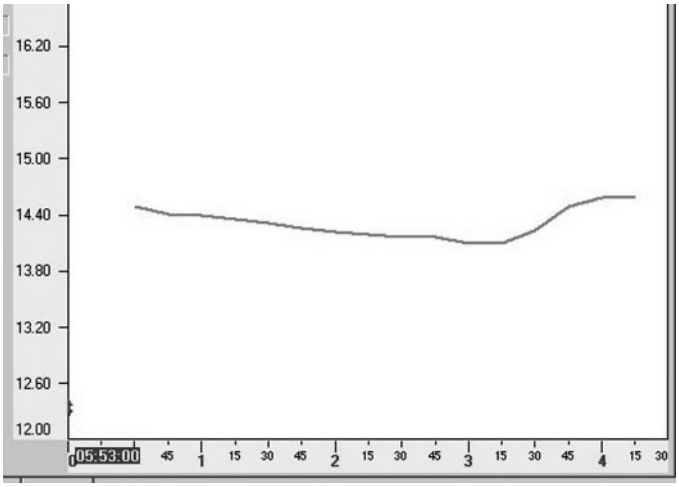

Figure 1. Example of a plasma conductivity curve during a dialysis session with thiosulfate infusion during the last hour of dialysis. Dialysate conductivity was kept constant at 14.0 mS/cm.

thiosulfate Cd = 14 mS/cm, *versus* 840 ± 240 ml/h with thiosulfate Cd = 13 mS/cm for the last hour, NS). Plasma conductivity during the sessions with thiosulfate increased during the infusion of thiosulfate whereas it remained stable during the last hour of the sessions without (Table 1). The mean increase in Cp during the third hour on thiosulfate was +0.38 ± 0.13 mS/cm *versus* + 0.001 ± 0.05 without thiosulfate ($P < 0.0001$). This increase was accompanied by an increase of the MBI from 385 ± 144 mmol for the sessions without thiosulfate to 493 ± 134 mmol with thiosulfate, Cd = 14 mS/cm ($P = 0.02$; Table 2). The mean difference between with-thiosulfate (Cd = 14mS/cm) and without-thiosulfate sessions was equal to 108 mmol. Additionally, the thiosulfate sodium load is responsible for a mean increase in Cp during the sessions of +0.24 ± 0.13 mS/cm. During the first 3 h of dialysis with thiosulfate, plasma conductivity decreased significantly more than during the period without (−0.143 ± 0.20 mS/cm with thiosulfate *versus* −0.0005 ± 0.19 mS/cm without thiosulfate, $P = 0.03$). This salt depletion was not enough to counterbalance the sodium load brought by thiosulfate, because the increase of Cp from start to end of dialysis was markedly greater with thiosulfate (+ 0.005 ± 0.13 mS/cm without thiosulfate *versus* + 0.24 ± 0.13 mS/cm with thiosulfate, $P = 0.0002$). The amount of sodium that caused this increase of nearly 2.4 mmol/L of natremia was equal to 79 mmol (Appendix 2). The total amount of sodium due to the infusion of thiosulfate was equal to 187 mmol (Table 2).

Subsequently, dialysate conductivity was decreased to 13.8 mS/cm. Increase in Cp from the third hour to the end of dialysis for 11 dialysis sessions was comparable to previous sessions with thiosulfate (0.43 ± 0.20 mS/cm *versus* 0.38 ± 0.13 mS/cm, NS). Cp decreased more during the first 3 h, with a value of 13.8 mS/cm, but the difference was negligible (−0.18 ± 0.18 mS/cm for Cd = 13.8 mS/cm *versus* −0.14 ± 0.20 mS/cm, NS). Finally, the variation of Cp from start to end was comparable with thiosulfate, with a Cd of 14.0 or 13.8 mS/cm (0.24 ± 0.22 mS/cm *versus* 0.24 ± 0.13 mS/cm, NS).

Subsequently, we tested a 14.0 mS/cm constant Cd during the session and a dramatic decrease to 13.0 mS/cm during the infusion of thiosulfate. The variation from start to end was reduced to 0.05 ± 0.14 mS/cm (*versus* 0.24 ± 0.13 mS/cm with thiosulfate and 14.0 mS/cm dialysate conductivity, $P = 0.005$), and the Cp increase during thiosulfate infusion reduced to 0.10 ± 0.17 mS/cm. The MBI was increased to 527 ± 136 mmol ($P = 0.001$ *versus* without thiosufate, Table 2) with a mean difference of 142 mmol between with and without thiosulfate. The per-dialytic variation of Cp became closer to the one without thiosulfate (0.005 ± 0.13 mS/cm without thiosulfate *versus* 0.05 ± 0.14 mS/cm, NS). This increase of 0.5 mmol/L of natremia corresponds to a sodium amount of 16 mmol (Appendix 2).

Table 1. Mean ± SD plasma conductivities (Cp) without thiosulfate (T−), with thiosulfate 25 g and 14.0 mS/cm dialysate conductivity (Cd) (T+, 14 mS/cm), with thiosulfate and 13.8 mS/cm Cd (T+, 13.8 mS/cm) and with thiosulfate and dialysate conductivity equal to 13.0 mS/cm during the last hour of dialysis (T+, 13 mS/cm)

		Cp (mS/cm)	Cp End to Cp Third Hour	Cp End to Start
T−	Start	14.02 ± 0.23		
$n = 20$	Third hour	14.02 ± 0.13		
	End	14.02 ± 0.10	+0.001 ± 0.05	+0.005 ± 0.13
T+, 14 mS/cm	Start	14.21 ± 0.26		
$n = 20$	Third hour	14.07 ± 0.14		
	End	14.46 ± 0.19	+0.38 ± 0.13*	+0.24 ± 0.13*
T+, 13.8 mS/cm	Start	14.13 ± 0.24		
$n = 11$	Third hour	13.94 ± 0.15		
	End	14.38 ± 0.15	+0.43 ± 0.20*	+0.24 ± 0.22*
T+, 13 mS/cm	Start	14.12 ± 0.11		
$n = 25$	Third hour	14.01 ± 0.13		
	End	14.17 ± 0.16	+0.10 ± 0.17	+0.05 ± 0.14

*$P < 0.001$ *versus* dialysis sessions without thiosulfate.

Table 2. Mass balance index (MBI) evaluated by Diascan and calculated from conductivity gradient during dialysis sessions with and without thiosulfate

Variable	MBI from Dialysis Monitor (mmol)	Calculated MBI (mmol)	Sodium Load not Dialyzed (mmol)	Sodium Load Not Dialyzed + Calculated MBI (mmol)	Sodium Load Not Dialyzed + Dialysis Monitor MBI (mmol)	Difference T+ and T− from Dialysis Monitor MBI (mmol)	Difference T+ and T− from Calculated MBI (mmol)
T−	385 ± 144	456	1.6	456	385	–	–
T+, Cd = 14 mS/cm	493 ± 134*	526	79	608	572	152	187
Thiosulfate+, Cd = 13 mS/cm during last hour	527 + 136*	587	16	603	543	147	158

Sodium load not dialyzed is evaluated from the mean variations of plasma conductivities (appendix 2). The difference of sodium load between sessions with and without thiosulfate is calculated from the dialysis monitor MBI and from the calculated MBI. The different calculations well estimate the amount of sodium content into 25 g thiosulfate (161 mmol).

The amount of sodium due to the thiosulfate infusion is equal to 158 mmol (Table 2).

Considering the sessions with thiosulfate, constant Cd, and according to Appendix 1, the dialyzed sodium amount was calculated for the first 3 h and the last hour considering the variations of Cp. The sodium dialyzed by diffusion was equal to 73 mmol and by convention to 453 mmol. The total calculated MBI was equal to 526 mmol (Table 2). In addition, the Cp increase from start to end was +0.24 mmol, corresponding to a sodium load already calculated of 79 mmol. The total sodium transfer and load is equal to 605 mmol (Table 2). The difference with the sessions without thiosulfate was equal to 149 mmol, matching the known amount of sodium in the infusion of thiosulfate (161 mmol).

For the sessions with a Cd = 13 mS/cm in the last hour, the sodium transfer increased from 526 mmol to 587 mmol compared with the sessions with thiosulfate, constant Cd and the sodium load was reduced from 79 to 16 mmol (Table 2). The sodium dialyzed by diffusion was nearly doubled by the change in Cd from 73 mmol with thiosulfate, constant Cd to 137 mmol with thiosulfate, Cd = 13 mS/cm the last hour.

Discussion

The importance of adequate sodium removal during hemodialysis has been known for a long time, both to avoid intradialytic hypotension induced by low-sodium dialysate and to avoid chronic sodium overload induced by high-sodium dialysate concentration. The monitoring of plasma conductivity allows the control of the diffusive sodium transfer. It successfully measured the significant sodium load induced by the thiosulfate infusion in the patients described here. We then were able to counterbalance the sodium load by decreasing the dialysate conductivity. A decrease of 0.2 mS/cm was not sufficient to fully counterbalance the sodium load. To avoid a more pronounced salt depletion before the thiosulfate infusion, we chose a marked decrease in dialysate conductivity during the infusion of thiosulfate that adequately compensated the sodium load.

Two real-time dialysis systems allow the monitoring of plasma conductivity. One is based on the measurement of both ionic dialysance and plasma conductivity. These measurements are available on dialysis monitors AK200 and Phoenix (Gambro), 4008H and 5008 (Fresenius), Innova and Integra (Hospal). A step change in inlet dialysate conductivity induces a change in the outlet dialysate conductivity that depends on ionic dialysance (ID) and Cp. The measurement of a couple of values of the inlet and outlet Cd allows the calculation of both ID and Cp. The second system uses paired-filtration dialysis (9). A double-chamber filter consists of a hemofilter without circulating dialysate and an hemodialyzer. This system physically separates convection and diffusion. A conductivity probe directly measures the ultrafiltrate conductivity. This system has the advantage of a continuous measurement.

With either system, and on the basis of the correlation between the conductivity and the sodium concentration, clinical applications have been proposed to match the sodium removal with the interdialytic sodium load. Because the sodium load varies from one patient to another and for the same patient from one session to another, the dialysate sodium prescription must be individualized. Cp measurement allows this to be performed for each dialysis session. Ultrafiltration is responsible for the main part of sodium removal but diffusive transfer could also significantly participate in sodium balance, in particular in cases with a large sodium gradient between the plasma and the dialysate. Two applications with biofeedback on dialysate concentration have been developed. The first biofeedback method is aimed at reaching a prescribed end plasma conductivity (10,11,12). The second one is termed isonatric dialysis. Dialysate conductivity is set to keep plasma conductivity constant during dialysis (13). In our reported experience with thiosulfate, control of the dialysate conductivity nearly doubled the diffusive sodium outflux and divided by nearly 5 the nondialyzed sodium load.

The mean increase in plasma conductivity during the thiosulfate infusion containing 3.7 g of sodium was equal to 0.38 mS/cm, roughly equivalent to 3.8 mmol/L of plasma sodium concentration. This is in agreement with the known increase in plasma sodium concentration after an injection of 2 g of hypertonic sodium chloride, containing 0.8 g of sodium, which has been estimated to be 1.1 mmol/L (14).

The measurement of MBI was validated in one study (13). Our calculated MBI are all superior to the ones calculated by the dialysis monitor (Table 2). Note that the Donnan effect was not taken into account in our calculations and is effectively responsible for a diminution of the sodium dialyzed. Both Diascan MBI and calculated MBI provide the sodium load of

thiosulfate, assuming a stable salt diet of both patients during the study period. The difference of sodium load during the period with and without thiosulfate calculated from Diascan MBI is very close to the calculated sodium content of thiosulfate: 187 mmol for constant Cd and 158 mmol for a Cd of 13 mS/cm in the last hour. This is even closer with the calculated MBI of 152 and 147 mmol, respectively. The uncertainty in this evaluation could be mostly due to the variation of the salt diet of the patients during the different study periods.

Under thiosulfate therapy, there is a sodium load of 3.7 g for 25 g of thiosulfate. The measurement of Cp permits estimation of this sodium load. The Cd should be lessened by 1 mS/cm during the 1-hr infusion of thiosulfate to counterbalance the sodium load. Real-time plasma conductivity measurement is inexpensive and does not require blood samples. It is sensitive enough to properly measure a 3.7-g sodium load, and thus can be used to monitor the sodium balance of hemodialysis patients. Other biofeedback applications based on this promising measurement technique should be studied.

Appendix 1

We assumed that the coefficients of proportionality between conductivity and sodium concentration are close and equal to 10 in the dialysate and in the blood. The amount of sodium dialyzed by diffusion during a period T is equal to $D \times (Cp - Cd) \times T$, where Cp is the logarithmic mean of Cp during the studied period and Cd is the dialysate conductivity. By ultrafiltration, the sodium dialyzed is equal to $UF \times T \times C$p.

Example

Considering the sessions without thiosulfate, Cp is equal to 14.02 mmol/L from start to end. The mean ionic dialysance is equal to 178 ml/min. The amount of sodium dialyzed by diffusion is equal to $0.178 \times (140.2 - 140) \times 4 \times 60 = 8$ mmol. By ultrafiltration, the dialyzed sodium amount is equal to $0.8 \times 4 \times 140.2 = 448$ mmol. The mean amount of sodium dialyzed is equal to 456 mmol.

Appendix 2

The apparent distribution volume of sodium is the total body water, nearly equal to $0.55 \times$ weight. The amount of sodium causing a natremia increase (Δn) is calculated as $\Delta n \times 0.55 \times$ weight.

Disclosures

None.

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