Differential Removal of Guanidinosuccinic Acid and Creatine by Hemodialysis and Continuous Ambulatory Peritoneal Dialysis

P.P.		De Deyn ^a
B.M.		Marescau ^a
R.D.		Swartz ^b
J.M.		Billiouw ^c
I.		Becaus ^c
W.		Lornoy ^c

^aLaboratory of Neurochemistry, Born-Bunge Foundation, University of Antwerp, and Department of Neurology, A.Z. Middelheim, Belgium; ^bDepartment of Nephrology, University of Michigan Medical Center, Ann Arbor, Mich., USA; ^cDepartment of Nephrology, OLV Ziekenhuis, Aalst, Belgium

Peter P. De Deyn, MD, PhD, Laboratory of Neurochemistry, Born-Bunge Foundation, UIA, Universiteitsplein 1, B-2610 Antwerp (Belgium)

Dear Sir,

In two previous reports, we presented serum guanidino compound (GC) levels and the clearances of GCs by continuous ambulatory peritoneal dialysis (CAPD) and the influence of a single hemodialysis (HD) on serum GC levels in steady-state patients with terminal renal insufficiency [1, 2]. Highly standardized dialysis procedures were performed. In hemodialyzed patients, guanidinosuccinic acid, among other GCs, remained markedly elevated and reached toxic levels before a dialysis session. In serum of patients who underwent CAPD, guanidinosuccinic acid, creatinine and methylguanidine reached levels associated with toxic effects in vitro. Serum creatine levels were lower in peritoneally dialyzed patients than in control subjects. In the peritoneal dialysis group, significantly different clearances were found for the different GCs ranging from 4.02 ± 1.08 ml/min for arginine to 7.94 ± 2.76 ml/min for creatine during a 3-hour exchange period. Also in the hemodialyzed group, substantial differences were found in the percent decrease of the different GCs, ranging from $25 \pm 13\%$ for arginine to $74 \pm 7.5\%$ for guanidinosuccinic acid.

Here, we assessed the interrelationships of parameters for the removal of the GCs and urea by HD [2] and by CAPD [1] by calculating the linear correlation coefficient. The GCs considered were: arginine, homoarginine, N- α -acetylarginine, guanidine, guanidinoacetic acid, creatinine, methylguanidine, argininic acid, guanidinosuccinic acid and creatine. The 3-hour equilibration percentage and the ratio (serum GC concentration before HD/serum GC concentration after HD) were used as parameters for the removal of ten different GCs and urea by CAPD and HD respectively. A weak, nonsignificant positive correlation ($r = 0.105$) was found between CAPD equilibrium percentage and the parameter for GC removal by HD (fig. 1). Omitting the values obtained for

12 3 4
 HD : [GC]_{PRE}/[GC]_{post}
 a
 L·J
 or
 IrO
 Q·Q <

Fig. 1. Correlation between the removal of arginine (Arg), homoarginine (Harg), N- α -acetylarginine (N- α -AA), guanidine (G), guanidinoacetic acid (GAA), creatinine (CTN), methylguanidine (MG), argininic acid (Arg A), guanidinosuccinic acid (GSA), creatine (CT) and urea by HD (shown in the abscissa) and CAPD (shown in the ordinate).

12 3 4
 HD : [GC]_{PRE}/[GC]_{post}

Fig. 2. Correlation between the removal of the GCs considered in figure 1, with exception of guanidinosuccinic acid and creatine, and urea by HD (shown in the abscissa) and CAPD (shown in the ordinate).

370

De Deyn/Marescau/Swartz/Billouw/Becaus/Lornoy

guanidinosuccinic acid and creatine from this analysis yielded a significant positive correlation ($r = 0.836$; $p < 0.05$) between the removal of the eight remaining GCs and urea by CAPD and HD (fig. 2). The statistically significant correlation found to exist between the removal of guanidinoacetic acid, N- α -acetylarginine, argininic acid, creatinine, arginine, homoarginine, guanidine, methylguanidine and urea by HD and CAPD indicates that these two dialytic procedures are equally efficient in dialyzing these substances. On the contrary, guanidinosuccinic acid seems to be more effectively removed by HD and creatine by CAPD. This differential removal might explain the lower serum levels of guanidinosuccinic acid and creatine in HD- and CAPD-treated patients respectively. Guanidinosuccinic acid reached serum levels as low as $3.58 \pm 1.87 \mu\text{mol/l}$ ($\bar{x} \pm \text{SD}$, $n = 30$) after a single HD session while levels remained around $14.5 \pm 4.2 \mu\text{mol/l}$ ($\bar{x} \pm \text{SD}$, $n = 15$) in CAPD-treated patients. Serum creatine concentrations in patients submitted to CAPD were approximately one third of the control values (42.1 ± 20.3 , $\bar{x} \pm \text{SD}$, $n = 52$).

A mechanistic explanation for the differences in the removal of guanidinosuccinic acid (MW= 175) and creatine (MW = 131) by HD and CAPD is not available yet. In general, it is well known that dialytic removal varies with molecular weight, protein binding, concentration gradient and hydrodynamic volume as well as other factors, such as possible active transport across biological membranes. Maybe, the latter factor accounts for some of the differences in efficacy of the two dialytic techniques in removing GCs. Indeed, the 10-hour equilibration percentage of 126.5 ± 32.0 ($\bar{x} \pm \text{SD}$, $n = 14$) for creatine in our CAPD group [1] could be in agreement with this hypothesis. Caution is indicated however: the creatine concentration shown to be higher in dialysate than in serum, after a 10-hour dwell period, could also be explained by local synthesis of this GC in the peritoneal cavity.

Although still controversial, guanidinosuccinic acid is believed to be related to the uremic bleeding diathesis [3, 4]. Moreover, guanidinosuccinic acid and creatine have been shown in vitro to increase hemolysis [5]. Furthermore, guanidinosuccinic acid, applied at concentrations

found in cerebrospinal fluid of terminal renal insufficient patients, inhibited responses to the inhibitory neuro-transmitters GABA and glycine on mouse neurons in cell culture by blocking the chloride channels [6]. Also, creatine was found to have a convulsive effect in animals when injected intracisternally [7, 8]. Finally, a deficiency of creatine could have pathophysiological implications [9]. At present, it remains difficult to predict whether the differences in the removal of guanidinosuccinic acid and creatine and the subsequent differences in their serum levels, have pathophysiological implications. Further studies, correlating clinical and chemical parameters, should be conducted in CAPD- and HD-treated patients in order to answer this question. Moreover, further studies should be performed to investigate whether the observed decrease of creatine in serum corresponds with decreases of creatine and phosphocreatine in muscle or brain.

References

- De Deyn, P.P.; Marescau, B.; Swartz, R.D.; Hogaerth, R.; Possemiers, I.; Lowenthal, A.: Serum guanidino compound levels and clearances in uremic patients treated with continuous ambulatory peritoneal dialysis. *Nephron* 54:307–312 (1990).
- De Deyn, P.P.; Marescau, B.; Lornoy, W.; Becaus, I.; Van Leuven, I.; Van Gorp, L.; Lowenthal, A.: Serum guanidino compound levels and the influence of a single hemodialysis. *Nephron* 45:291–295 (1987).
- Stein, I.M.; Cohen, B.D.; Horowitz, H.I.: Guanidinosuccinic acid: The ‘X’ factor in uremic bleeding? *Clin. Res.* 16:397 (1968).
- Horowitz, H.I.; Cohen, B.D.; Martinez, P.; Papayouanou, M.F.: Defective ADP-induced platelet factor 3 activation in uremia. *Blood* 30:331–340 (1967).
- Giovannetti, S.; Cioni, L.; Balestri, P.L.; Biaginin, M.: Evidence that guanidines and some related compounds cause haemolysis in chronic uremia. *Clin. Sci.* 34:141–148 (1968).
- De Deyn, P.P.; Macdonald, R.L.: Guanidino compounds that are increased in uremia inhibit GABA and glycine responses on mouse neurons in cell culture. *Ann. Neurol.* (in press).
- Jinnai, D.; Mori, A.; Mukawa, J.; Ohkusu, H.; Hosotani, M.; Mizuno, A.; Tye, L.: Biochemical and physiological studies on guanidino compounds induced convulsions. *Jap. J. Brain Physiol.* 706:3668–3673(1969).
- Mori, A.: Biochemistry and neurotoxicology of guanidino compounds. History and recent advances. *Pavlov J. Biol. Sci.* 22: 85–94 (1987).