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ANIONIC POLY(METHYL METHACRYLATE) (PMMA) MEMBRANE FOR RAPID DIALYSIS

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With the increase in the number of chronic dialysis patients, improving their rehabilitation has been more seriously discussed not only based upon their desire but also from the financial viewpoints of the health care. Although increasing the efficiency and/or reducing the time of this treatment are important approaches to solve this problem, a concern is often raised that rapid dialysis may worsen the balance of body fluids and solutes including acid-base homeostasis. In order to realize a rapid and comfortable therapy, therefore, we have focused our attention on acid-base balance and measured the membrane permeability of bicarbonate (HCO_3^-) and acetate (CH_3COO^-) ions and its reflection on the change in acid-base parameters in a patient.

MATERIALS AND METHODS

Dialyzers and Controller. Two kinds of cellulosic hollow fiber dialyzers, Cellulose-A (0.8 m^2) and Cellulose-B (2.1 m^2) and anionic PMMA hollow fiber dialyzer, TK-201 (2.1 m^2) were mainly used in this study. UFR controller, "UFC-11"[1] was used in in vitro and clinical evaluations where precise UFR control was needed.

Patients. Eight (3 males and 5 females; age: 38 to 80 yrs) and 4 (1 male and 3 females; age: 34 to 59 yrs) patients participated in the preliminary and long-term evaluations, respectively. The latter 4 patients had no residual renal function and their predialysis HCO_3^- concentration was between 17 to 21 mEq/L. In the long-term evaluation, dietary protein and fluid intake was not restricted.

In in vitro evaluations, physiologic aqueous solutions were substituted for a patient.

Dialysis Procedures. Dialysis treatment time was reduced stepwise from 5 hrs in the control phase to 4 and then 3 hrs. On switching from 4 to 3 hr treatment, blood flow rate (Q_B) was increased by 10% from 200 to 220 ml/min. Acetate (CH_3COO^- 37 mEq/L) and bicarbonate (CH_3COO^- 6, HCO_3^- 30) dialysates were used.

In the long-term evaluation of rapid dialysis, the durations of the phases of 5, 4 and 3 hrs were 7, 7 and 16 wks, respectively.

Chemical Measurements. For measurements of acid-base parameters (pH, pCO_2, pO_2 and HCO_3^-) a blood gas analyzer, "Corning-175" was used, where HCO_3^- was calculated according to the Henderson-Hasselbach equation.

As discrepancy from calculated values was observed when aqueous samples were analyzed with this analyzer as previously reported[2], we calculated HCO_3^- in the aqueous samples such as dialysate based upon TCO_2 (total CO_2) measured with a TCO_2 analyzer, "Corning-965" and pCO_2 with "Corning-175" according to the following equation: $HCO_3^- = TCO_2 - 0.03\ pCO_2$.

CH_3COO^- concentration in blood and aqueous samples was measured by ion chromatography with Dionex's "System 14."

Technicon's "AutoAnalyzer II" was used for measurement on urea nitrogen (UN) and creatinine (Cr).

Calculations. Dialysance (D; ml/min), and overall mass transfer coefficient (K_0; cm/min) were calculated as reported[3]. Unless otherwise stated, D was measured at the blood, dialysate (Q_D) and ultrafiltrate flow rates of 200, 500 and 0-15 ml/min, respectively. Based upon the results of the mass balance verification, D and K_0 for HCO_3^- and CH_3COO^- were calculated as whole blood as well as urea nitrogen (UN). Reduction rate (%) was defined as follows:

$$\text{Reduction rate} = [(C_0 - C_t) / C_0] \times 100 \ (\%)$$

where C_0 : pretreatment concentration
C_t : post-treatment concentration.

Calculations on UN kinetics were carried out as previously reported[1,4].

Clinical Symptoms. Although it was difficult to quantitatively evaluate the extent of dialysis-related symptoms, we tried to express them in terms of the frequency and the amount of normal saline infusion during treatment, because normal saline was often infused to treat hypotension, nausea, vomiting or cramps. Thus, analyzed data coincided well with the comments from patients and nurses.

RESULTS

Effect of Shortening Treatment Time on Removal of UN and Cr. We considered it prerequisite to keep the pretreatment levels of UN and Cr when shortening the treatment time. Table I summarizes the change in the reduction rates of UN and Cr in rapid dialysis. These results suggest that use of the larger surface area

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TABLE I. CHANGE IN REDUCTION RATES OF UREA NITROGEN (UN) AND CREATININE (Cr) BY SHORTENING TREATMENT TIME

Dialyzer	Area (m^2)	Rx Time (hr)	Reduction Rate (%) Mean ± SD (n) UN	Cr
Control Phase	0.8-1.2	5	65.1 ± 9.6 (27)	57.8 ± 8.1 (27)
TK-201	2.1	4	66.4 ± 5.7 (58)	59.2 ± 5.6 (58)
Cellulose-B	2.1	4	66.2 ± 6.8 (36)	60.9 ± 6.2 (36)
TK-201	2.1	3	58.9 ± 3.8 (28)	54.3 ± 4.0 (28)
Cellulose-B	2.1	3	59.8 ± 4.1 (15)	57.7 ± 3.4 (15)

dialyzers compensated the reduction in the treatment time from 5 to 4 hrs and that not 10 but 25% increase of Q_B on switch from 4 to 3 hrs should have been prescribed to obtain the same level of the reduction rates as predicted by the kinetic modeling.

Figure 1 shows the change in the pretreatment levels of UN and Cr for 4 patients. Despite the decrease in the reduction rate on transfer from 4 to 3 hr treatment, change in the pretreatment levels of these solutes were not consistent.

Four patients, T.M., Y.K., Y.T. and K.K. in Figure 1, had the UN generation rates of 6.5, 3.7, 4.2 and 5.4 mg/min, respectively, in the control phase. Their relative generation rates in the 3 hr treatment to those in the control phase were 92, 122, 110 and 111 % with TK-201 and, 91, 114, 124 and 96 % with Cellulose-B, respectively, and significant change was not observed.

Effect of Improved Efficiency as to UN, Cr Removal on Acid-Base Balance. What effects on acid-base balance are exerted by the increase in the surface area of a dialyzer and/or the enhancement of Q_B should be carefully checked. Table II lists K_0 for UN, Cr and HCO_3^- and the ratios of K_0 of Cr and HCO_3^- to that of UN observed with Cellulose-A, Cellulose-B and TK-201 having the wall thickness (wet) of the membrane of 26, 29 and 25 μ, respectively. K_0 of Cellulose-A is larger than that of Cellulose-B for these 3 solutes, which may be partially explained by the difference in the wall thickness. Two dialyzers which have the same surface area, Cellulose-B and TK-201, have the same levels of UN and Cr permeability. However, suppressed HCO_3^- permeability of TK-201 is noted. These relationships are depicted in Figure 2. It is again demonstrated that HCO_3^- permeability of anionic PMMA membrane is suppressed compared with that of the cellulosic membrane despite the quite similar permeability of Cr, a nonionic solute. From the data plotted in Figure 2, no difference in K_0 of HCO_3^- between in the aqueous solution and blood is shown.

TABLE II. IN VITRO OVERALL MASS TRANSFER COEFFICIENTS (K_0) OF UREA NITROGEN (UN), CREATININE (Cr) AND HCO_3^-, AND THE RATIOS OF K_0 OF Cr AND HCO_3^- TO THAT OF UN

Dialyzer	n	Overall Mass Transfer Coefficient K_0 (cm/min), Mean ± SD: UN	Cr	HCO_3^-	$(K_0)_{Cr}/(K_0)_{UN}$	$(K_0)_{HCO_3^-}/(K_0)_{UN}$
1. Cellulose-A	3	0.044 ± 0.003	0.029 ± 0.002	0.034 ± 0.001	0.66 ± 0.02	0.79 ± 0.07
2. Cellulose-B	3	0.029 ± 0.005	0.020 ± 0.003	0.021 ± 0.002	0.69 ± 0.04	0.73 ± 0.06 ┐ $p < 0.001$
3. TK-201	5	0.031 ± 0.003	0.020 ± 0.001	0.015 ± 0.001	0.66 ± 0.03	0.49 ± 0.03 ┘

Although not listed here, the mass balance error[5] of HCO_3^- was checked in the calculation of D and found to be less than 7% not only in aqueous (in vitro) but also clinical settings.

In Figure 3, changes of pH, pCO_2 and HCO_3^- during acetate dialysis are plotted. Note that plasma HCO_3^- was kept at a higher level with TK-201 than with Cellulose-B and that HCO_3^- level with TK-201 approximated that in the control phase with the smaller surface area dialyzers. The pCO_2 dropped sharply during dialysis with Cellulose-B, whereas it remained relatively stable during dialysis with TK-201. As to change in pO_2, significant difference between 2 membranes was not observed. These behaviors can be interpreted as follows: anionic membrane, TK-201, has a reduced HCO_3^- permeability despite the enhanced UN or Cr permeability by the increase in the surface area and, therefore, with TK-201, rapid loss of HCO_3^- from the patient's blood to the dialysate can be prevented. As dialytic loss[2] mainly occurs via HCO_3^-, drop of pCO_2 with Cellulose-B is considered to be caused by rapid loss of HCO_3^- across that membrane.

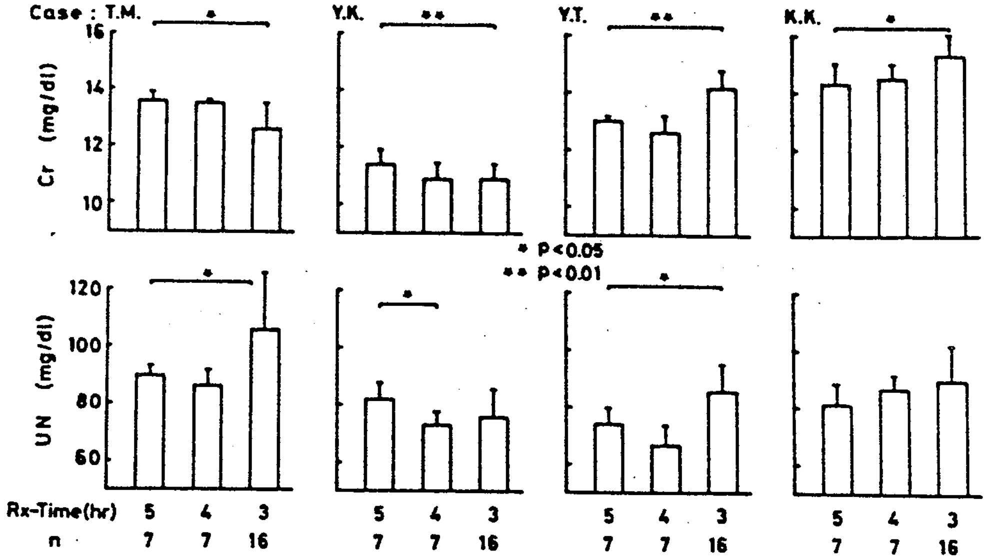

Figure 1. Change in the pretreatment plasma concentrations (mean ± SD) of urea nitrogen (UN) and creatinine (Cr) in 4 patients by shortening treatment time. Chemical measurements were performed on the first day each week.

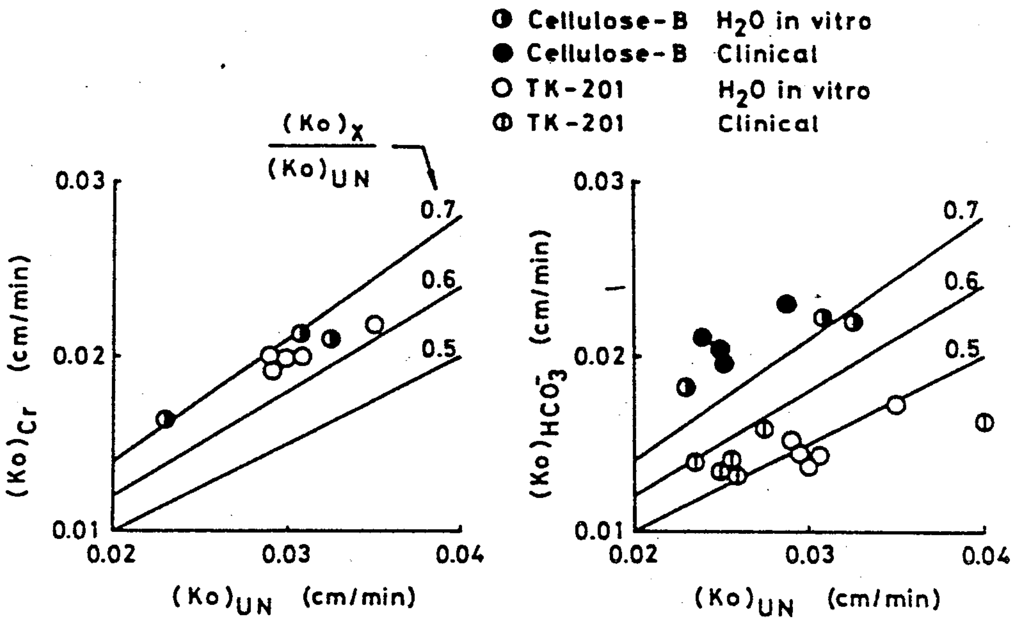

Figure 2. Relationship between the overall mass transfer coefficient (K_0) of urea nitrogen (UN) and K_0 of creatinine (Cr) and HCO_3^- measured at "blood" and dialysate flow rates of 200 and 500 ml/min, respectively, and at a negligible ultrafiltration rate.

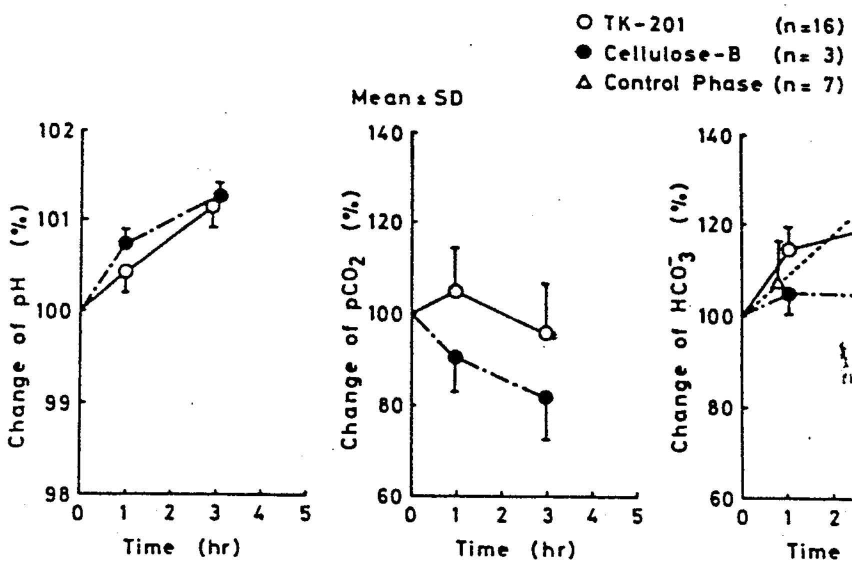

Figure 3. Changes of pH, pCO_2, HCO_3^- in plasma during the dialysis treatment.

Together with loss of HCO_3^-, rapid inflow of CH_3COO^- into the body especially in rapid dialysis, is another item to which attention should be paid. If the metabolic processing of CH_3COO^- is the rate-determining step, too rapid inflow of CH_3COO^- from dialysate may cause various adverse effects. $(K_0)_{CH_3COO^-}/(K_0)_{UN}$ ratios clinically observed (mean ± SD) were 0.358 ± 0.098 (n = 8), and 0.575 ± 0.213 (4) ($p < 0.05$) for TK-201 and Cellulose-B, respectively. Figure 4 depicts the increase in CH_3COO^- concentration in the blood during acetate dialysis. These preliminary results suggest that the difference of CH_3COO^- permeability between membranes was reflected on the difference of CH_3COO^- accumulation in the latter part of the treatment.

Change in Clinical Symptoms Associated with Rapid Dialysis. Figure 5 shows the frequency (times per treatment) and the volume (ml per treatment) of normal saline infusion as an index of clinical symptoms. Table III lists χ^2 test on the frequency of normal saline infusion during treatment. Significantly less infusion with TK-201 than with Cellulose-B both in acetate and bicarbonate dialyses is noted and less infusion (χ^2 test; $p < 0.001$ for Cellulose-B, $p < 0.01$ for TK-201) with bicarbonate dialysis than with acetate treatment is also shown. These 2 comparisons strongly suggest that acid-base balance plays a significant role in the occurrence of dialysis-related symptoms.

TABLE III. SALINE INFUSION DURING TREATMENT

Dialyzer	Rx Time (hr)	Frequency (times/Rx) 0	Frequency (times/Rx) ≥1	χ^2 Test	Frequency (times/Rx) 0	Frequency (times/Rx) ≥1	χ^2 Test
Control Phase	5	28	8	$p > 0.5$			
TK-201	3	77	28		87	32	$p < 0.001$
Cellulose-B	3				3	11	

DISCUSSION

Several attempts have been made to shorten treatment time. In the National Cooperative Dialysis Study[6], blood UN (BUN) concentration was selected as an index for adequacy of dialysis and it was concluded that as long as BUN concentration was maintained at a lower level, treatment time could be reduced from 4.5 or 5 hrs to 3 hrs without significant change in morbidity. To maintain BUN level in shortened dialysis, use of large surface-area or high flux dialyzers and/or the enhancement of operational conditions such as raising Q_B and/or Q_D are needed. Increased efficiency of dialysis with acetate dialysate, however, may have an adverse effect on patients due to rapid loss of HCO_3^- at the initial phase of the treatment and accumulation of CH_3COO^- toward the end of the treatment[7,8]. Substituting bicarbonate for acetate dialysate in an efficient treatment can prevent the occurrence of a transient hypocapnia, but it renders treatment more cumbersome and expensive and it may raise another concern for alkalosis. If it becomes possible to independently control removal rates of nonionic solutes, such as urea, and ionic substances, such as HCO_3^-, by using a dialysis membrane with selective permeability without changing the composition of dialysate, it may be advantageous. Effect of the charge fixed to membranes to retard the permeability of ionic substances is theoretically known, but such an ionic dialysis membrane has not been available. Therefore, we made anionic PMMA membrane, TK-201, and investigated its characteristics comparing with a cellulosic membrane with surface area and UN permeability identical to those of TK-201. In our study, performance of TK-201 and Cellulose-B to remove UN and Cr without increasing their pretreatment levels in shortened dialysis was confirmed.

As to the effect on acid-base balance, however, significant difference was demonstrated between these 2 dialyzers. K_0 of HCO_3^- and CH_3COO^- with TK-201 was lower than that of Cellulose-B. Compared with a metabolic rate of CH_3COO^- (300 mEq/hr) already reported[7], the difference of CH_3COO^- permeability between 2 membranes was relatively small. However, as Kaiser et al pointed out[8], slight difference of permeability might cause critical clinical difference. According to our data, when $D_{HCO_3^-}/BW$ exceeded 2.7 ml/min/kg, the frequency of normal saline infusion rapidly increased, and slight discrepancy between D_{UN}/BW and $D_{HCO_3^-}/BW$ in rapid dialysis may create a significant effect.

Occurrence of clinical symptoms during treatment is multifactorial and, for example, biocompatibility, small and middle molecules permeability, and sterilization method of dialysis membranes may be contributing factors to it. In our study, significant difference in clinical symptoms was observed between TK-201 versus Cellulose-B and bicarbonate versus acetate dialysate. In these 2 comparisons, dialyzer or technique with which plasma HCO_3^- was maintained at a higher level, the patients became less symptomatic. Furthermore, to confirm that effect, anionic PMMA membrane with higher flux (H_2O in vitro UFCO; 70 ml/hr · mm Hg) than TK-201

(8.0 ml/hr · mm Hg) was tested with the same patients in long-term evaluations. This module had HCO_3^- permeability comparable to that of Cellulose-B, $[(K_0)_{HCO_3^-}/(K_0)_{UN} = 0.70]$, and during treatment with this module HCO_3^- level was low. Occurrence of clinical symptoms approximated that with Cellulose-B. These observations strongly suggest that acid-base control is one of the essential factors responsible for clinical symptoms in rapid dialysis.

Although our study was still preliminary, membrane with selective permeability based upon the charge fixed to it can be considered to be an important step to a dialysis membrane of the second generation.

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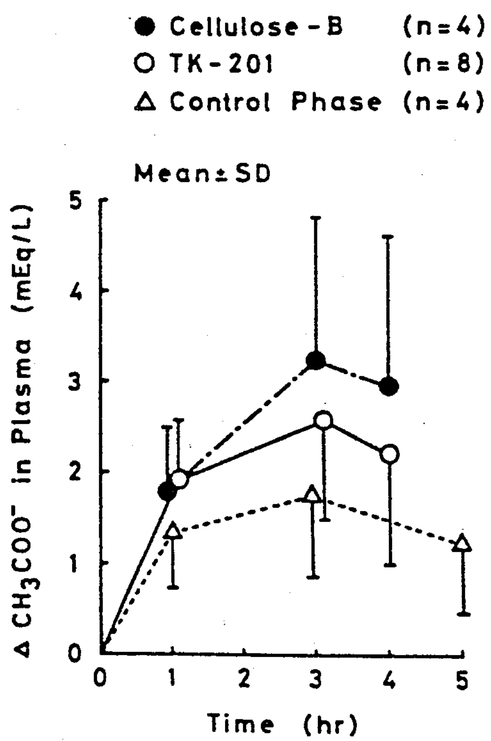

Figure 4. Increase in the plasma CH_3COO^- concentration during the treatment.

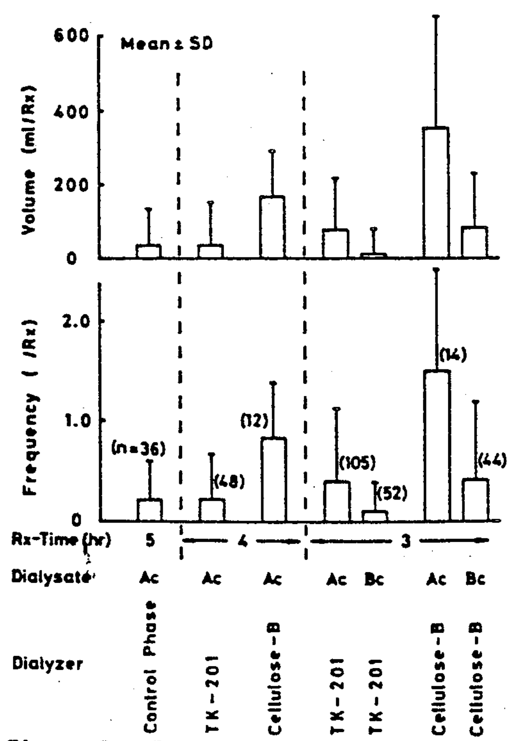

Figure 5. Frequency and volume of normal saline infusion during the treatment as one index of dialysis-related symptoms. (Ac and Bc mean acetate and bicarbonate dialysates, respectively.)