Biologicals 44 (2016) 591–595

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Short paper

Study of twenty preparations of human albumin solution which failed in quality control testing due to elevated sodium content, a poor internal quality control at manufacturing unit

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ARTICLE INFO

Article history:
Received 26 October 2015
Received in revised form
7 August 2016
Accepted 5 September 2016
Available online 10 October 2016

Keywords:
Human albumin solution
Sodium
Quality control
Trend analysis

ABSTRACT

Current study is conducted in our laboratory due to failure in quality control testing of twenty batches of Human Albumin solution in which sodium content is higher than the prescribed limit. These batches are received in short duration from indigenous manufacturer and is the first incident of failure of Human albumin preparation in sodium content of manufacturer. On request of manufacturer, study is conducted to rule out the cause. Repeat testing of each out of specification batch is conducted and a trend analysis is drawn between our findings and manufacturer's results, also study of trend analysis of manufacturer for the last one year. Trend analysis data indicated towards poor consistency of batches with major shift at various time intervals in sodium content of human albumin preparation. Further analysis rule out that non-traceable quality of standard used in the internal quality control testing by manufacturer is the root cause of the problem.

1. Introduction

Albumin is a major constituent of plasma protein contributing around 60% in a normal healthy human. It has a molecular weight of around 67 KD, low serum viscosity with a highly soluble net negatively charged molecule. Albumin is accountable for about 70% of plasma oncotic pressure [1] and plays critical role in regulating distribution of fluid between body compartments. Albumin has the ability to bind with both cations and anions; therefore, it can function as a carrier for a large number of metabolites including fatty acids, ions, thyroxine, bilirubin and amino acids [1]. Albumin plays a vital role in human homeostasis and disease state. Human albumin solution are intended in clinical condition such as Hemorrhagic & Nonhemorrhagic Shock, Hepatic Resection, Cerebral Ischemia, Thermal Injury, Nutritional Intervention, Cardiac Surgery, Hyper-bilirubinemia of the newborn, Nephrotic syndrome, Organ transplantation and Plasmapheresis [2]. Human Albumin solution is mainly manufactured by the Cohn-Oncley cold ethanol fractionation or chromatography separation process of large volume of Human plasma followed by ultra- and infiltration followed by pasteurization. Such blood derived products require regulatory authority approval and certificate of analysis for standard quality before releasing into the market. These regulatory agencies maintain stringent quality control testing for each batch of blood derived biological received for testing as per their respective Pharmacopial monograph for ensuring of safety of end-user. Human Albumin solution (HAS) as per Indian Pharmacopeia 2014 [3] requires in total 16 biological and chemical testing before releasing the finished product in the market. Sodium content is one of the critical parameter and its prescribed limit is $\leq$ 160 mmol/L [3]. National Institute of Biologicals (NIB) was established under the Ministry of Health & Family Welfare (MOHFW)-Government of India with the financial & technical help of USAID & OECA Japan for assuring the availability of high standard and good quality biological products for consumption in India and for exports. Blood products laboratory under NIB is the only central drug testing laboratory for eight blood derived products like Human albumin, Immunoglobulins, and Blood Clotting Factor VIII, Factor IX, Anti-thrombin III and Fibrin sealant kits in India. During April 2014–May 2015, NIB received 196 batches of Human Albumin Solution 20% (HAS) from one of the indigenous manufacturer for batch quality testing and out of which

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http://dx.doi.org/10.1016/j.biologicals.2016.09.001
1045-1056/

20 batches were not of standard quality due to high sodium content in it which leads to a huge financial loss for the manufacturer and shortage of Human Albumin preparation in local markets moreover, If such out of specification (OOS) quality of biologicals were consumed by patients, it could be life threatening specially drugs which are directly intravenous infused which causes rapid onset & progress of adverse reaction. In case of Human albumin, with such high sodium content transfused lead to Hypervolemia and if not treated on time may cause congestive heart failure, kidney and liver failure. As, it is the first ever case in our testing laboratory in which albumin found to be not of standard quality due to high sodium content in huge number, indicating any quality control lapse during manufacturing processing or testing. This indigenous manufacturers is producing HAS for the last five years and NIB has not found any non-compliance in a large volume of batches received previously. So, the current study was conducted to rule out the root cause and suggest a preventive action to the manufacturer to strengthen indigenous manufacturing and to come out in favor of public health. From, human plasma fractionation to 20% (IV) Human normal albumin preparation, major source of sodium contributors are sodium caprylate used as stabilizer and sodium chloride. Sodium chloride is added in final preparation in such a calculated adjustment so that the sodium content must be up to 145 mmol/L, only exceptions are low sodium preparation keeping this as the main focus, Pharmacopial and various National Regulate Authority has set the prescribed limit up to 160 mmol/L for sodium content in human albumin preparation. Major source of error can be pre analytical during preparation of bulk and bulk to 20% human albumin preparation like wrong calculation or over weighing of these contents. Second analytical fault in measuring instrument, control, diluent, standard and last post analytical after packaging some leaching from container.

2. Material method

2.1. Sample receiving, coding & decoding

NIB has a Sample Receiving & Report Dispatching Unit (SRRDU) which works totally as a separate unit with testing laboratory. SRRDU receives required quantity and document of samples as stated on institutional web site along with referred letter by Central Drugs Standard Control Organization (CDSCO) office or State Drug Control office with consent manufacturing product document like manufacturing process documents, source of plasma pool, and method of viral inactivation, certificate of analysis finished product. SRRDU receives the samples and issues receipt of the same after verifying the quantity of vials, and document required for testing. SRRDU enter the details in consent register and computer format along with box number assigned for keeping document labels and storage box details. SRRDU removes or hides the labels & carton pack form sample to be sent for testing in laboratory (with non-transparent & non removable tape) and place a unique coding identity number on each vial of batch received. Each label is removed; inserted and cartons are placed with other document to respective box and retain samples in respective storage box for storage as per manufacturer's instruction. Sample to test is then forwarded to the testing laboratory along with sample receipt register containing some details like type of product, concentration of product as per label claim. During coding and transportation of sample, cold chain is maintained by using cooling box or box with dry ice for maintaining the cold chain. As in case of human normal albumin, eight vials 50 ml or 100 ml are required. SRRDU keeps 4 vials to be retained with them and 4 are sent to the testing laboratory. Testing laboratory number the vial (01/04 to 04/04) which received from SRRDU and uses 02/04 vial for sterility testing, 03/04 pyrogen testing, 04/04 abnormal toxicity and from vial no 01/04 further 10 sub aliquot of 1.5 ml (01/10-10/10) are prepared in aseptic condition for testing protein concentration, identification, protein composition, sodium, potassium, pH, Heam content, Transfusion transmitted infection like HIV 1&2, anti HCV and HBs Ag tests. Vial 01/04 cap further seal with parafilm and stored at referred temperature. Test laboratory performs the test in HAS and then submit their results through tamper proof computer software online and a hard copy of all results in a file is sent to SRRDU for decoding. SRRDU generates the analysis report for coded sample placed with them in hard copies of result and close the file. Now, coded file is sent to the decoded section of SRRDU which keeps the records and issues the consent box containing labels & protocol documents of respective batch. SRRDU places them in a file and sends it to the concerned lab for protocol scrutiny & generation of Certificate of Analysis, the concerned lab generates the Certificate of Analysis approved & verified by concerned authority and then sends it to archive department and for online release at our official web site.

2.2. Sodium estimation & repeat testing protocol for out of specification batches

Sodium estimation is performed by atomic absorption spectroscopy using Thermo Scientific™ iCE™ 3000 AAS and AccTrace reference lot no 212115084 tractability with National Institute of Standards & Technology Reference Material. In brief, a standard graph was plotted with reference standard using concentration 0.0 ppm, 0.6 ppm, 0.8 ppm, 1.0 ppm and 2.0 ppm with regression coefficient more than 0.995 as shown in Fig. 3. Along with an In-house control validated against international reference standard [4]. Each test is performed in duplicate. If any test result is found out of specification, then Repeating of out of specification is performed as per standard operating procedure Title “Repeat testing protocol [5] for out of specification samples” in short two retain bottles from SRRDU were collected for repeat testing, then two different analyst were deputed for testing, each analyst performed the test from these three bottles in replicate.

2.3. Trend analysis plotting

Trend analysis charts are prepared between out-of specification HAS sodium content results of indigenous manufacturers and NIB as shown in Fig. 1, both results were Statistical analysis using GraphPad Prism 7.0, mean, standard deviation, standard error of mean & %RSD followed by the student t-test. Significance was considered at the $P < 0.05$ level as shown in Table 1. Second, Levey-Jennings (LJ) Control Chart plotted between data from April 2014–May 2015 in-house control with $\pm$ 2SD limit and NIB results of indigenous manufacturer. All the suggestive trends recorded and analysis as shown in Fig. 2.

3. Results

3.1. Sodium estimation & repeat testing

Total 20 HAS batches of indigenous manufacturer are found to be OOS as shown in Table 1 out of 197 batches tested. All the results for the In-House controls are obtained within the specified limits and standard curve regression coefficient obtained more than 0.995 for each of the tested batch. Repeat testing of out of specification of samples confirm that these 20 batches are not of standard Quality as a result shown in Table 1.