Beta-2 Microglobulin Removal During Continuous Ambulatory Peritoneal Dialysis (CAPD)

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Beta-2 microglobulin (B2M) handling in continuous ambulatory peritoneal dialysis (CAPD) was characterized in acute and chronic clinical studies. Average clearance rate was 0.7 mL/min and mean mass transfer coefficient, KoA, was calculated to be 0.95 cm²/min; these values are in the range expected from extrapolation of published data for other large solutes. In chronic studies with both anuric and oliguric populations, CAPD was shown to be much more effective than conventional hemodialysis in removing B2M and, in fact, CAPD removal rates were equivalent to those reported for high flux dialysis therapies. However, this greater extraction was not associated with any clinically significant reduction in circulating plasma concentrations. These trends remained valid in both the anuric and oliguric subsets of the study population.

KEY WORDS: β2 microglobulin; amyloidosis; mass transport; hemodialysis; KoA.

Beta-2 microglobulin (B2M) remains a major topic in contemporary hemodialysis literature with special emphasis upon the ability of different devices and circuits to influence its generation, distribution, and removal. B2M is considered far less often in connection with continuous ambulatory peritoneal dialysis (CAPD), despite the putative capacity of this therapeutic modality to more effectively remove intermediate molecular weight uremic toxins than does conventional hemodialysis.

B2M, a polypeptide, is synthesized in the body as a subunit of the class I major histocompatibility antigens found on the cell surface of cells. It also occurs as a 12 kilodalton monomer in plasma and urine. Since the concentration of B2M is normally regulated by the kidney, the elevated levels found in renal failure are not surprising. Hyperbeta-2-microglobulinemia is not a simple retention disease but the detailed pathways by which decreased B2M removal leads to elevated plasma levels and then to amyloidosis remain to be elucidated; and current therapeutic strategies for interrupting these progressions are at best speculative.

In the late seventies, Yorioka (1) and Vincent (2), employing laborious column chromatography analysis, first reported the elevated plasma levels of B2M in uremia. Following the introduction of more convenient radioimmunoassay techniques, B2M permeability was frequently utilized to characterize “upper middle” molecular weight transport in both hemodialysis (3,4) and CAPD (5-11). In 1985 through 1986, the status of B2M was upgraded from that of a marker molecule to a likely uremic toxin by the finding of Geyjo (12, 13) and Gorevic (14) that B2M was a primary constituent of the amyloid deposits in the carpal tunnel and skeletal joints of long-term hemodialysis patients. Considerable research has since been devoted to the clinical and device-oriented aspects of this syndrome, with special emphasis upon devising hemodialyzers and hemodialysis-like circuits capable of enhanced B2M removal and thus, putatively, of a concomitant reduction in circulating B2M levels and amyloidosis.

Enthusiasm remains high, individual case reports are optimistic, and several excellent reviews (15-19) have recently appeared. However epidemiologic studies to date have failed to support the suggestion that selection of high permeability devices will lower steady-state B2M levels (20) or reduce the incidence of carpal tunnel syndrome or similar osteoarthritic symptoms (21). Moreover, quantitative analysis suggests that the maximum amounts of B2M removable by high-permeability hemodialysis (400-500 mg/wk (22)) or even hemofiltration (700-900 mg/wk (23)) is less than the approximate mean weekly generation rate of 1000 to 1500 mg/week, determined in uremic turnover studies (24) or in collection of normal urine (25).

So far as amyloidosis and hyperbeta-2-microglobulinemia in CAPD are concerned, Ballardie et al. (26) reported in 1986 that circulating plasma levels in a group of 25 CAPD patients with a mean time on therapy of 1.5 years was 34 &plusmn; 12 mg/L vs. 33 &plusmn; 13 mg/L in a control group of hemodialysis patients utilizing regenerated cellulose membranes on therapy for 2.3
transport co-efficient for B2M was characterized, and daily carpal tunnel syndrome, as their hemodialysis counterparts. Afflicted by similar osteoarthritic pathologies, including common clinical wisdom that long-term CAPD patients are A recent report from Bardin measured B2M loss in residual urine of the CAPD patients. Neither Saito nor Blumberg have recently reported a very similar value of 232 mg/week transperitoneal removal. Neither Saito nor Blumberg measured B2M loss in residual urine of the CAPD patients. Saito et al. (29) have recently reported a very similar value of 232 mg/week transperitoneal removal. Neither Saito nor Blumberg measured B2M loss in residual urine of the CAPD patients. A recent report from Bardin et al. (30) confirms the common clinical wisdom that long-term CAPD patients are afflicted by similar osteoarthritic pathologies, including carpal tunnel syndrome, as their hemodialysis counterparts.

We report here on studies in which the peritoneal mass transport co-efficient for B2M was characterized, and daily mass balances, including residual renal function, for CAPD patients were obtained and compared to similar determinations for hemodialysis patients.

EXPERIMENTAL METHODS

MASS TRANSFER COEFFICIENTS

Established procedures (31) were employed to obtain the data needed for determination of mass transfer co-efficients. The experimental protocol was repeated on 2 consecutive days on the same five stable, peritonitis-free patients who had been enrolled in the study from the chronic CAPD population at St. Vincent's Hospital in Melbourne, Victoria, Australia. Patients presented and drained their overnight fluid in the normal fashion. One liter of 1.5% Dianeal (Baxter) was infused and removed with no dwell to rinse the peritoneum. A 2-L solution of 2.5% Dianeal was infused; the exchange was considered to start halfway through the infusion. Two hundred milliliters of effluent was withdrawn and sampled immediately after infusion, every 20 min for the first 2 h, and every 30 min thereafter. Serum samples were collected prior to infusion and every 90 min during the exchange. Samples were centrifuged and the serum was frozen at 4°C prior to analysis by RIA (β2-Micro, Pharmacia). Initial infusion volume was taken as the difference in weight between the full and empty infusion bag; drain volume was measured gravimetrically.

Hemodialysis was conducted with Cuprophan regenerated cellulose or with cellulose diacetate devices from a variety of manufacturers. Dialysis duration was from 4 to 6 h; the mean value of urea KT IV, here excluding any contribution from residual renal function, was 0.95. Blood samples were drawn (a) before 24 h spent dialysate to their periodic checkup along with any urine passed in the preceding 24-h period. A sample of blood was taken at this checkup. The volumes of the urine and of the drain bags, after bulking, were measured in graduated cylinders. Beta-2 microglobulin was again measured by RIA (β2-Micro, Pharmacia) in the blood, urine, and peritoneal effluent. Samples were stored at 4 oC for no more than 1 week between collection and measurement. Mass removed per 24 h in CAPD effluent and urine was calculated as the product of the respective volume and B2M concentration; clearance was obtained by dividing the rate of mass removal by plasma concentration.

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| Table 1. Patient Characteristics—Mass Balance Study |
|-----------------|-----------------|
|                 | CAPD (n = 30)   | HD (n = 35)    |
| Age             | 52 ± 3          | 56 ± 2         |
| Weight (kgs)    | 67 ± 3          | 67 ± 2         |
| Gender (F/M)    | 18/12           | 18/17          |
| Time on therapy (months) | 26 ± 3 | 37 ± 6 |
| Kr, mL/min      | 2.0 ± 0.2       | 0.7 ± 0.3      |

Reported values are mean ± SEM. Kr is residual creatinine clearance.
after the patient's midweek dialysis; they were analyzed for B2M, along with any urine the patients had produced since their preceding dialysis, following the same procedures employed for CAPD. Spent hemodialysate was occasionally sampled for B2M; none was found. B2M levels post dialysis averaged 6.3 mg/L (15%) higher than the corresponding pre-dialysis levels, presumably due to fluid compartment shifts insofar as the increase correlated with the degree of weight loss. Accordingly, and because the literature strongly suggests that dialysis with regenerated cellulose or cellulose diacetate membranes does not remove B2M (33-35), hemodialysis clearance was taken as zero. Residual renal mass removal rate and clearance were calculated in the same manner as for the CAPD group.

HUMAN SUBJECTS APPROVAL

All patients participated in these studies on a fully voluntary basis after being informed of the risks and inconveniences. The experimental procedures were conducted according to protocols which had been approved by the appropriate ethical review boards at the participating institutions.

RESULTS

Figure 1 contains plots of peritoneal B2M concentration vs. dialysate dwell time for the five patients participating in the mass transfer experiment; a single regression line is drawn through the data points from duplicate experiments for each patient. Figure 2 is an averaged, normalized plot of the same data presented as the ratio of dialysate to plasma concentration. The dialysate remains sufficiently dilute in B2M so that first order regression (straight lines) fit the data quite satisfactorily. Circulating plasma levels, plasma clearance, and net mass removal for the hemodialysis and CAPD groups are presented in Table 2; net mass removal is further illustrated in Figure 3.

DISCUSSION

Considerable patient-to-patient variability is evidenced in Figure 1: the higher transport rates do not correspond to higher plasma concentrations and thus greater driving forces for transport but must reflect the intrinsic intrapatient differences in peritoneal area or permeability for large molecules. The mean mass transfer coefficient, KoA, for the ten data sets is 0.95 mL/min ± 0.28 (SEM). This value is unremarkable for a 12 kilodalton permeant and in fact falls quite close to values predicted from published regressions (36) of KoA vs. molecular weight. The possibility that some of the B2M collected in the dialysate is being generated in the peritoneal cavity, rather than being transported across the peritoneal membrane, cannot be fully excluded; however, comparison of the data in this report with published correlations for neighboring molecules suggests that transport considerations alone are sufficient to account for the quantities observed in the dialysate.

The method of Garred et al. to estimate mass

![Graph](http://www.pdlconnect.com/)

**Figure 1**—Increase of dialysate concentration of \( \beta_2 \) microglobulin during 6-h exchanges for five patients. The rise in concentration is nearly linear. Differences in rates between patients do not correspond to differences plasma concentrations.
transfer coefficient (32) essentially assumes that unselective ultrafiltration is the only convective process occurring during CAPD. Consideration of sieving would raise the calculated value of KoA, while incorporation of lymphatic flow would lower it. In any event, the imprecision introduced by these assumptions is believed slight.

Differences between the plasma concentrations reported in Table 2, 34 ± 2.4 (SEM) mg/L for CAPD vs. 43 ± 2.1 for hemodialysis, are unlikely to be of clinical significance although they just reach statistical significance (p < 0.05). These results are both quantita
tively and qualitatively similar to those reported elsewhere by Ballardie et al., Gagnon et al., and Blumberg et al. (25-27). Plasma concentration showed no significant variation with time on treatment for either the CAPD (r = 0.21) or the HD (r = 0.34) cohorts.

As is also clear from Table 2, both residual renal function and dialytic removal contributed to net weekly B2M clearance in CAPD whilst residual renal function was the only mechanism of removal in hemodialysis. CAPD patients experience a much higher level of B2M clearance than do those being treated by conventional hemodialysis and the relative advantage

<table>
<thead>
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<th>Table 2</th>
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Comparison of Anuric and Oliguric Subsets

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<th>Full Study</th>
<th>Anuric</th>
<th>Oliguric</th>
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<tbody>
<tr>
<td></td>
<td>CAPD</td>
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</tr>
<tr>
<td>N</td>
<td>30</td>
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<td>Kr, mL/min</td>
<td>2.0 ± 0.4</td>
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<td>Plasma B2M, mg/L</td>
<td>34 ± 2.4</td>
<td>43 ± 12</td>
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<td>Clearance, L/week</td>
<td>Via urine</td>
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<td>Dialytic</td>
<td>7.4 ± 3.8</td>
<td>10.1 ± 2.0</td>
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<td>Total</td>
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<td>3.4 ± 0.4</td>
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<tr>
<td>Mass removal, mg/wk</td>
<td>In urine</td>
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<td>Dialytic</td>
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<tr>
<td></td>
<td>Total</td>
<td>389 ± 29</td>
<td>147 ± 42</td>
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Reported values are mean ± SEM. Kr is residual creatinine clearance.
is amplified at low values of residual renal function. High flux hemodialysis is capable of providing B2M clearances of 20 to 60 mL/min, or roughly 12 to 36 L per week, but these values are not directly comparable to CAPD. Hemodialysis is a short intermittent therapy: the blood compartment is rapidly depleted of B2M in the first 15 to 45 min of treatment and solute-poor blood is being "cleared" for the remainder of the treatment session. In contrast, during CAPD, B2M is being cleared at its endogenous concentration over the full course of treatment.

Rate of mass removal is listed in Table 2 and shown for clarity in the bar graph in Figure 3. It is comprised of a residual renal and a dialytic fraction for CAPD and of a residual renal fraction only for Cuprophan hemodialysis. The mean weekly transperitoneal removal is 239 ± 28 mg; curiously, Blumberg (25) and Saito (28) also reported weekly dialytic removals of between 230 and 240 mg/week in CAPD. This quantity, corresponding to 0.51 mg/kilo-day of removal, is equivalent to the quantities removed by the most permeable, and incidentally most expensive, dialyzers currently available in conventional hemodialysis circuits (22). CAPD thus represents an attractive and cost effective alternative to clinicians interested in increasing B2M removal, especially in anuric patients. It also offers between 50% and 80% of mass removals reported for aggressive hemofiltration or hemodiafiltration (23), although these therapies are infrequently employed outside the investigative or acute setting, especially in North America.

Mean residual renal function, estimated from creatinine clearance, was higher in the CAPD group (2.0 ± 0.2 mL/min SEM) than in the HD group (0.7 ± 0.3 mL/min SEM). Rottembourg (37) and Cancarini (38) has observed that GFR declines more slowly on CAPD than on hemodialysis; and this "sparing" of residual function by CAPD might account for the differences between the two groups. Alternatively, patients with low GFR might gravitate toward hemodialysis because of its higher net small solute clearance, although no such patient selection was deliberately practiced by the participating centers. In any event, Table 2 also contains a full breakout of results by the anuric and oliguric subsets in both HD and CAPD cohort groups. As would be expected, anuric patients...
evidenced slightly higher circulating plasma levels of B2M and thus slightly higher mass-removal rates. However these differences are numerically quite modest and, most importantly, all of the trends seen in the original CAPD and HD groups are preserved in both the oliguric and non-oliguric subsets. Stated differently, B2M clearance will be higher in CAPD than in HD at any comparable level of GFR; the higher mean GFR of the CAPD patients in this study population was an added bonus.

The mass balance studies agree satisfactorily but not perfectly with the acute mass transport determinations. In the case of solutes whose dialysate concentration remains much lower than plasma concentration (D/P ≤ 1.0), mass transfer coefficient and clearance rate are almost numerically equal. This should be the case with B2M and, in fact, clearance was 0.7 mL/min and Koa was 0.95 mL/min. Moreover, the D/P curve suggests that efficient concentration should reach about 15% of plasma concentration, which in the population studied would lead to an estimated weekly removal rate of 320 mg/week (63 L/week effluent X 34 mg/L concentration X 0.15) vs. a measured value of 259 mg/week.

Available evidence (24, 25) suggests that B2M is generated at a rate of about 1000 to 1500 mg/week and thus the quantities removed in CAPD, even the combined dialytic and renal losses, are inadequate to provide a negative balance. (The same holds true for other high flux dialytic and renal losses, are inadequate to provide a maximum fluid concentration is reached, must be removed by a value of D/P &leq; 1.0).

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REFERENCES


