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Nurol Arık[a]
Hakan Yüksel[a]
Bahattin Adam[b]
Tekin Akpolat[a]
Oktay Özdemir[c]

Departments of
[a] Nephrology and
[b] Biochemistry, Ondokuz Mayıs University School of Medicine and
[c] Hacettepe University School of Medicine, Department of Hematology, Ankara, Turkey

May Colchicine Therapy Be of Value in the Prevention of Dialysis Amyloidosis?

Dear Sir,

Dialysis-related amyloidosis (DA) is a major complication of long-term hemodialysis (HD) inducing carpal tunnel syndrome, diffuse osteoarthropathy, bone cysts, and pathologic fractures with soft tissue involvement [1–4]. β_2-Microglobulin (β_2m) polymers are the principal constituents of this form amyloidosis [1, 5, 6]. β_2m is expressed on the cell surface of all nucleated cells and is also released from intragranular stores by degranulating granulocytes as occurs during HD with complement-activating membranes [5, 7, 8]. The exact pathogenetic mechanisms of DA have not been determined in HD patients dialysed by cuprophane membrane, but some biocompatibility factors such as increased synthesis and release of β_2m by granulocytes, release of proteases and reactive oxygen species which favor polymerization of β_2m into amyloid and failure of clearance of β_2m from the circulation by low-flux cellulosic membranes have been suggested as the possible hypothetical factors in the genesis of DA [9]. Colchicine, a drug commonly considered as one of the most potent inhibitors of granulocyte degranulation, has been reported to inhibit the decrease of circulating granulocytes during HD [10]. Besides this agent was reported to be able to prevent HD-induced polymorphonuclear neutrophil (PMN) degranulation [10].

In view of the latter data and the increased release of β_2m by PMNs during HD, which was suggested as one of the main causative mechanisms of DA, we wondered whether colchicine might be of value in the prevention of DA via inhibition of β_2m release from PMN during HD.

We studied 15 patients (5 men, 10 women) ranging in age from 17 to 57 (mean ± SD, 39.3 ± 14.0). All patients were on regular HD, performed for 4 h, 3 times a week with acetate-containing dialysate and cuprophane membrane. Informed consent was obtained from all patients prior to the study. A preliminary study was performed with parallel-plate dialyzers and hollow-fiber dialyzers, whereafter colchicine, at a total dose of 3 mg/24 h, was administered orally to all the patients. Just after the last dose of colchicine, we repeated the same protocol with only hollow-fiber dialyzers. Blood samples for plasma β_2m levels and white blood cell (WBC) counts were drawn from the arteriel site of the dialyzer at 0, 15, 60, 240 min after connecting the patients to the dialysis unit. As to the interpretation of β_2m levels, in order to avoid the errors originating from volume changes during HD, plasma β_2m levels were expressed as values corrected for hemoconcentration. Hematocrit (Hct) correction factor was calculated from the quotient $(100 - Hct_{postdialysis})/(100 - Hct_{predialysis})$. Plasma β_2m levels were determined by a commercially available immunoenzymatic assay (Abbott Laboratories).

Repeated-measures analysis of variance with two within-subject effects (time and membrane type; time and treatment) was performed. Difference contrast was performed for comparison of group means of β_2m and WBCs. Difference contrasts were used for pairwise comparisons. Statistical significance was assigned to p values <0.05 for repeated-measures analysis of variance. Student's t test for paired samples was used for comparison of means at different times. Statistical significance was assigned to p values <0.016 (0.05/3) (Bonferroni modification) in order to avoid an increase in type I error.

The changes in plasma β_2m levels and WBC counts during HD before and after colchicine therapy are shown in tables 1 and 2. β_2m levels and WBC counts changed with time on HD with parallel-plate and hollow-fiber dialyzers (time effect, $p < 0.05$). Neither type of membrane nor colchicine therapy affected the β_2m alteration profile during HD (tables 3, 4). (p: 0.74, p: 0.34). The parallelism of the time curves of β_2m levels did not change with different types of membrane and short-term cholchicine therapy (p: 0.54, p: 0.31).

There were marked drops in mean WBC counts with two types of membrane at 15 min; subsequently, in dialyses with hollow-fiber dialyzers, mean WBC count returned to predialysis level at 60 min and remained so at 240 min. On the contrary, marked leukopenia persisted during all the measurements in dialyses performed with parallel-plate membranes ($p < 0.05$). We did not observe any effect of colchicine on mean WBC counts during the study (p: 0.09).

Mean baseline β_2m level at 0 min was 47.2 ± 13.8 mg/l before colchicine therapy

KARGER
E-Mail karger@karger.ch
Fax + 41 61 306 12 34

0028–2766/96/0732–0365$10.00/0

Nurol Arık
Ondokuz Mayıs Üniversitesi
Tıp Fakültesi, Nefroloji Bölümü
55139 Kurupelit
Samsun (Turkey)

Table 1. Mean plasma β_2m levels during hemodialysis (mg/l)

	Time			
	0 min	15 min	60 min	240 min
A	46.4	49.5	50.5	57.7*
B	47.2	46.7	50.1	56.9*
C	49.1	49.8	49.4	57.4*

A = Mean plasma β_2m levels with parallel-plate dialysers; B = mean plasma β_2m levels with hollow-fiber dialzyers (pretreatment); C = mean plasma β_2m levels with hollow-fiber dialzyers (postreatment).

* $p < 0.05$.

Table 2. Mean WBC counts during hemodialysis (mm^3)

	Time			
	0 min	15 min	60 min	240 min
D	6,173	2,613*	4,893*	5,273*
E	6,187	2,773*	6,113	6,663
F	6,000	2,280*	5,353	6,380

D = Mean WBC counts with parallel-plate dialyzers; E = mean WBC counts with hollow-fiber dialyzers (pretreatment); F = mean WBC counts with hollow-fiber dialyzers (posttreatment).

* $p < 0.05$.

Table 3. Repeated-measures analysis of variance

	β_2m	WBC
Membrane effect	0.74	0.035
Time effect	0.001	0.001
Paralellism	0.54	0.02

Table 4. Repeated-measures analysis of variance

	β_2m	WBC
Colchicine effect	0.34	0.09
Time effect	0.002	0.001
Paralellism	0.31	0.74

with hollow-fiber dialyzers. Corrected mean β_2m level rose to 56.9 ± 10.7 at 240 min (p: 0.002). Mean plasma β_2m levels at 15 and 60 min did not differ statistically from the baseline value (p: 0.73, p: 0.11).

The precise mechanisms of the development of DA is not well understood; it has thus been difficult to prevent and no established effective treatment is available. Considering the complex physiopathologic picture of DA, we did not expect, colchicine to solve all the practical matters related to the prevention of DA in this preliminary study, but we wondered whether it might be of any value in the conservative management of DA.

Unfortunately, colchicine administration did not affect the β_2m alteration profile during HD with cuprophane membranes in the present study. In other words, although colchine was suggested to be a helpful drug in in the prevention of some HD-associated events originating from the interaction of cellulosic membrane with blood constituents, our results do not encourage us to use it for the prophylaxis of β_2m amyloidosis [10]. In analogy to the favorable results obtained with colchicine in AA amyloidosis associated with FMF, a short-term study undertaken in a limited number of HD patients to determine the role of colchicine in the prevention of β_2m release was reported before [11]. The results of that latter study were not very encouraging either. The role of long-term colchicine treatment in the prophylaxis of DA has not been documented and could be worth studying.

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