Development of New Plate-Type Hemofiltration Filter, Daicel "HemoFresh"
Design and Its Evaluation

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The generation rate of urea for HF patients (0.28±0.06g/hr) were compared with that for HD patients (0.38±0.05g/hr). Considering the removal of accumulated amount of urea for the term of treatments (14g), the suitability of HF treatment of 20 L. substitution was established. On the standpoint mentioned above, the new plate-type hemofiltration filter with high performance, DAICEL "HemoFresh" was developed. From the clinical test results for it, very high and stable performance, good biocompatibility were confirmed. All treatments were completed within 5 hrs with comfortable feeling of patients.

Key Words: Urea generation,
Urea removal,
DAICEL "HemoFresh"

(Introduction)

Recently hemofiltration (H.F.) has clinically been applied as a blood purification method for treatment of chronic renal failure. This new method has favorable effects on anemia, Ca and P metabolic disorders, lipid metabolic abnormalities, dialysis-resistant hypertension in long-term dialysis patients, and so called "dialysis difficulties" which develops during hemodialysis (H.D.).

Though 20 L. of substitution of body fluid in 5 hrs. has experimentally been adopted in HF treatment from the standpoint of solute removal.

We have been compelled to use two filters in series in a very complicated way to obtain a sufficient amount of ultrafiltration rate (UFR) because no satisfactory HF filter has been available.

By comparing of urea removal with urea generation, we tried to ensure the efficiency of the post-dilution mode by use of a new-type high performance HF filter "HemoFresh" developed by Daicel Chemical Industries, Ltd.

(Method and Patients)
The details of the hemofiltration machine and the technical procedures were previously reported by Yamagami, et al.

(1) To estimate the effects of the urea-nitrogen removal in HF patients, we compared it with that in HD patients.

The plasma urea-nitrogen concentration during the procedure was measured by sampling the blood every thirty minutes through the arterial line of the dialyzer and the filter. In respect to the body weight, residual renal function, the urea-nitrogen and protein concentrations in plasma, there were no significant differences between two groups. The removal rate was calculated from the pre- and post-treatment urea-nitrogen concentrations in plasma, there were no significant differences between two groups. The removal rate was calculated from the pre- and post-treatment urea-nitrogen concentrations in plasma. The amount of total removal of urea-nitrogen was calculated also from the total collection of dialysate during HD and filtrate during HF treatment, respectively. The total removal of urea-nitrogen was compared between dialyzers on the hollow-fiber-type artificial kidney and the coil-type one.
The urea generation rate was calculated from the amount of urea-nitrogen accumulated during the interval between treatments; 65% of body weight was assumed as the amount of total body fluid, and the urea space was assumed as one-pool of the body. There was no significant difference in residual function, protein concentration, or body weight loss between patients treated by HD and those by HF.

To evaluate Daicel "HemoFresh", ultrafiltration rate and sieving coefficient for several solutes were measured in vitro, ex vivo and in vivo. The amounts of residual blood and protein in the filter as well as the amount of protein lost in the filtrate were also measured.

(a) Model solutions were prepared to determine the solute permeability. The compositions of the test solutions were as follows: In vitro: albumin (molecular weight 46,000), 0.2%; vitamin B₁₂ (MW 1,355), 0.002%; and urea (MW 60), 0.1%. The concentration was measured by high performance aqueous G.P.C. Ex vivo (mongrel dogs of 10-15kg): cytochrome-C (MW 12,800), inulin (MW 5,000), vitamin B₁₂ (MW 1,355) and creatinine. Concentrations of albumin and cytochrome-C in the blood and filtrate were measured by high performance aqueous G.P.C., that of inulin by resorcinol-thiourea colorimetry, those of vitamin B₁₂ and creatinine by reversed phase HPLC.

(b) The amounts of residual protein and blood in the filter were determined on the basis of cynomethohemoglobin values after washing by circulating with a 0.04% NH₃ solution. Even small coagula was dissolved by this method. Residual protein in the filter was determined by Lowry's method. Protein loss in the filtrate during HF treatment was determined by the Bio Rad protein assay method.

(4) Patients.

For clinical evaluation of HF and performance of "HemoFresh", seventeen stable patients were treated with the artificial kidney for more than a year at the Dept. of H.D., Tadaoka Public Hospital. Chronic glomerulonephritis was the underlying disease that led to renal insufficiency in all patients.

(Results)

(1) The total amount of the urea-nitrogen removal by HF treatment was 14.29±5.13g (M±S.D.N=15) and that by HD treatment using the hollow fiber kidney was 23.16±5.46g (M±S.D.N=7). The plasma extraction ratio for urea was 49.93±2.83% by HF. The ratio was significantly lower than that by HD, being 58.29±5.08% (P<0.005). As shown in Fig.1, however, the amount of urea removed on the coil-type dialyzer was almost the same as that by HF; whereas the plasma extraction ratio by HD was significantly higher than that by HF.

The urea-nitrogen-decay curve during HF was slightly different from that during HD as shown in Fig.2.

-- (2) The urea generation rates for
the patients treated by HD and those by HF are shown in Fig. 3. There was no significant difference in the pre-treatment urea-nitrogen concentration between HD and HF patients. The post-treatment urea-nitrogen concentration was lower in HD than in HF patients. From the urea generation rate during the interval of 48 hrs. between treatments, therefore, the generation rate for HD patients seems to be significantly higher than that for HF patients.

(3) The specifications of Daicel "HemoFresh" are shown in Table 1. The membrane is made of cellulose diacetate; the effective membrane surface area is 0.7m². It is a modified plate-type filter with a built in colgate spacer that keep the thickness fo blood compartment. The priming volume is 70ml. The residual blood after application averaged 0.26ml and the residual protein in the filter 0.12g.

The solute permeabilities both in vivo and ex vivo are shown in Fig. 4. In vitro permeabilities of urea, vitamin B₁₂, inulin, cytochrome C in the protein solution through this filter were 100%. In the study of canis ex vivo, the permeabilities of these solutes were 100%, 98%, 68% and 43%, respectively.

The relationship between serum protein concentration and UFR is shown in Fig. 5.

The ultrafiltration rate decreased as function of the total protein concentration.

(4) The decay curve of UFR is shown in Fig. 6.

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**Table 1** SPECIFICATION OF DAICEL "HemoFresh"

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DAICEL HemoFresh</th>
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</thead>
<tbody>
<tr>
<td>MATERIAL</td>
<td>MODIFIED PLATE</td>
</tr>
<tr>
<td>WALL THICKNESS</td>
<td>200µ</td>
</tr>
<tr>
<td>SURFACE AREA</td>
<td>0.7m²</td>
</tr>
<tr>
<td>PRIMING VOLUME</td>
<td>70ml</td>
</tr>
<tr>
<td>RESIDUAL BLOOD</td>
<td>0.26±0.07ml M±SD N=5</td>
</tr>
<tr>
<td>RESIDUAL PROTEIN</td>
<td>0.12±0.05g M±SD N=5</td>
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Fig. 6. When Q(B) was 200 ml/min, the filtrate decreased from 89±7 ml/min to 74±9 ml/min in 4 hrs. UFR decreased only by 17% of the initial value. The protein loss in the filtrate was 1.7±0.4 g (N=5, M±S.D.)

(5) Changes in each electrolyte, in blood cell counts and in hemoanalysis were as follows: Na 139±3 mEq/L, K 4.5±0.9, Ca 4.6±0.4, Mg 3.2±0.4 mg/dl, P 6.6±1.5. Each constituent of blood: Ht (%) 20.3±3.0, RBC (10^6/mm) 221±49, WBC (10^2/mm) 66±24, Hb (g/dl) 6.6±0.9, thrombocytes (10^4/mm) 15.6±3.2, BUN (mg/dl) 81.6±16.6, Cr (mg/dl) 14.0±1.1, uric acid (mg/dl) 9.4±2.3.

(Discussion)

Quellhorst, et al. proposed that 20 L of substitution fluid is enough comparing corrected pre- and post-treatment values of serum solute concentrations and removal rates of metabolic wastes with those in HD patients.

Clearance is a function of UFR if the sieving coefficients of the solute is 1.0. The total removal rate by HF can not be estimated by only clearance, because the solute transfer between the compartments was quite different from that in HD. Based on the middle molecular hypothesis by Babb and Scibner, it can be expected that HF removing much more middle molecular solutes than does HD is clinically more effective than HD. HF may be better if a required amount of such small molecular solutes can be eliminated by 20 L substitution, though it is believed generally that HD is a better treatment for removal of the small molecular solutes.

More than 23 g of urea is remove by a single HD treatment, but only 14 g of urea seems to be removed by a single HF treatment. Such a small amount of urea removed, however, is enough for HF treatment because the generation rate of urea in HF patients is lower by 0.1 g/h than that in HD patients and the amount of urea generated in 48 hrs is about 14 g.

From this fact, the urea-nitrogen removal by HF is considered to induce physiological effect on metabolism of urea and other substances.

From the standpoint considered above, we developed a new plate-type filter to substitute more than 20 L within 5 hrs. The mean value of ultrafiltrate rate is 77 ml/min, UFR changed from 87±7 ml/min to 74±9 ml/min and the final UFR is about 83% of initial UFR. It may depend both on the gel layer formed on the membrane surface and on the increased protein concentration caused by water removal. In anyway, substitution of 22 to 24 L can be performed by HF in 5 hrs. by filtration at on UFR of 77 ml/min. From the result of in vivo tests, protein loss is 1.7 g per treatment and residual blood is only 0.26±0.07 ml (M±S.D., N=5)

As to the influence on blood, there are no significant differences between Daicei "HemoFresh" and other filters used for HF and HD. Daicei "HemoFresh" may have proper biocompatibility. Biocompatibility for the artificial kidney, however, should be concluded from long-term tests, therefore further investigations seem necessary.

(References)