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Evaluation of Aluminum Concentration in Albumin Products Prepared by Blood Fractionation

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ABSTRACT

Human Serum albumin as well as other biological products prepared by blood fractionation for clinical purposes, was found to contain different amount of aluminum in different commercially available human albumin solutions. It has been reported that interaction of chemicals with the container material can occur during plasma collection, manufacture and storage, so aluminum is introduced into albumin products. Albumin solution is produced by Cohn fractionation. These solutions were analyzed and albumin content was measured by atomic absorption spectrometry, using electrothermal atomizer (Graphite Furnace) and the aluminum concentration in final products and in-process fractions in 21 batch of albumin 20% and 8 batch of albumin 5% were investigated. Also the content of aluminum was determined after 3 months storage in glass container. We found that the aluminum content in all investigated containers had remarkably reduced during the fractionation process. Only in one stage the aluminum content has been increased, and it is probably due to the filters and other chemicals which are used to adjust pH and electrolyte concentration. On the other hand concentration may have an important role in increasing aluminum content in this stage. Aluminum overload may result in development of some diseases, so indicating the need to monitor aluminum level in the albumin to avoid the potential hazard.

Keywords: *Aluminum, Albumin, Atomic absorption, Plasma fractionation*

Human serum albumin is the most plentiful plasma protein, and considered as the most physiological solution for volume loading, can be widely used in patients with renal, cardiac and respiratory injuries. Human Serum albumin products are used to treat hypoalbuminaemia or hemorrhagic shock. The contamination of albumin by metals especially by aluminum, is a major concept in preparing albumin solutions, because aluminum toxicity in human being has been increased in patients receiving hemodialysis, and patients who had died with dialysis encephalopathy syndrome had brain gray matter aluminum levels that were 3 times higher the normal [1].

Aluminum is introduced into albumin products via materials (Diatomaceous earth filters aid or diatomaceous containing depth filters) used in manufacturing process, resulting in a high aluminum level in the final product [2]. Sodium citrate, anticoagulant, contributes significantly to the aluminum load of source plasma and therefore to the aluminum content of products such as albumin derived from plasma [3].

Diatomaceous earth filter aid, as a material used in manufacturing process, also increase aluminum in the solution. Although appropriate procedures of manufacturing can reduce aluminum in albumin products [4]. Leaching of aluminum from glass containers during storage has also been reported [5].

Recently the relationship between aluminum and some diseases, for example, bone disease or nervous disorders in patients on chronic hemodialysis, have drawn much attention. They may be caused by dialysis solutions with a high aluminum level [6-11].

The European Pharmacopoeia monograph specifies that the aluminum concentration in albumin products used for patients on hemodialysis and premature infants shall be 200 μg/L or less. So evaluation of aluminum concentration in albumin product is a basic and useful parameter. Albumin solution is produced by Cohn fractionation.

The aim of this study was setting a method for aluminum measurement in albumin solution (5% and 20%) by atomic absorption spectrometry, using electrothermal atomizer (Graphite Furnace) in Iran for the first time and evaluation the aluminum content in intermediate products, final products and also after 3 months storage these products in glass container, because it is important

Table 1. Comparison of aluminum concentration (μg/L) in different stages of batch production.

Batchs of Alb 20%	1	2	3	4	5	6	7	8
No . 1	843	224	101	160	220	360	498	414
No . 2	894	705	807	603	300	450	669	879
No . 3	1044	654	140	121	274	306	431	441
No . 4	852	549	156	495	397	286	501	522
No . 5	795	159	192	65	204	210	540	579
No . 6	832	119	166	44	250	164	414	318
No . 7	747	142	121	56	283	196	255	332
No . 8	756	164	155	426	450	268	371	339
No . 9	792	178	177	333	168	152	347	360
No . 10	777	204	447	88	286	228	354	288
Mean ± SD	833.2 ± 67.1	309.8 ± 230.1	246.2 ± 219.5	239.1± 207.3	283.2 ± 85.5	262 ± 92.8	438 ± 117.9	447.2 ± 178
CV%	10.5	74.3	89.1	86.7	30.2	35.4	45	39.8

1: Primary Plasma
2: After dissolution of paste V
3: After Ultrafiltration
4: Before Dialysis
5: After Dialysis
6: After Concentration
7: After pH Adjustment
8: Final Bulk Product

to determine the aluminum concentration in albumin products for the patients undergoing dialysis or the premature infants.

MATERIALS AND METHODS

Samples were collected from routine fractionation process in albumin production. These fractions were:

1. Primary pooled plasma
2. After dissolution of paste V in buffer solution
3. After ultrafiltration
4. Before Dialysis
5. After dialysis with distilled buffer
6. After concentration of the solution
7. After pH adjustment
8. Final bulk product before filling

Samples from 10 production run were examined, and also the ordinary albumin products including 21 batches of albumin 20% and 8 batches of albumin 5% were analyzed for the content of aluminum.

A Graphite furnace Atomic Absorption Spectrometer (AA-680 Japan) was used to measure the aluminum concentration in the solutions. The samples were diluted with the sample diluent solution (0.5 ml of HNO_3 0.5% in 100 ml 0.15% Triton X-100) before measuring the aluminum concentration. The fractions and albumin 5% were diluted 1:3 and albumin 20% were diluted 1:5. The working standard solutions (50, 100, 200 and 300 μg/L aluminum) were prepared by diluting with the sample diluent solution from aluminum stock solution 1 ppm. All of the samples and standards were prepared in plastic containers. The instrument was set to measure each sample in 309.3 nm 2 times and if CV was over 20% the third measurement was done. If the CV after third injection was more than 20% the sample was repeated.

RESULTS

Table 1 shows the concentration of aluminum in 8 fractions of 10 batches. The concentration of aluminum in primary plasma was in its highest rate (833.2± 87.11 μg/L). After fractionation the content of aluminum was decreased about 3 folds (309.8 ± 23 μg/L) and it has been maintained constant in other steps of manufacturing process. Only concentration can increase aluminum content in this process (447±17).

Table 2 shows concentration of aluminum in final albumin 20% solution (247 ± 88.7 μg/L) and Table 3 shows concentration of aluminum in albumin 5% (157.5 ± 57.1 μg/L).

The glass containers which are used in the company for the albumin solution were examined for aluminum leakage. They were tested 3 months after the first measurement. The results in Table 4 show no significant change in aluminum during this period (215.9 ± 49.9).

DISCUSSION

We have set up a method for aluminum measurement in albumin solutions in Iran for the first time.

We also have examined different stages in albumin purification to measure the aluminum concentration in albumin products. The high concentration of aluminum in primary plasma is probably due to the usage of anticoagulants which may introduce a high level of aluminum. We found that the aluminum concentration in albumin solution is remarkably reduced in fractionation process. Only in one stage the aluminum content has

Table 2. Aluminum concentration in albumin 20% solution.

Batch of albumin 20%	Aluminum concentration (μg/L)
No. 1	228
No. 2	287
No. 3	354
No. 4	150
No. 5	214
No. 5	275
No. 7	468
No. 8	360
No. 9	197
No. 10	376
No. 11	200
No. 12	266
No. 13	272
No. 14	266
No. 15	263
No. 16	210
No. 17	187
No. 18	169
No. 19	91
No. 20	215
Mean ± SD	247 ± 88.7
CV%	35.9

Table 3. Aluminum concentration in albumin 20% solution.

Batch of albumin 5%	Aluminum concentration (µg/L)
No. 1	166
No. 2	35
No. 3	180
No. 4	75
No. 5	60
No. 6	240
No. 7	252
No. 8	252
Mean ± SD	157.5 ± 69.9
CV%	57.1

Table 4. Aluminum content of albumin 20% (µg/L) solution before and after 3 months.

Batches of albumin 20	Before 3 months	After 3 months
No. 1	287	279
No. 2	354	248
No. 3	275	206
No. 4	170	175
No. 5	197	160
No. 6	376	300
No. 7	272	285
No. 8	263	210
No. 9	210	205
No. 10	187	188
No. 11	139	160
No. 12	175	175
Mean ± SD	241±74.7	215.9 ± 49.9
CV%	22.3	23.1

been increased and it is probably due to the filters and other chemicals which are used to adjust pH and electrolyte concentration. On the other hand concentration may have an important role in increasing aluminum content in this stage.

The content of aluminum in final products in most cases is lower than that stated in European Pharmacopoeia. They have recommended that not more than 200 µg/L must be measured, if the albumin solution is intended for administration to patients under dialysis or to premature infants, and otherwise it must be mentioned on the label.

Storage of albumin products in glass containers used in Iran has no significant effect on aluminum concentration in albumin products during storage and therefore they are recommended for further use.

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